UNIVERSITY OF SOUTHAMPTON

FACULTY OF Natural and Environmental Sciences

School of Chemistry

Towards the Total Synthesis of Chrysophaentin F

by

Jean-Baptiste Vendeville

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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This thesis describes the synthetic work towards the natural product Chrysophaentin F which has been extracted from the alga *Chrysophaeum taylori*. This bisdiarylbutene macrocycle exhibits antimicrobial properties against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF) (MIC_{50} (MRSA) = 4.2 ± 1.3 μg/mL).

Investigation of the key steps on an unchlorinated analogue allowed us to determine what strategy would be best to access the natural product. The formation of the desired core structure relied on a Chan-Lam-Evans coupling reaction, a Pd catalysed coupling reaction and a RCAM reaction to create the pivotal bonds of the complex scaffold. The investigation on a model system to form the vinyl chloride bridge has also been performed bringing insight on the possible regioselectivity of the necessary late stage hydrochlorination reaction.

Finally the synthesis towards the chlorinated macrocycle was started and advanced enough to access some key intermediates which despite some unforeseen difficulties proved that the natural product is now at reach following the strategy developed for the unchlorinated analogue.

Contents

DECLARATION OF AUTHORSHIP

I, Jean-Baptiste Vendeville

declare that the thesis entitled

Towards the Total Synthesis of Chrysophaentin F

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. 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;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- 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;
- none of this work has been published before submission.

Signed: ……..

Date:…….

Acknowledgements

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“Make the most of yourself...for that is all there is of you”

Ralph Waldo Emerson

Definitions and Abbreviations

ACN	acetonitrile
App.	apparent
ARAP	A*STAR research attachment programme
A*STAR	agency for science, technology and research
BBBPy	4,4′-di-tert-butyl-2,2′-dipyridyl
br	broad
conc.	Concentrated
cp	cyclopentadienyl
COD	1,5-cyclooctadiene
d	doublet
DCM	dichloromethane
DIBALH	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DME	dimethoxyethane
DMF	dimethyl formamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide

dppf	1,1'-bis(diphenylphosphino)ferrocene
EI	electron ionisation, electron impact
equiv.	equivalents
ES	electrospray
FDA	food and drug administration
FT	fourier transformation
FtsZ	Filamenting temperature sensitive mutant Z
GC	gas chromatography
GTP	guanosine triphosphate
HMBC	heteronuclear multiple-bond correlation
HMQC	heteronuclear single-quantum correlation
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
ICES	Institute of Chemical and Engineering Sciences
IR	infra red
LiHMDS	lithium hexamethyldisilazide
LRMS	low resolution mass spectrometry
LTMDA	lithium N,N,N′-trimethylethylenediamine

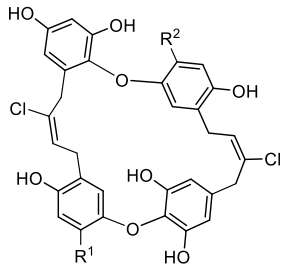
MOM	methoxy methyl
MP	melting point
MRSA	methicillin resistant *Streptococcus aureus*
NBS	*N*–bromosuccinimide
NCS	*N*–chlorosuccinimide
NMR	nuclear magnetic resonance spectroscopy
PDC	pyridinium dichromate
PMA	phosphomolybdic acid
ppm	parts per million
Py	pyridine
RCAM	ring closing alkyne metathesis
RCM	ring closing metathesis
RT	room temperature
sat.	saturated
S_NAr	nucleophilic aromatic substitution
sol.	Solution
TBAF	tetra–*n*–butylammonium fluoride
TBAI	tetra–*n*–butylammonium iodide
Tf	trifluoromethanesulfonyl

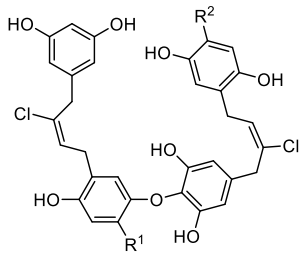
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMS	trimethylsilyl
TPE	tetraphenylethylene
p-TSA	p-toluenesulfonic acid
UV	ultraviolet
VREF	vancomycin resistant *Enterococcus faecium*
δ	chemical shift
Δ	heating at reflux
μW	microwave

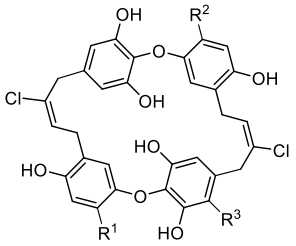
1. Introduction

1.1 Chrysophaentin F

The project was undertaken as a partnership between Chemistry at The University of Southampton and the Institute of Chemical and Engineering Sciences (ICES) in the A*STAR institute, Singapore, as part of the A*STAR Research Attachment Programme (ARAP). The aim was to develop a robust route towards chrysophaentin F **1.8** that would give access to other chrysophaentins and facilitate the pharmacomodulation of chrysophaentin F. Chrysophaentin F **1.8** was isolated from the marine Chrysophyte alga *Chrysophaeum Taylori* in 2010 by Bewley *et al.*, along with chrysophaentins A–H (Figure 1.1).[1, 2] Extracts of this alga had shown interesting biological activity against multi-drug resistant bacteria, inhibiting the growth of *S. aureus* and *E. faecium*.[2]







A : $R^1 = R^2 = Cl$ **1.1**
B : $R^1 = Br\ R^2 = Cl$ **1.2**
C : $R^1 = Cl\ R^2 = Br$ **1.3**
D : $R^1 = R^2 = Br$ **1.4**

E : $R^1 = R^2 = Cl$ **1.5**
E_1 : $R^1 = Cl\ R^2 = Br$ **1.6**
E_2 : $R^1 = Br\ R^2 = Cl$ **1.7**

F : $R^1 = R^2 = Cl\ R^3 = H$ **1.8**
G : $R^1 = Cl\ R^2 = Br\ R^3 = H$ **1.9**
H : $R^1 = R^2 = Cl\ R^3 = Br$ **1.10**

Figure 1.1. Chrysophaentin A–H

1.2 The threat of resistant bacteria

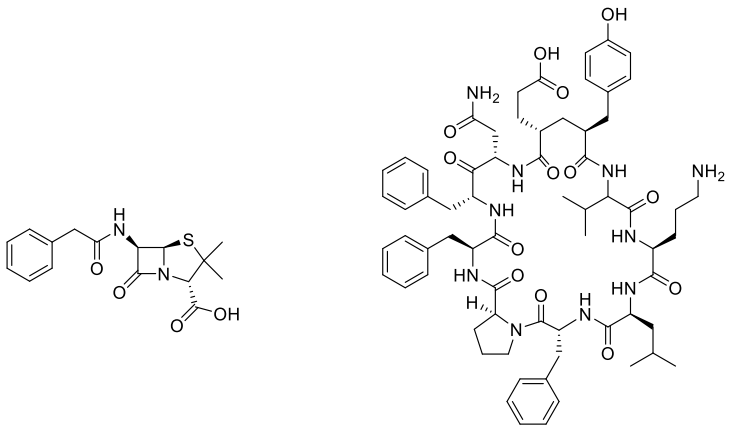
A vast number of antibacterial agents act by stopping the replication process (bacteriostatic) or by provoking cell death (bactericidal). The chrysophaentins appeared to belong to the bacteriostatics class, effectively hampering the replication of bacteria, thereby controlling the spread of the infection by stopping its propagation. These compounds proved particularly effective against multiresistant strains, which is currently of global concern.

1.2.1 The first antibiotics

Since the 19th century, scientists have tried to control bacterial strains in order to improve life conditions for billions of people. Though most microorganism are harmless and non life-threatening, some can lead to infections with fatal outcomes especially in individuals weakened by illness. The growing interest in anti-infectives started when Pasteur showed that anthrax cultures were inactivated in presence of aerobic microbes, such that soil could serve to neutralise these deadly bacteria. Half a century later, before the rediscovery of penicillin **1.11** by Florey, Dubos found samples of soil that were able to break the polysaccharide capsule of pneumococcal bacteria. His first results were published in 1930, where he reported the isolation of a capsule-degrading enzyme that he'd named S III enzyme.[3] Alas, this breakthrough could not be transferred to the medical field as the S III enzyme worked poorly on patients. The focus of Dubos' research then switched to countering gram-positive bacteria with the isolation of an active artificial strain from a fermentation broth

including a mixture of tyrothricin **1.12** (Figure 1.2) and gramicidin. These substances were identified with the help of Hotchkiss. The latter proved toxic when administered by direct injection but proved effective by topical application and, during World War II, prevented many casualties. Indeed, this was the first systematic study of an antibacterial and opened the field for further development.[4]

Fleming first reported on the antibacterial properties of penicillin in 1929 and foresaw its use as a biological tool to help in the isolation of influenza strains. In 1940, the realisation that penicillin was of potential therapeutic interest led to a thorough investigation of its effectiveness in animals. The study showed that penicillin was harmless in animals, even at high doses, so it was soon adopted for the treatment of systemic infections by Gram-positive bacteria. In the meantime, the first report of a penicillin resistant strain of bacillus was reported in *Nature* in 1940, an omen to the widespread resistance that became evident some 15 years later.[5]



1.11

Penicillin G

1.12

tyrothricin

Figure 1.2. Penicillin G **1.11** and tyrothricin **1.12**

1.2.2 Current situation in respect of drug-resistance

The widespread use of antibiotics, often for unrelated diseases, prompted the appearance of resistant strains. Indeed, the problem of bacterial resistance is of worldwide concern to the extent that the British government has made its resolution the target of the 2014 longitude prize. The aim of the prize is to stimulate research leading to the creation of a cost-effective, accurate, rapid and easy-to-use test for bacterial infections that will allow health professionals worldwide to administer the right antibiotics at the right time. Similarly, other organisations have started to provide incentives to advance this cause. For example, the Infectious Diseases Society of America has been seeking to put in place a means to develop more antibacterials, through its establishment as a common aim with related societies and institutions. They hope that through their engagement with key players in the field, they will be able to develop 10 safe and effective new antibiotics by 2020.

1.2.3 A tough enemy

The root cause of the problem is the ability of bacteria to adapt and survive a hostile environment. Since the discovery of antibiotics, their overuse has placed undue pressure on bacteria to survive, triggering the so called “arms race” to evolve. It has led to a situation where resistance to each newly introduced drug develops within a few decades or, on occasions, a few years. Staying ahead of

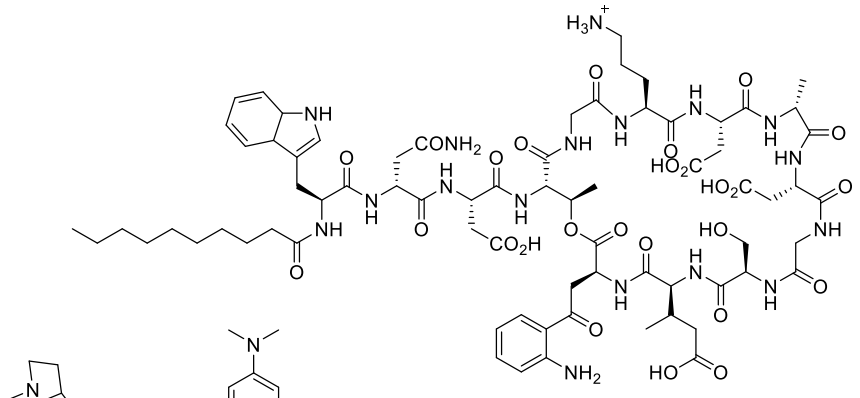
evolving bacterial strains requires new antibiotics with new scaffolds targeting new biological modes of action. However, in reality, the pharmaceutical industry has largely stepped back from the field in favour of research with better chances of providing a good return upon investment, as the patent cliff renders the whole pharmaceutical world chaotic and increasingly challenging.[6] The cost of developing a new antibiotic, coupled with the low chance of approval by the FDA, makes this field unattractive to major pharmaceutical companies. As a consequence, few antibiotics are being developed to counter drug-resistant strains. To make the matter worse, any new drug approved by the FDA is likely to be kept as the drug of last resort in order to slow the development of resistance. Though sensible from the perspective of long-term management of the problem, it annihilates any chance of profit for the commercialised drug, leading to inertia. For this reason, many have seen the need to put in place a global strategy to fight bacteria if we are to overcome the current impasse. Otherwise, even basic medical procedures will continue to bear a significant risk of fatal infection from hostile bacteria.[7]

1.3 Chrysophaentins and the therapeutics

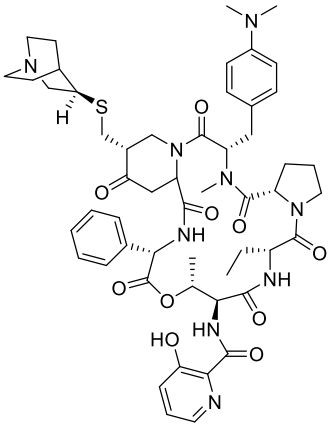
In this context, a number of questions arise. Where can we find new antibiotics? What is required in a new drug candidate to fight the development of a resistance? Do the new candidates, such as the chrysophaentins, fulfil the necessary criteria?

From the inception of the field, natural products have proven to be a good source of antibacterial agents. Indeed, many of the newly introduced antibiotics originate from the natural pool, usually being produced by fungi or bacteria and extracted on an industrial scale. Fragment design synthesis provides an alternative entry. Here, an active site is screened for interaction with a library of small fragments before "hits" are combined to form more complex molecules with improve activity.[8] The technique has its own limitations as the need to obtain a crystal of the target for docking studies to confirm binding misses a wide range of unknown or uncrystallisable targets.

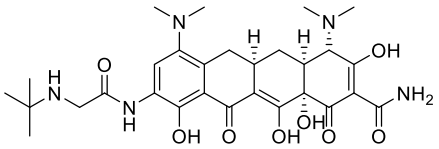
Ideally, a drug candidate should also operate through a new mode of action, one that other drugs don't target. Otherwise, a mutation in the target (protein/enzyme/receptor) is likely to develop resistance to both drugs in a far shorter time than it would take to counter two drugs operating by different mechanisms. Likewise, it is usually beneficial to introduce a drug based on a different scaffold to those employed by existing drugs as it is known that resistance can be extended to a whole class of compound. Thus, a perfect drug candidate would have a novel mode of action and be based on a new scaffold. The chrysophaentins meet both criteria so are good candidates for development. As examples of natural product inspired drugs; Daptromycin **1.13**, Qinupristin **1.14** and Tiglecycline **1.15**, all commercialised drugs, display the general complexity that can be attained by mimicking nature (figure 1.3).



1.13
Daptomycin, Eli Lilly



1.14
Qinupristin, Rhône-Poulenc



1.15
Tiglecycline, Wyeth

Figure 1.3. Daptomycin **1.13**, Qinupristin **1.14** and Tiglecycline **1.15**

1.3.1 A new scaffold

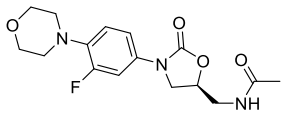
As noted above, drug resistance can be associated to a whole class of drugs, as has been seen for many common antibiotic families such as the penicillins, cephalosporins and sulfonamides. The chrysophaentins are bisdiarylbutene macrocycles from the methanol extract of the alga *Chrysophaeum Taylori*. Interestingly, geolocalisation of that alga was shown to impact on the nature of the methanol extract, in some cases leading to the isolation of new chrysophaentins, such as chrysophaentins E1 **1.6** and E2 **1.7**. Chrysophaentin A **1.1** is the most potent member of the family identified to date (MIC_{50} (MRSA) =

1.5 ± 0.7 μg/mL), with chrysophaentin F **1.8** coming a close second (MIC_{50} (MRSA) = 4.2 ± 1.3 μg/mL). Interestingly, these are based on different scaffolds, though both are believed to originate from a common intermediate. Three linear chrysophaentins (E, E1-2, **1.5**, **1.6** and **1.7**) have also been reported and these could be precursors to both the non-symmetrical cyclic scaffold found in chrysophaentins A-D (**1.1**, **1.2**, **1.3** and **1.4**) or the symmetrical scaffold found in chrysophaentins F-H (**1.8**, **1.9** and **1.10**).

In terms of novelty, these scaffolds are unprecedented in nature and form a new class of natural products. Indeed, these scaffolds are different from any found in drugs used against VRE and MRSA.[9] Infections due to VRE and MRSA are a nosocomial problem in hospitalized or immuno-compromised individuals as well as healthcare professionals.[10-11] The organisms are often resistant to multiple antibiotics and the last two decades has witnessed a rapid increase in the incidences of VRE infections, as well as a dramatic increase in the incidences of MRSA infections. As their virulence is greater than community acquired strains, it often causes or accelerates the death of infected patient.[11]

To stress further the rapid mutation that can happen in bacteria and the subsequent resistance Linezolid **1.16** presents a good case. Linezolid **1.16**, an antibiotic targeting MRSA and VRE, was given the FDA approval in 2000 and was the first drug in over 40 years introduced into the US market for the treatment of MRSA and VRE infections. However, a year later drug resistance began to be observed, highlighting the rapidity with which bacteria evolve and survive.[12] This again emphasizes the acute need to identify antibiotics to combat resistant bacteria so that clinicians and practitioners can prevent the spread of the

resistant strains and the scourge of untreatable infections acquired during benign surgery.



1.16

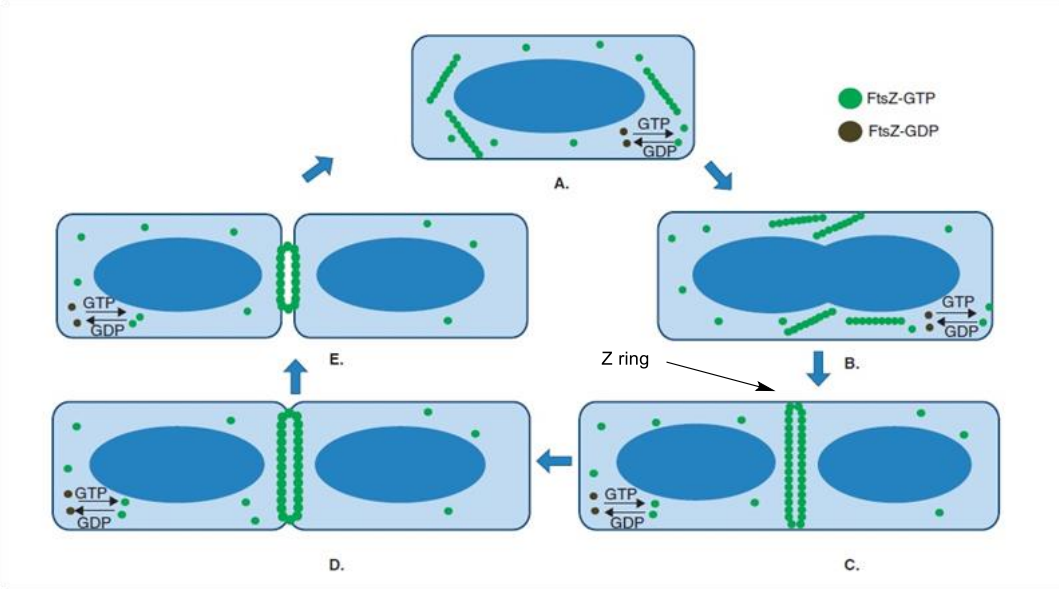
Figure 1.4. Linezolid **1.16**

1.3.2 FtsZ protein: A fresh target.

The biological target of chrysophaentin F has been shown to be the filamentous temperature sensitive mutant Z (FtsZ) protein. This was deduced using NMR, TEM and *in silico* studies by Bewley *et al.* and explains the broad range of antibacterial activity shown by the chrysophaentins against gram positive bacteria. The FtsZ protein has been described as a tubuline analogue for gram positive bacteria since in 1995 by Erikson and co-worker.[13] In fact, although based on a different protein sequence, the folding and function of FtsZ appeared to be closely related to its eukaryotic counterpart.

The activity of the FtsZ protein was summarised well in a recent review by Ojima *et al.*[14] Of particular note was the realisation that FtsZ is a highly conserved protein in prokaryote cells. Since FtsZ is well preserved in various bacteria, FtsZ targeting agents are likely to act as broad-spectrum antibacterial agents in addition to their use against particular bacteria, especially drug-resistant

strains. The tubulin-like protein interacts with GTP during cytokinesis in order to form the Z-ring, which is essential for the separation of the two cells (Figure 1.5). FtsZ protein, in the presence of GTP, starts to polymerise to form protofilaments. In turn, the protofilaments migrate to the mid-cell forming a Z ring that induces separation of the nucleus and the chromosomes. The Z ring then contracts, leading to separation of the newly formed cells.



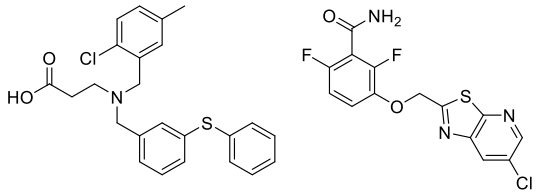
A. Bacterial cell prior to the beginning of cell division B. Cell elongation and chromosome segregation: FtsZ protofilaments start localizing at the mid cell C. Formation of the Z-ring D. Formation of the septum E. Constriction of the Z-ring, leading to cell division FtsZ, filamentous temperature sensitive mutant Z; GTP, guanosine triphosphate; GDP, guanosine diphosphate

Figure 1.5. Role of FtsZ during cell division

1.3.3 FtsZ targeting drugs

Although protein FtsZ is common to all bacteria, very few drugs have been developed to target it. Chrysophaentin A **1.1**, PC170942 **1.17** and PC190723 **1.18** have been found to inhibit the FtsZ protein by binding in the GTP binding site.[15] Other inhibitors of FTsZ have been discovered that bind the protein in

other areas, such as the filaments. Interest in this mode of action, together with the complex macrocyclic structure of chrysophaentin F **1.8**, makes it an interesting target for total synthesis. A total synthesis of chrysophaentin F **1.8** may aid in the development of related molecules with improved characteristics while helping to probe further the biological pathway it disrupts.



1.17 **1.18**

Figure 1.6. PC170942 **1.17** and PC190723 **1.18**

1.4 Related natural products

Most of the chrysophaentins are macrocyclic structures. Though unique, they have a number of features in common with the bisbibenzyl family of natural products that are usually found in the liverworts and other bryophytes.[16] Both families are based on macrocyclic structures in which four arenes are tethered by carbon chains and ether linkages. The common cores identified in the bisbibenzyl series are depicted in Figure 1.7.[17]

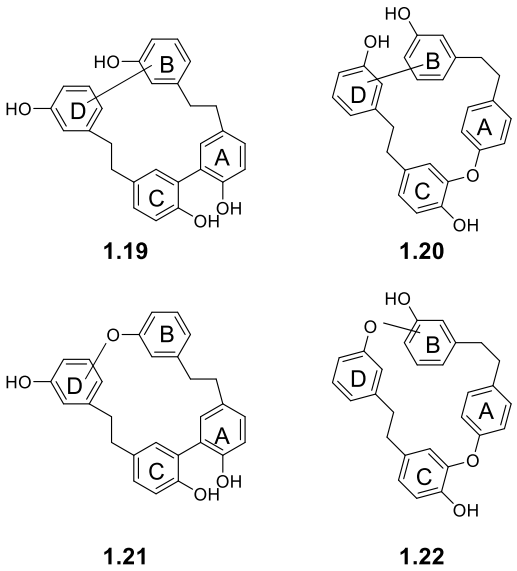
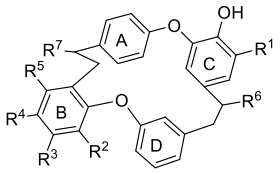


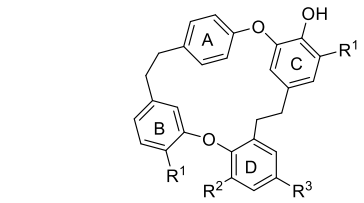
Figure 1.7. Bisbibenzyl family pattern

A key difference between the chrysophaentins and the bisbibenzyls is seen in the respective aliphatic linkages. In the chrysophaentins both are chlorobutene subunits while in the bisbibenzyls these are shorter, ethane-based subunits. The bis-ether that is ubiquitous within the macrocyclic chrysophaentins, is less common within the bisbibenzyl family. Nonetheless, it is seen among the marchantins, isomarchantins and neomarchantins, in ptychantols and in pakyonol **1.23** – **1.46** (Figure 1.8).

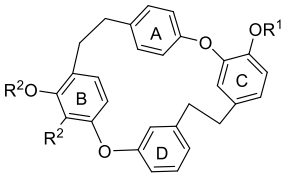


Marchantins

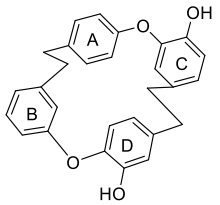
		R^1	R^2	R^3	R^4	R^5	R^6	R^7
A	**1.23**	OH	OH	H	H	H	H	H
B	**1.24**	OH	OH	OH	H	H	H	H
C	**1.25**	H	OH	H	H	H	H	H
D	**1.26**	OH	OH	H	H	H	OH	H
E	**1.27**	OH	OH	H	H	H	OMe	H
F	**1.28**	OH	OH	OH	H	H	OH	H
G	**1.29**	OH	OH	H	H	H	=O	H
H	**1.30**	H	OH	OH	H	H	H	H
I	**1,31**	H	H	H	OMe	H	H	H
J	**1,32**	OH	OH	H	H	H	OEt	H
K	**1.33**	OH	OH	OH	H	OMe	H	H
L	**1.34**	OH	OH	H	H	H	H	OH
M	**1.35**	H	OMe	H	H	OH	H	H
O	**1.36**	H	OMe	H	H	H	H	H



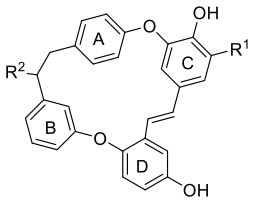
Isomarchantin B **1.37** $R^1 = R^2 = OH$, $R^3 = H$
Isomarchantin C **1.38** $R^1 = R^3 = H$, $R^2 = OH$
Dihydroptychantol **1.39** A $R^1 = R^2 = H$, $R^3 = OH$



Pakyonol **1.40** $R^1 = Me$ $R^2 = H$
Neomarchantin A **1.41** $R^1 = R^2 = H$
Neomarchantin B **1.42** $R^1 = H$ $R^2 = OH$



Riccardin B **1.43**



Ptychantol A **1.44** $R^1 = R^2 = H$
Ptychantol B **1.45** $R^1 = OH$ $R^2 = H$
Ptychantol C **1.46** $R^1 = R^2 = OH$

Figure 1.8. Bisdiaryl ethers from the bisbibenzyl family

Similarly, subclasses within the bisbibenzyl family display a high degree of chlorination, in common with the chrysophaentin. This is unsurprising for natural products with a marine origin given the higher halogen content of their environment. The bazzanin family, for example, are polychlorinated bisbibenzyl macrocycles with as many as eight chlorine atoms decorating the core structure. A vinyl chloride moiety can also be seen in bazzanins B–I and in bazzanin R a double chlorinated alkene linkage is present. Similarly, the isoplagiochin subfamily has four chlorinated siblings. As the Harrowven group has

considerable experience relating the synthesis of the bisbibenzyl family of natural products, the chrysophaentin family were especially interesting targets.

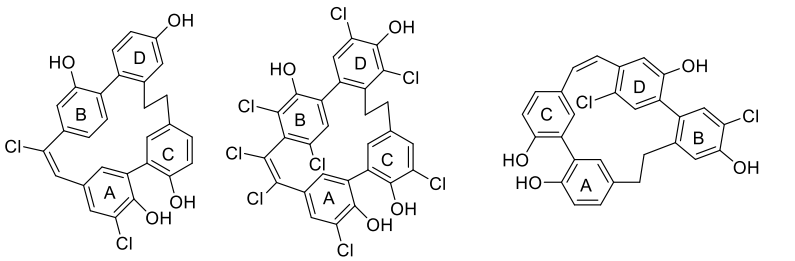
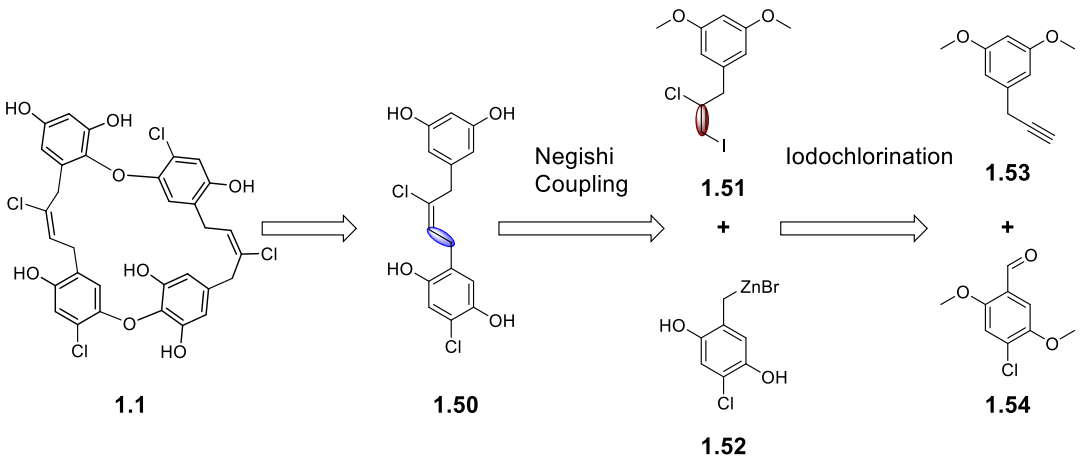


Figure 1.1. Bazzanin B **1.47**, bazzanin R **1.48** and 12,10'-dichloroisoplagiochin C **1.49**.

1.5 Wipf and Bewley semi synthesis

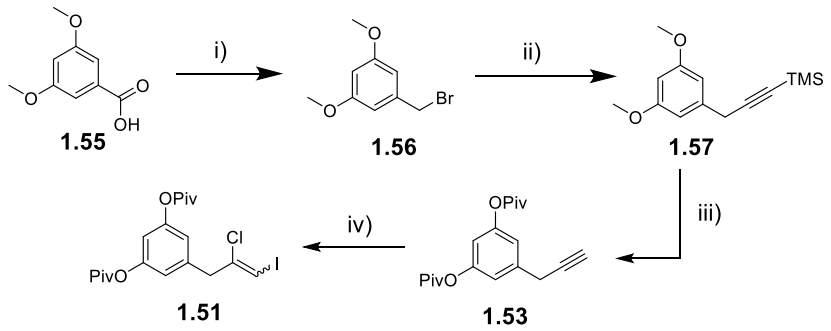
To the best of our knowledge, no total synthesis of any chrysophaentin has been reported. However the synthesis of a key fragment of chrysophaentin A was published in 2012 by Bewley *et al.* as part of their studies towards the chrysophaentins and related molecules exhibiting similar biological properties.[2]

Their approach was inspired by the presumed biosynthetic pathway, which is believed to involve dimerisation of subunit **1.50** (Scheme 1.1). Their plan was to link a vinyl iodide **1.51** with a benzylzinc species **1.52** using a Negishi coupling. The two fragments **1.51** and **1.52** would in turn be accessed in few steps from the previously described alkyne **1.53** and benzaldehyde **1.54**.



Scheme 1.1. Retrosynthetic route to access chrysophaentin A **1.1**

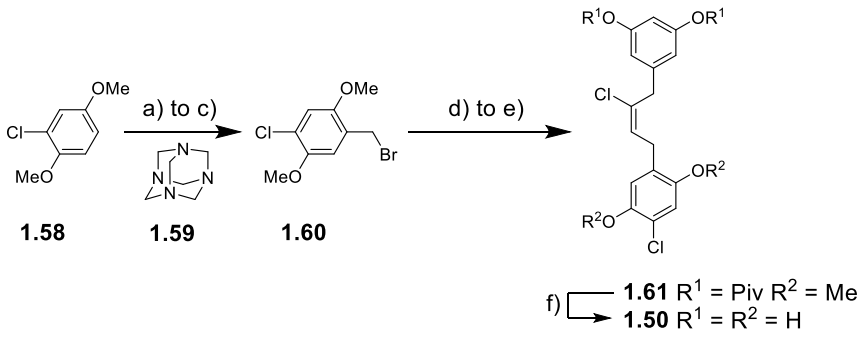
In order to access the pivotal synthon **1.51** at first acid **1.55** was reduced to the alcohol then brominated to obtain benzyl bromide **1.56**. In turn a copper-catalysed alkynylation was performed. At this stage the TMS and the methoxy groups were deprotected in order to access terminal alkyne **1.53** after reprotection with pivaloyl groups. **1.51** was then formed after iodochlorination of propynyl **1.53**, affording the desired target in a ratio of 2 : 1 of isomers (scheme 1.2).



Reagents & conditions : i) (a) LAH, THF, 0 °C, 97%; (b) PBr_3, CH_2Cl_2, 92%; ii) EtMgBr,ethynyltrimethysilane, CuBr, THF, Δ, quant. iii) (a) TBAF, AcOH, THF, quant. (b) BBr_3, CH_2Cl_2, (c) PivCl, CH_2Cl_2 82% (2 steps) iv) ICl, DCM 95%

Scheme 1.2. Synthesis of intermediate **1.51**

The second synthon **1.52** was also synthesised in a few steps from 1-chloro-2,5-dimethoxybenzene **1.58**. Its formylation, reduction and bromination afforded benzyl bromide in 96% overall yield reported. Subsequent treatment with activated zinc then facilitated a Negishi coupling with $Pd(OAc)_2$ as catalyst to give the advanced precursor **1.59**. Deprotection with BBr_3 then gave the hemichrysophaentin **1.50** in 96% yield (Scheme 1.3).



Reagents & conditions :a) **1.59**, TFA, 95 °C, quant. b) $NaBH_4$, EtOH, 96% c) HBr, CH_2Cl_2, quant. d) Zn, DMF, **1.51**, $Pd(OAc)_2$ (10 mol%), P(*o*-Tol)$_3$ (10 mol%), μW, 120 °C, 4 min e) Cs_2CO_3, MeOH, CH_2Cl_2 (40-51% over two steps) f) BBr_3, CH_2Cl_2, 0 °C to RT, 96%

Scheme 1.3. Formation of Hemichrysophaentin **1.50** by Wipf

The strategy proved a useful means of accessing the hemichrysophaentin **1.50**, however a lack of selectivity of the iodo-chlorination reaction, **1.53** to **1.51**, led to a drastic loss in the overall yield. It also proved necessary to deprotect and reprotect intermediate **1.57**, adding two unproductive steps to the sequence.

The longest linear sequence *en route* to intermediate **1.50** was 9 steps, with an overall yield of 22%. The major drawback of this approach was the 2:1 ratio of isomers given during the formation of chloroalkene **1.51**. An end-game leading to a chrysophaentin has yet to be reported and the authors noted that the hemichrysophaentin **1.50** proved less potent than the target (MIC_{50} from 20 to 31 μM against various strains of resistant and mustiresistant *Streptococcus Aureus*), but sufficient to warrant further optimisation.

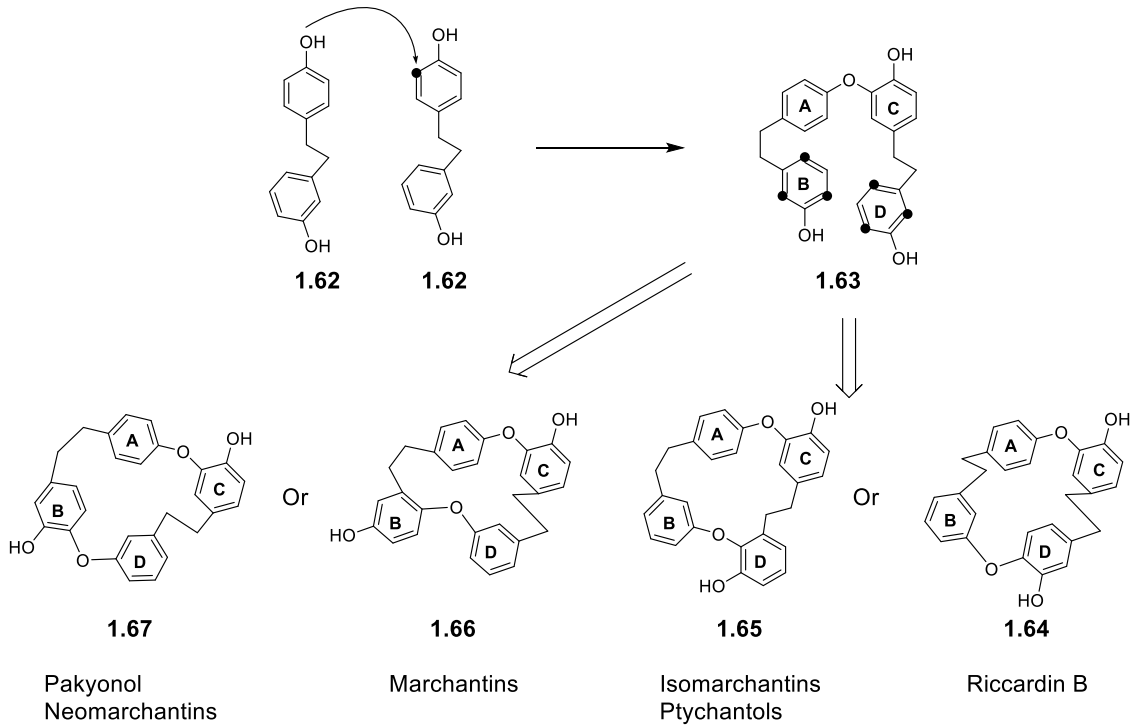
1.6 Bisbiaryl ether synthesis

As noted previously, the chrysophaentins closest relatives in the natural products sphere are in the bisbibenzyl family where there are a number of macrocyclic compounds bearing two diaryl ether bridges. These have smaller macrocycles than the chrysophaentins as they have ethano bridges linking the arenes rather than the buteno bridges seen in the chrysophaentins. Herein, the reported syntheses of such compounds are described as they provide some useful insights into the transformations and strategies applicable when developing a synthesis of chrysophaentin F **1.8**.

To date very few approaches to these macrocyclic bisdiaryl ethers have been reported. Riccardin B **1.45** has proven a popular target. It is unique among the riccardins as it bears two diaryl ether linkages instead of one. As such, it has attracted the attention of the Iyoda, Kodama and Nógrádi groups.[18,19,20] Similarly, the marchantin family has raised the interest of the synthetic chemists with syntheses of marchantins A, C and I (**1.23**, **1.25** and **1.31**, respectively) having been described by Kodama, Nógrádi, Speicher and Eicher.[21,22,23,24] Synthesis of pakyonol **1.40** and dihydroptychantol **1.39** have also been described by the groups of Nógrádi and Lou respectively.[25,26]

1.6.1 Classification and biosynthetic pathway

Within the bisbibenzyl family, a subgroup of macrocyclic bisdiaryl ethers akin to the chrysophaentins can be identified. Each consists of two diaryl ether units linked by two ethano or ethylene bridges. The bisdiaryl ether family consists of four core structures resulting from the oxidative macrocyclisation of perrottetin E **1.63** with formation of an ether linkage between arenes *B* and *D* (Scheme 1.4). Though much work has been devoted to the biosynthesis of macrocyclic bisbibenzyls in general, precise details of the biosynthetic pathway have yet to be established.[27]

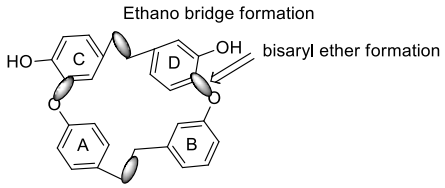


Scheme 1.4. Postulated cyclisation pathways leading to the different scaffolds found within the bisbiaryl ether family.

Asakawa developed a commonly used nomenclature to systematically classify all of the bisbibenzyl natural products by relating each back to perrottetin E, from which all were derived. Thus, the *para* substituted aromatic ring of perrottetin E is designated as the *A* ring and the *meta* substituted arene is ring *C*.[28] Then, by convention, the ethano bridges link ring *A* to ring *B* and ring *C* to ring *D*.

1.6.2 General strategies

As the natural macrocyclic bisdiaryl ethers all have a similar structure, it is of no surprise to witness similar strategies being used to access different siblings (Figure 1.10). Commonly, the diaryl ether linkages have been made through Ullmann type couplings and macrocyclisation has involved construction of an ethano bridge. The strategies employed for macrocyclisation have all employed Wittig type olefination or benzylic coupling reactions.



1.43

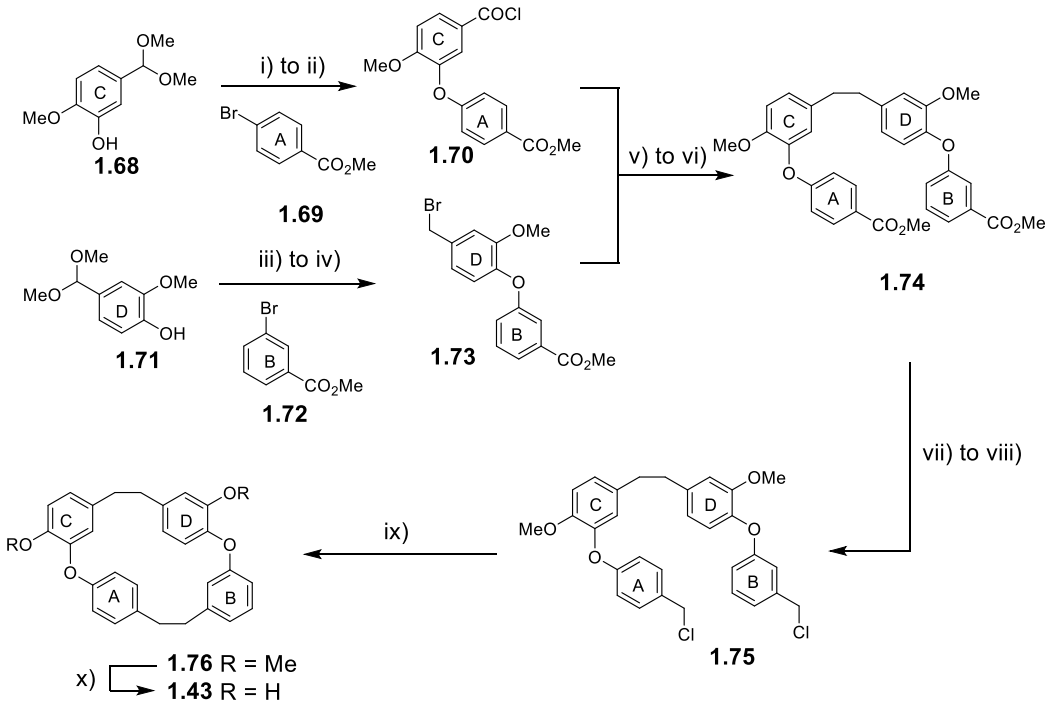
Riccardin B

Figure 1.10. Bisbiaryl ethers common disconnections

1.6.3 Riccardin B synthesis

Iyoda and co-workers described the first synthesis of riccardin B **1.43** in 1985 (Scheme 1.5).[18] Their synthesis began with the construction of the *AC* and *BD* fragments, **1.70** and **1.73**, *via* Ullmann coupling reactions. These were then coupled using a Fujisawa reaction between acyl chloride **1.70** and the benzyl bromide **1.73**. Next, a Clemensen reduction gave the expected tetraarene **1.74**

which, by a sequence of functional group interconversions, was transformed into bisbenzyl chloride **1.75**, a precursor for the macrocyclisation. The critical cyclisation was carried out with $NiBr_2(PPh_3)_2$ (2 equiv.), zinc (15 equiv.) and tetraethylammonium iodide (4 equiv.) in THF to afford macrocycle **1.76** in an impressive 88% yield. A global deprotection using BBr_3 completed the synthesis of riccardin B **1.43**. The main drawback with this approach was associated with the Fujisawa coupling reaction as it proved low yielding and required an additional step to reduce the superfluous ketone moiety.

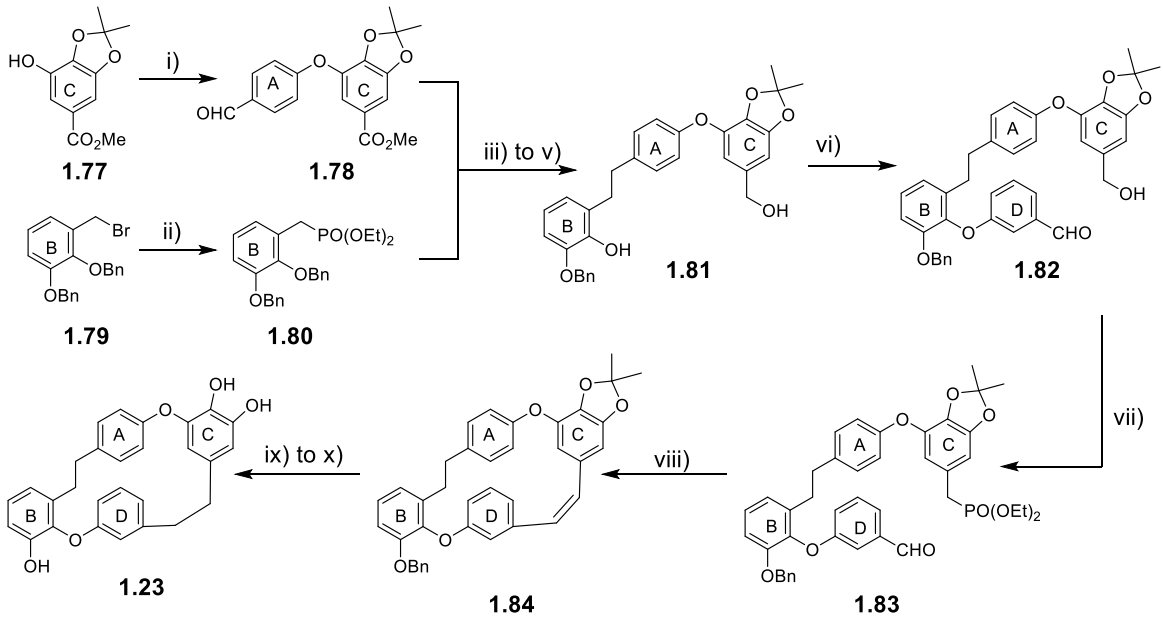


Reagents & conditions : i) CuCl, Py, 20 h 82% ii) CrO_3 then oxalyl chloride (97% over two steps) iii) CuCl, Py, 20 h 74% iv) $NaBH_4$ then PBr_3-Py, (72% over two steps) v) $PdCl_2(PPh_3)_2$, Zn, DME 50% vi) Zn-Hg, HCl 91% vii) $LiAlH_4$, 88% viii) $SOCl_2$, 84% ix) $NiBr_2(PPh_3)_2$, Zn, Et_4NI, 88% x) BBr_3, DCM, -78 °C, 95%

Scheme 1.5. Synthesis of riccardin B **1.43** by Iyoda

1.6.4 Marchantin A synthesis

In 1985, Kodama and co-worker also described syntheses of riccardin B and marchantin A **1.23** following similar strategies.[19,21] The formation of the ether linkages used the ubiquitous Ullmann coupling reaction while formation of the two ethano bridges was achieved using the Horner-Wadsworth-Emmons (HWE) reaction. For marchantin A **1.23** (Scheme 1.6), the HWE reaction was used to couple the *AC* fragment **1.78** with arene *B* **1.80** to give triarene **1.81** after hydrogenation. A second Ullmann reaction was then undertaken to bring in the last arene, giving tetraarene **1.82** in low yield (42%). Sequential bromination and an Arbusov reaction to form phosphonate **1.83** then set up the macrocyclisation reaction, which was performed with potassium *tert*-butoxide at high dilution (C = 1.4 mM) and yielded the expected macrocycle **1.84** in 60% yield. Reduction of the resulting alkene and deprotection then afforded marchantin A **1.23** in good yield.



Reagents & conditions : i) K_2CO_3, CuO, Py, *p*-bromobenzaldehyde, Δ, 68% ii) $P(OEt)_3$, 74% iii) ^tBuOK, DMF, 71% iv) H_2/Pd-C then BnBr 61% over two steps v) $LiAlH_4$, 94% vi) K_2CO_3, CuO, Py, quinoline, 3-hydroxybenzaldehyde, Δ, 42% vii) $SOBr_2$ then $P(OEt)_3$ 60% viii) tBuOK, DMF 60% ix) H_2/ Pd-c 87% x) HCl 80%

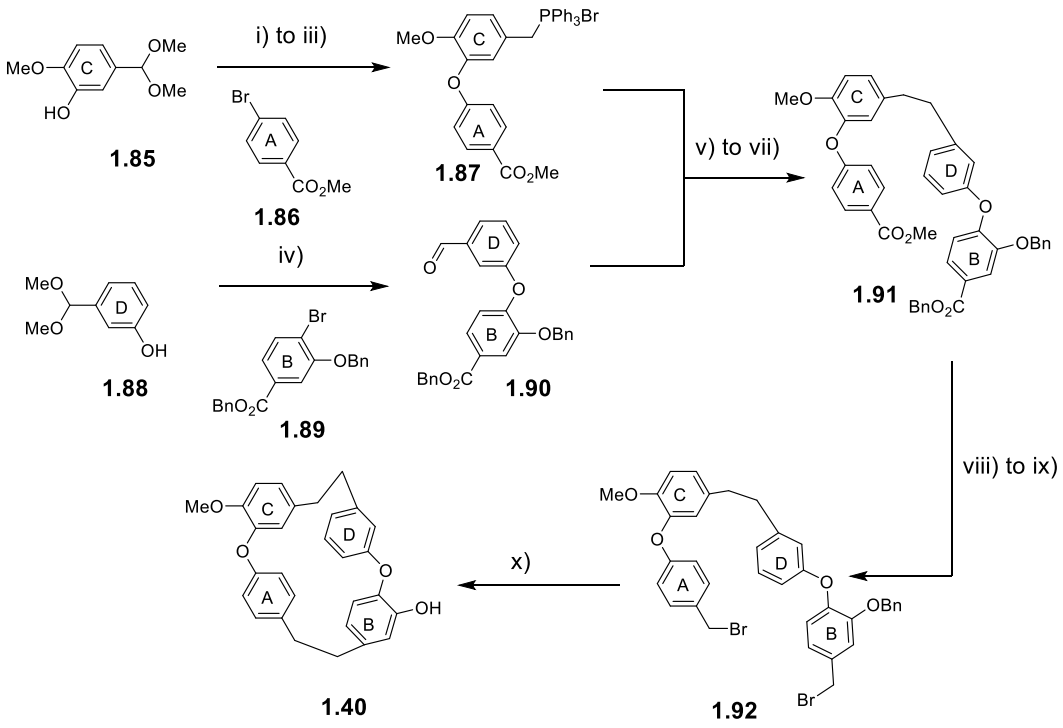
Scheme 1.6. Synthesis of marchantin A **1.23** by Kodama

The main drawbacks with this approach were the necessity to reprotect the phenolic position after the first reduction step and the inefficiency of the second Ullmann coupling, which had a dramatic impact on the overall yield. It was also noted that the macrocyclisation step afforded a dimer in substantial amounts when performed at higher concentration.

1.6.5 Pakyonol synthesis

Over a two year period, 1989 and 1990, Nógrádi *et al.* described the synthesis of three bisdiaryl ethers: marchantin I **1.31**, pakyonol **1.40** and riccardin B

1.45.[20,22,25] The syntheses all followed the same strategic lines in that they relied on Ullmann coupling reactions to form the *AC* and *BD* fragments, a Wittig olefination reaction to couple these fragments together and a Wurtz coupling to induce closure of the macrocycle. Their synthesis of pakyonol **1.40** is representative (Scheme 1.7) and began with the formation of fragments *AC* **1.87** and *BD* **1.90** using low yielding Ullmann coupling reactions in conjunction with a short sequence of functional group transformation. The fragments **1.87** and **1.90** were next conjoined using a Wittig olefination performed with sodium methoxide and provided the expected adduct in good yield (74%). A reduction followed by benzyl reprotection then gave intermediate **1.91** in high yield. Reduction of the two ester moiety followed by bromination next afforded bisbenzyl bromide **1.92** which underwent a Wurtz coupling in presence of sodium and tetraphenylethylene (TPE) to afford the target in low yield (15%).



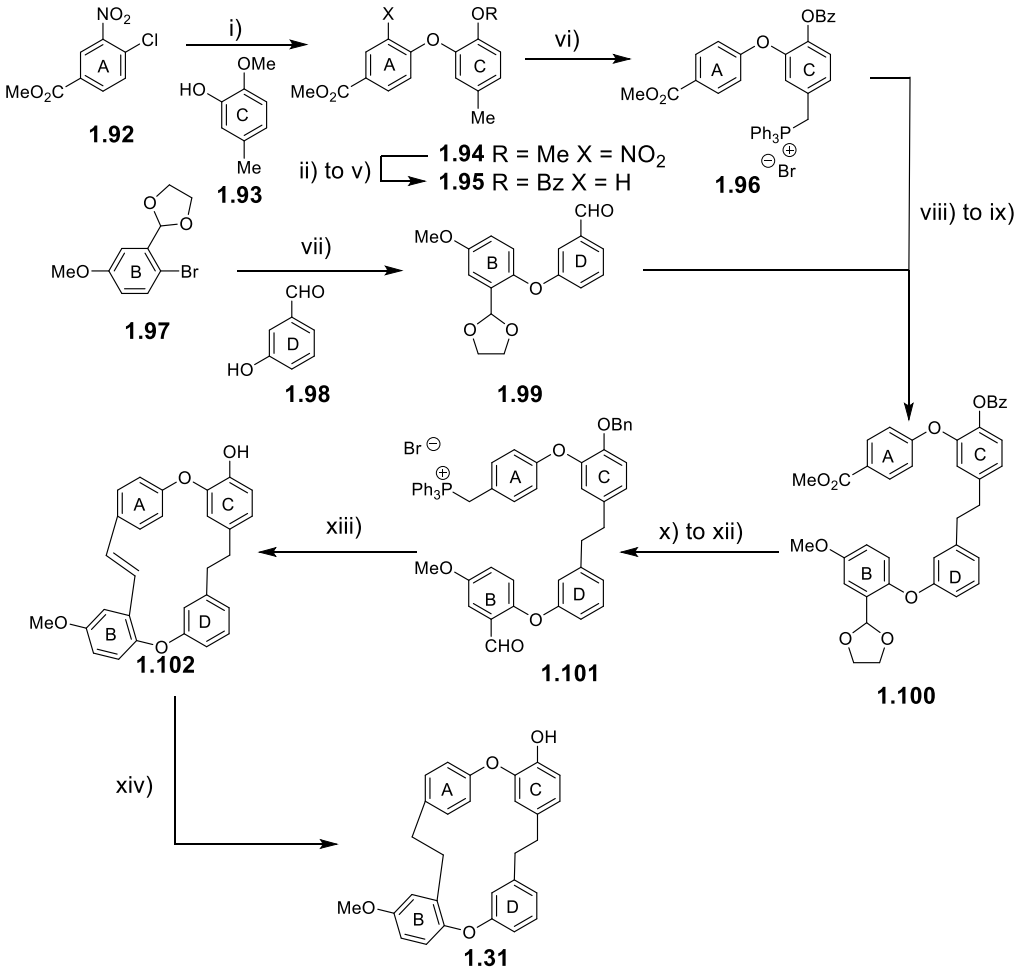
Reagents & conditions : i) CuO, K_2CO_3, Py, Δ, 30% ii) $NaBH_4$, 90% iii) PBr_3 then PPh_3 76% iv) CuO, K_2CO_3, Py, 27% v) NaOMe, 74% vi) Raney Ni, H_2, EtOAc, EtOH, 92% vii) NaI, BnBr, K_2CO_3, acetone 74% viii) $LiAlH_4$, THF, 85% ix) PBr_3, benzene, 85% x) TPE, Na, THF, 24 h, 15%

Scheme 1.7. Synthesis of pakyonol **1.40** by Nógrádi

The main drawback with this strategy is the macrocyclisation reaction. In all cases the low yield attained for the Wurtz coupling had a crippling impact on the overall yield of the synthesis. Though it gave direct access to the final product, this does little to counterbalance the inefficiency displayed.

1.6.6 Marchantin I synthesis

In 1998, Eicher and co-workers described the synthesis of marchantin I **1.31** (Scheme 1.8).[24] Their synthesis used an S_NAr reaction to generate the *AC* fragment **1.94** in good yield (87%). This was followed by removal of the nitro group in two steps, bromination of the tolyl position and an Arbusov reaction to afford the phosphonium **1.96**. Contemporaneously, the *BC* fragment **1.99** was formed in moderate yield (60%) by an Ullmann coupling of bromide **1.97** and phenol **1.98**. The *AC* and *BC* fragments were then coupled in a Wittig reaction, to afford tetraarene **1.100** after hydrogenation. Phosphonium salt **1.101** was then synthesised via standard functional group manipulations. A Wittig reaction with sodium methoxide then induced macrocyclisation to **1.102**, with a high yielding hydrogenation reaction completing the synthesis of marchantin I **1.31**.



Reagents & conditions : i) NaH, DMF, 87% ii) H_2, Pd-C, 85% iii) $NaNO_2$, HCl then H_3PO_2, 84% iv) $AlCl_3$, 81% v) BzCl, Na_2CO_3, 81% vi) NBS, AIBN then PPh_3, 68% vii) CuO, K_2CO_3, Py, 60% viii) K_2CO_3, DCM, 18-crown-6, 89% ix) H_2, Pd-C, 94% x) $LiAlH_4$, 86% xi) BnCl, K_2CO_3, 88% xii) HBr, AcOH then PPh_3, 75% xiii) NaOMe, DCM, 81% xiv) H_2, Pd-C, 90%

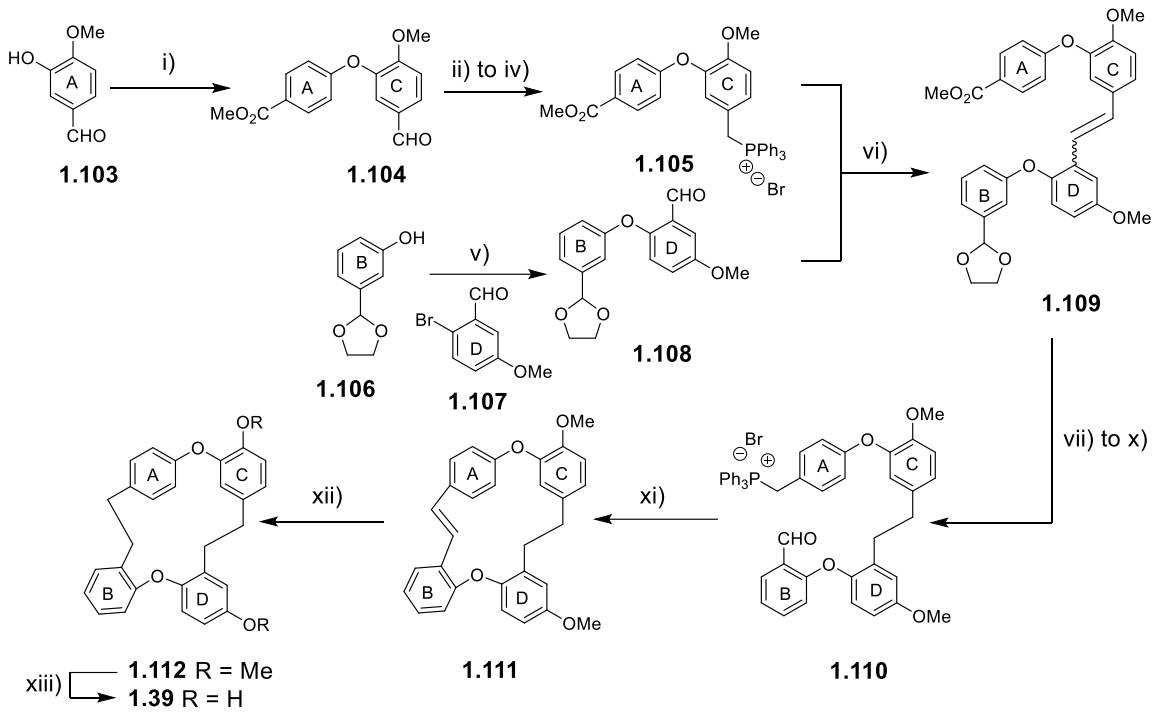
Scheme 1.8. Synthesis of marchantin I **1.31** by Eicher

In this case the main drawback is the need to employ a nitro group to facilitate the S_NAr reaction. Though the S_NAr reaction proves more efficient than the Ullmann coupling, two additional steps are needed to remove the nitro group, lessening the overall appeal of this tactic. The protection and deprotection

sequences with the benzoyl and benzyl groups also add steps and reduce the efficiency of the synthesis overall.

1.6.7 Dihydroptychantol synthesis

More recently, Lou and co-workers described a synthesis of dihydroptychantol **1.39** (Scheme 1.9).[26] Their synthesis started with the formation of the *AC* and *BD* fragments **1.105** and **1.108**. Fragments *AC* and *BD* were then coupled in a Wittig reaction using K_2CO_3 in presence of a crown-ether to give tetraarene **1.109** as a mixture of *cis* and *trans* isomers. The resulting stilbenes **1.109** were then advanced through a hydrogenation reaction and a standard sequence of functional group interconversion to obtain phosphonium salt **1.110**. Macrocyclisation to *trans*-stilbene **1.111** followed on treatment with sodium methoxide and was accomplished in an impressive 78% yield. Reduction of the stilbene followed by global deprotection then completed the synthesis of dihydroptychantol A **1.39**.



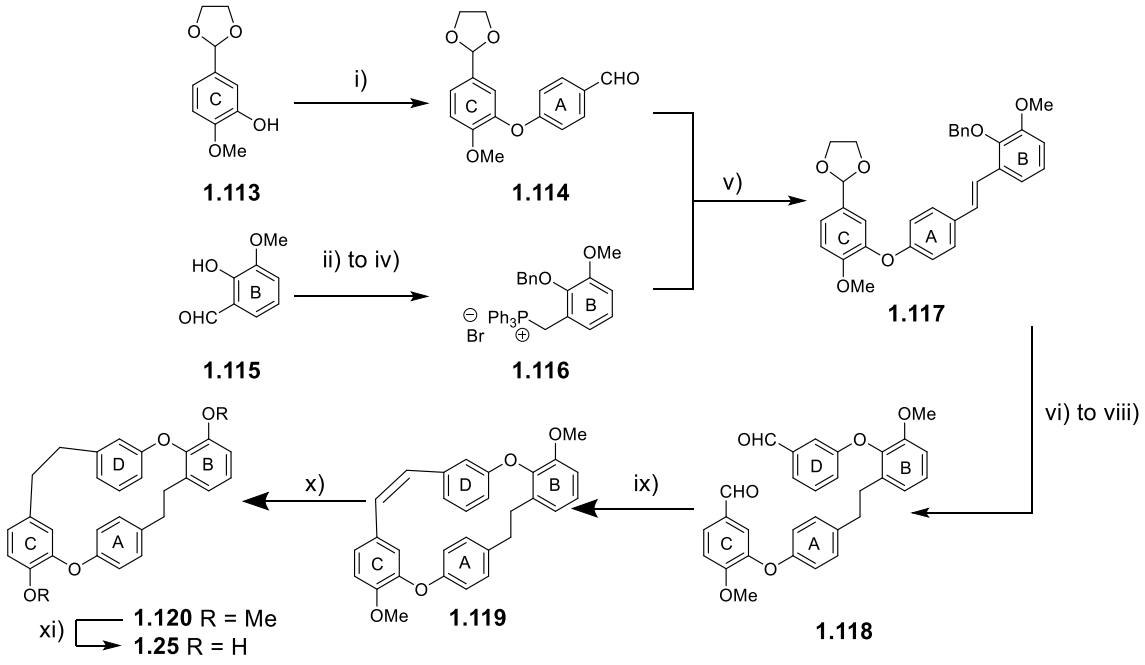
Reagents & conditions : i) 2-bromo-5-methoxybenzaldehyde, K_2CO_3, CuO, Py, Δ, 65% ii) $NaBH_4$, THF, 88% iii) CBr_3, PPh_3, DCM, 0 °C, 88% iv) PPh_3, Toluene, Δ, 98% v) K_2CO_3, CuO, Py, Δ, 62% vi) K_2CO_3, 18-crown-6, DCM, Δ, 86% vii) H_2, Pd/C, Et_3N, AcOEt, 98% viii) $LiAlH_4$, THF, 30 °C then H^+/H_2O, 87% ix) CBr_4, PPh_3, DCM, 0 °C, 79% x) PPh_3, Toluene, Δ, 98% xi) NaOMe, DCM, 78% xii) H_2, Pd/C, AcOEt, 96% xiii) BBr_3, DCM, -78 °C, 73%

Scheme 1.9. Synthesis of dihydroptychantol **1.39** by Lou

1.6.8 Marchantin C synthesis

The latest synthesis to be reported was described by Speicher and co-worker, who accessed marchantin C **1.25** following a strategy similar to that described by Kodama for marchantin A **1.23**.[23] A key difference was their use of a McMurry reaction to induce macrocyclisation, which was inspired by earlier syntheses of cavicularin and riccardin C.[29] The *AC* fragment **1.114** was first prepared using an S_NAr reaction between the protected isovanillin **1.113** and *p*-

fluorobenzaldehyde. Fragment **1.114** was then reacted with the phosphonium salt **1.116** (derived from the *o*-vanillin **1.115** to obtain triarene **1.117**. Hydrogenation and an Ullmann coupling then gave tetraarene **1.118** in an impressive 97% yield before the aldehyde on ring *D* was unmasked to set up the critical McMurry reaction. That was performed with a low-valent titanium reagent formed from by reduction of $TiCl_4$ with Zn and provide the expected macrocycle **1.119** in a modest 47% yield. Hydrogenation of the stilbene and deprotection of the phenols completed the synthesis of marchantin C.



Reagents & conditions : i) *p*-fluorobenzaldehyde, K_2CO_3, DMF, 165 °C, 12 h, 97% ii) BnBr, K_2CO_3, THF, Δ, 12 h, 95% iii) $NaBH_4$, EtOH, 0 °C to RT, 12 h, 92% iv) PPh_3, HBr, ACN, 95 °C, 12 h, 85% v) K_2CO_3, 18-crown-6, DCM, Δ, 12 h, 62% vi) H_2, Pd/C, 24 h, 98% vii) 3-bromobenzaldehyde, CuO, K_2CO_3, Py, 160 °C, 12 h, 97% viii) 2 M HCl/THF, RT, 12 h, 97% ix) Zn, $TiCl_4$, THF, -10 °C to reflux, 47% x) H_2, Pd/C, 24 h, 96% xi) BBr_3, DCM, -78 °C to RT, 12 h, 85%

Scheme 1.10. Synthesis of marchantin C **1.25** by Speicher

The main drawback of this approach was the modest yield attained in the McMurry reaction. Additionally, the Wittig reaction leading to **1.117** also gave a modest yield.

In summary, all of these syntheses follow a similar pattern in that they construct two diaryl ether moieties then conjoin them using a Wittig type reaction to form one of the ethano bridges. The main issues encountered have been with low yielding Ullmann reactions leading to the diaryl ether fragments, a problem that also extends to many of the subsequent macrocyclisation reactions. These concerns are likely to arise in syntheses of a chrysophaentin skeleton based on a similar strategy.

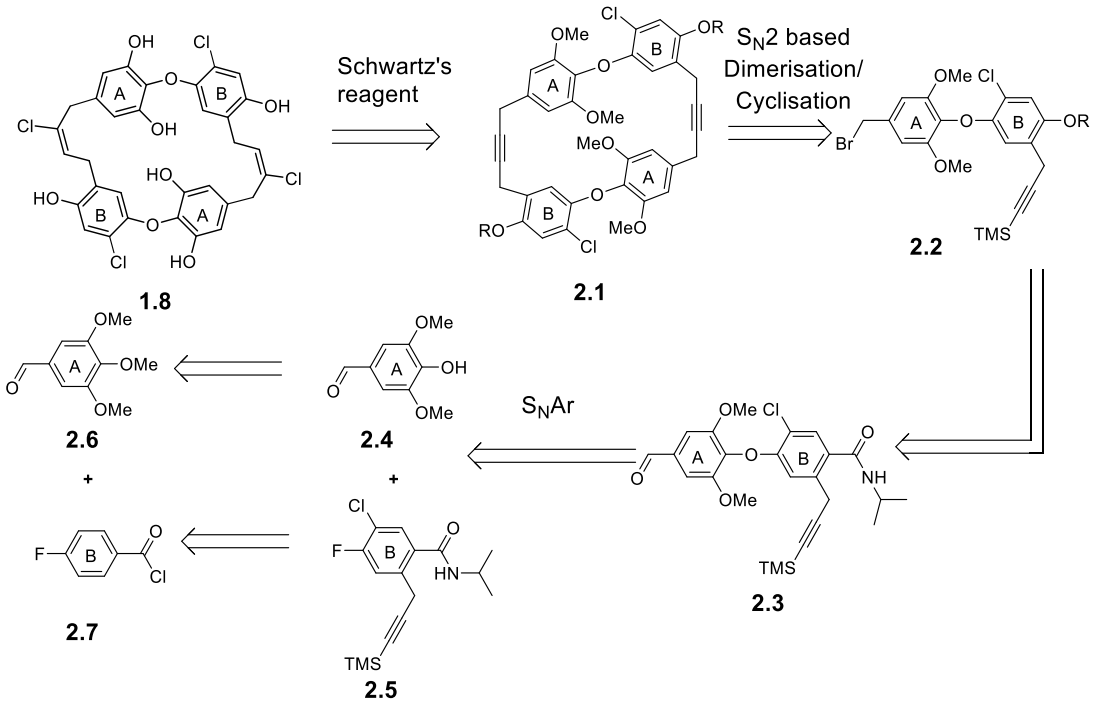
1.7 Aims and objectives

The aims of this project are a) to achieve the first total synthesis towards chrysophaentin F and evaluate its biological activities; b) develop synthesis towards other chrysophaentins or chrysophaentin analogues. The strategy relies on a S_NAr reaction to install the ether linkage and on a S_N2 reaction to perform the macrocyclisation reaction. Previous studies in the group on bisbibenzyl family and insights from the literature allowed us to develop the synthetic pathway to our targets which is presented in chapter 2 (scheme 2.2).

2. An alkynyl S_N2 strategy

2.1 Strategy rationale

As detailed in the retrosynthetic analysis (Scheme 2.1), our initial approach to the synthesis of chrysophaentin F **1.8** sought to take advantage of the symmetry in this molecule. It was hoped that the target could be made from the macrocyclic diyne **2.1** through selective hydrochlorination of the two alkynes and global deprotection. In turn a dimerisation/cyclisation of silylacetylene **2.2** could be used to construct the core of the natural product. In turn, silylacetylene **2.2** might be prepared from benzamide **2.3** by functional group interconversions, implicating an S_NAr reaction between phenol **2.4** and fluoroarene **2.5** as a third key step. Thus, our approach would begin with phenol **2.4** a known deprotection of benzaldehyde **2.6** and the development of a short sequence to transform benzyl chloride **2.7** into the required fluoroarene **2.5**.



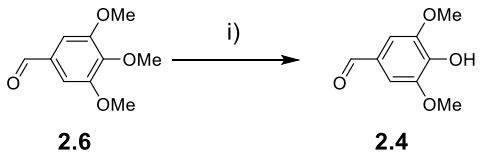
Scheme 2.1. Retrosynthetic analysis of chrysophaentin F **1.8**

2.2 Results and Discussion

2.2.1 S_NAr reaction

The starting point for our investigation was the coupling of phenol **2.4** and benzamide **2.5**. Phenol **2.4** could be obtained from commercially available benzaldehyde **2.6** following literature procedures. Three Lewis acids, $AlCl_3$, BCl_3 and MgI_2, were screened for the selective demethylation of **2.6** under different

conditions.[30,31,32] The most effective method employed MgI_2 without solvent and afforded the desired phenol **2.4** in 68% yield (Scheme 2.2).

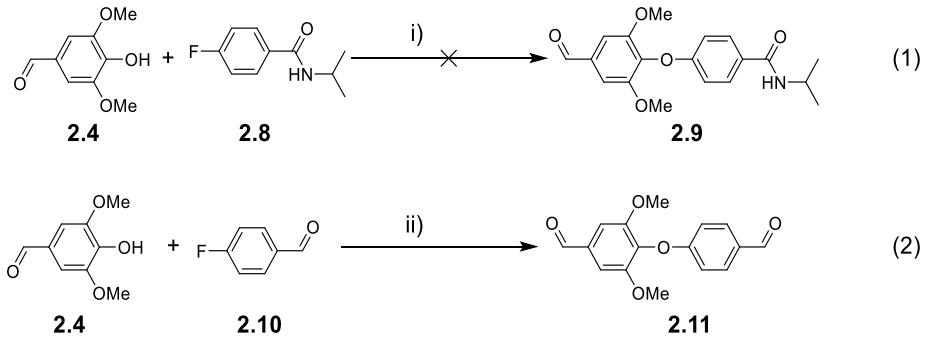


2.6 **2.4**

Reagents & conditions : i) MgI_2, 68%

Scheme 2.2. Selective demethylation of **2.4**

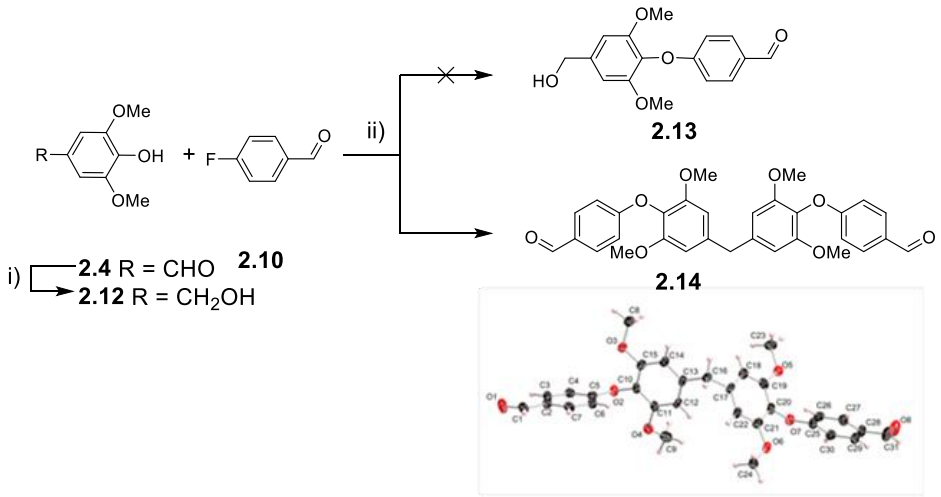
Our attention next turned to the S_NAr reaction. We first decided to investigate the coupling of commercially available benzamide **2.8** and phenol **2.4** in order to establish whether an amide was able to activate an aryl fluoride sufficiently to facilitate nucleophilic attack by a phenolate derived from **2.4**. In the event, all the conditions we examined returned both of the starting materials suggesting that the amide group was not sufficiently electron withdrawing to facilitate fluoride displacement. To test that hypothesis, the coupling of 4-fluorobenzaldehyde **2.10** and **2.4** was examined and gave diaryl ether **2.11** in 11% isolated yield after three days (Scheme 2.3).



Reagents & conditions : i) K_2CO_3, Δ, DMF, 0%; ii) K_2CO_3, 3 d, Δ, DMF, 11%

Scheme 2.3. S_NAr reaction of phenol **2.4** with fluoroarenes **2.8** and **2.10**

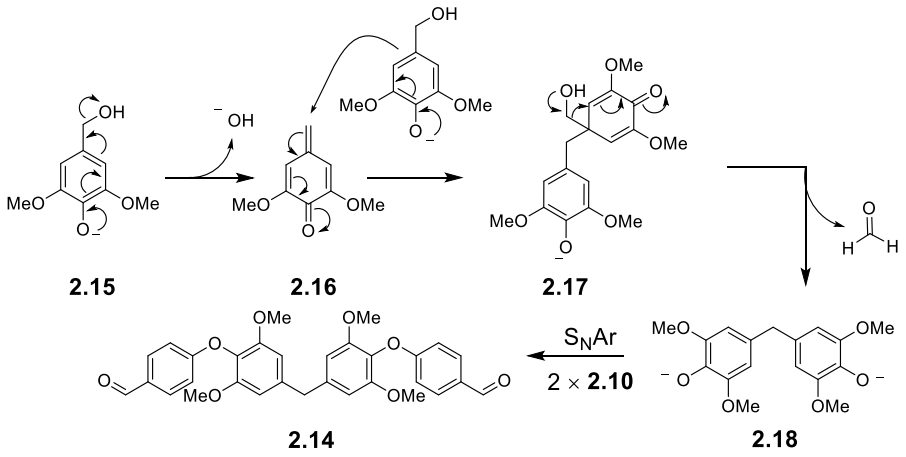
As the poor yield could be attributed to either adverse steric demand or the poor nucleophilicity of the phenoxide we next decided to reduce the aldehyde moiety in **2.4** to alcohol **2.12** in order to enhance the nucleophile. The coupling reaction of **2.12** with 4-fluorobenzaldehyde **2.10** was then undertaken under microwave irradiation.[33] Alas, the reaction gave none of the expected product **2.13** and produced instead tetraarene **2.14** in a moderate yield (52%) – the identity of which was confirmed by X-Ray crystallographic analysis (Scheme 2.4).



Reagents & conditions : i) $NaBH_4$, 0 °C, 1 h, MeOH, 62%, ii) K_2CO_3, 150 °C, 90 min, , μw, DMF, 52%

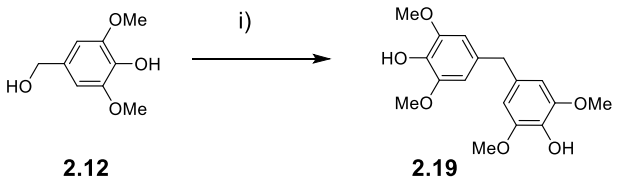
Scheme 2.4. S_NAr reaction between **2.12** and **2.10**

The formation of tetraarene **2.14** is likely to proceed by the dimerisation of phenol **2.12** *via* quinone methide **2.16** (Scheme 2.5). Loss of a molecule of formaldehyde from intermediate **2.17**, followed by a double S_NAr reaction of the resultant bisphenolate **2.18** with 4-fluorobenzaldehyde **2.10**, completes the sequence. This postulate was inspired from the bakelite formation patented in 1909 by Dr. Baekeland.[34]



Scheme 2.5. Proposed mechanism for formation of tetracycle **2.14**

Support for this mechanism was provided by subjecting phenol **2.12** alone to the aforementioned conditions. As expected, it gave dimer **2.19** in 52% yield (Scheme 2.6).

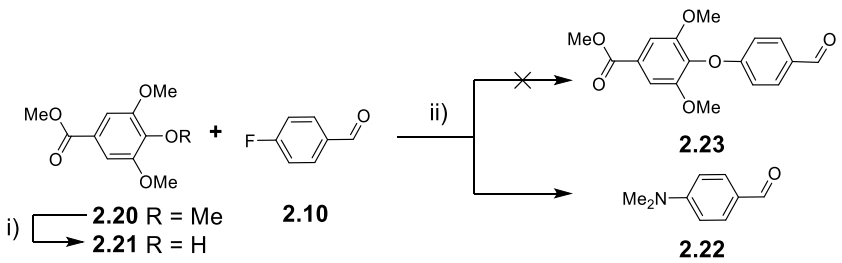


Reagents & conditions : i) K_2CO_3, μW, 150 °C, 90 min, DMF, 52%

Scheme 2.6. Dimerisation of **2.12**

To avoid the complications associated with using benzyl alcohols in the S_NAr reaction, ester **2.21** was identified as an alternative starting point. It was obtained in excellent yield (98%) from commercially available ester **2.20** *via* the deprotection method as described above for the aldehyde **2.6** (Scheme 2.2).[32]

Phenol **2.21** was then examined as a substrate for the S_NAr reaction under microwave irradiation, but gave no evidence of the desired reaction. Indeed, 4-dimethylaminobenzaldehyde **2.22** was observed as the main product in most reactions, together with recovered starting materials. The dimethylamine needed for the displacement of fluoride from **2.10**, was generated from the degradation of DMF under the conditions of the reaction.[35]



Reagents & conditions : i) MgI_2, 30 min, 98%, ii) K_2CO_3, DMF, 150 °C, 90 min, μW, 0%

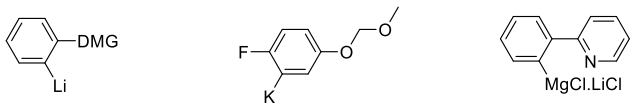
Scheme 2.7. S_NAr reaction of ester **2.31** with **2.14**

The problems we had encountered with the S_NAr reaction, prompted us to investigate alternative means of creating the ether linkage. These are described in the following Chapter.

2.2.2 Studies on the synthesis of fragment 2.5

Whilst investigating the S_NAr reaction, work towards the synthesis of the required fluorinated fragment **2.5** was also under development using *ortho*-metallation

strategies. Directed *ortho*-metallation has been extensively described in the literature and is widely used to functionalise aromatic compounds at positions that would be difficult to address under normal conditions. The main principle is to control the site of deprotonation of an aromatic ring using an appropriate directing group. The seminal work of Snieckus did much to delineate the requirements for directing groups in *ortho*-lithiation reactions.[36] Related work involving other organometallic species, particularly from the groups of Knochel and Schlosser, has brought new reactivities to light and given methods to functionalise *ortho*-positions on both electron-rich and electron-poor aromatic rings (Figure 2.1).[37,38]

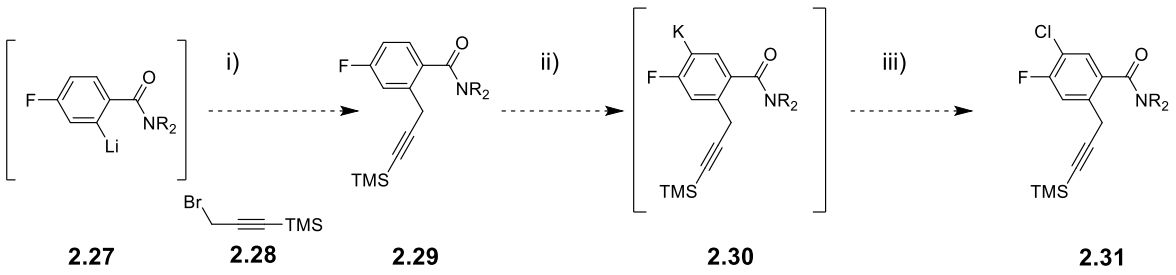


2.24 **2.25** **2.26**

Snieckus Schlosser Knochel

Figure 2.1. Common types of *ortho*-metalation reactions

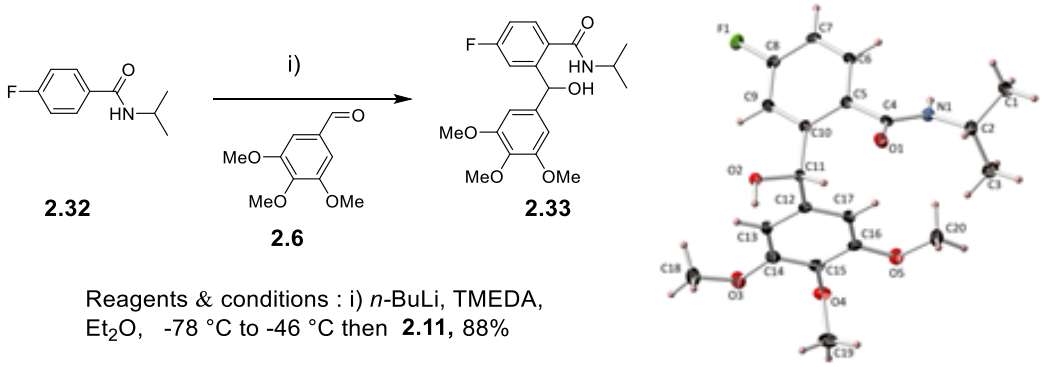
Of particular interest to us was Schlosser's finding that the use of organopotassium "superbases" could change the course and selectivity of directed *ortho*-metallation reactions. In particular, he had found that deprotonation next to a fluorine atom was more facile when compared to most directed lithiation reactions. Indeed, these would generally favour deprotonation *ortho*- to the amide group due to the strong Lewis acid – Lewis base interaction between a lithium centre and an amide.



Reagents & conditions : i) **2.28**, THF ii) *n*-BuLi, *t*-BuOK, solvent iii) NCS, THF

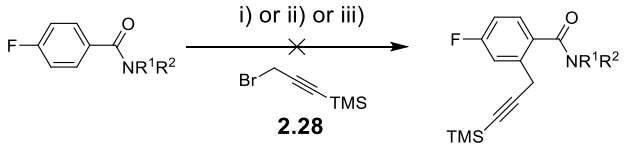
Scheme 2.8. Strategy for the selective functionalisation of position 2 and 5 of **2.27**

We decided to investigate the *ortho*-lithiation step using a secondary amide as the directing group as it is known to be very efficient for directing lithiation. In addition, by using an *iso*-propyl amide, nucleophilic attack of the amide by the lithiating species is minimal due to the formation of the imidate intermediate. Before attempting the experiment with the TMS propargylic bromide **2.28**, a quick test of the reaction was carried out to establish an efficient protocol for the formation of the desired dilithiated intermediate. Thus, 3,4,5-trimethoxybenzaldehyde **2.6** was added to the reaction mixture after addition of butyllithium and to our satisfaction the expected adduct **2.33** was isolated in excellent yield (88%). The single X-ray crystallography could be performed on the adduct, confirming the structure and providing a clear picture of the regioselectivity of the reaction.



Scheme 2.9. *Ortho*–lithiation with **2.11**

Encouraged by the successful model reaction the same conditions were next applied using 3–bromo–1–(trimethylsilyl)–1–propyne **2.28** as the electrophile (Scheme 2.10). Alas, this failed to give the expected arene propyne **2.35**, returning only the starting benzamide **2.34**. This reaction was repeated several times, varying the reaction parameters, but each time the outcome was the same. At this juncture we wondered if the aryllithium intermediate was too hard to react efficiently with the propargyl bromide. The corresponding organocopper reagent was therefore generated but it too failed to give the expected alkyne **2.35**. *Ortho*–cupration by the method described by Wheatley *et al*.[39] was also attempted but produced a complex mixture of compounds in low yield that could not be separated.



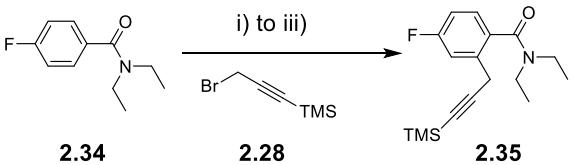
2.32 R^1 = iPr, R^2 = H
2.34 R^1 = R^2 = Et

2.33 R^1 = iPr, R^2 = H
2.35 R^1 = R^2 = Et

Reagents & conditions : i) *n*-BuLi, TMEDA, Et_2O, -78 °C to -46 °C then **2.28**; ii) *n*-BuLi,TMEDA, -78 °C to -46 °C, CuCN -78 °C to RT, then **2.28**, -78 °C to RT; iii)) $MeCuCN(TMP)Li_2$, 0 °C then **2.28**

Scheme 2.10. *Ortho*–metalation with **2.33** and **2.34**

Finally a protocol developed by Groth *et al.*[40] was attempted involving the formation of a copper reagent by transmetalation of a zincate by copper(I) cyanide. This type of reagent has been extensively described by Knochel to perform a plethora of addition reactions on diverse electrophiles.[41] The outcome of the reaction was promising as it gave the desired alkylated product **2.34**, albeit in low yield. Attempts to optimise the reaction further failed to improve on this initial finding so we decided to focus on the reactivity of organolithium **2.27** with other suitable electrophiles more prone to react with harder electrophiles than bromide **2.28**.

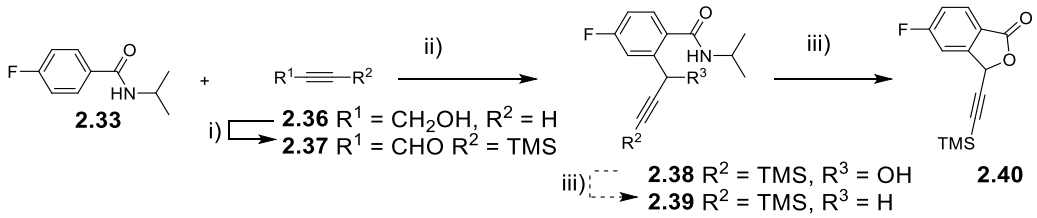


2.34 **2.28** **2.35**

Reagents & conditions : i) *s*-BuLi, TMEDA, -78 °C; ii) $ZnCl_2$, -78 °C to RT; iii) CuCN.2LiCl, -78 °C to RT; iv) **2.28**, -78 °C to RT, 30%

Scheme 2.11. Alkylation of **2.34** *via* the zincate species

Having established the conditions for nucleophilic addition to benzaldehyde **2.6** (scheme 2.9), we decided to examine the addition of the same imidate species to 3-(trimethylsilyl)propiolaldehyde **2.37**. Propiolaldehyde **2.37** was obtained from the propargyl alcohol **2.36** following a two-step literature procedure involving protection with TMSCl then oxidation with PDC (75%).[42] It is worth noting that aldehyde **2.37** was highly unstable at RT and was best to synthesise it from the propargyl alcohol **2.36** immediately prior to its use the addition step. The addition step was carried out under similar conditions to those established in the test reaction and afforded our target **2.38** in moderate yield (53%).



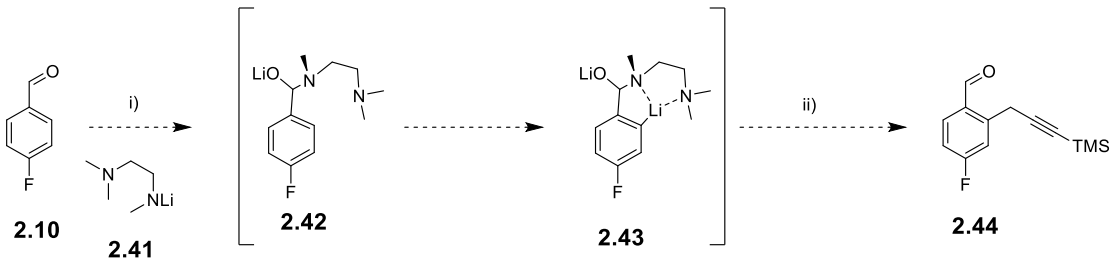
Reagents & conditions : i) *n*-BuLi, THF, -78°C, TMSCl then HCl 2M; PDC, DCM (75% over two steps) ii) *n*-BuLi, TMEDA, Et_2O, -78 °c to -46 °C then **2.37,** 53% iii) TFA, Et_3SiH, DCM, 36%

Scheme 2.12. Formation of the benzylic alcohol **2.38** and lactone **2.40**

As compound **2.38** had an unwanted hydroxyl group at the benzylic position, we next examined methods to effect its reductive removal. The first protocol attempted employed boron trifluoride and triethylsilane as a mild hydride donor, but returned only the starting material.[43] Using trifluoroacetic acid and triethylsilane, by contrast, provided lactone **2.40**.[42]

2.2.3 Alternative propargylation reaction: aldehyde directed *ortho*-lithiation and Suzuki coupling

At this juncture we decided to switch our focus as the carbons of the amide and the benzyl alcohol in **2.38** were both at a higher oxidation level than we required. Our new plan was to perform the *ortho*-lithiation on aldehyde **2.10** using an *in situ* protection method developed by Comins *et al.*[45] He was able to show that lithium amide **2.41** could simultaneously act as a protecting group and an *ortho*-directing group for aromatic aldehydes (Scheme 2.13). In essence, its addition to the aldehyde function first gave adduct **2.42** which, on treatment with *s*-BuLi underwent *ortho*-metalation to form aryllithium **2.43**. Addition of an electrophile next would provide the *ortho*-substituted benzaldehyde **2.44** on aqueous work-up.



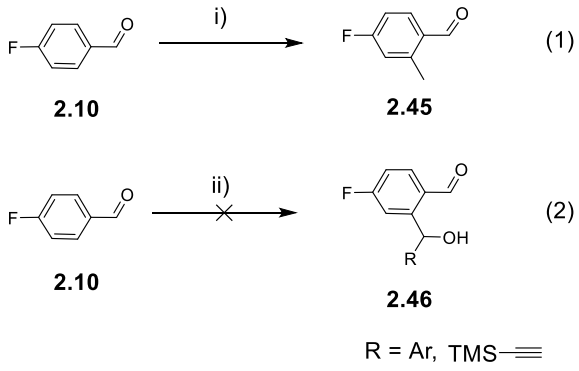
2.10 **2.41** **2.42** **2.43** **2.44**

Reagents & conditions : i) **2.41**, -78 °C, THF then *s*-BuLi, ii) **2.28**, -78 °C, THF then H^+

Scheme 2.13. Comin's aldehydes protection

Following an application of the aforementioned procedure by Cushman *et al.*[46] we carried out a test reaction on 4-fluorobenzaldehyde **2.10** using methyl iodide as an electrophile. Analysis of the product mixture by NMR showed the presence

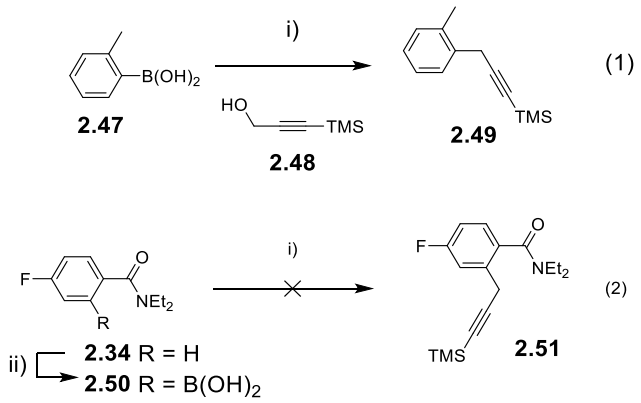
of the expected methylated product **2.45** in 70% yield with the remaining mass balance being recovered 4-fluorobenzaldehyde **2.10**. Unfortunately, this success was not mirrored when propynal **2.37** and benzaldehyde **2.6** were used as electrophiles, as we saw no evidence for formation of alcohols **2.46** in either reaction.



Reagents & conditions : i) LTMDA, -78 °C, THF, then *s*-BuLi then MeI, 70% (NMR yield)
ii) LTMDA, -78 °C, THF, then *s*-BuLi then **2.37** or **2.6**

Scheme 2.14. Cushman's *ortho*-lithiation on **2.10**

Another means to install a propargyl moiety was reported by Yoshida *et al.*[47] involving a Suzuki-Miyaura type coupling between a propargyl alcohol and an aryl boronic acid, *e.g.* **2.47** + **2.48** → **2.49** (Scheme 2.15). To apply their conditions on our system, boronic acid **2.50** was synthesised in good yield by adding trimethyl borate to the aryllithium species derived by deprotonation of amide **2.34** with *s*-BuLi. Unfortunately, attempts to replicate Yoshida's chemistry returned benzamide **2.34**, the result of the protodeborylation of **2.50**.



Reagents & conditions : i) $Pd(PPh_3)_4$ (10 mol%), Δ, dioxane, 76% **2.48** ii) *s*-BuLi then $B(OMe)_3$ quant.

Scheme 2.15. Suzuki-Miyaura coupling between **2.50** and **2.48**

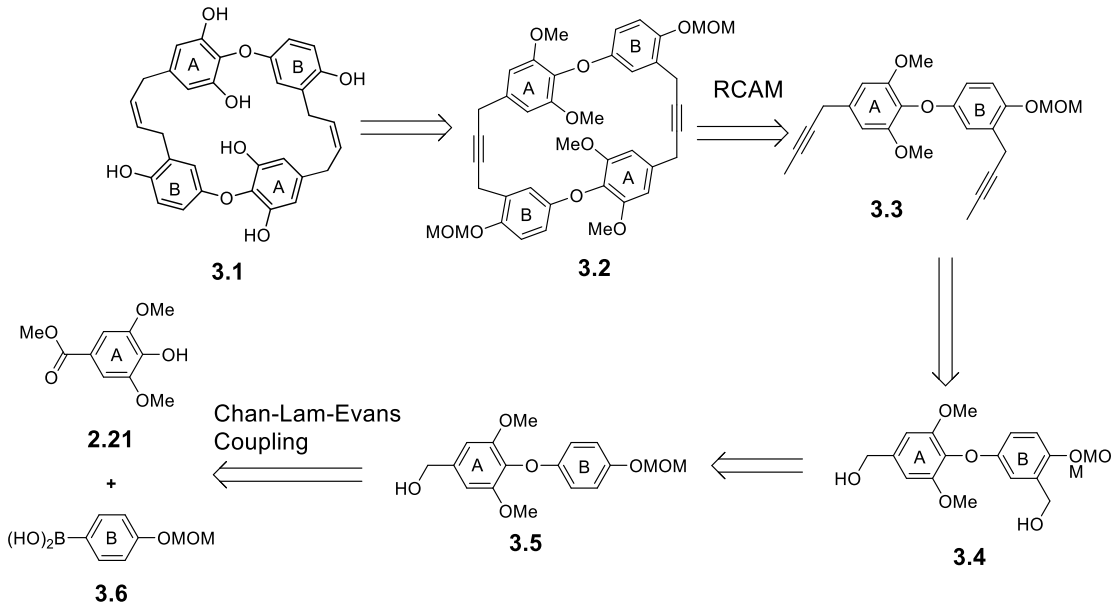
Thus, our preliminary investigations provided some useful insights into the early steps and shown that both the S_NAr reaction and the envisioned *ortho*-alkylation steps were likely to prove unproductive. Consequently, the decision was taken to review our synthetic plan and to develop an alternative approach avoiding these troublesome methodologies.

3. Chan-Lam-Evans coupling and Ring Closing Alkyne Metathesis

3.1 A new strategy

The strategy described in Chapter II relied on an S_NAr reaction and a propargylation to form the key fragment for a dimerization/cyclisation step. Both key steps proved troublesome prompting us to re-assess and redesign our synthesis. This chapter details the alternative approaches examined to form the ether linkage and achieve the macrocyclisation reaction. As our end game had never been examined, this was retained in the hope that our target could be made by selective hydrochlorination of macrocyclic diyne **3.2**.

The key step we envisioned sought to effect a dimerization of dialkyne **3.3** with concomitant ring closing alkyne metathesis reaction (RCAM). In turn, this key fragment **3.3** was to be derived in two steps from bisbenzylalcohol **3.4**. We hoped that the benzylic alcohol moiety on ring B could be installed using an *ortho*-metallation reaction to direct the introduction of a formyl group. The required diaryl ether **3.5** could in turn be envisioned from a Chan-Lam-Evans coupling reaction between boronic acid **3.6** and phenol **2.21** which are both accessible from commercial starting materials.

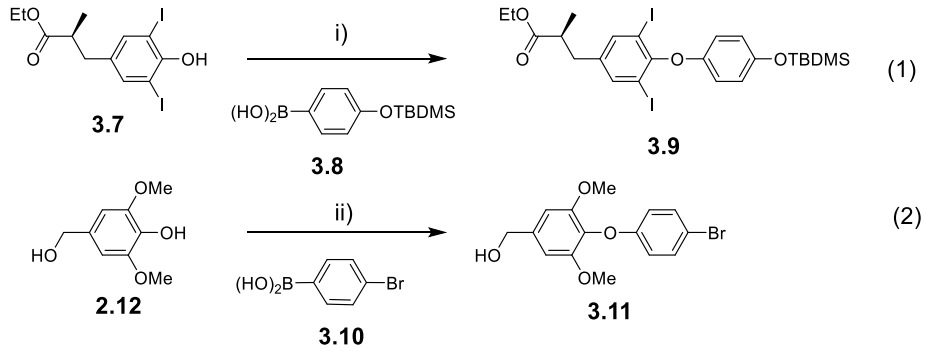


Scheme 3.1. Retrosynthetic plan featuring a Chan-Lam-Evans reaction and a RCAM

3.2 Formation of biaryl ether

As formation of the congested ether linkage in chrysophaentin F **1.8** was a crucial early step, an extensive literature survey was carried out to identify a good means of achieving that transformation. The Chan-Lam Evans coupling reaction was soon identified as a candidate as it had been shown to perform well under mild conditions with systems leading to the formation of hindered aryl ether and amino linkages. The reaction was reported by Chan, Lam and Evans in 1998 in three consecutive papers.[48,49,50] Each described the coupling of arylboronic acids with phenols or anilines mediated by stoichiometric copper(II) salts. It proved particularly effective for hindered 2,6-disubstituted substrates as demonstrated in the synthesis of biaryl ether **3.9** during a synthesis of thyroxine (scheme 3.2).

To test the effectiveness of the reaction in our hands, the original conditions were applied to the coupling of phenol **2.12** and the commercially available boronic acid **3.10**. Pleasingly, the reaction yielded the expected adduct **3.14**, albeit in a low isolated yield (30%).

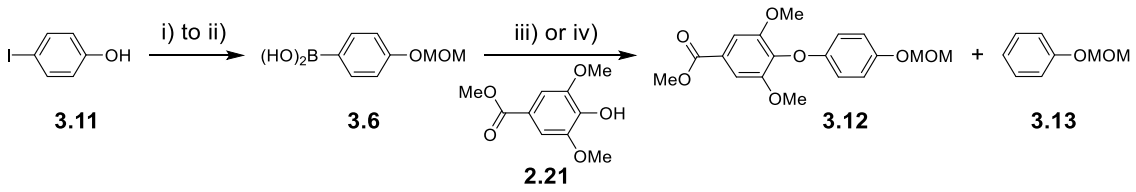


Reagents & conditions : i) $Cu(OAc)_2$, Py, 4 Å sieves, DCM, 84%
ii) $Cu(OAc)_2$, Et_3N 4 Å sieves, DCM, 24 h, 30%

Scheme 3.2. Model reaction using Chan-Lam-Evans original conditions

Having identified the Chan-Lam-Evans reaction as a suitable candidate for the formation of the hindered ether linkage in chrysophaentin **1.8**, we next needed to establish optimal conditions to achieve the coupling of boronic acid **3.6** and phenol **2.21**. Thus, methoxymethoxyphenyl boronic acid **3.6** was synthesised in two steps from commercially available iodophenol **3.11** in 93% yield following literature procedures described by Kajiwara and van Heerden (Scheme 3.3).[51] The coupling of boronic acid **3.6** and phenol **2.21** was then examined using the conditions disclosed in the original papers. Pleasingly, the major product formed was the expected biaryl ether **3.12**, and was isolated in 46% yield. However, the deborylated product **3.13** was also observed in significant quantity.

A better yield was subsequently achieved for the coupling of boronic acid **3.6** and methyl benzoate **2.21** (70%). However, to achieve this the reaction required the addition of 1 equiv. of copper(II) acetate and 1 equiv. of boronic acid each day for four days. Therefore, despite the high yield in respect of phenol **2.21**, the reaction was wasteful of time and resources. In 2001, Lam described a catalytic protocol for the coupling reaction when conducted under an oxygen atmosphere.[52] The reaction was thus attempted using 20 mol% copper(II) acetate and gave biaryl ether **3.12** in 63% yield. Though the yield was lower than the stoichiometric procedure, the reaction proceeded more rapidly and was more economical in respect of the boronic acid **3.6** (2.5 equivalents used instead of 4 equivalents).

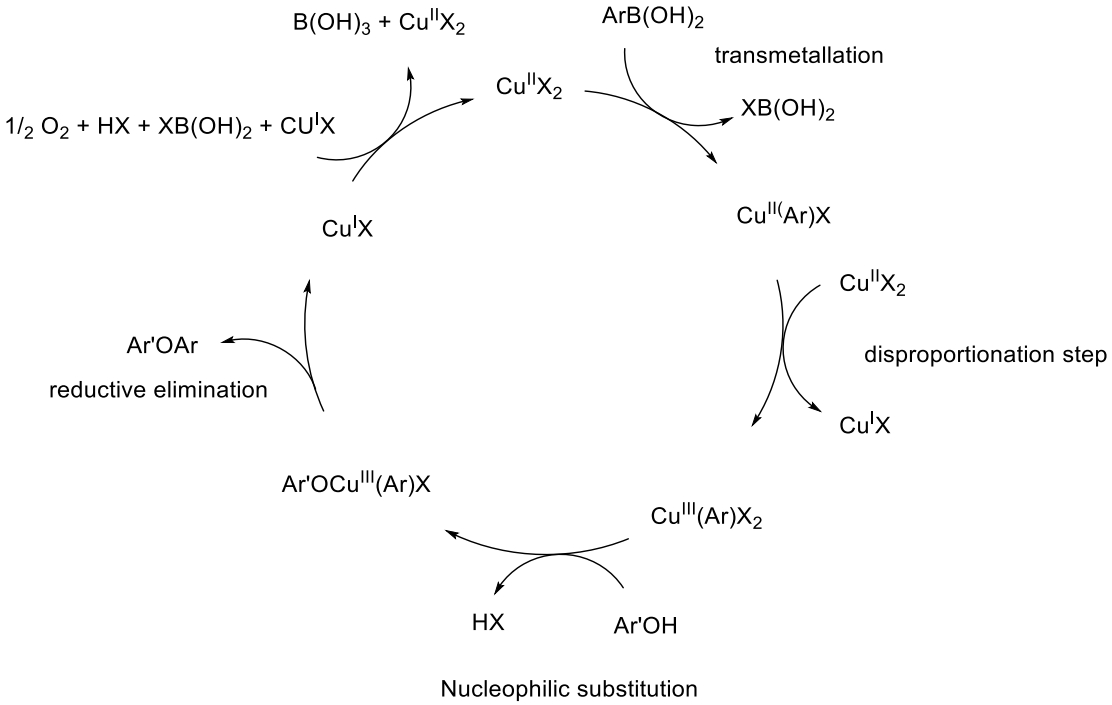


Reagents & conditions : i) NaH, THF then MOMCl ii) $B(O^iPr)_3$, *n*-BuLi (93% over 2 steps) iii) $Cu(OAc)_2$, 4 Å sieves Et_3N, DCM, 4 days, 70% iv) 20% $Cu(OAc)_2$ 4 Å sieves, O_2 Py, DMF, 50 °C 24 h, 63%

Scheme 3.3. Synthesis of diarene **3.12**

The accepted mechanism starts with a copper(II) species and its coordination to the nucleophile through transmetallation with the boronic acid.[53] Next, a disproportionation reaction with another copper(II) species generates a copper(I) and a copper(III) species. This is important as organocopper(II) species do not perform reductive elimination reactions efficiently. The copper(III) species can then undergo an nucleophilic substitution with the phenolate followed by a reductive elimination step generating a copper(I) species and forming the

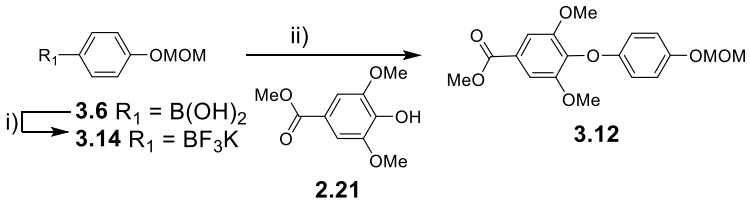
desired ether linkage between the two aryl substrates. The copper(I) species is then reoxidised to reform the catalytically active copper(II) species.



Scheme 3.4. Catalytic cycle for the Chan-Lam-Evans reaction

At this stage the stability of the boronic acid **3.6** was questioned, as the formation of the deborylated product indicated that a facile side-reaction was occurring. Therefore, the reaction was attempted using the corresponding trifluoroborate salt, which has been shown to be a useful surrogate for boronic acids in many reactions, including the Chan-Lam-Evans coupling.[54] Trifluoroborate **3.14** was synthesised in excellent yield from boronic acid **3.6** (Scheme 3.5) and then reacted with **2.21**. Unexpectedly, it gave the desired product **3.12** in a modest 36% yield. Indeed, as we had already identified a

protocol able to deliver diarene **3.12** in gram quantities, we decided to conduct no further optimisation at this stage.



Reagents & conditions : i) KHF_2, MeOH, 95%, ii) $Cu(OAc)_2$, DMF, O_2, 4 ÅMS

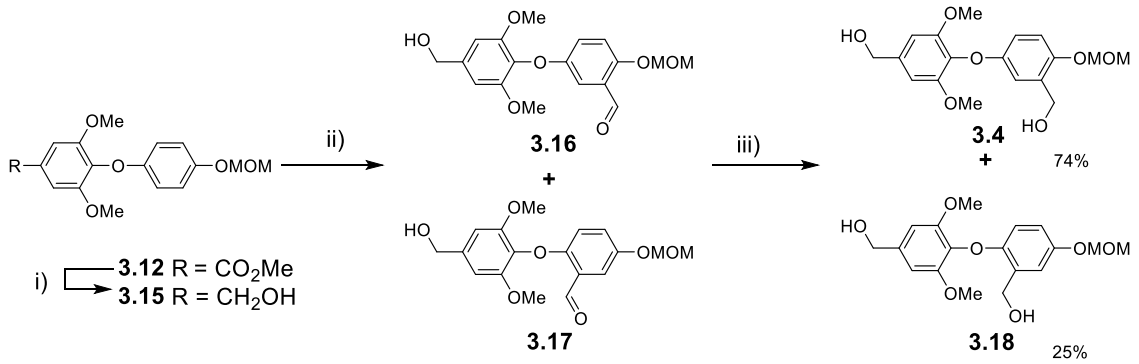
Scheme 3.5. Formation of trifluoroborate salt and Chan-Lam-Evans reaction

3.3 Propynylation

3.3.1 Access to benzyl alcohol 3.4

At this stage our focus turned to the efficient installation an aldehyde *ortho*- to the MOM directing group. Our plan was to use an *ortho*-lithiation reaction, so it seemed sensible to first reduce the ester function to eliminate side-reactions such as nucleophilic addition. The reduction readily accomplished by addition of an ether solution of $LiAlH_4$ to **3.12** at 0 °C, providing the expected benzyl alcohol **3.15** in high yield. Benzyl alcohol **3.15** was then lithiated in presence of 2.4 equivalents of *s*-BuLi, and TMEDA and after 40 min the reaction was quenched with DMF to form the expected aldehyde **3.16** on work up. A second aldehyde was detected in the crude product mixture and co-eluted when this was purified column chromatography. As a consequence, identification of the isomeric aldehydes was only possible after reduction of the product mixture to

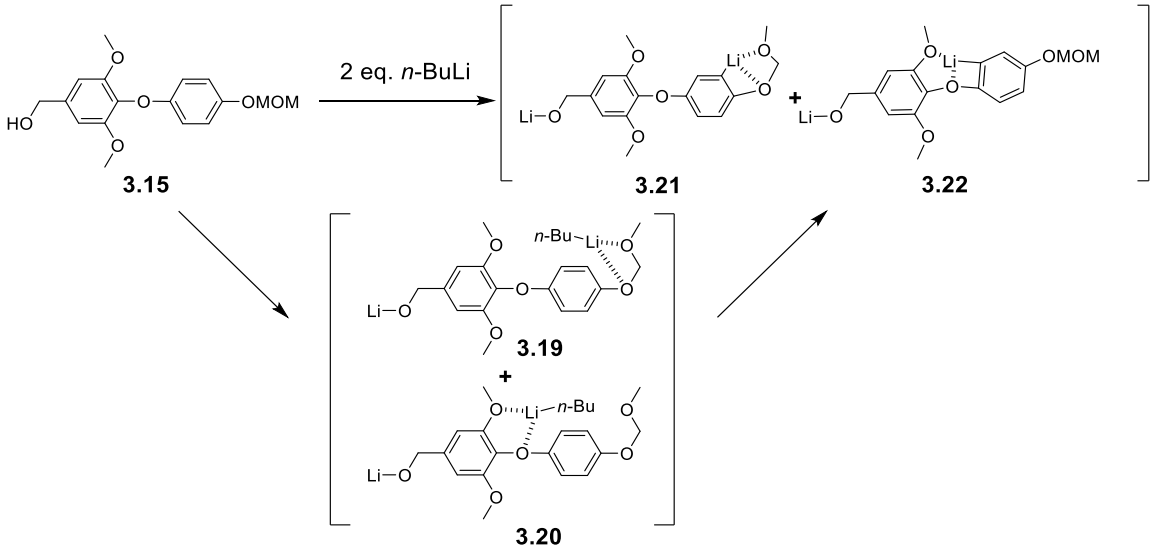
the corresponding benzyl alcohols with $NaBH_4$. Separation was then achieved using a combination of column chromatography and HPLC. ^{1}H and ^{13}C NMR analysis of the two products showed few notable differences, suggesting that we had formed the regioisomers **3.4** and **3.18**.



Reagents & conditions : i) $LiAlH_4$, Et_2O, 0 °C, 84% ii) *s*-BuLi, TMEDA, THF, -78 °C then DMF iii) $NaBH_4$, MeOH

Scheme 3.6. Formation of benzyl alcohols **3.4** and **3.18**

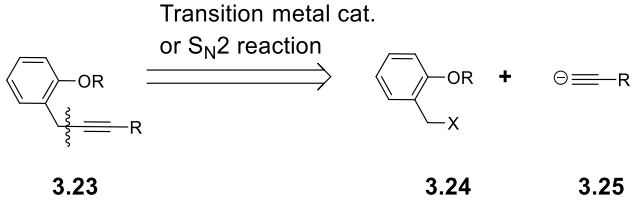
Through recourse to NOE and 2D NMR (HMBC and HMQC) experiments, we were able to confirm that the major product was the expected bisbenzyl alcohol **3.4** and the side-product was its regioisomer **3.18**. Undoubtedly, its formation was due to the chelation of butyllithium between the aryl ether and the proximal methyl ether leading to the pre-reaction complex **3.22** (Scheme 3.7). This must compete with the pre-reaction complex formed with the MOM, thereby determining the ratio of the products formed.



Scheme 3.7. Alternative deprotonation

3.3.2 Alkynylation

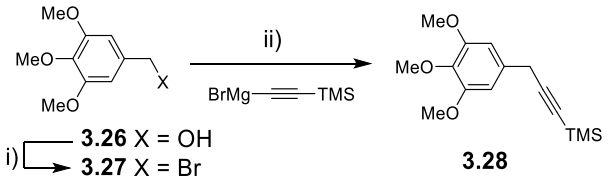
Last modification in this new strategy was the method used to install the propargyl moiety onto the arene rings. Instead of performing an aromatic metallation followed by nucleophilic addition to propargylic species, we decided to employ a benzylic synthon **3.24** and couple it with an alkynyl anion **3.25**. Appropriate methodology has been described in the literature, employing either the direct displacement of a leaving group at the benzylic carbon or by means of transition metal promoted coupling akin to the Sonogashira reaction.



Scheme 3.8. Alkynylation reaction disconnection

3.3.3 Alkynyl Grinard reagent method

To determine the best option for us to explore, the model benzyl bromide **3.27** was used as a starting point for the first part of this investigation, **3.27** being available in high yield through treatment of benzyl alcohol **3.26** with NBS and PPh_3. Displacement of the bromide with TMSethynylmagnesium bromide was readily achieved in the presence of 20 mol% Cu(I)Br afforded TMS protected alkyne **3.28** in 74% isolated yield.[55]

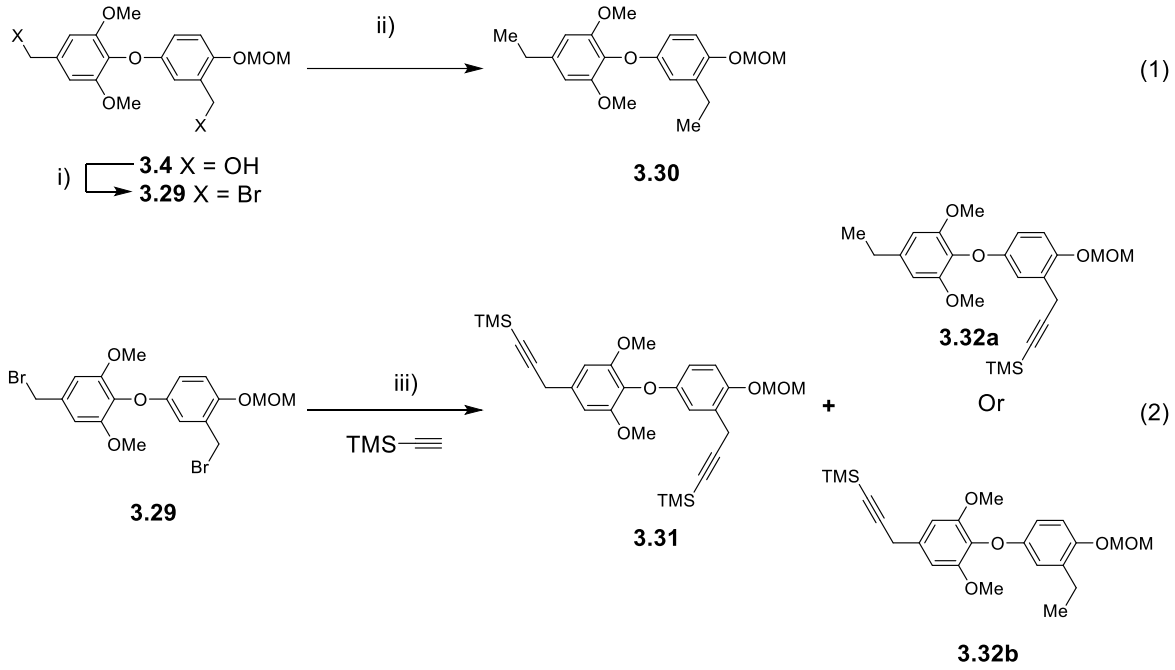


Reagents & conditions : i) PPh_3, NBS, THF, 0 °C, 86% ii) Cu(I)Br (20 mol%), THF, Δ,12 h, 74%

Scheme 3.9. Formation of the propargylic compound **3.28**

This protocol was next applied to bisbenzyl bromide **3.29** which was similarly obtained from the corresponding bisbenzyl alcohol **3.4** in excellent yield (Scheme 3.10). It is worth noting that compound **3.29** proved to be light sensitive with degradation occurring in a matter of hours. Consequently, it was found necessary to store this intermediate under argon in a freezer or to use it directly in the next step.

Next, attempts to prepare the methyl capped alkyne **3.3** were undertaken. A solution of MeMgBr in THF was placed under a positive pressure of propyne then catalytic copper(I) bromide and bisbenzyl bromide **3.29** were sequentially added. Alas, the reaction produced the methylated adduct **3.30** instead of the diyne **3.3**, indicating that deprotonation of propyne had not taken place. This may have been due to a slow deprotonation reaction or poor dissolution of propyne in THF. To address the issue of volatility, trimethylsilylacetylene was used in place of propyne gas. Under the aforementioned conditions, formation of a mono alkynylated product, **3.32a** or **3.32b**, was witnessed at low yield. The regiochemistry of alkyne addition was not determined due to the small amount of product isolated. Pleasingly, when the reaction was repeated using an excess of trimethylsilylacetylene (5 equiv.) the desired product **3.31** was isolated, albeit in 23% yield. The low yield was attributed to the instability of the bisbenzyl bromide **3.29**, and its propensity for degradation on prolonged heating.



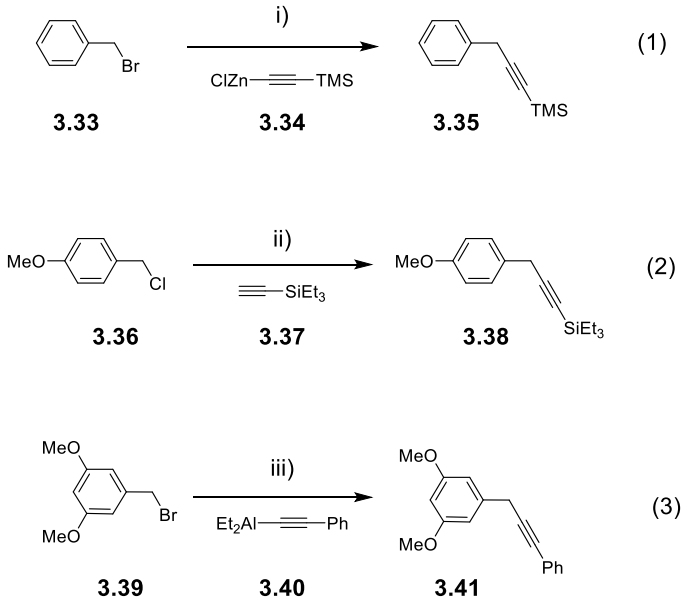
Reagents & conditions :i) PPh_3, NBS, THF, 0 °C, 94% ii) propyne, MeMgBr, 40% Cu(I)Br, Δ, THF, 75% iii) MeMgBr, 40% Cu(I)Br, Δ, THF, 23%

Scheme 3.10. Attempted alkynylation of bisbenzyl bromide **3.29**

3.3.4 Transition metal investigation

As an alternative to the anionic displacement method, which had proven challenging, we decided to investigate protocols involving transition metal catalysed coupling reactions to generate propynyl arenes. Methods for forming an sp^3 – sp bond at a benzylic position *via* palladium catalysed coupling were described by Negishi, Buchwald and Gau, in 2005, 2006 and 2011 respectively.[56,57,58] All reports included examples related to our model of study, suggesting this was a reasonable approach to follow. Negishi *et al.* described a coupling between benzyl bromide **3.33** and an alkynyl zinc species **3.34**, while

Buchwald *et al.* described a Heck-type alkynylation between an electron-rich benzyl chloride **3.36** and triethylsilylacetylene **3.37** and Gau reported a nickel-catalysed coupling of electron rich benzyl bromide **3.39** and aluminium acetalide **3.40**. Their study was large in scope, particularly in respect of the benzyl bromides species, and included an example that was particularly close to our system (Scheme 3.11).



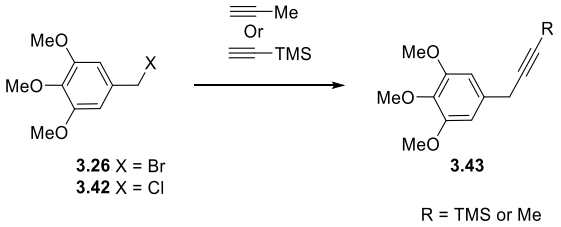
Reagents & conditions : i) Pd(DPEPhos)Cl_2 (1 mol%), THF, RT, 10 h, 88% ii) $PdCl_2(CH_3CN)_2$ (2 mol%), XPhos (6 mol%), K_2CO_3, MeCN, 65 °C, 16 h, 99% iii) $NiCl_2(PPh_3)_2$ (4 mol%), Et_2O 94%

Scheme 3.11. Reported alkynylation methods by (1) a Negishi-type coupling, (2) a Heck-type alkynylation and (3) a Nickel catalysed coupling.

Conditions were screened on the model halides **3.26** and **3.42** to establish the most efficient coupling reaction in our hands. Though all worked to some extent, yields were modest for both the Heck- and Negishi-type alkynylation reactions. By contrast, Gau's procedure afforded the expected alkyne **3.43** in

high yield in a short time frame under mild conditions. It is worth noting that the coupling described by Buchwald and co-workers was later conducted in the ICES' laboratory (Singapore) and afforded **3.43** in a quantitative yield. We have no inkling as to the origin of this discrepancy, as it was due to an unseen variable.

Table 3.1. Pd and Ni - catalysed coupling alkynylation



X	R	time	Catalyst	%
Br	TMS	1d	$PdCl_2(CH_3CN)_2$	17[a]
Cl	TMS	2d	$PdCl_2(CH_3CN)_2$	27[a]/99[d]
Br	Me	2d	$Pd(DPEPhos)Cl_2$	21[b]
Br	Me	2d	$Pd(DPEPhos)Cl_2$	25[b]
Br	Me	1d	$Pd(DPEPhos)Cl_2$	40[b]
Cl	Me	1d	$Pd(DPEPhos)Cl_2$	25[b]
Br	**TMS**	**3 h**	**$NiCl_2(PPh_3)_2$**	**72**[c]

(a) Heck-alkynylation: TMS acetylene, K_2CO_3, $PdCl_2(CH_3CN)_2$ (2 mol%), XPhos (6 mol%), 65 °C

(b) Negishi coupling: Propyne, *n*-BuLi then $ZnCl_2$, then **25**, $PdCl_2$(DPEPhos) (3 mol%), rt

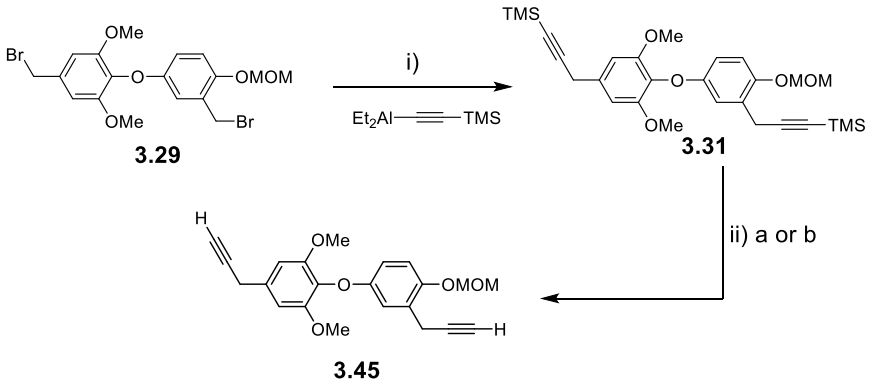
(c) Gau couling: $NiCl_2(PPh_3)_2$ (4 mol%), Et_2O

(d) Performed in ICES, Singapore

Following this investigation, the nickel catalysed coupling reaction was selected as the most suitable for our system. The mild conditions and the rapidity with

which it could be realised were key factors in the decision, along with the high yield witnessed on the model system. Thus, analogous conditions were applied to the coupling of bromide **3.29** dissolution and TMS acetalyde **3.44** to yield the required bis-alkyne **3.31** in a satisfying 76% yield.

Formation of fragment **3.31** heralded our entry to the end-game phase of the synthesis as the key macrocyclisation step was now in sight. To that end, removal of the TMS groups was investigated using two different protocols. A classic protocol, described by Wipf and co-workers in 2012, used TBAF in a buffered solution of THF and AcOH in order to avoid any isomerisation of terminal alkyne **3.45** to the corresponding allene.[2] It proceeded in 71% yield. Another protocol, described by Pale and co-workers in 2005,[59] employed silver triflate catalytically in a mixture of DCM, MeOH and water (ratio of 7/4/1 respectively). It gave the fully deprotected product **3.45** in a comparable 70% yield.



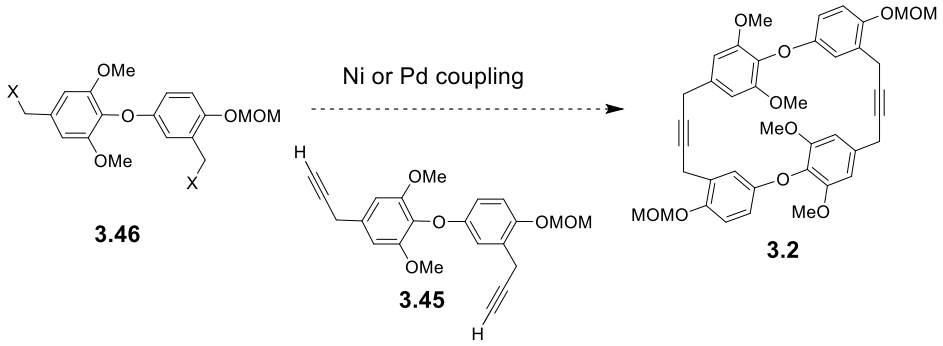
Reagents & conditions : i) $NiCl_2(PPh_3)_2$ (14 mol%), 0 °C to RT, Et_2O/pentane, 76%
ii) a)TBAF, AcOH 88%; b) AgOTf 71%

Scheme 3.12. Formation of methyl capped dialkyne **3.3**

3.4 Macrocyclisation strategies

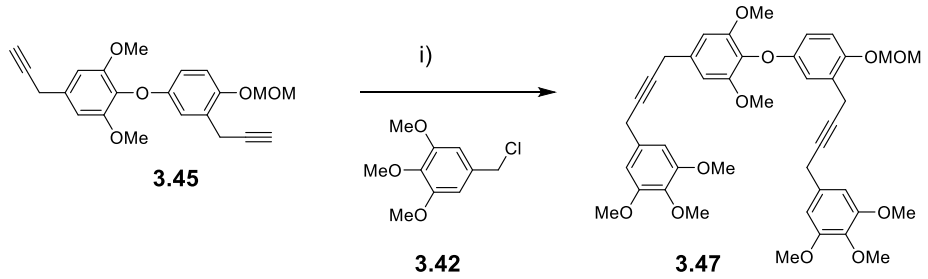
3.4.1 Macrocyclisation by alkynylation

As we were investigating the transition metal catalysed reactions between a benzylic position and terminal alkynes, the idea of using this reaction for macrocyclisation was examined. The principle was similar to that of the dimerization/macrocyclisation protocol presented earlier in this chapter (Scheme 3.1). However, in this case one of the fragments would bear two benzyl halide functionalities while the second would contain two terminal alkynes. In this way the two fragments might be coupled, under nickel or palladium catalysis, to form macrocycle **3.2** (Scheme 3.13).



Scheme 3.13. Macrocyclisation by alkynylation

A palladium catalysed Heck-alkynylation developed by Buchwald *et al.* was the first method to be evaluated. A model reaction conducted between diyne **3.45** and benzyl chloride **3.42** was first examined in presence of bisacetonitrile dichloro palladium and led to the expected tetracyclic product **3.47** in 55% yield.

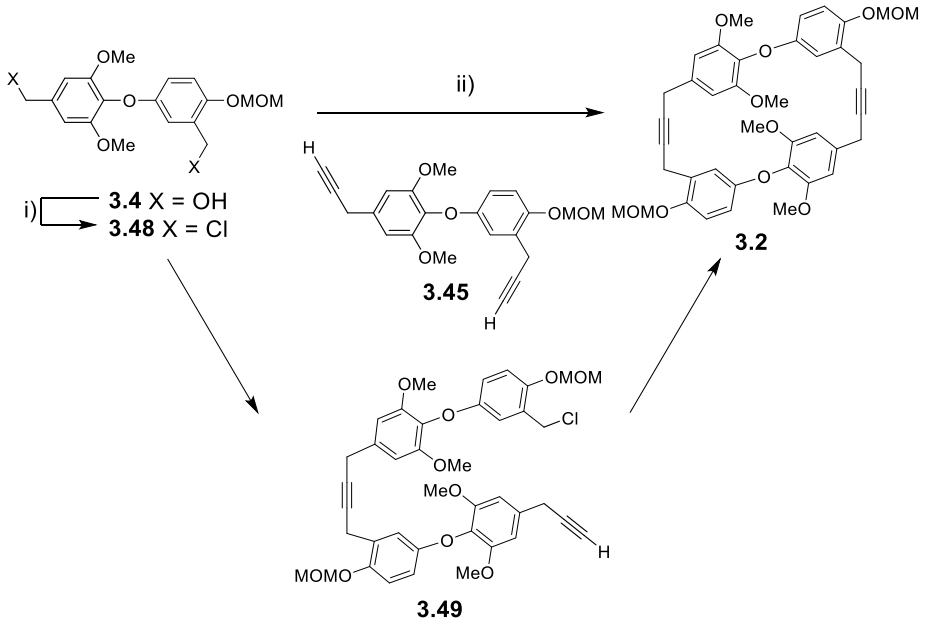


Reagents & conditions : i) $PdCl_2(CH_3CN)_2$, XPhos, 70 °C, acetonitrile, 55%

Scheme 3.14. Formation of tetra aromatic species **3.47**

Buoyed by this success, our attention turned to the synthesis of macrocycle **3.2**, which required the preparation of bisbenzyl chloride **3.48**. Surprisingly, treatment of bisbenzyl alcohol **3.4** under our usual conditions (NCS, Ph_3P) provided **3.48** in a disappointing 21% yield. Furthermore, in the palladium

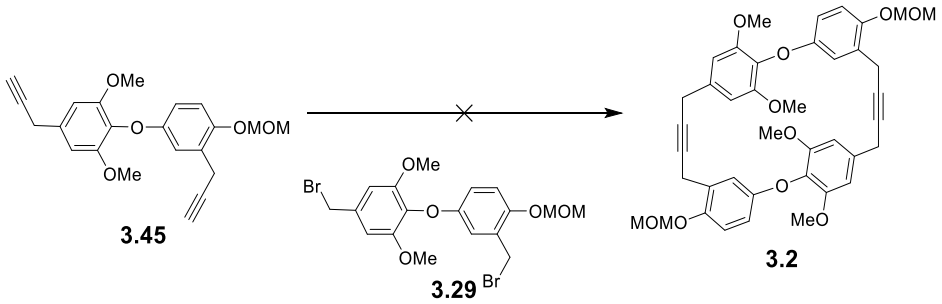
catalysed coupling reaction with diyne **3.45**, many products were formed in very low yield. Analysis of the crude product mixture by LC-MS showed a peak at 703 corresponding to the expected mass of macrocycle **3.2** plus sodium ($[M+Na]^+$). However, attempts to isolate the desired product were unsuccessful. Another prominent component exhibited a mass of 739, providing tantalising evidence for the presence of the intermediate linear dimer **3.49** (as this would correspond to $[M(^{35}Cl)+Na]^+$).



Scheme 3.15. Palladium catalysed macrocyclisation

A similar sequence was attempted using Gau's method to couple diyne **3.45** and bisbenzyl bromide **3.29** in the presence of $NiCl_2(PPh_3)_2$. In this case, we attained no evidence for the formation of macrocycle **3.2** and attribute failure to

precipitation of the deprotonated diyne from the non-polar solvent during the course of the reaction. No other solvents were investigated with this coupling.

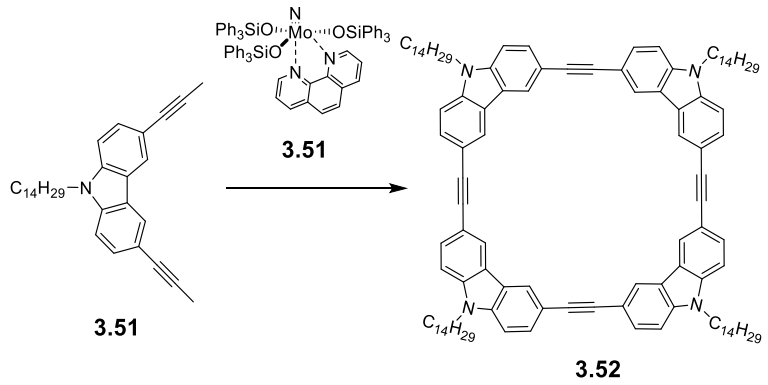


Reagents & conditions : i) *n*-BuLi, pentane, 0 °C, 20 min then $ClAlMe_2$, 0 °C, 20 min then Et_2O, $NiCl_2(PPh_3)_2$ (14 mol%)

Scheme 3.16. Macrocyclisation using Gau's alkynylation method

3.4.2 Ring-closing alkyne metathesis (RCAM)

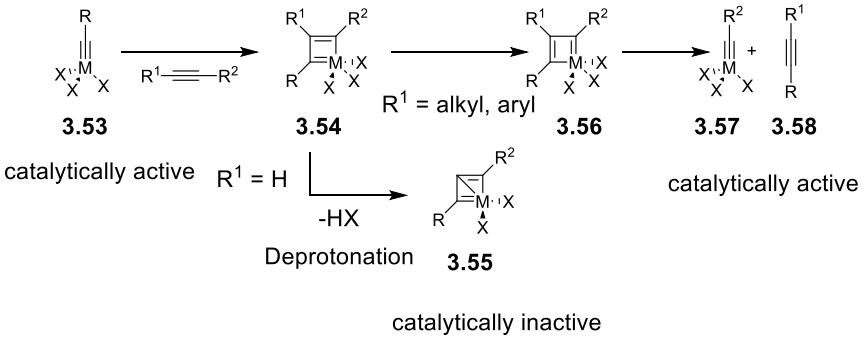
While assessing our options for the macrocyclisation step, we came across a paper by Fürstner *et al.*[60] in which alkyne metathesis was used to prepare macrocyclic tetrayne **3.52** from diyne **3.50** in high yield (Scheme 3.17). Cyclisation was mediated by the stable phenantroline-silyloxy molybdenum catalyst **3.51**.



Reagents & conditions : $MnCl_2$ (10 mol%), **3.52** (10 mol%), 30 min, Δ, Toluene, 83%

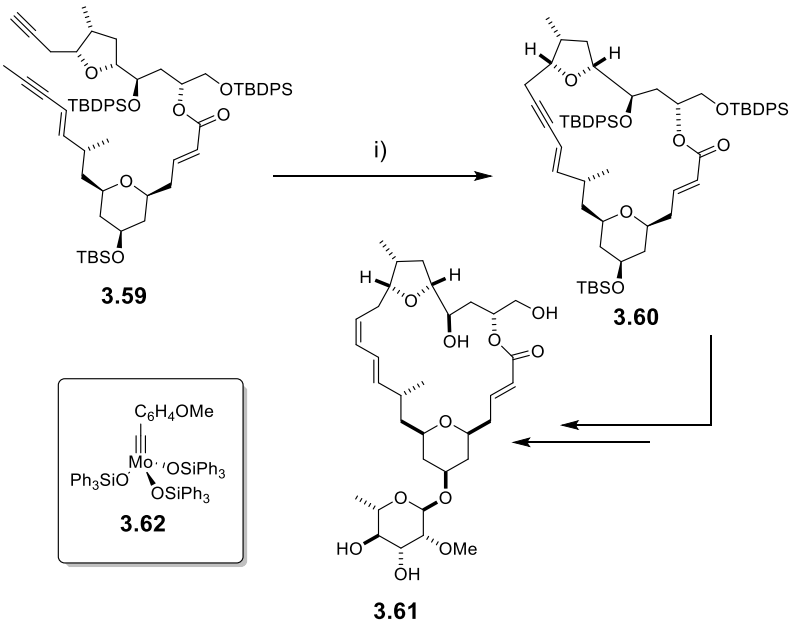
Scheme 3.17. Formation of tetrayne macrocycle **3.52** by ring-closing alkyne metathesis

Usually, methylated alkynes are used a precursors in alkyne metathesis in order to eliminate a common side reaction witnessed with terminal alkynes. The side reaction occurs following formation of the metallocyclobutadiene intermediate **3.54**. Substrates prone to deprotonation generally give metallacycles **3.55**, which are catalytically inactive. By contrast, substituted alkynes proceed to metallocyclobutadienes **3.56** in a fashion similar to that seen in olefin metathesis. A cycloreversion reaction then provides alkyne **3.58** and the alkylidyne complex **3.57**. Recently Tamm and co-workers have developed a catalyst to perform terminal alkyne metathesis,[61] broadening the scope and applicability of the method considerably.



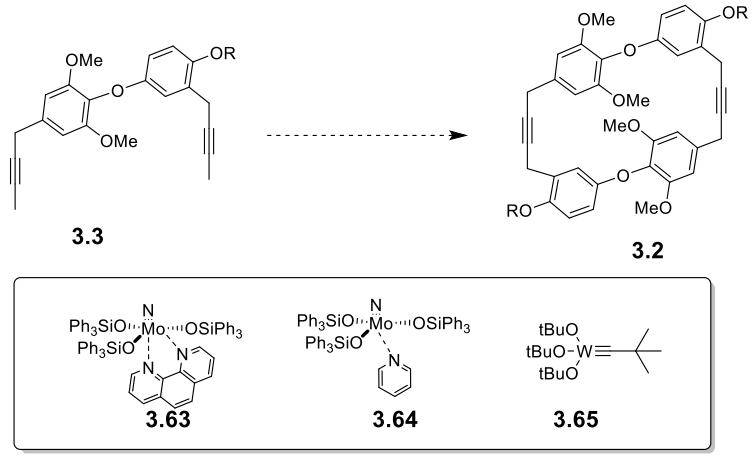
Scheme 3.18. Alkyne metathesis reaction mechanism

Using this procedure, Fürstner and co-workers developed a route towards the natural product mandelalide A **3.61** (Scheme3.19).[62] Notably, a mixed alkyne metathesis between a terminal alkyne and a methyl substituted alkyne was the pivotal step.



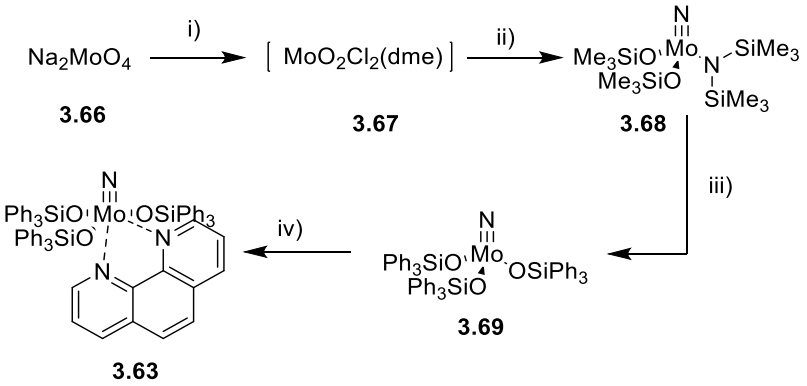
Scheme 3.19. Synthesis of Mandelalide A proposed structure by RCAM

This encouraging precedence inspired us to explore new strategy for assembling the chrysophaentin core that offered good prospects for high efficiency and a low step-count. Our plan was to combine the dimerization and macrocyclisation reactions into one step, **3.3** → **3.2**, through application of the aforementioned alkyne metathesis reaction (Scheme 3.20).



Scheme 3.20. RCAM strategy to build chrysophaentin core structure **3.2**

Before embarking on the RCAM reaction with diyne **3.3**, it was necessary to choose an appropriate alkyne metathesis catalyst. The candidate catalysts, **3.63**, **3.64** and **3.65**, were identified following a survey of literature. Catalyst **3.63** was not a commercial entity so had to be prepared by a procedure described by Fürstner et al.[60] Surprisingly, the synthesis of catalyst **3.63** proved to be more involved than that described in the paper as the final purification step failed to provide the pure catalyst. However, characteristic peaks for the expected molybdenium species were clearly seen by NMR and led us to wonder if it would still be catalytically competent.

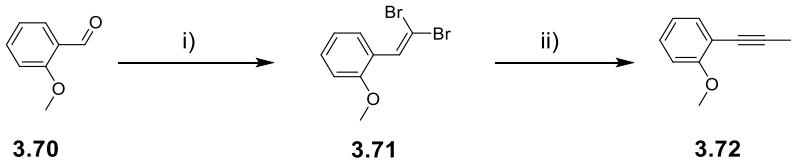


Reagents & conditions : i) TMSCl, 1,2-dimethoxyethane (DME), Δ,
ii) LiHMDS, hexane, iii) Ph_3SiOH, toluene, 80 °C, iv) 1,10-phenantroline

Scheme 3.21. Catalyst **3.63** synthesis

A test alkyne metathesis reaction was therefore conducted using alkyne **3.72** as a model compound (having been used by Fürstner *et al.* in alkyne metathesis reactions).[60] (2-methoxyphenyl)propyne **3.72** was thus prepared in good yield

using a protocol described by Barton *et al*.[63] This centred on the formation of dibromostyrene **3.71** from benzaldehyde **3.70** followed by a Corey-Fuchs reaction with a methyl iodide quench (Scheme 3.22).



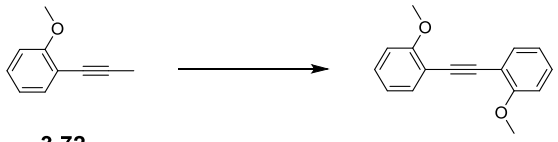
3.70 **3.71** **3.72**

Reagents & conditions : i) CBr_4, PPh_3, 79% ii) *n*-BuLi then MeI, THF, 88%

Scheme 3.22. Formation of phenylacetylene **3.72**

In the sequence of model reaction examined, diarylacetylene **3.73** was formed in modest yield using the Schrock catalyst **3.65**. By contrast, catalysts **3.63** and **3.64** showed no reactivity and returned only starting material

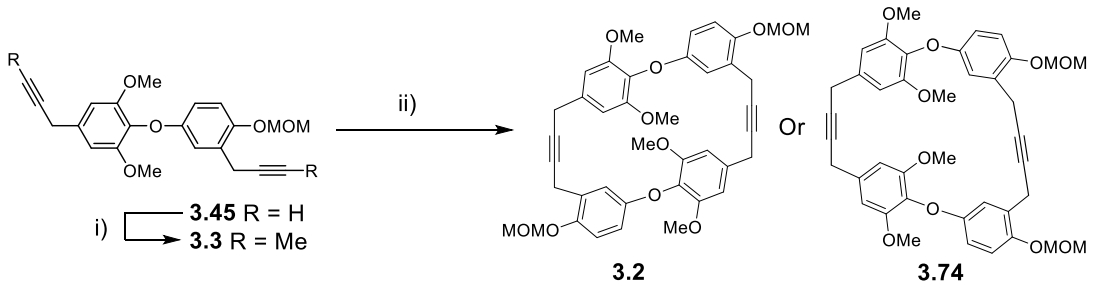
Table 3.1. Dimerisation of phenyl acetylene **3.72** to form adduct **3.73**



3.72 **3.73**

Catalyst (10 mol%)	Conditions	%
3.65	Toluene, 80 °C, $MnCl_2$	0
3.66	Toluene, 80 °C	0
3.67	Toluene, 80 °C	60%

Diyne **3.3** was accessed by treating terminal alkyne **3.45** with *n*-BuLi (2.5 equiv.) yielding the desired methylated alkyne in 59% yield (Scheme 3.23). Diyne **3.3** was next exposed to the Schrock catalyst **3.65** using the conditions established in our model study. Alas, the reaction led to a complex product mixture from which seven components could be isolated by HPLC (no recovered starting material was seen). Amongst these, one macrocyclic component was isolated following reverse phase preparative HPLC. However, its identity could not be established with certainty as the isomers **3.2** and **3.74** can each be formed in the reaction and these would be expected to display very similar spectral characteristics.



Reagents & conditions : i) *n*-BuLi, THF then MeI, 59% ii) **3.65**, toluene, 80 °C, C = 0.002 M, 6%

Scheme 3.23. Macrocyclisation using a RCAM reaction

Thus, a relevant sequence of reactions led us to form the desired macrocyclic structure. An efficient ether formation step was developed along with an alkynylation reaction which afforded the key fragment to explore the RCAM step. However, despite the confirmation that the RCAM reaction could be used to access the desired structure the low yields obtained so far led us to consider a more thorough investigation of the reaction conditions for the RCAM and it required a large amount of starting material. Thus, we decided to carry an optimization on the route to access dialkyne **3.3** in order to have an efficient and scalable synthesis for the macrocyclisation precursor.

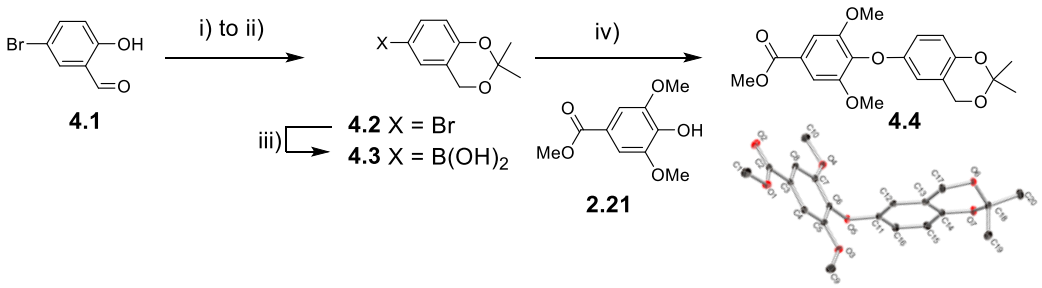
Chapter 3: Chan-Lam-Evans coupling and RCAM

4. Optimisation of the synthesis

Our primary task at this juncture was to resolve the main drawbacks with our current strategy. Thus, it was clearly necessary to investigate the macrocyclisation reaction further as it was low yielding and proceeded with an uncertain outcome. Other problems identified in the synthesis as a whole were the lack of regioselectivity during the *ortho*-lithiation reaction (**3.15** → **3.4**), the instability of boronic acid **3.6** and the alkynylation step, **3.29** → **3.3**, where three steps were needed to form the methyl substituted alkyne **3.3** from the corresponding benzyl bromide. Fixing these issues would allow us to attain the precursors needed for a study of the macrocyclisation reaction and in the quantities needed to progress the synthesis further.

4.1 Solving the *ortho*-lithiation selectivity

To solve the problem of regioselectivity in the *ortho*-lithiation step, **3.15** → **3.4** (scheme 3.7), we decided adapt our strategy and have the benzylic position attached to the arene before embarking on the Chan-Lam-Evans coupling reaction. Thus, our plan was to prepare diaryl ether **4.4** through coupling of the salicyl derived boronic acid **4.3** and phenol **2.21**. Pleasingly, the approach worked well and afforded the expected diaryl ether in 90% yield (Scheme 4.1).



Reagents & conditions : i) $NaBH_4$, MeOH, 79% ii) DMP, acetone, Na_2SO_4, 98%
iii) *n*-BuLi then $B(OiPr)_3$, 78% iv) 20% $Cu(OAc)_2$ 4 Å sieves, O_2 Py, DMF, 50 °C 24 h, 90%

Scheme 4.1. Formation of diaryl ether **4.4**

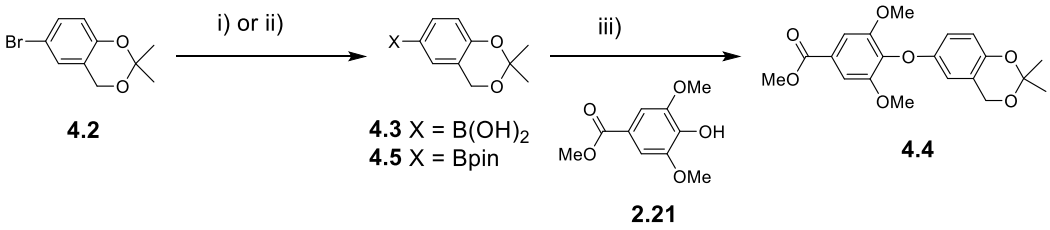
Boronic acid **4.3** also proved unstable in our hands and it proved necessary to employ two equivalents of it in the Chan-Lam-Evans coupling reaction to obtain good yield. We therefore felt obliged to address this issue before we looked to scaling up the synthesis.

4.2 Solving boronic acid 4.3 instability.

To solve the instability of boronic acid **4.3** we decided to employ a more stable surrogate. As we already explored the use of trifluoroborate previously with limited success our attention was drawn towards the use of pinacol boronate **4.5** as an equivalent of boronic acid **4.3**. This has been shown to be an effective surrogate in various coupling reactions generally being more stable than boronic acids and more reactive than their trifluoroborates equivalents, additionally they are easily chromatographed and recovered. Thus, a Miyaura borylation was performed on bromoarene **4.2** and gave the expected boronic ester **4.5** in high yield. Its performance in the Chan-Lam-Evans coupling reaction, **4.5** + **2.21** →

4.4, was then assessed in different solvents (DMF and EtOH) and with different sources of copper [$Cu(OAc)_2$, $Cu(OTf)_2$ and Cu(II)-TMEDA].[64] The system using 1 equivalent of phenol **2.21** and 1 equivalent of boronic ester **4.5** in EtOH mediated by $Cu(OTf)_2$ was selected as the most suitable due to the high yield attained (76%) and the facile recovery of unreacted starting materials from the product mixture.

Table 4.1. Chan-Lam-Evans optimisation



4.2 **4.3** X = $B(OH)_2$ **4.5** X = Bpin **2.21** **4.4**

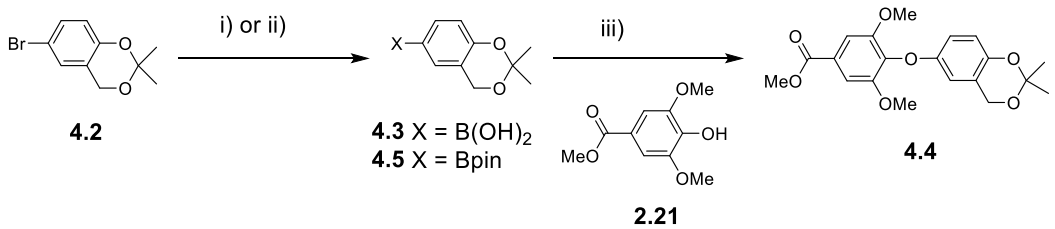
Reagents & conditions : i) $B(O^iPr)_3$, *n*-BuLi ii) B_2Pin_2, KOAc, $Pd(dppf)Cl_2$ (20 mol%) , THF, 60 °C, 16 h, quant. iii) see table

X	Equivalents	Catalyst	Solvent	loading	Yield (%)
$B(OH)_2$	1.9	$Cu(OAc)_2$	DMF	20%	45 to 90
$B(OH)_2$	1.9	$Cu(OTf)_2$	DMF	20%	38
Bpin	1.0	$Cu(OAc)_2$	DMF	20%	0
Bpin	1.4	$Cu(OTf)_2$	DMF	20%	25
Bpin	**1.0**	**$Cu(OTf)_2$**	**EtOH**	**20%**	**76**
Bpin	1.0	Cu-TMEDA	EtOH	10%	23

4.3 Direct alkynylation reaction.

4.3.1 Access to bisbenzyl-bromide 4.8

Our next task was to address the difficulties associated with the formation of a 2-butynyl species **3.3** by developing an efficient coupling reaction between bisbenzyl-bromide **3.29** and a metallated propyne. However, before we could address that problem we needed to develop a route to bisbenzyl bromide **4.8**, the precursor for our double alkynylation reaction. To that end, diaryl ether **4.4** was deprotected to benzyl alcohol **4.6** and its phenol reprotected with benzyl bromide to give **4.7**. Bisbenzyl bromide **4.8** then prepared in two steps by reduction with $LiAlH_4$ and a double bromination. Importantly, all of these reactions could be performed on a multi-gram scale with consistent yields.



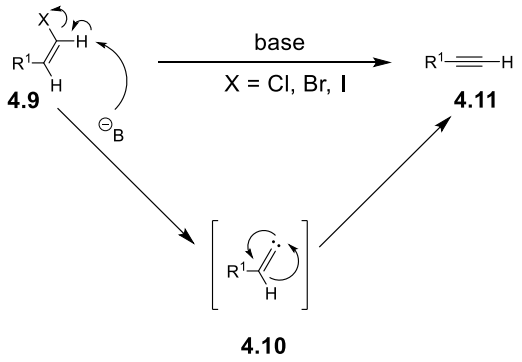
4.2 **4.3** X = $B(OH)_2$ **4.5** X = Bpin **2.21** **4.4**

Reagents & conditions : i) $B(O^iPr)_3$, *n*-BuLi ii) B_2Pin_2, KOAc, $Pd(dppf)Cl_2$ (20 mol%) , THF, 60 °C, 16 h, quant. iii) see table

Scheme 4.2. Synthesis of bisbenzyl-bromide **4.8**

4.3.2 Methyl capped alkyne

With bisbenzyl-bromide **4.8** in hand we could now investigate the crucial double propynylation reaction. The problems we had encountered led us to synthesise the desired methylated alkyne **3.3** in three steps instead of one. To address this we needed a convenient way of forming a metallated propyne capable of performing well in the Gau coupling reaction and, interestingly, a reaction developed at the end of the 19th century emerged as a possible solution. First described by Fritsch, Buttenberg and Wiechell in 1894,[65] the rearrangement of vinyl halides to alkynes in presence of a strong base gives access to alkynes (Scheme 4.3).

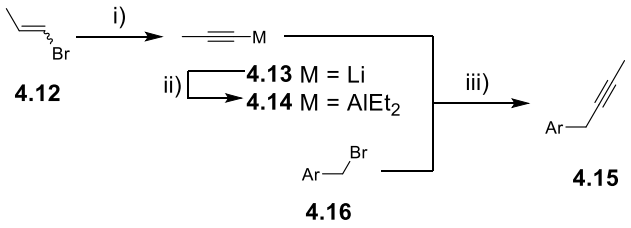


Scheme 4.3. The Frisch-Buttenberg-Wiechell rearrangement

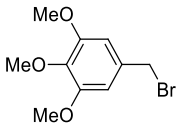
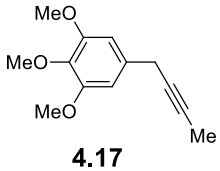
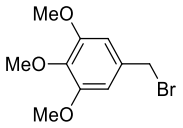
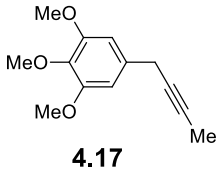
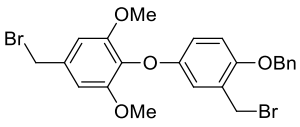
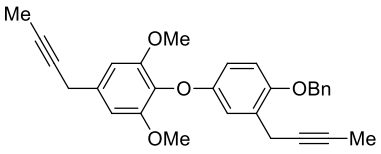
Importantly, the method was used by Toussaint and co-workers to access propynyl lithium from propenyl bromide **4.12** in THF using 1.5 equivalent of *n*-

BuLi.[66] Although they commented that the reaction did not occur in Et_2O, we decided to attempt it in a mixture of Et_2O and pentane (1 : 1) so as to make it compatible with Gau's chemistry. To our delight, formation of propynyl lithium **4.13** was soon evidenced when transmetallation to the corresponding organoaluminium species followed by reaction with benzyl bromides **3.27** and **4.8** under nickel catalysis formed the propynylated adducts **4.17** and **4.18** in modest yields (Table 4.2).

Table 4.2. Propynylation using the Frisch-Buttenberg-Wiechell rearrangement

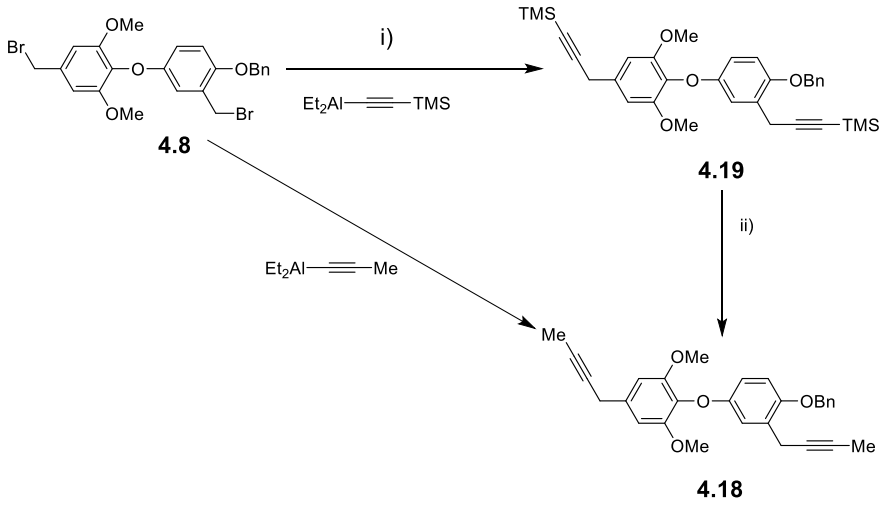


Reagents & conditions : i) *n*-BuLi, -78 to 0 °C, Et_2O/pentane (1 :1) ii) Et_2AlCl, 0 °, EtO/pentane (1 ; 1) ii) $NiCl_2(PPh_3)_2$, 0 °C to RT, Et_2O/pentane (1 :1)

substrate	Product	*n*-BuLi equivalents	Yield (%)
 **3.27**	 **4.17**	1.5	64
 **3.27**	 **4.17**	2	44
 **4.8**	 **4.18**	1.5	43

A comparison of the two strategies for the double propynylation of **4.8** to diyne **4.18** (Scheme 4.4) showed that the modest 43% yield attained using the Frisch-

Buttenberg-Wiechell approach was substantially higher than that given by our three-step protocol (23% overall).



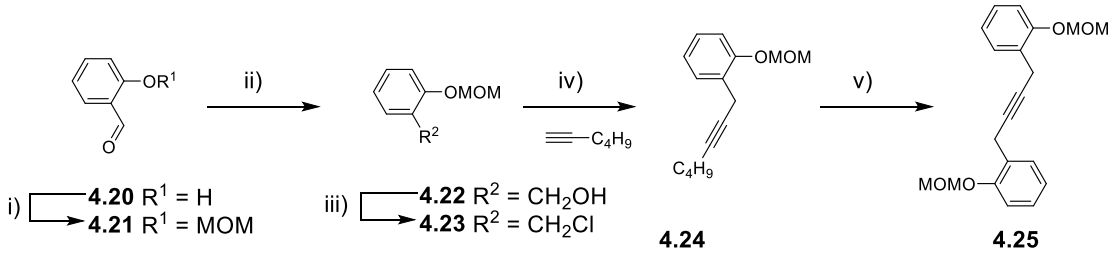
Reagents & conditions : i) $NiCl_2(PPh_3)_2$ 14%, Et_2O/pentane (1 : 1) 72% ii) AgOTf, MeOH/H_2O/DCM (3 : 1 : 4); *n*-BuLi, MeI, 0 °C to RT, THF (23% over two steps) iii) $NiCl_2(PPh_3)_2$ 14%, Et_2O/pentane (1 : 1), 43%

Scheme 4.4. Comparison of the procedures used to access diyne **4.18**

4.3.3 Butyne substituted alkyne

We next wondered if use of a longer chain alkyne might offer an even simpler means of resolving this issue by allowing us to employ direct deprotonation instead of the Frisch-Buttenberg-Wiechell rearrangement. Our analysis of the key macrocyclisation reaction suggested that the favoured outcome of RCAM could still be driven by entropy towards the macrocyclic diyne **3.2**. In effect, high dilution could be used to ensure that macrocyclisation (a first order reaction) would outpace dimerisation (a second order reaction). Moreover, as macrocyclisation leads to a more chaotic state, this outcome would also be

favoured on thermodynamic grounds. To test this hypothesis alkyne **4.22** was synthesized, in a short sequence of high yielding reactions (Scheme 4.5), then subjected to alkyne metathesis reaction in presence of catalyst **3.65**. After heating in toluene at 80 °C for 15 h we were encouraged to witness the formation of dimer **4.23** in 48% of yield.



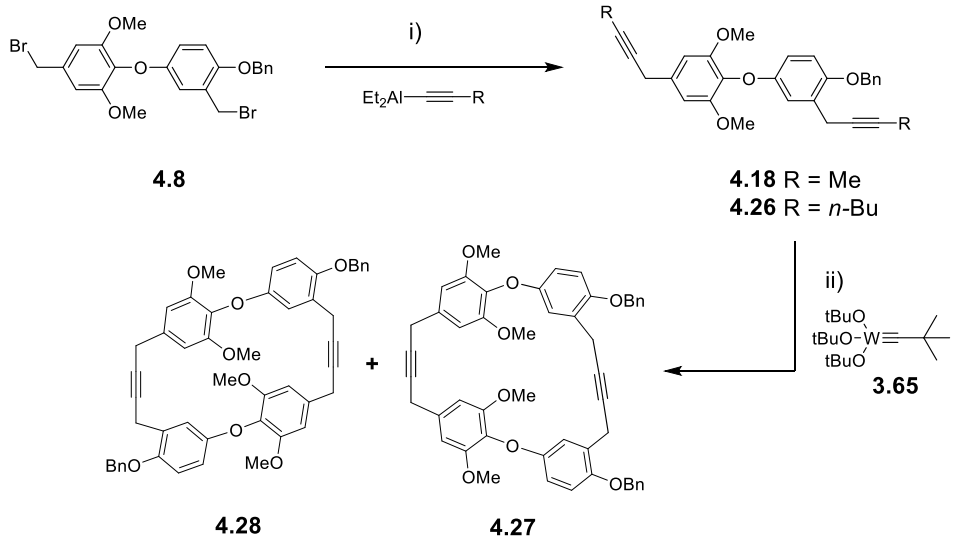
Reagents & conditions : i) MOMCl, DIPEA, 0 °C to RT, DCM, quant. ii) $NaBH_4$, 0 °C to RT, MeOH quant. iii) NCS, PPh_3, 0 °C to RT, THF 79% iv) $PdCl_2(CH_3CN)_2$, XPhos, 65 °C, ACN 88% v) **3.65**, 80 °C, toluene 48%

Scheme 4.5. Dimerisation of alkyne **4.24**

4.4 Macrocyclisation reaction

Our next task was to develop this sequence for the preparation of the macrocyclic diyne **4.28**, giving entry to the end-game. Thus, bis-alkynylation of bisbenzyl-bromide **4.8** with hexyne using Gau's alkynylation procedure afford the corresponding diyne **4.26** in good yield 78%. With diynes **4.18** and **4.26** in hand, their performance in the RCAM reaction was studied. Thus, diyne **4.18** and catalyst **3.65** were heated in toluene at 80 °C under normal heating and with microwave irradiation. Alas, in common with our previous attempts, only traces

of a macrocyclic product, **4.27** or **4.28**, were formed as evidenced by an LC-MS analysis of the crude product mixtures. Moreover, diyne **4.26** gave a similar outcome following treatment in this fashion, with LC-MS showing components with masses equal to that of macrocycles **4.27** and **4.28**, and the dimeric precursors. Though evidenced, these products could not be isolated in pure form from the product mixture.



Reagents & conditions : i) $NiCl_2(PPh_3)_2$ 14%, Et_2O/pentane (1 : 1) 78%
ii) **3.65**, toluene, 80 °C, C = 0.002 M, traces

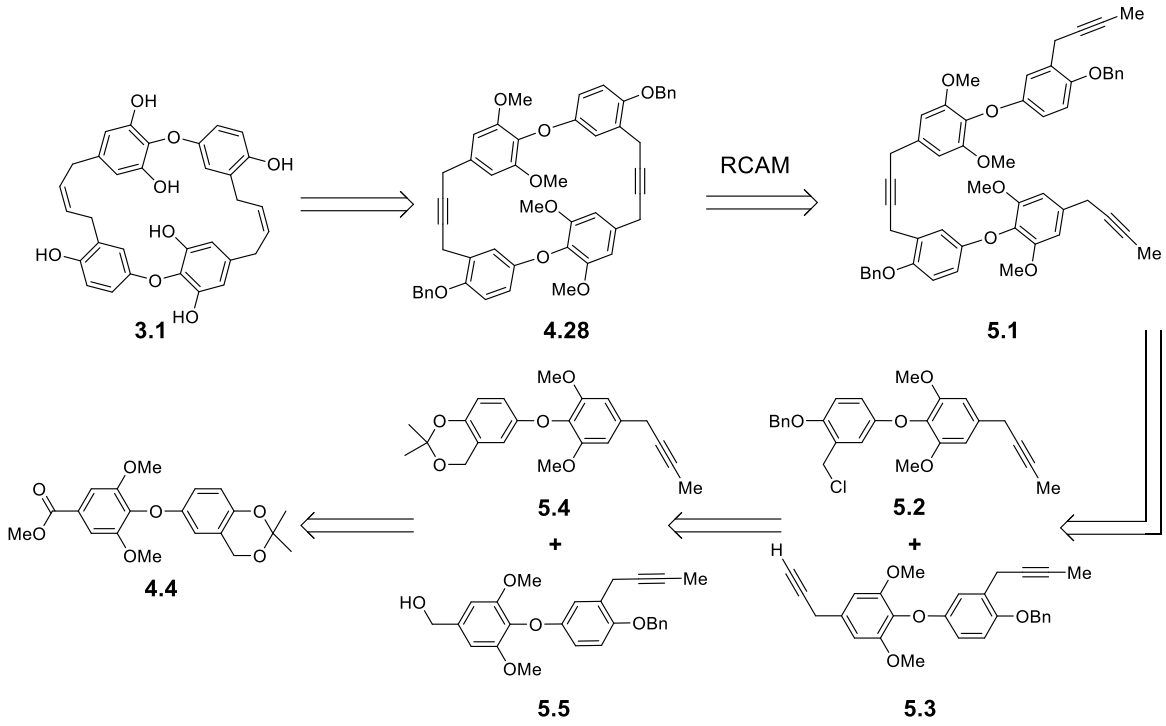
Scheme 4.6. RCAM reaction with dialkynes **4.18** and **4.26**

After these attempts to form the macrocyclic core structure using a dimerisation/macrocyclisation strategy, we decided to rethink our strategy. In particular, we wondered if the optimal conditions for dimerisation were different for those required for macrocyclisation conditions. If so, a step-by-step approach might prove more rewarding, as described in the next Chapter.

5. 'Dimerisation' then macrocyclisation strategy

5.1 A Novel approach

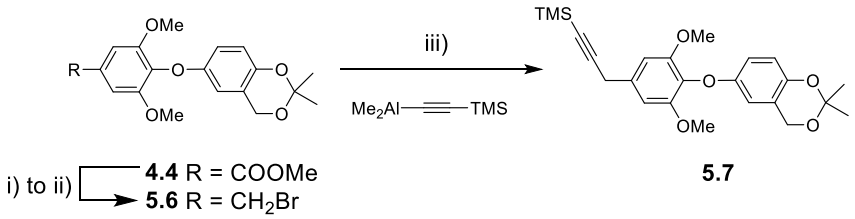
The strategies discussed in Chapters 3 and 4 confirmed that the dimerisation-RCAM strategy could be used to access advanced macrocyclic precursors, albeit in low yield. However, it was clear that a more efficient protocol was needed for us to progress the synthesis further. Our revised strategy sought to assemble the cyclisation precursor **5.1** in a distinct step prior to its macrocyclisation to **4.28** (Scheme 5.1). In turn, assembly of triyne **5.1** could be envisioned through a palladium catalysed coupling reaction between terminal diyne **5.2** and benzyl chloride **5.3**. Further analysis indicated benzyl chloride **5.2** could be synthesized in a few steps from dioxine **5.4** while diyne **5.3** could be synthesized from benzyl alcohol **5.5**. Importantly, it seemed plausible to access both of these subunits **5.4** and **5.5** from diaryl ether **4.4**, allowing us to capitalise on prior art generated by our earlier endeavour.



Scheme 5.1. A strategy involving stepwise 'dimerisation' and macrocyclisation

5.1.1 Accessing 5.5

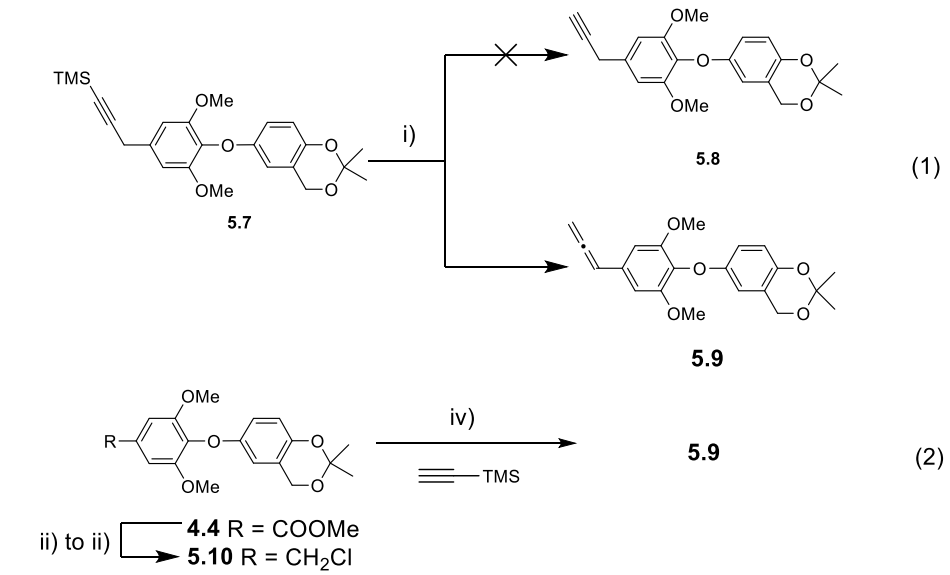
Thus, our first task was to develop a route to alkyne **5.4** from diaryl ether **4.4**. Following a sequence used earlier, diaryl ether **4.4** was reduced with $LiAlH_4$ in THF then brominated using NBS and PPh_3. Alkynylation of the resulting benzyl bromide **5.6** using Gau's procedure, dimethyl(TMSalkynyl)aluminium and catalytic $NiCl_2(PPh_3)_2$ afforded the expected alkyne **5.7** in moderate yield.



Reagents & conditions : i) $LiAlH_4$, 0 °C to RT, THF, 98% ii) NBS, PPh_3, 0 °C to RT, THF 78%
iii) $NiCl_2(PPh_3)_2$, 90 min, 0 °C to RT, Et_2O/pentane (1 : 1) 49%

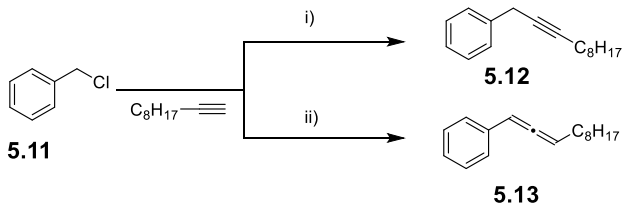
Scheme 5.2. Access to alkyne **5.7**

Our next task was to effect the TMS deprotection of **5.7** to terminal alkyne **5.8**. Unfortunately, when this was attempted with TBAF, allene **5.9** was obtained as the primary product in 74% yield. Moreover, this facile isomerisation was also observed in an attempt to prepare **5.7** using a palladium catalysed reaction between benzyl chloride **5.10** and TMSacetylene, described by Buchwald (Scheme 5.3). Indeed, the isomerisation had been observed by Buchwald in reactions conducted above 80 °C, where it was found necessary to employ a large excess of base to achieve selective allene formation (*e.g.* Scheme 5.4). Thus, it seemed reasonable to suggest that allene **5.9** is stabilised by conjugation to the electron rich arene present in our system and that this promotes isomerisation at 65 °C under the conditions employed for the alkynylation reaction.



Reagents & conditions : i) TBAF, THF, 74% ii) $LiAlH_4$, 0 °C to RT, THF, 52%
iii) NBS, PPH_3, 0 °C to RT, THF % iv) Cs_2CO_3, $PdCl_2(CH_3CN)_2$, XPhos, 65 °C, CH_3CN 68%

Scheme 5.3. Formation of allene **5.9** over terminal alkyne **5.8**



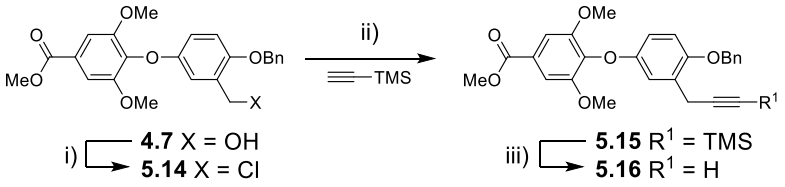
Reagents & conditions : i) Cs_2CO_3 (1.05 eq.), $PdCl_2(CH_3CN)_2$, XPhos 65 °C, THF 96%
iv) Cs_2CO_3 (2.5 eq.), $PdCl_2(CH_3CN)_2$, XPhos, 80 °C, CH_3CN 68%

Scheme 5.4. Alkyne vs allene formation reported by Buchwald and co-workers

5.2 Accessing fragment 5.4

Our synthesis of fragment **5.4** from benzyl alcohol **4.7** began with its transformation into benzyl chloride **5.14**. A palladium-catalysed coupling with TMSacetylene next gave protected alkyne **5.15** in quantitative yield. It is worth

noting that no isomerisation to the corresponding allene was witnessed with this substrate. Indeed, deprotection of the alkyne using TBAF in a buffered acetic acid solution afforded the desired terminal alkyne **5.16** in good yield.

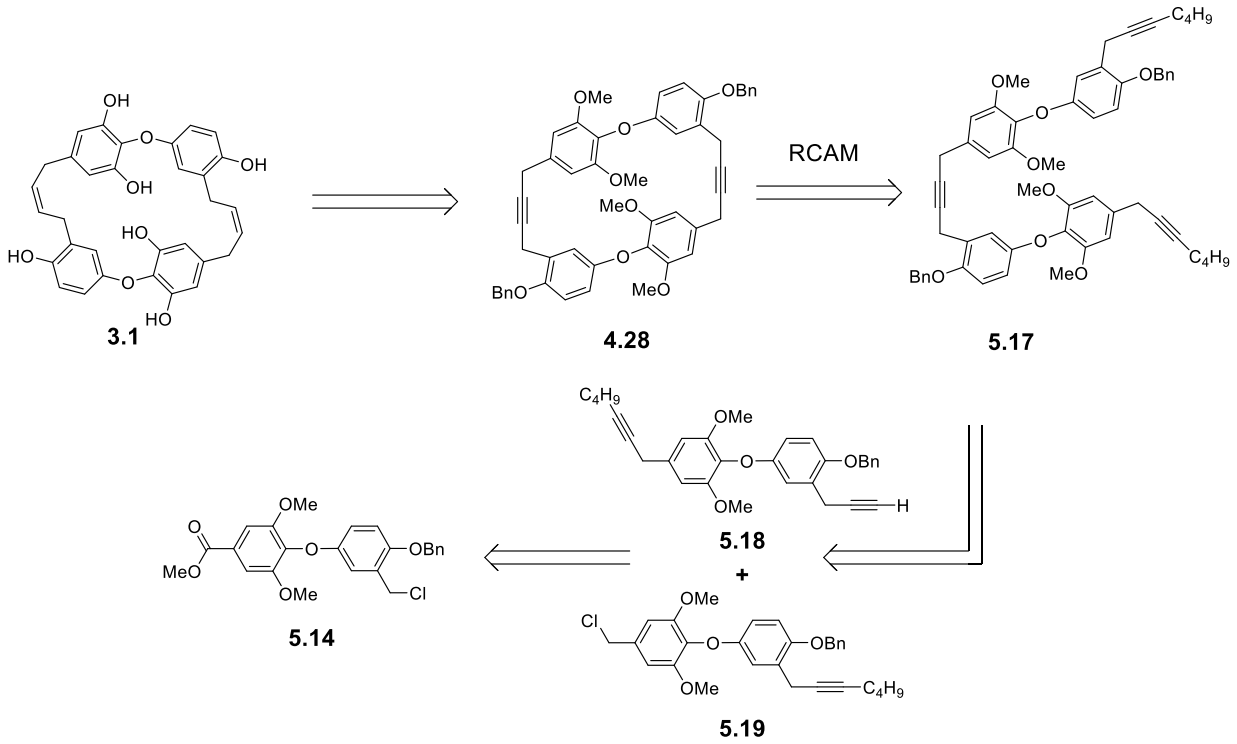


Reagents & conditions : i) NCS, PPh_3 THF, 79% ii) $PdCl_2(CH_3CN)_2$, XPhos ACN, 65 °C, quant. iii) TBAF, AcOH, THF, 79%

Scheme 5.5. Synthesis of alkyne **5.16**

5.3 Retrosynthetic analysis

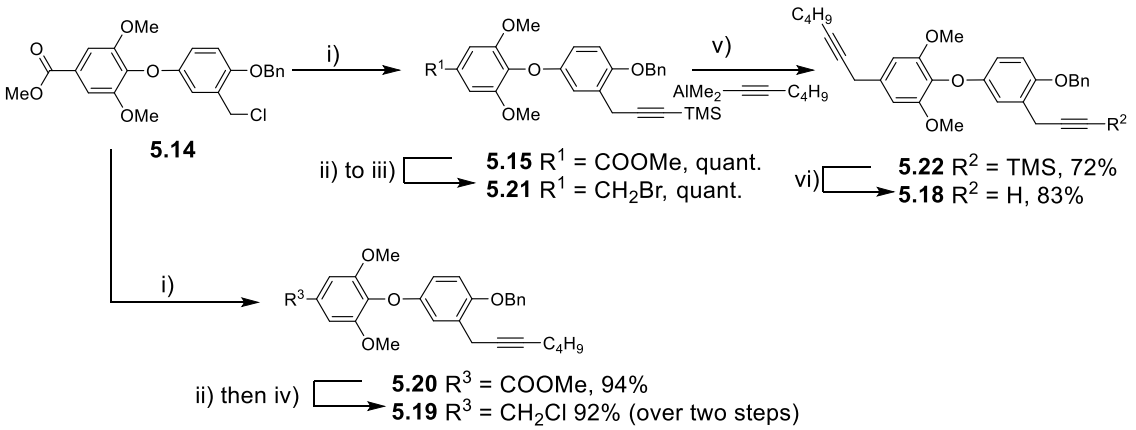
As our approach to key fragment **5.5** was proving difficult, we decided to modify our strategy. In particular, we wondered if benzyl chloride **5.14** could serve as the pivotal point in our synthesis, as it would give us the handle needed to develop a divergent approach to the crucial fragments **5.18** and **5.19** (Scheme 5.6). Thus, our new approach sought to generate macrocycle **3.1** by selective *cis*-hydrogenation of the corresponding diyne **4.28**. As before, diyne **4.28** could be formed by RCAM of the triyne intermediate **5.17**. In turn, access to this intermediate could be given by a coupling of terminal alkyne **5.18** and benzyl chloride **5.19**, each of which should be available from benzyl chloride **5.14**.



Scheme 5.6. Reviewed retrosynthesis of macrocycle **3.1**

5.4 Synthesis of fragments 5.18 and 5.19

Subjecting benzyl chloride **5.14** to the Heck–alkynylation method in presence of hexyne or TMSacetylene gave access to the expected alkynes **5.20** and **5.15** in good yields (Scheme 5.7). Each was then subjected to reduction and halogenation to provide the key building blocks **5.21** and **5.19** in good overall yield (respectively 60% and 87%). Benzyl bromide **5.21** was then transformed into diyne **5.22** using a nickel-catalysed coupling reaction with dimethyl(hexynyl)aluminium. Finally, TMS deprotection with catalytic silver triflate provided terminal alkyne **5.18**.

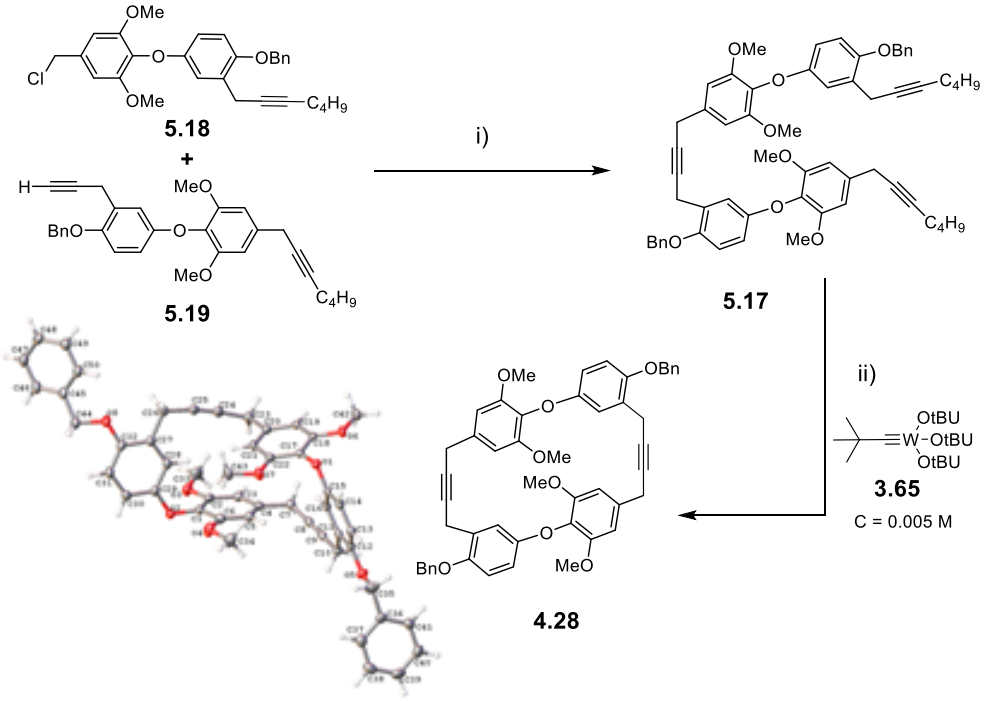


Reagents & conditions :i) $PdCl_2(CH_3CN)_2$ (5% mol), XPhos (15% mol), Cs_2CO_3, ACN, 65 °C ii) $LiAlH_4$, 0 °C to RT, THF iii) NBS, PPh_3, 0 °C to RT, THF iv) NCS, PPh_3, 0 °C to RT, THF v) $NiCl_2(PPh_3)_2$, 0 °C to RT, Et_2O/pentane (1 : 1) vi) AgOTf, MeOH/H_2O/DCM (3 : 1 : 4)

Scheme 5.7. Access to fragments **5.18** and **5.19**

Fragments **5.18** and **5.19** were then coupled using the previously developed Heck–alkynylation conditions to give the ring closing metathesis precursor **5.17**. Pleasingly, its isolation from the product mixture was easily achieved in spite of the modest yield (49%). Moreover, unreacted benzyl chloride **5.19** could also be recovered and reused. Macrocyclisation of triyne **5.17** to the advanced intermediate **4.28** was then undertaken using Schrock's alkylidyne catalyst **3.65** in toluene at 80 °C for 12 h under conditions of high-dilution (5×10^{-3} M). Pleasingly, cyclisation provided the expected macrocycle **4.28** smoothly and in high yield. Alas, isolation of the product in a high state of purity proved challenging due to its sensitivity to most separation media. Consequently, it was critical to employ a short silica column and rapid elution to achieve efficient separation. In this way, isolation of macrocyclic diyne **4.26** could be realised in near quantitative yield. A crystal was then grown by holding an EtOAc and

petroleum ether solution of **4.28** at -20 °C, facilitating X-ray analysis and a robust confirmation of its structure.



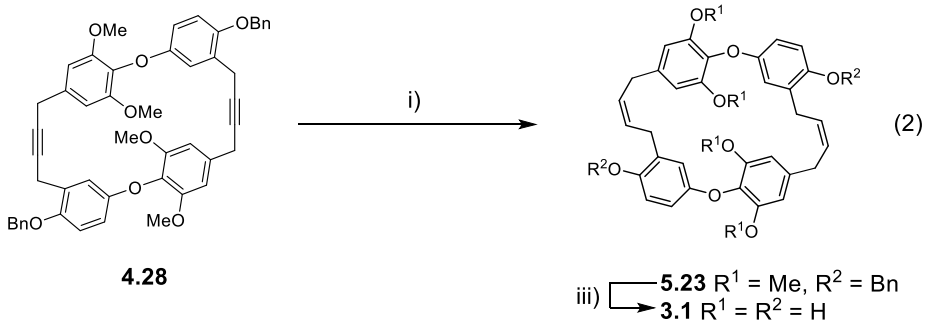
Reagents & conditions : i) $PdCl_2(CH_3CN)_2$ (5% mol), XPhos (15% mol), Cs_2CO_3, ACN, 65 °C, 49% ii) **3.65**, toluene, 80 °C, quant.

Scheme 5.8. Dimer **5.17** formation and following cyclisation

With the cyclised product **4.28** in hand, our attention next turned to the partial hydrogenation of the two alkyne bridges. The selective cis-hydrogenation was thus carried out using Lindlar's catalyst in a mixed EtOAc/methanol solvent system containing quinoline under a hydrogen atmosphere. This gave the core of chrysophaentin F, **5.23**, in 68% yield with recovered starting material accounting for much of the remaining mass balance

One drawback of the reduction was variability in the time needed to achieve optimal yield, which ranged from 6 to 48 hours. The final stage of the synthesis

involved the removal of the 4 methyl and 2 benzyl ether protecting groups. Several procedures were examined. First, a protocol using $AlBr_3$ and EtSH was attempted, as it had been used by Nicolaou and Boger respectively to effect the deprotection of 6 ethers in a total synthesis of hybocarpone and 8 ethers in a synthesis of some teicoplanin derivatives.[67] In our hands this protocol proved unsuccessful. An alternative method by Coe *et al.*, using BCl_3 in conjunction with tetrabutylammonium iodide (TBAI),[68] proved more rewarding. Indeed, a ^{1}H-NMR spectrum of the crude product mixture showed that we had achieved global deprotection to the desired product **3.1** but it was contaminated by residues from the tetrabutylammonium salt. Purification by reverse phase HPLC was unable to effect their removal so an amberlyst 15® ion exchange column was employed, with success, to trap out the residual ammonium salt. Preparative HPLC then afforded the pure product **3.1** in near quantitative yield, completing the synthesis of the chrysophaentin F **1.8**, G **1.9** and H **1.10** core.



Reagents & conditions : i) H_2, Lindlar, quinoline, EtOAc/MeOH (1 : 1), 68%
iii) BCl_3, TBAI, DCM, 0 °C to RT, quant.

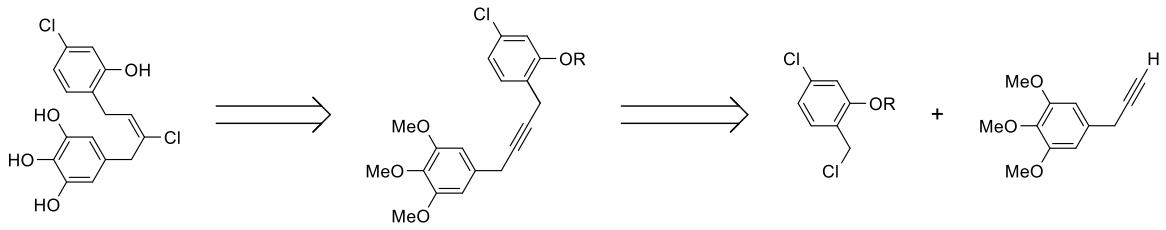
Scheme 5.9. Deprotection of Chrysophaentin F analogue **3.1**

At this juncture, the challenge of effecting the selective hydrochlorination reaction remains.

6. Towards Chrysophaentin F

6.1 The Hydrochlorination reaction

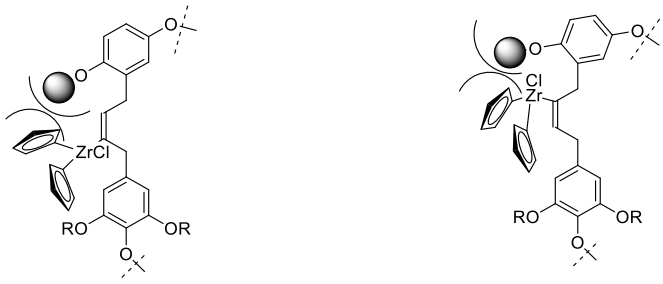
One of the challenges remaining in our synthesis of chrysophaentin F **1.8** was formation of the vinyl chloride bridge. At this juncture we decided to examine ways to install this in a regioselective manner leading to the desired (*E*)-geometry. As macrocycle **4.28** was precious, we chose to perform the investigation on a hemichrysophaentin as this could be accessed in quantity in a few steps and seemed a suitable model. The hemichrysophaentin targeted, **6.1** (Scheme 6.1), would be obtained from the corresponding alkyne **6.2** *via* a hydrozirconation and treatment with a chlorinating agent. In turn, alkyne **6.2** could come from a coupling between benzyl chloride **6.3** and the terminal alkyne **6.4**, each available in a few steps from commercial starting materials.



Scheme 6.1. Retrosynthesic analysis for hemichrysophaentin **6.1**

6.1.1 Hydrozirconation rationale

Our decision to employ the hydrozirconation reaction to form the vinyl chloride from an alkyne was based on the known cis-addition of the Schwartz reagent across alkynes. This methodology has been applied to many different acetylenes and, when using iodide as an electrophile, leads to exclusive formation of the corresponding (*E*)-iodo-alkene.[69] We hoped that the proximity of the *ortho*-phenolic residue might provide a handle to control the regioselectivity of this reaction when protected with a bulky residue. Steric hindrance would direct the addition of zirconium to the more distal carbon centre leading to **6.5** instead of **6.6** (Scheme 5.2). Similarly, replacing iodine with *N*-chlorosuccinimide (NCS) should lead to the desired (*E*)-chloroalkene.



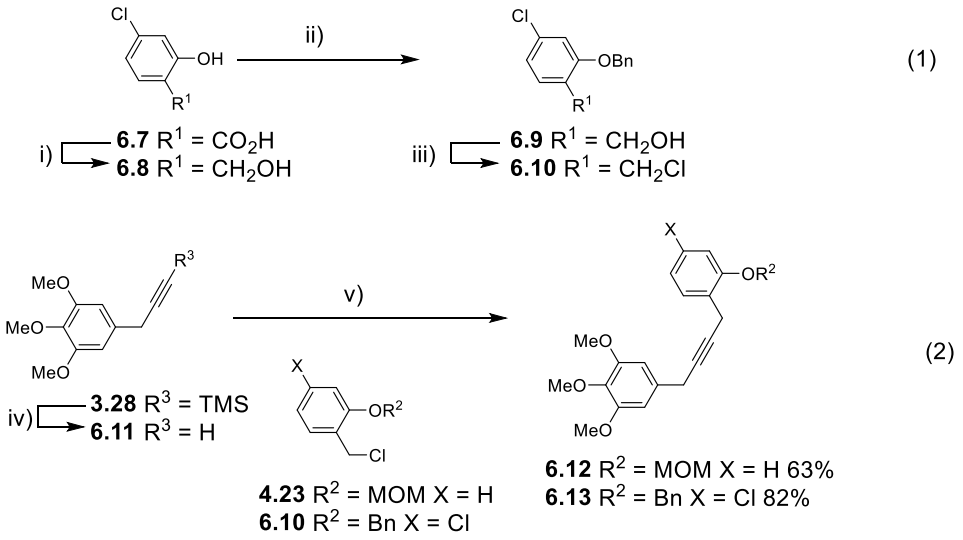
6.5 **6.6**

Distal position Proximal position

Figure 6.1. Distal versus proximal position during the hydrozirconation

6.1.2 Rapid synthesis of model alkynes 6.11 and 6.12

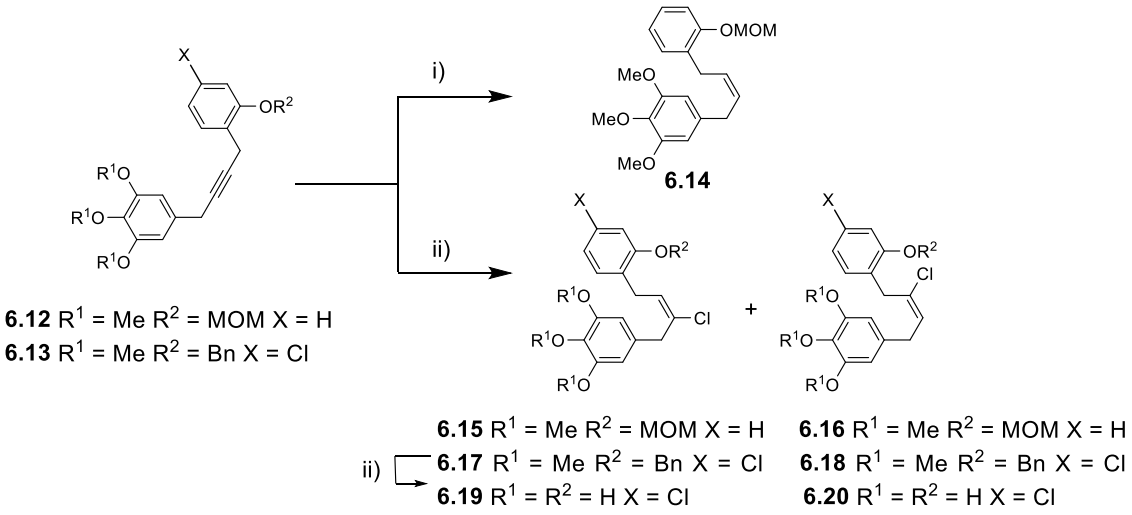
To investigate the influence of protecting group size on the course of the hydrozirconation reaction the MOM and Bn protected phenols, **6.12** and **6.13**, were targeted. Conveniently, the MOM protected benzyl chloride **4.23** had been synthesised earlier (Chapter 4) from aldehyde **4.20** so it seemed sensible to use this as our starting point. For the analogous benzylated benzyl chloride **6.10,** 5-chlorosalicylic acid **6.7** seemed a more convenient starting point as it could be reduced to the corresponding benzyl alcohol **6.8** with borane. In the event, its reduction with borane.DMS complex proceeded in a modest 46% yield.[70] Using $LiAlH_4$, a nearly quantitative yield could be achieved by heating the reaction at 40 °C for 4 h. Benzylation of the phenol next provided **6.9** in high yield (96%), with chlorination affording the required fragment **6.10** in good yield (81%). Benzyl chlorides **6.8** and **6.9** were each reacted with alkyne **6.10** in presence of $PdCl_2(CH_3CN)_2$ to give the desired hemichrysophaentins **6.12** and **6.13** in 63% and 82% yield respectively.



reagents and conditions: i) $LiAlH_4$, 0 °C to 40 °C, THF, 96% ii) K_2CO_3, BnBr, 40 °C, acetone, 89% iii) NCS, PPh_3, 0 °C to RT, THF, 81% iv) TBAF, AcOH, 18 h, THF, quant. v) Cs_2CO_3, $PdCl_2(CH_3CN)_2$, XPhos, **4.21** or **6.10**, 65 °C, CH_3CN

Scheme 6.2. Synthesis of alkynes **6.11** and **6.12**

With alkynes **6.12** and **6.13** in hand, the hydrochlorination reaction could be investigated. Using Negishi's original procedure with alkyne **6.12** yielded none of the expected product **6.15**. Rather, it gave a mixture of the unchlorinated alkene **6.14** and recovered starting material. Indeed, for hydrozirconation to reach completion, it was found necessary to heat the reaction at 40 °C for 1 h. Addition of NCS then gave a 1 : 1 mixture of vinyl chlorides **6.15** and **6.16** in 57% yield after 18 h at RT. Hydrochlorination of the benzylated analogue, alkyne **6.13**, proved more rewarding as it gave a 2 : 1 mixture of vinyl chlorides **6.17** and **6.18** in near quantitative yield. The mixture proved inseparable by column chromatography so was converted to the hemichrysophaentins **6.19** and **6.20** by removal of the ethereal protecting groups. Alas, these too proved inseparable by column chromatography and preparative HPLC.



Reagents & conditions : i) **6.12**, $ZrCl_2Cp_2$, DIBALH, 0 °C, 1 h, then NCS, -78 °C ii) $ZrCl_2Cp_2$, DIBALH, 0 to 40 °C, 1 h, then NCS, RT, 18 h, 57% for **6.15** and **6.16** (1 : 1) quant. for **6.17** and **6.18** (2 : 1) ii) BCl_3, TBAI, DCM 0 °C to RT, 7% for **6.19** and **6.20** (3 : 1)

Scheme 6.3. Hydrochlorination of alkynes **6.12** and **6.13**

From this model study we concluded that the selective formation of the desired vinyl chloride should be performed through hydrozirconation. Indeed, it seems likely that the steric interactions governing the regiochemical course of the reaction will be more significant when applied to a macrocyclic precursor, such as **4.28**, as the system would have less degree of freedom available to counter adverse steric interactions.

6.1.3 Selectivity

The identity of the major and minor regioisomers formed by this sequence, **6.19** and **6.20** respectively, was determined by NMR. 2D experiments (HMQC, HMBC) were first used to attribute all of the resonances observed in the ^{1}H NMR

spectrum. HMBC proved particularly useful as it was able to show an interactions between the singlet at δ_H 3.60 ppm (C10 in Scheme 6.4) and the 2H aromatic singlet at δ_H 6.29 ppm (C12 and C16 in Scheme 6.4). Similarly, an interaction between the doublet at 3.48 ppm (C7) and the 1H aromatic doublet at δ_H 7.02 ppm (C6) was witnessed, strongly suggesting that vinyl chloride **6.17** had been formed as the major regioisomer.

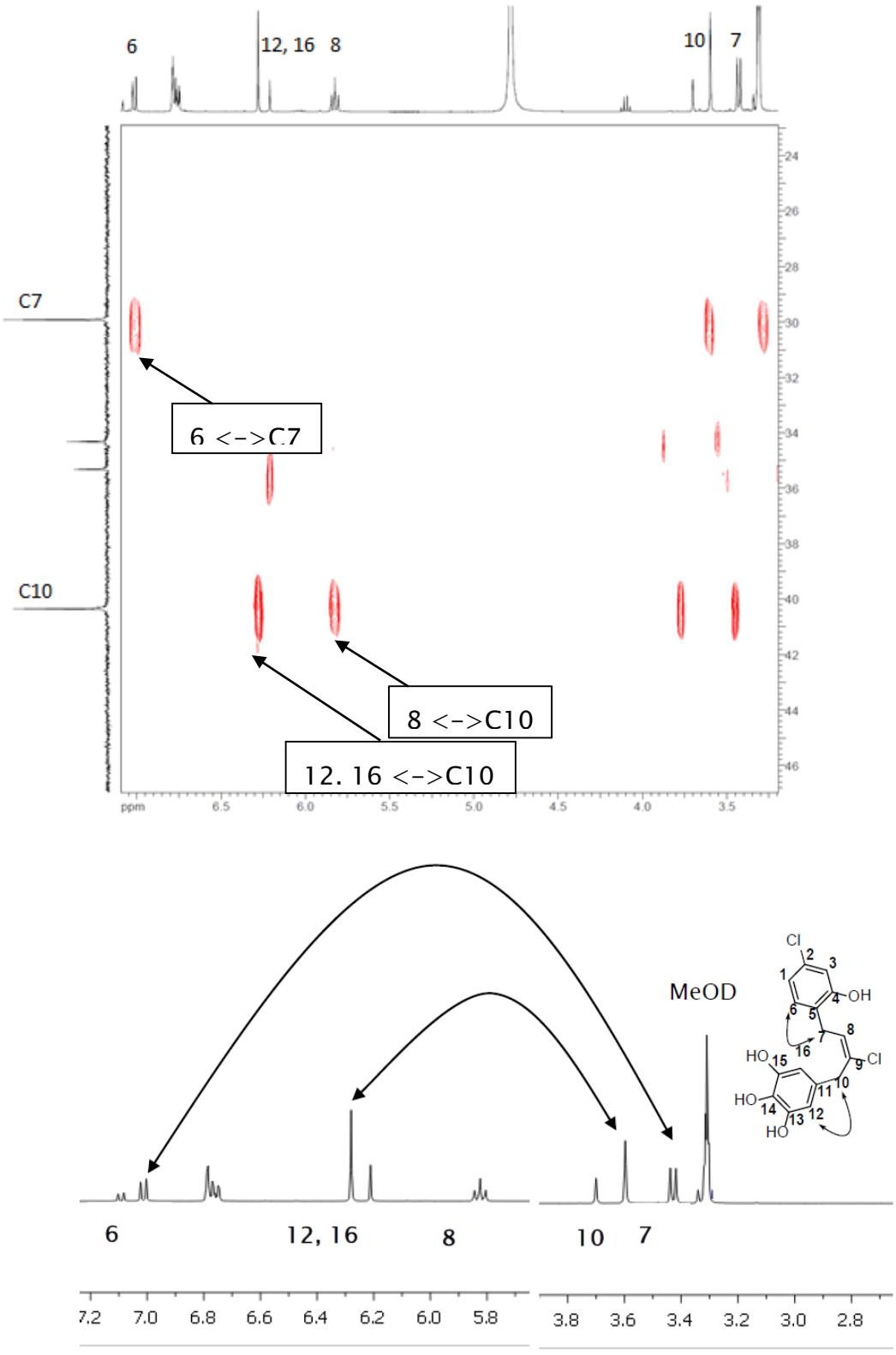
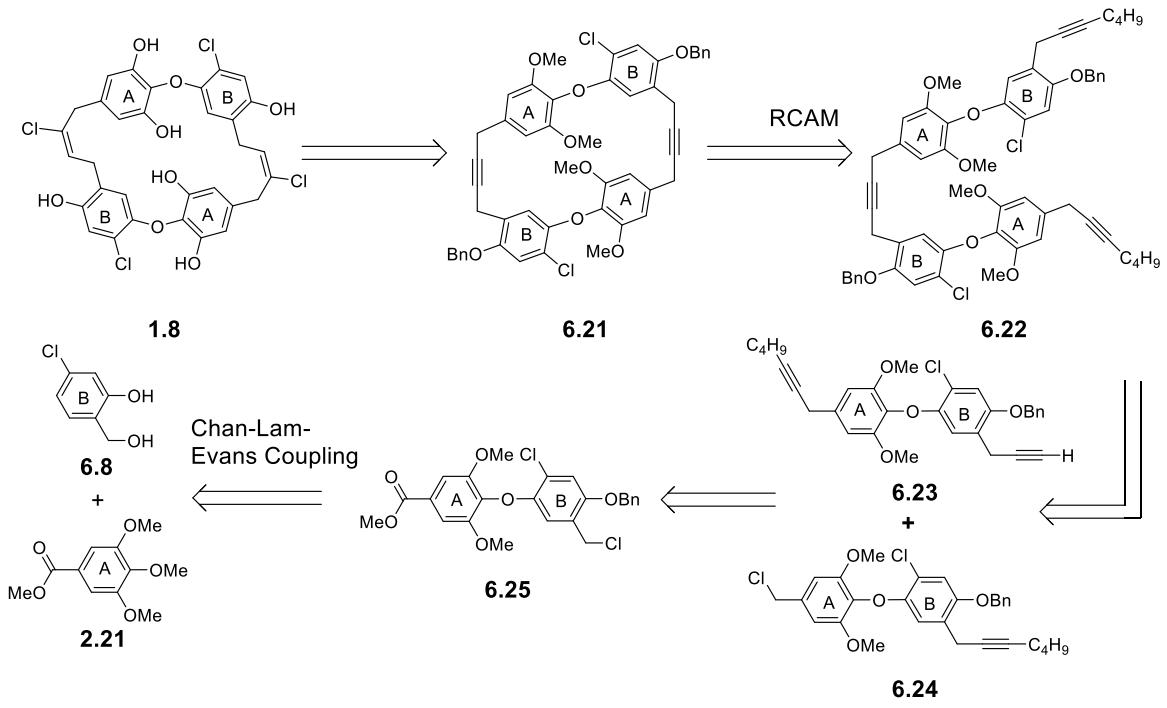


Figure 6.2. HMBC interactions

6.2 Towards Chrysophaentin F 1.8

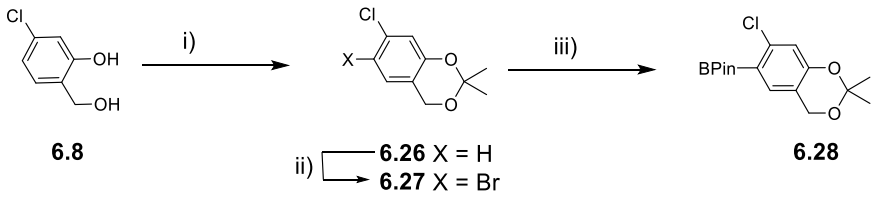
With a pathway towards chrysophaentin F **1.8** now established, we also needed to incorporate the two additional chlorine atoms in the aromatic region. Thus, our plan was to target chrysophaentin F **1.8** *via* macrocyclic diyne **6.21** through a selective double hydrochlorination reaction (Scheme 6.4). In turn, a macrocyclisation step through RCAM reaction leads us back to the key triyne **6.22**, which could be accessed from terminal alkyne **6.23** and benzyl chloride **6.24** through a palladium catalysed Heck-alkynylation. Syntheses of intermediates **6.23** and **6.24** can both be envisioned from a common benzyl chloride **6.25**, which in turn might come from 3-chlorosalicylic acid **6.8** and methyl 3,4,5-trimethoxybenzoate **2.21** using a Chan-Lam-Evans coupling.



Scheme 6.4. Retrosynthetic rationale of Chrysophaentin F **1.8**

6.2.1 Towards diarene 6.25

Our synthesis started with the protection of salicyl alcohol **6.8** using dimethoxypropane in presence of catalytic *p*-TSA and proceeded in 71% yield. The resulting acetal **6.26** was then treated with NBS in acetonitrile at different temperatures to find the most suitable conditions to deliver bromide **6.27**. At RT the reaction gave a reasonable 55% yield after 18 h, which increase to 64 % yield when conducted at 60 °C. A Miyaura borylation of **6.27** was then carried out using the conditions we had established previously with **4.2**. However, the presence of the *ortho*-chloro-substituent had a significant impact, with the expected boronic ester **6.28** formed in a disappointing 20% yield.

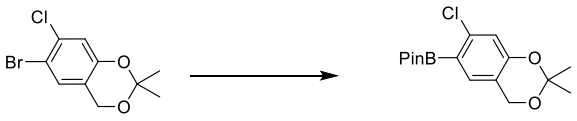


Reagents & conditions : i) DMP, acetone, Na_2SO_4, 71%, ii) NBS, ACN, 60 °C, 65% iii) B_2Pin_2, KOAc, $Pd(dppf)Cl_2$ (20 mol%) , THF, 60 °C, 20%

Scheme 6.5. Synthesis of boronic ester **6.28**

The experiment was examined under microwave irradiation but showed no improvement in yield. Indeed, it appeared to reach a plateau after 1 h with further time failing to improve the yield. A halogen-lithium exchange reaction was then investigated using bispinacolatodiboron as a quench. Pleasingly, this gave the expected boronic ester **6.28** in 53% yield when conducted at -78 °C and quantitative yield when conducted at -100 °C. The improvement gained was attributed to the propensity for aryne formation at elevated temperatures.

Table 6.1. Accessing **6.28**

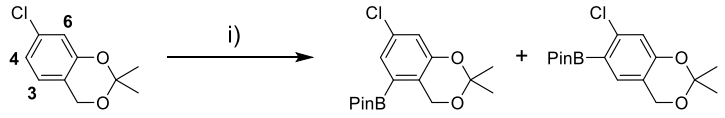


6.25 **6.26**

Conditions	Catalyst loading	Reaction time	Temperature	yield
B_2Pin_2, $PdCl_2(dppf)$, KOAc, THF	10% mol	16 h	60 °C	20%
B_2Pin_2, $PdCl_2(dppf)$, KOAc, μw, THF	10% mol	0.5 h	65 °C	10%
B_2Pin_2, $PdCl_2(dppf)$, KOAc, μw, THF	10% mol	1 h	65 °C	20%
B_2Pin_2, $PdCl_2(dppf)$, KOAC, μw,THF	10% mol	5 h	65 °C	20%
DMSO, $PdCl_2(dppf)$, KOAc, B_2Pin_2	10% mol	5 h	95 °C	23%
dioxane, $PdCl_2(dppf)$, NEt_3, HBPin	4% mol	20 h	80 °C	10%
n–BuLi, B_2Pin_2, THF	N. A.	70 min	-78 °C	53%
n–BuLi, B_2Pin_2, THF/ Et_2O	N. A.	70 min	-100 °C	Quant.

6.2.2 C-H borylation investigation and Chan-Lam-Evans coupling

As an alternative to the bromination/borylation strategy we investigated the possibility of using a direct C-H activation to afford the desired boronic ester **6.28**. The dimethoxyiridium COD catalyst is known to insert into unencumbered aryl CH bonds when in presence of the BBBPY ligand. Thus, we wondered if, with arene **6.26**, it would favour reaction at C3 or C4. Alas, on running the experiment we found that the C3 adduct **6.29** formed as the major product in a 7:1 ratio with the desired C4 adduct **6.28** (Scheme 6.6).

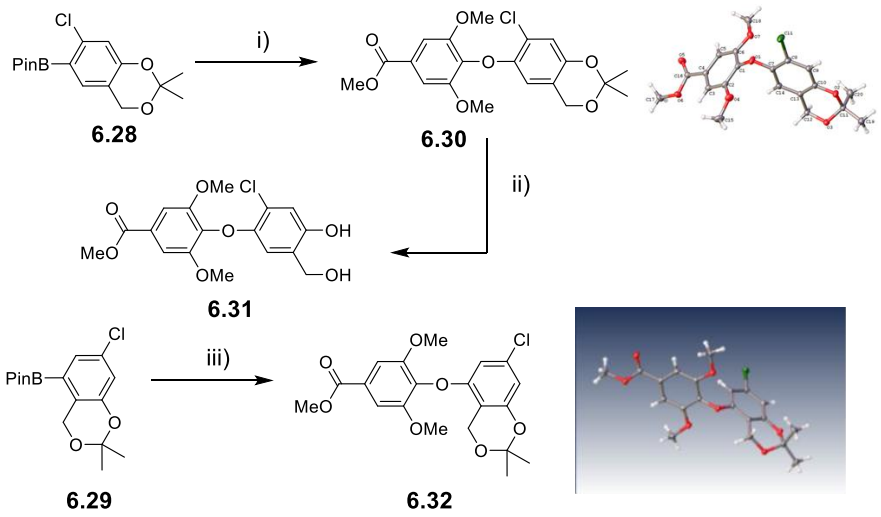


6.26 **6.29** **6.28**

Reagents & conditions : i) $[Ir(COD)(MeO)]_2$, BBBPY, B_2Pin_2, dioxane, 100 °C, **6.29** (51%), **6.28** (7%)

Scheme 6.6. C-H activation borylation reaction

The Chan-Lam-Evans coupling reaction was investigated next for the coupling of phenol **2.21** with the freshly prepared boronic esters **6.28** or **6.29**. Both reactions afforded the expected aryl ethers **6.30** and **6.32** (Scheme 6.7), though the former was higher yielding (83%) that its regioisomer (38%). Deprotection of **6.30** to the free phenol **6.31** was readily accomplished using acetic acid and water at 70 °C, albeit in low yield (44%). Although this could doubtless be improved, contemporaneous studies had delivered a more efficient approach to an advanced intermediate so further work on this approach was deemed inappropriate.

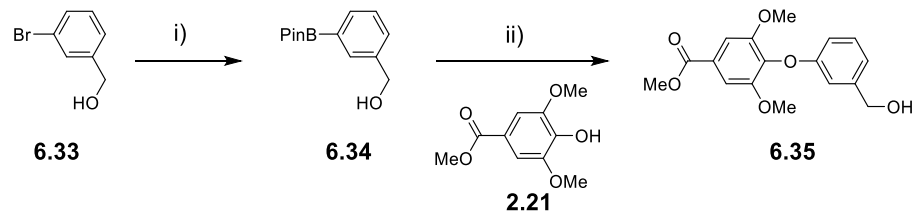


Reagents & conditions : i) 20% $Cu(OTf)_2$, **2.21**, 4 Å sieves, O_2, Py, EtOH, 65 °C, 15 h, 83% ii) AcOH, H_2O, 70 °C, 44% iii) 20% $Cu(OTf)_2$, **2.21**, 4 Å sieves, O_2, Py, EtOH, 65 °C, 15 h, 30%

Scheme 6.7. Chan-Lam-Evans coupling on **6.28** and **6.29**

6.2.3 A direct access to benzyl alcohol 6.38

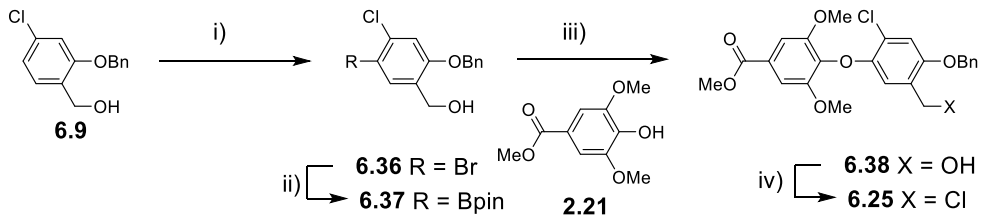
The alternative approach began with a Miyaura-borylation of benzyl alcohol **6.33** to boronic ester **6.34** which proceeded in ~80% yield and delivered the product contaminated with some recovered starting material **6.33**. Though separation at this stage proved intractable, the mixture could be used directly in a Chan-Lam-Evans coupling with phenol **2.21** to afford the expected diarene **6.35** in 60% yield (Scheme 6.8).



Reagents & conditions : i) B_2Pin_2, KOAc, $Pd(dppf)Cl_2$, 65 °C, 16 h , 80%,
ii) $Cu(OTf)_2$ (20% mol), 4 Å sieves, O_2, Py, EtOH, 65 °C, 20 h, 60%

Scheme 6.8. Miyaura borylation then Chan-Lam-Evans coupling reaction from **6.33**

Following this precedent, benzyl alcohol **6.9** was reacted with NBS to give bromoarene **6.36**. A Miyaura borylation reaction then provided the expected boronic ester **6.37**, albeit in moderate yield (31%). The yield was elevated to 54% by increasing the catalyst loading to 20 mol% and leaving the reaction to run for 5 days. Then, through recovery of starting material **6.36** and recycling it through a repeat reaction, the overall yield was increased to 79%. A Chan-Lam-Evans coupling with phenol **2.21** next gave the expected diaryl ether **6.38** in 87% yield, providing access to the pivotal benzyl chloride **6.25** following chlorination with NCS and PPh_3.



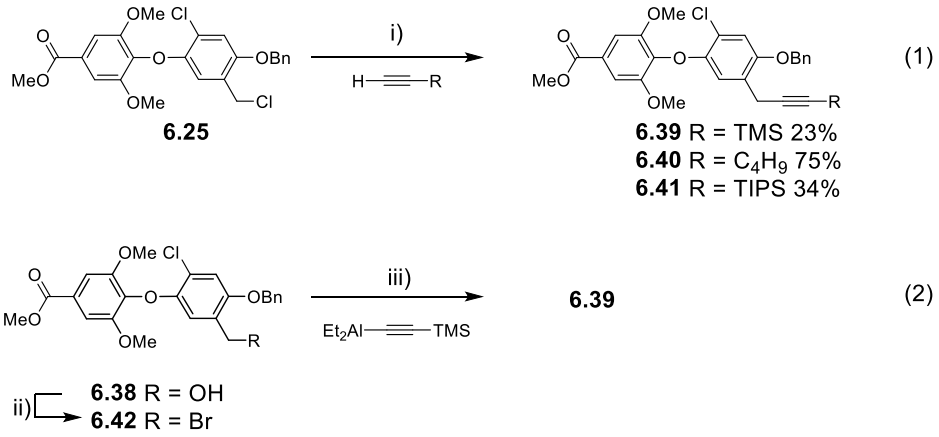
Reagents & conditions : i) NBS, 60 °C, acetonitrile 60% ii) $Pd(dppf)Cl_2$, B_2Pin_2, K_2CO_3, THF, 79% (brsm) iii) $Cu(OTf)_2$ (20% mol), 4 Å sieves, O_2, Py, EtOH, 65 °C, 15 h, 87%, iv) NCS, PPh_3, THf, 0 °C to RT, 80%

Scheme 6.9. Access to benzyl chloride **6.25**

6.3 The alkynylation step

Benzyl chloride **6.25** was then reacted with hexyne and TMSacetylene using Buchwald's conditions to effect a Heck-alkynylation reaction. With hexyne the desired product **6.40** was formed in a satisfying 75% yield, but with TMSacetylene this dropped to a poor 23% yield for alkyne **6.39**. Several variations of the reaction parameters were examined, including fresh batches of catalyst, but to no avail. A switch to using the TIPS protected alkyne afforded some improvement with alkyne **6.41** formed in 34 % yield (Scheme 6.10).

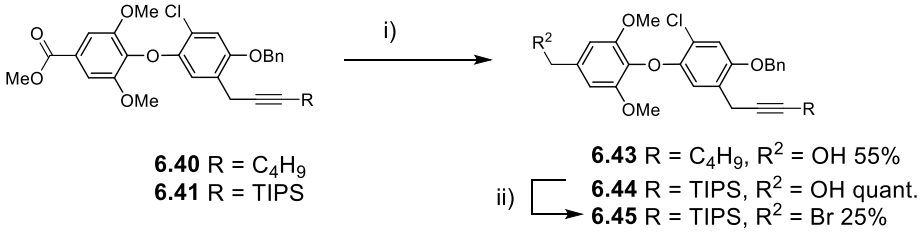
To address the low yield, an alternative approach to alkyne **6.39** was sought. To that end, benzyl bromide **6.42** was prepared and subjected to a $NiCl_2(PPh_3)_2$ catalysed Negishi coupling with dimethyl(hexynyl)aluminium. However, though this yielded the expected product **6.39**, it was formed in a 15% yield as part of a complex product mixture.



Reagents & conditions : i) $PdCl_2(CH_3CN)_2$ (5% mol), XPhos (15% mol), Cs_2CO_3, ACN, 65 °C, 16 h i) NBS, PPh_3, 0 °C to RT quant. iii) $NiCl_2(PPh_3)_2$, Et_2O, Pentane, 0 °C to RT, 15%

Scheme 6.10. Alkynylation of benzyl halides **6.25 and 6.42** with hexyne, TMSacetylene and TIPSacetylene

The synthesis was then carried on with alkynes **6.40** and **6.41**. A reduction with $LiAlH_4$ provided the corresponding benzyl alcohols **6.43** and **6.44** then the TIPS protected alkyne **6.44** was treated with NBS and PPh_3 to afford benzyl bromide **6.45** in low yield. Alas, this put a stop to further progression of this route.

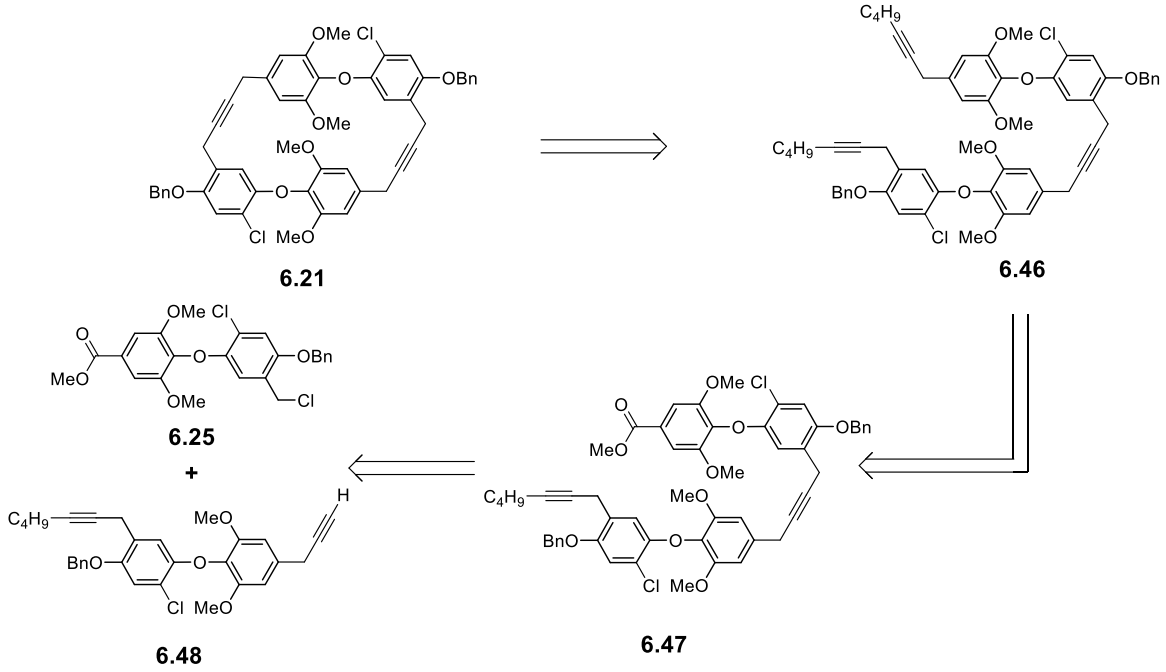


Reagents & conditions : i) $LiAlH_4$, THF, 0 °C to RT, ii) NBS, PPh_3, THF, 0 °C to RT

Scheme 6.11. Access to **6.43** and **6.45**

6.3.1 An alternative approach to macrocyclisation

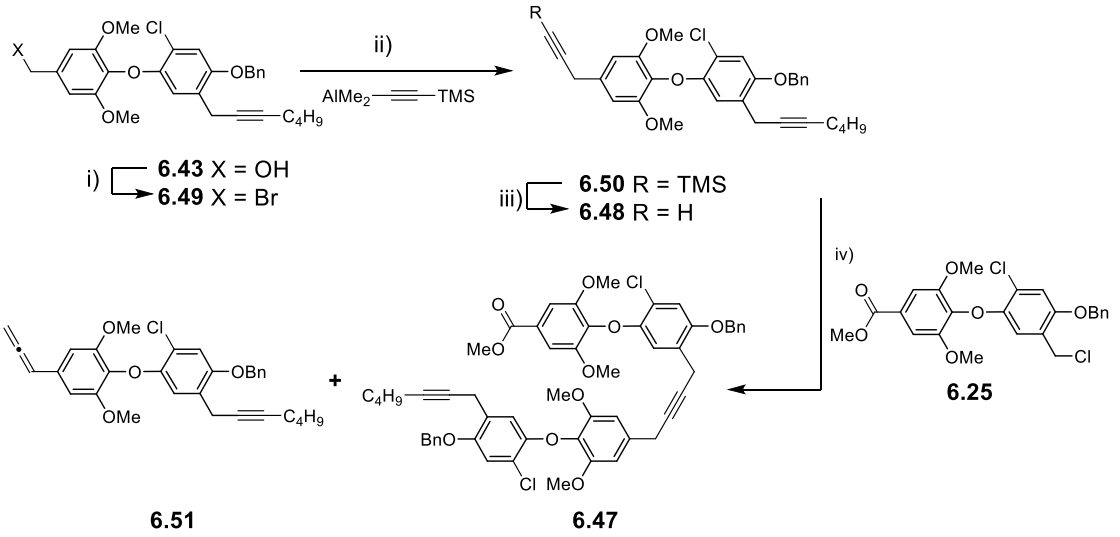
It was postulated that four arenes could be conjoined at an earlier stage in the synthesis, leaving some functional group interconversions to be performed prior to macrocyclisation. The strategy would seek to advance benzyl chloride **6.25** and diyne **6.46** to tetraarene **6.45** from which macrocyclisation to **6.21** could be envisioned (Scheme 6.12).



Scheme 6.12. Retrosynthetic analysis of tetraaromatic **6.45**

Accessing alkyne **6.48** from benzyl alcohol **6.43** was accomplished in three steps. First, bromination to **6.49** was performed to facilitate a nickel catalysed coupling with TMSacetalyde. Pleasingly, this afforded the desired diyne **6.50** in 80% yield. TMS deprotection with catalytic AgOTf then afforded the desired

terminal diyne **6.48** in 77% yield. Diyne **6.48** and benzyl chloride **6.25** were now coupled to form tetraarene **6.47** in less than 25% isolated yield as evidenced by mass spectrometry and ^{1}H-NMR. Allene **6.51** was also identified as a constituent of the product mixture. Unfortunately due to time constraints the investigation had to be stopped at this juncture.



Reagents & conditions : i) NBS, PPh_3, THF, 0 °C to RT, 70% ii) $NiCl_2(PPh_3)_2$ (7% mol), Et_2O, pentane, 0 °C to RT, 80% iii) AgOTf, MeOH/H_2O/DCM (3 : 1 : 4), 77% iv) $PdCl_2(CH_3CN)_2$ (5% mol), XPhos (15% mol), Cs_2CO_3, ACN, 65 °C, 25%

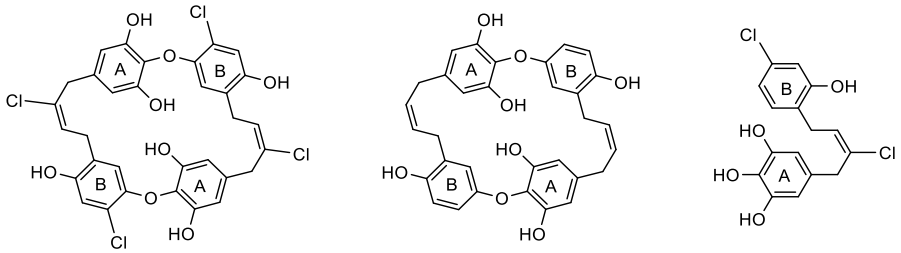
Scheme 6.13. Access to terminal alkyne **6.47**

6.4 Conclusion and future work

6.4.1 Conclusion

During the course of this Ph.D. our studies towards chrysophaentin F **1.8** have culminated in a synthesis of the unchlorinated analogue **3.1** *via* a strategy

involving 'dimerisation' and macrocyclisation steps (Scheme 5.6). Additionally, our investigations have provided a strategy for introducing the vinyl chloride. This led to the synthesis of hemichrysophaentins **6.19** and **6.20** and displayed the desired regioselectivity albeit the reaction remains to be attempted and optimised on the real system.

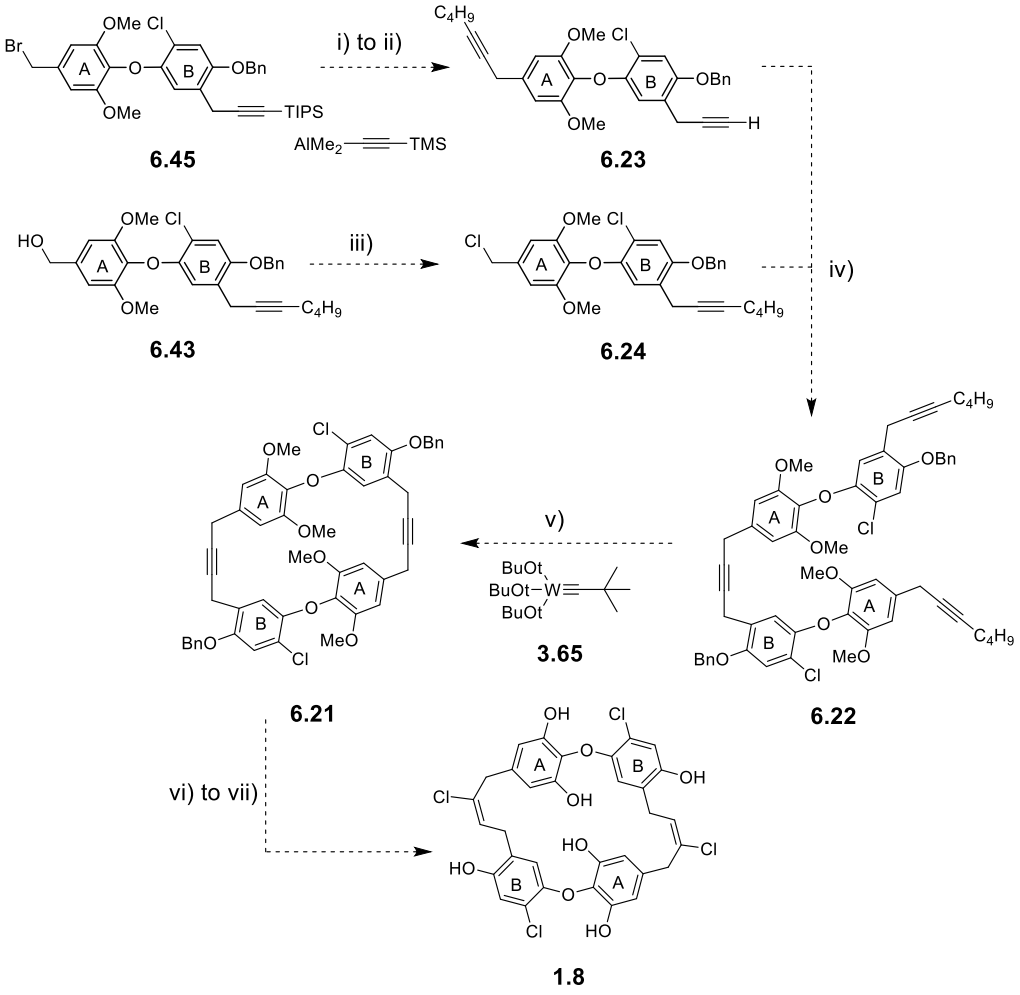


1.8 **3.1** **6.19**

Figure 6.2. Chrysophaentin F **1.8**, Chrysophaentin analogue **3.1** and hemichrysophaentins **6.19**.

The synthesis of the chlorinated structure was design such as to mimic as closely as possible to the the synthesis of macrocycle **3.1.** This strategy afforded easily fragment **6.25**, a few steps from the dimerisation reaction. However the alkynylation reaction with TMS acetylene proved surprisingly difficult and hindered our efforts towards chrysophaentin F **1.8**. To circumvent this problem two strategies were designed and could not be fully investigated due to time constraints. To realise a synthesis of chrysophaentin F **1.8** we plan to subject benzyl bromide **6.45** to a nickel catalysed alkynylation with hexyne to afford terminal alkyne **6.23** after TIPS removal. Contemporaneously, a chlorination reaction on benzyl alcohol **6.43** will afford the required benzyl chloride **6.24**.

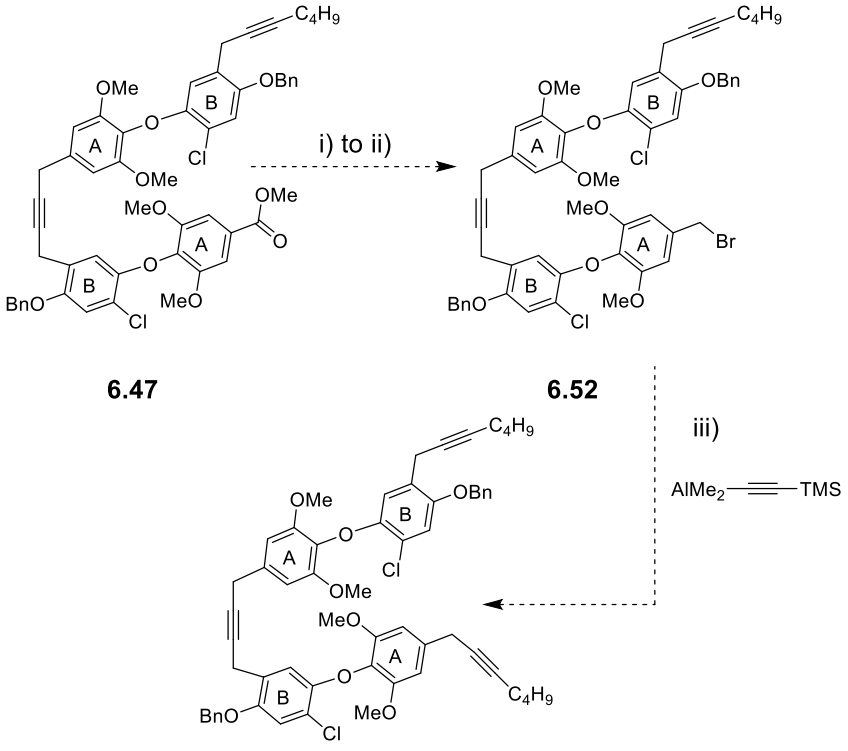
Fragments **6.23** and **6.24** will then be combined in a palladium-catalysed coupling reaction to afford triyne **6.22** then subjected to macrocyclisation by alkyne metathesis to reach macrocycle **6.21**. We then hope to apply the hydrozirconation-chlorination strategy to install the vinyl chloride moieties and induce global deprotection to attain chrysophaentin F **1.8**.



Reagents & conditions : i) $NiCl_2(PPh_3)_2$ (7% mol), Et_2O, pentane, RT ii) TBAF, AcOH, THF iii) NCS, PPh_3, THF, 0 °C to RT iv) $PdCl_2(CH_3CN)_2$ (5% mol), XPhos (15% mol), Cs_2CO_3, ACN, 65 °C v) **3.65**, toluene, 80 °C, C = 0.002 M vi) $ZrCl_2Cp_2$, DIBALH, 0 to 40 °C, 1 h, then NCS, RT, 18 h vii) BCl_3, TBAI, DCM 0 °C to RT

Scheme 6.14. Completing the synthesis of chrysophaentin F **1.8**

An alternative approach can be envisioned from ester **6.47**. Its advancement to benzyl bromide **6.52** should facilitate a nickel catalysed reaction to the aforementioned macrocyclisation precursor **6.21** (Scheme 6.15).



6.47 **6.52** **6.21**

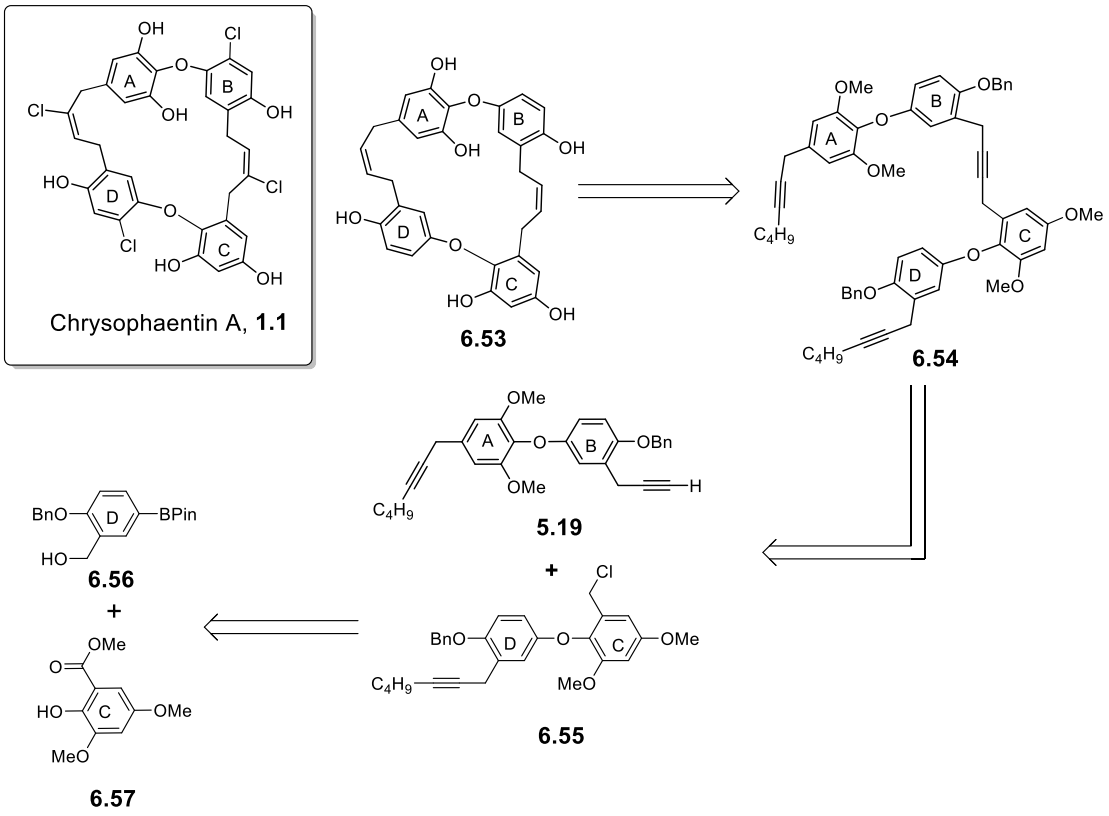
Reagents & conditions : i) $LiAlH_4$, THF, 0 °C to RT, ii) NBS, PPh_3, THF, 0 °C to RT iii) $NiCl_2(PPh_3)_2$ (7% mol), Et_2O, pentane, 0 °C to RT

Scheme 6.15. Alternative access to triyne **6.21**

6.4.2 Comprehensive synthesis of chrysophaentins core structures

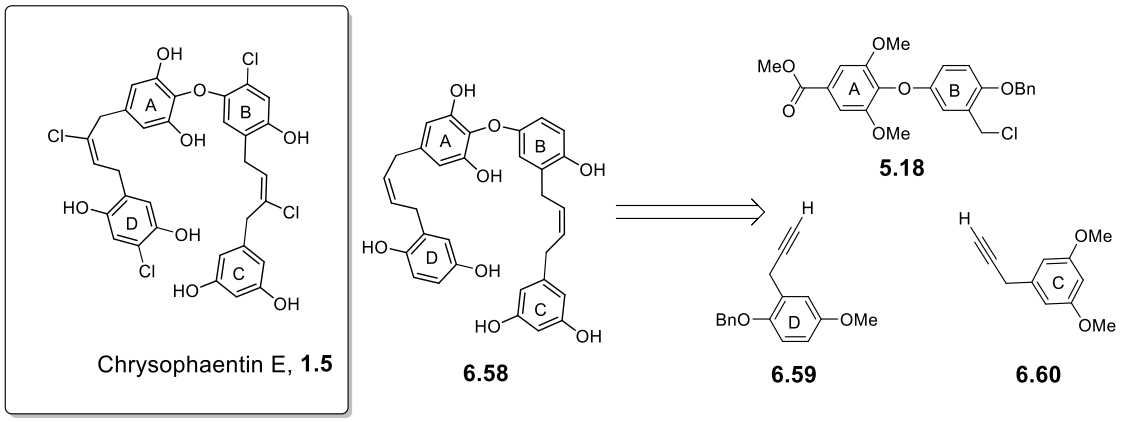
In a same family of compounds it is usual to recognise similar pattern which allow for a comprehensive synthesis of all the members of the family if a common set of subunits can be identified. The work of Bruke and co-worker in 2014 is a good example of how,[71] theoretically, with a set of 12 subunits we can access the whole polyene family. The question is can we identify the necessary subunits for the comprehensive synthesis of the chrysophaentin family?

Thus, it was investigated to what extend the chemistry/strategy developed in this Ph.D. would be transferable to build the rest of Chrysophaentins. Here we choose the core structure of chrysophaentin A **1.1** as a theoretical example. It is envisaged to form the desired target from triyne **6.54** using an RCAM reaction followed by a partial reduction and global deprotection to access the desired scaffold **6.53.** In turn triyne **6.54** is envisioned to be synthesised by a palladium catalysed reaction between terminal alkyne **5.19** and benzyl chloride **6.55**. It was analysed that benzyl chloride **6.55** could be synthesized from boronic ester **6.56** and phenol **6.57**. Boronic ester **6.56** can be accessed easily from bromo-salicylaldehyde **4.1** and the synthesis of phenol **6.57** has been described by Wang and co-workers in 2007.[72]



Scheme 6.16. Retrosynthetic analysis of Chrysophaentin A scaffold

Applying the same reasoning to the linear chrysophentin E **1.5** we envisaged that the core structure could be synthesised by reacting benzyl chloride **5.18** with terminal alkynes **6.59** and **6.60** in two consecutive palladium catalysed coupling followed by partial reduction and a global deprotection to give the core structure **6.58**. Alkynes **6.59** and **6.60** have both been reported in the literature.[2, 73]



Scheme 6.17. Retrosynthesic analysis of Chrysophaentin E core structure **6.58**

7. Experimental

7.1 General method

All solvents were distilled prior to use. Tetrahydrofuran, diethyl ether, hexane and pentane were all distilled from sodium benzophenone ketyl under argon. Dichloromethane was distilled from calcium hydride under argon. All air sensitive reactions were carried out under argon using flame or oven dried apparatus.

All reactions were monitored by TLC on Merck Silica Gel 60 Á F TLC plates. Plates were visualised with 254 nm UV followed by aqueous 1% $KMnO_4$, ethanolic PMA, DNPH or iodine. Flash chromatography was performed under pressure on davisil 35-70 μm 60 Å silica.

Reaction and chromatography solvents were removed using a rotary evaporator with diaphragm pump.

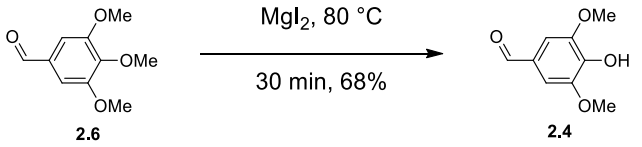
NMR spectroscopy was performed using a Bruker 300 MHz and 400 MHz. $CDCl_3$ was stored over dried K_2CO_3 to neutralise trace acidity. Chemical shifts are quoted as δ values in ppm. Residual solvent peaks are used as the reference, the primary reference being TMS proton at 0 ppm. Coupling constants *J* are given in Hz and multiplicity is described as follows: s-singlet, d-doublet, t-triplet, q-quartet, qi-quintet, m-multiplet, br-broad.

Electrospray mass spectrometry was performed on a directly injected Waters quadrupole MSD using ESI+ or ESI- ionisation with MeOH 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 $\times$ 0.25 mm $\times$ 0.25 μm column run from 40 °C to 200 °C over 18 min.

Infrared spectroscopy was performed on a Bio-Rad FTIR instrument using a golden gate window. Spectra were acquired from pure samples or evaporated solution in $CDCl_3$. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}). The abbreviations describing their intensity are as follows: s-strong, m-medium, w-weak, br-broad.

7.2 Experimental Chapter 2

4-Hydroxy-3,5-dimethoxybenzaldehyde (2.4)



2.6 $C_{10}H_{12}O_4$ MW: 196.20

2.4 $C_9H_{10}O_4$ MW: 182.17

Adapted from the protocol of Zhang et al.[31] To magnesium turnings (64.9 mg, 2.67 g-atom) in diethyl ether (5 mL) at 0 °C was added iodine (602 mg, 2.37 mmol). The reaction mixture was then stirred at reflux for 2 h (controlled with an ice bath) then a solution of methyl 3,4,5-trimethoxybenzaldehyde **2.6** (212 mg, 1.08 mmol) in DCM (10 mL) was added. The solvent was removed *in vacuo* then the temperature was raised to 80 °C. After 30 min water (10 mL), sodium

thiosulfate (10% aqueous solution, 10 mL) and EtOAc (20 mL) were added then the phases were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) then the organic phases were combined, washed with water (20 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 30% EtOAc in petroleum ether) to yield the title compound **2.4** (134 mg, 0.74 mmol, 68%) as a pale yellow solid.

The physical and spectroscopic data were in agreement with reported values.[74]

MP: 105 – 107 °C (EtOAc) [Lit. 113 – 114 °C].[75]

IR ν_{max} (neat, cm^{-1}) 3154 br, 2989 m, 2939 m, 2839 m, 2248 m, 1666 s, 1602 s, 1583 s, 1514 m, 1461 s, 1423 m, 1366 m, 1327 s, 1209 m, 1145 s, 1110 s, 727 s.

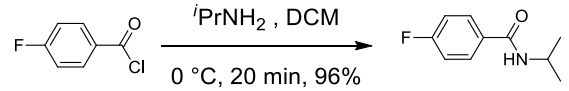
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 9.82 (1H, s, C**H**O), 7.15 (2H, s, 2 × Ar**H**), 6.14 (1H, s, O**H**), 3.97 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 190.7 (**C**HO), 147.3 (**C**), 140.8 (**C**), 128.4 (**C**), 106.7 (**C**H), 56.4 (**C**H$_3$).

LRMS (HPLC–MS; ES^-): 181 ($[M-H]^-$, 100%)

HRMS (ES^-) Calcd. for $C_9H_9O_4^-$ $[M-H]^-$: 181.0506, found: 181.0503.

4-Fluoro-*N*-isopropylbenzamide (2.8)



7.1

C_7H_4ClFO
MW: 158.5575

2.8

$C_{10}H_{12}FNO$
MW: 181.21

To a solution of 4-fluorobenzoyl chloride **7.1** (1.59 g, 10.0 mmol) in DCM (20 mL) at 0 °C was added isopropylamine (1.18 g, 20.0 mmol) dropwise over 5 min. After 20 min water (15 mL) was added then the aqueous phase was separated and extracted with EtOAc (2 × 15 mL). The organic phases were combined, washed with 2M HCl (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **2.8** (1.75 g, 9.64 mmol, 96%) as a white powder. The product was used without further purification.

The physical and spectroscopic data were in agreement with reported values.[76]

MP: 110 – 112 °C ($CHCl_3$) [Lit.118 – 119 °C].[74]

IR ν_{max} (neat, cm^{-1}): 3306 br, 2978 m, 2940 m, 2878 m, 1631 s, 1600 s, 1532 s, 1500 s, 1454 m, 1326 s, 1222 s, 886 s.

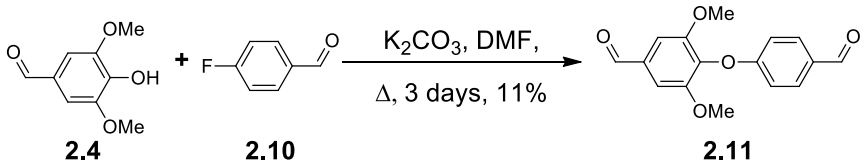
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.77 (2H, dd, *J* = 8.6, 5.3 Hz, 2 × Ar**H**), 7.10 (2H, t, *J* = 8.6 Hz, 2 × Ar**H**), 5.92 (1H, br. s, N**H**), 4.28 (1H, app. oct, *J* = 6.6 Hz, C**H**), 1.27 (6H, d, *J* = 6.6 Hz, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.2 (**C**O), 164.3 (d, *J* = 204 Hz, **C**F), 131.1 (d, *J* = 4 Hz, **C**H), 129.1 (d, *J* = 43 Hz, **C**H), 115.5 (d, *J* = 22 Hz, **C**), 42.0 (**C**H), 22.8 (**C**H$_3$).

LRMS (HPLC–MS; ES^+): 245 ($[M+Na+MeCN]^+$, 100%).

HRMS (ES^+) Calcd. for $C_{10}H_{12}FNNaO^+$ $(M+Na)^+$: 207.0795, found: 207.0794.

<u>4-(4-Formylphenoxy)-3,5-dimethoxybenzaldehyde (2.11)</u>



2.4 $C_9H_{10}O_4$ MW: 182.17 **2.10** C_7H_5FO MW 124.11 **2.11** $C_{16}H_{14}O_5$ MW: 286.28

To a solution of phenol **2.4** (182 mg, 1.00 mmol) and 4-fluorobenzaldehyde **2.10** (0.13 mL, 1.20 mmol) in deoxygenated DMF (2 mL) was added potassium carbonate (138 mg, 1.00 mmol). After 3 d at reflux, water (2 mL) and diethyl ether (2 mL) were added. The aqueous phase was separated and extracted with Et_2O (2 × 3 mL). The organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 30% EtOAc in petroleum ether) to yield the title compound **2.11** (32.0 mg, 0.11 mmol, 11%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 3066 w, 2951 w, 2819 m, 2820 m, 2733 m, 1692 s, 1596 s, 1578 s, 1493 s, 1464 s, 1234 s, 1128 s, 831 s.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 9.96 (1H, s, C**H**O), 9.90 (1H, s, C**H**O), 7.82 (2H, d, J = 8.7 Hz, 2 × Ar**H**), 7.23 (2H, s, 2 × Ar**H**),

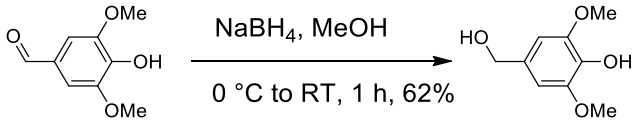
6.96 (2H, d, J = 8.7 Hz, 2 × Ar**H**), 3.86 (6H, s, 2 × C**H**$_3$).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 190.8 (**C**HO), 190.7 (**C**HO), 162.6 (**C**), 153.6 (**C**), 136.2 (**C**), 134.0 (**C**), 131.8 (**C**H), 131.2 (**C**), 115.3 (**C**H), 106.4 (**C**H), 56.4 (**C**H$_3$).

LRMS (GC–MS; EI): 286 ([M]$^+$, 100%).

HRMS (ES$^+$) Calcd. for $C_{16}H_{14}NaO_5^+$ [M+Na]$^+$: 309.0733, found: 309.0739.

4-Hydroxy-3,5-dimethoxybenzylalcohol (2.12)



2.4
$C_9H_{10}O_4$
MW: 182.17

2.12
$C_9H_{12}O_4$
MW: 184.19

Adapted from the procedure of Snyder *et al.*[77] To a solution of 4-hydroxy-3,5-dimethoxybenzaldehyde **2.4** (910 mg, 5.00 mmol) in methanol (25 mL) at 0 °C was added sodium borohydride (380 mg, 10.0 mmol). After 1 h at RT, water (20 mL), 2 M HCl (10 mL) and EtOAc (40 mL) were added. The aqueous phase was separated and extracted with EtOAc (4 × 40 mL), then the organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 50 to 70% EtOAc in petroleum ether) to afford the title compound **2.12** (572 mg, 3.11 mmol, 62%) as an off-white solid.

The physical and spectroscopic data were in agreement with reported values.[78]

MP: 113 – 115 °C (EtOAc) [Lit.132 – 134°C].[77]

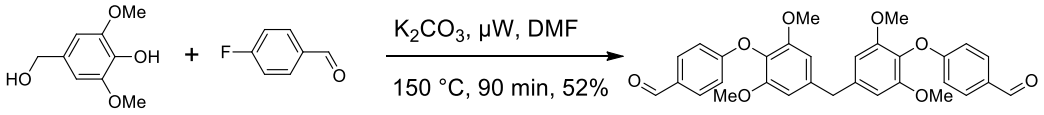
IR ν_{max} (neat, cm^{-1}) 3465 s, 3150 br, 2939 m, 2840 m, 1611 m, 1515 s, 1458 m, 1280 s, 1215 s, 1147 s.

^{1}H NMR (300 MHz; CD_3OD): δ ppm 6.64 (2H, s, Ar**H**), 4.51 (2H, s, C**H$_2$**), 3.84 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; CD_3OD): δ ppm 149.3 (**C**), 136.0 (**C**), 133.6 (**C**), 105.6 (**C**H), 65.7 (**C**H$_2$), 56.8 (**C**H$_3$).

LRMS (HPLC–MS; ES^-): 183 ($[M-H]^-$, 100%).

4,4'-((Methylenebis(2,6-dimethoxy-4,1-phenylene))bis(oxy))dibenzaldehyde (2.14)



2.12 $C_9H_{12}O_4$ MW: 184.19

2.10 C_7H_5FO MW: 124.11

2.14 $C_{31}H_{28}O_8$ MW: 528.55

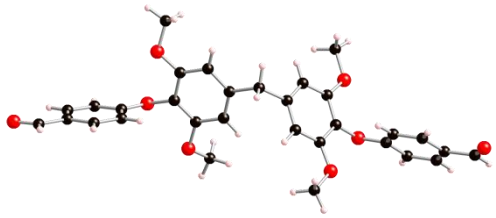
A solution of 4-fluororbenzaldehyde **2.10** (75.0 mg, 0.60 mmol), 4-hydroxy-3,5-dimethoxybenzaldehyde **2.12** (92.0 mg, 0.50 mmol) and K_2CO_3 (69.0 mg, 0.50 mmol) in deoxygenated DMF (2 mL) under argon was irradiated in a microwave reactor at 150 °C for 90 min. Water (2 mL) was added then the aqueous phase was separated and extracted with EtOAc (3 × 4 mL). The organic phases were combined, washed with water (4 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* then purified by column chromatography (silica, 0 to 5%

EtOAc in DCM) to afford the title compound **2.14** (70.0 mg, 1.32 mmol, 52%) as an off-white solid.

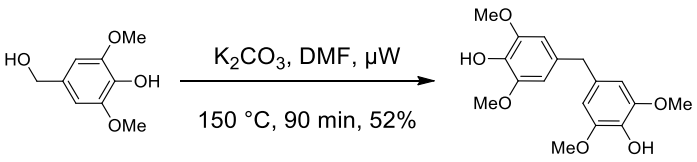
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 9.88 (2H, s, 2 × C**H**O), 7.80 (4H, d, *J* = 8.6 Hz, 4 × Ar**H**), 6.98 (4H, d, *J* = 8.6 Hz, 4 × Ar**H**), 6.54 (4H, s, 4 × Ar**H**), 4.02 (2H, s, C**H$_2$**), 3.76 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 190.8 (**C**HO), 163.5 (**C**), 152.9 (**C**), 138.7 (**C**), 131.8 (**C**H), 130.7 (**C**), 129.6 (**C**), 115.2 (**C**H), 105.1(**C**H), 56.2 (**C**H$_3$), 42.5 (**C**H$_2$).

X-ray:



4,4'-Methylenebis(2,6-dimethoxyphenol) (2.19)



2.12

$C_9H_{12}O_4$
MW: 184.19

2.19

$C_{17}H_{20}O_6$
MW: 320.34

A solution of 4-hydroxy-3,5-dimethoxybenzaldehyde **2.12** (92.0 mg, 0.50 mmol) and K_2CO_3 (69.0 mg, 0.50 mmol) in deoxygenated DMF (2 mL) under argon was irradiated in microwave reactor at 150 °C for 90 min then sat. NH_4Cl (2 mL) was then added. The aqueous phase was separated and extracted with

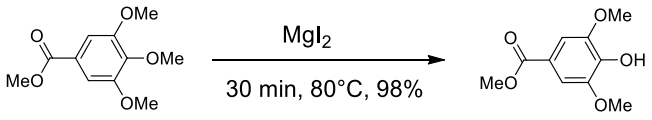
EtOAc (3 × 4 mL), then the organics phases were combined, washed with water (4 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 30 to 40% EtOAc in petroleum ether) to afford the title compound **2.19** (42.0 mg, 1.31 mmol, 52% yield) as a brown oil.

The physical and spectroscopic data were in agreement with reported values.[79]

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 6.40 (4H, s, 4 × Ar**H**), 3.85 (14H, s, C**H$_2$** and 4 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 147.0 (**C**), 133.0 (**C**), 132.2 (**C**), 105.5 (**C**H), 56.3 (**C**H$_3$), 41.9 (**C**H$_2$).

Methyl 4-hydroxy-3,5-dimethoxybenzoate (2.21)



2.20

$C_{11}H_{14}O_5$
MW: 226.23

2.21

$C_{10}H_{12}O_5$
MW: 212.20

Adapted from the protocol of Zhang *et al.*[32] To magnesium turnings (3.65 g, 0.150 g-atom) in Et_2O (100 mL) at 0 °C was added iodine (19.2 g, 75.6 mmol). The reaction mixture was heated at reflux for 2 h (controlled with an ice bath) then a solution of methyl 3,4,5-trimethoxybenzaldehyde **2.20** (7.92 g, 35.0 mmol) in DCM (50 mL) was added. The solvent was removed *in vacuo* then the temperature was raised to 80 °C. After 30 min water (100 mL), sodium

thiosulfate (10% aqueous solution, 20 mL) and EtOAc (40 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 40 mL) then the organic phases were combined, washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **2.21** (7.30 g, 34.4 mmol, 98%) yield as a yellow solid which was used without further purification.

The physical and spectroscopic data were in agreement with reported values.[81]

MP: 83 – 86°C (EtOAc) [lit. 106 – 107 °C].[81]

IR ν_{max} (neat, cm^{-1}) 3303 br, 2944 m, 2840 m, 1694 s, 1611 m, 1594 m, 1518 m, 1459 m, 1371 s, 1277 s, 1232 s, 1180 s, 1103 s, 845 s.

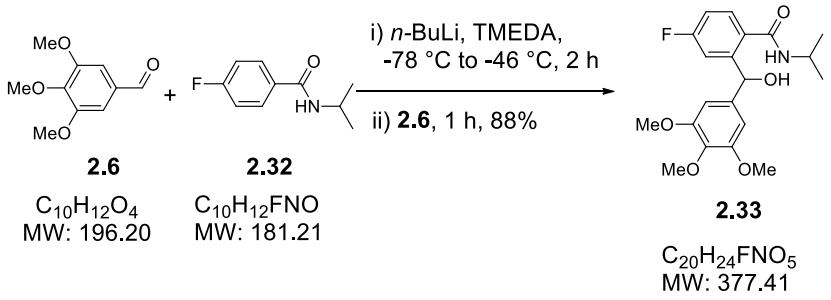
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.33 (2H, s, 2 × Ar**H**), 5.95 (1H, br. s, O**H**), 3.94 (6H, s, 2 × C**H$_3$**), 3.90 (3H, s, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.8 (**C**O), 146.6 (**C**), 139.2 (**C**), 121.0 (**C**), 106.6 (**C**H), 56.4 (**C**H_3), 52.1 (**C**H_3).

LRMS (HPLC–MS; ES^-): 211 ($[M-H]^-$, 100%).

HRMS (ES^-): Calcd. for $C_{10}H_{11}O_5^-$ $[M-H]^-$: 211.0612, found: 211.0613.

4-Fluoro-2-(hydroxy(3,4,5-trimethoxyphenyl)methyl)-*N*-isopropylbenzamide (2.33)



2.6
$C_{10}H_{12}O_4$
MW: 196.20

2.32
$C_{10}H_{12}FNO$
MW: 181.21

2.33
$C_{20}H_{24}FNO_5$
MW: 377.41

To a solution of 4-fluoro-*N*-isopropylbenzamide **2.32** (362 mg, 2.00 mmol) and TMEDA (0.66 mL, 4.40 mmol) in Et_2O (17 mL) at -78 °C was added *n*-BuLi (2.40 M in hexane, 2.10 mL, 5.04 mmol) dropwise over 10 min. The reaction mixture was stirred for 1 h at -78 °C and 1 h at -46 °C then a solution of 3,4,5-trimethoxybenzaldehyde **2.6** (589 mg, 3.00 mmol) in THF (2 mL) was added dropwise over 10 min. After 1 h at -46 °C sat. NH_4Cl (5 mL) was added. The aqueous phase was separated and extracted with EtOAc (3 × 10 mL), then the combined organic phases were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 50% EtOAc in petroleum ether) to give the title compound **2.33** (0.67 g, 1.76 mmol, 88%) as a white solid.

MP: 140 – 145 °C ($CHCl_3$).

IR ν_{max} (neat, cm^{-1}) 3392 br, 3307 br, 2972 m, 2936 m, 2837 m, 1643 s, 1590 s, 1491 s, 1456 m, 1327 s, 1230 s, 887 s.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.42 (1H, dd, *J* = 8.8, 5.5 Hz, Ar**H**), 7.05 – 6.97 (2H, m, 2 × Ar**H**), 6.56 (2 H, s, 2 × Ar**H**), 5.82

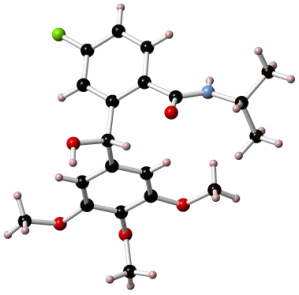
(1H, br. d, J = 4.8 Hz, N**H**), 5.74 (1H, br. d, J = 7.7 Hz, O**H**), 5.55 (1H, br. d, J = 6.2 Hz, C**H**), 4.08 (1H, app. oct, J = 6.6 Hz, C**H**), 3.81 (6H, s, 2 × C**H**$_3$), 3.82 (3H, s, C**H**$_3$), 1.19 (3H, d, J = 6.6 Hz, C**H**$_3$), 1.04 (3H, d, J = 6.6 Hz, C**H**$_3$).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 169.2 (**C**O), 168.2 (d, J = 190 Hz, **C**F), 153.0 (**C**), 146.6 (**C**), 137.7 (**C**), 137.0 (**C**), 131.9 (d, J = 4 Hz, **C**), 129.6 (d, J = 9 Hz, **C**H), 117.1 (d, J = 22 Hz, **C**H), 114.5 (d, J = 21 Hz, **C**H), 103.7 (**C**H), 74.2 (**C**H); 60.8 (**C**H$_3$), 56.2 (**C**H$_3$), 42.3 (**C**H), 22.5 (**C**H$_3$), 22.4 (**C**H$_3$).

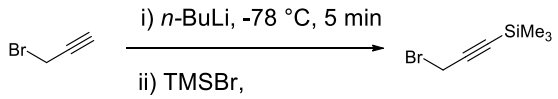
LRMS (HPLC–MS; ES$^+$): 441 ([M+Na+MeCN]$^+$, 100%), 400 ([M+Na]$^+$, 25%), 360 ([M–OH]$^+$, 11%).

HRMS (ES$^+$): Calcd. for $C_{20}H_{24}FNNaO_5^+$ [M+Na]$^+$: 400.1531, found: 400.1539.

X-ray



(3-Bromoprop-1-yn-1-yl)trimethylsilane (2.28)



7.2 **2.28**

C_3H_3Br
MW: 118.96

$C_6H_{11}BrSi$
MW: 191.14

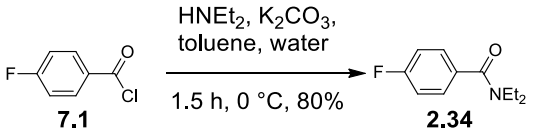
To a solution of propargyl bromide **7.2** (2.25 mL, 25.2 mmol) in THF (80 mL) at −78 °C was added *n*−BuLi (2.40 M in hexane, 5.25 mL, 12.6 mmol) dropwise over 5 min. TMSBr (3.33 mL, 25.2 mmol) was then added dropwise over 5 min and the solution warmed to RT. After 1 h water (40 mL) and Et_2O (40 mL) were added. The aqueous phase was separated and extracted with Et_2O (2 × 30 mL) then the organic phases were combined, washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by distillation under reduced pressure (0.1 mmHg, 23 °C) to give the title compound **2.28** (1.23 g, 6.40 mmol, 26%) as a colourless liquid.

The physical and spectroscopic data were in agreement with reported values.[82]

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 3.92 (2H, s, C**H$_2$**), 0.19 (9H, s, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 99.9 (**C**), 92.3 (**C**), 14.7 (**C**H$_2$), -0.4 (3 × **C**H$_3$).

N,N-Diethyl-4-fluorobenzamide (2.34)



7.1 C_7H_4ClFO MW: 158.56

2.34 $C_{11}H_{14}FNO$ MW: 195.23

Following the protocol of Gosselin *et al.*[83] To a solution of diethylamine (0.57 mL, 5.50 mmol) in water (2.5 mL) was added K_2CO_3 (415 mg, 3.00 mmol) and toluene (5 mL). The reaction mixture was cooled to 0 °C and 4-fluorobenzoyl chloride **7.1** (0.59 mL, 5.00 mmol) was added dropwise over 5 min. The reaction mixture was warmed to RT and after 1.5 h the aqueous phase was separated and extracted with Et_2O (2 × 5 mL). The organic phases were combined, washed with water (5 mL), sat. $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 30 to 50% EtOAc petroleum ether) gave the title compound **2.34** (785 mg, 4.02 mmol, 80%) as a colourless oil.

The physical and spectroscopic data were in agreement with reported values.[83]

IR ν_{max} (neat, cm^{-1}) 2975 m, 2937 m, 1625 s, 1511 m, 1427 s, 1287 m, 1221 s, 1094 m, 846 s.

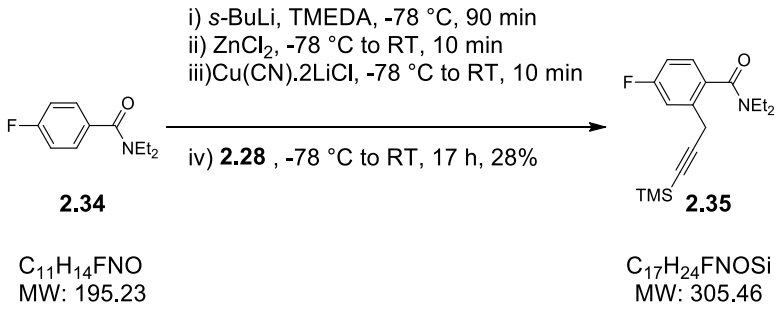
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.37 (2H, dd, J = 8.6, 5.5 Hz, 2 × Ar**H**), 7.07 (2H, app. t, J = 8.6 Hz, 2 × Ar**H**), 3.51 (2H, br. s, C**H$_2$**), 3.27 (2H, br. s, C**H$_2$**), 1.18 (6 H, app. br. s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 170.3 (**C**O), 163.0 (d, *J* = 250 Hz, **C**F) 133.2 (d, *J* = 8 Hz, **C**), 128.4 (d, *J* = 9 Hz, **C**H), 115.4 (d, *J* = 21 Hz, **C**H), 43.3 (**C**H_2), 39.4 (**C**H_2), 14.2 (**C**H_3), 12.8 (**C**H_3).

LRMS (HPLC-MS; ES^+): 259 ($[M+Na+MeCN]^+$, 100%), 196 ($[M+H]^+$, 12%).

HRMS (ES^+) Calcd. for $C_{11}H_{15}FNO^+$ $[M+H]^+$: 196.1132, found: 196.1135.

***N,N*-Diethyl-4-fluoro-2-(3-(trimethylsilyl)prop-2-ynyl)benzamide (2.35)**



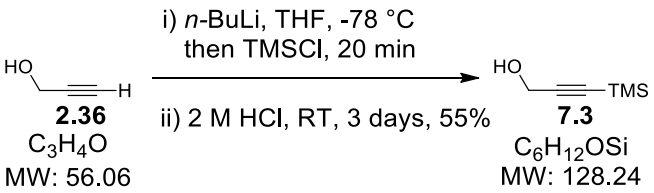
Adapted from a procedure by Groth *et al.*[40] To a solution of TMEDA (0.16 mL, 1.05 mL) in THF (3 mL) at -78 °C was added *s*-BuLi (1.3 M in cyclohexane, 0.85 mL, 1.1 mmol) dropwise over 2 min. A solution of benzamide **2.34** (195 mg, 1.00 mmol) in THF (1 mL) was added over 2 min followed after 90 min by a solution of flame dried zinc chloride (200 mg, 1. 47 mmol) in THF (2 mL). The solution was warmed to 0 °C for 10 min, then cooled to -78 °C. A solution of CuCN.2LiCl [from CuCN (99.0 mg, 1.10 mmol) and LiCl (94 mg, 2.2 mmol)] in THF (2 mL) was added over 2 min. The reaction was warmed to 0 °C and after 10 min was cooled back to -78 °C, whereupon a solution of propargyl bromide **2.28** (250 mg, 1.30 mmol) in THF (1 mL) was added. After 1h the reaction

mixture was allowed to warm to RT over 16 h then sat, NH_4Cl (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 × 15 mL) then the organic phases were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10% EtOAc in petroleum ether) to afford the title compound **2.35** (85.0 mg, 0.28 mmol, 28%) as yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.30 (1H, d, *J* = 9.6 Hz, Ar**H**), 7.14 (1H, app. t, *J* = 7.1 Hz, Ar**H**), 6.95 (1H, app. t, *J* = 8.3 Hz, Ar**H**), 3.33–3.88 (4H, m, NC**H$_2$** and ArC**H$_2$**), 3.12 (2H, q, *J* = 6.9 Hz, NC**H$_2$**), 1.25 (3H, t, *J* = 6.9 Hz, C**H$_3$**), 1.05 (3H, t, *J* = 6.9 Hz, C**H$_3$**), 0.17 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 169.3 (**C**O), 162.8 (d, *J* = 260.6 Hz, **C**), 135.8 (d, *J* = 8.1 Hz, **C**), 132.2 (d, *J* = 2.9 Hz, **C**), 127.1 (d, *J* = 7.3 Hz, **C**H), 116.1 (d, *J* = 23.6 Hz, **C**H), 113.6 (d, *J* = 20.5 Hz, **C**H), 102.4 (**C**), 87.9 (**C**), 43.0 (**C**H_2), 39.0 (**C**H_2), 23.4 (**C**H_2), 14.0 (**C**H_3), 12.7 (**C**H_3), −0.1 (**C**H_3).

3-(Trimethylsilyl)prop-2-yn-1-ol (7.3)



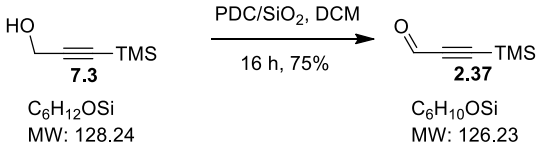
Adapted from the protocol of Schmalz *et al.*[42] To a solution of propargyl alcohol **2.36** (1.04 mL, 17.8 mmol) in THF (80 mL) at −78 °C was added *n*-BuLi (2.40 M in hexane, 16 mL, 38.4 mmol) dropwise over 5 min. After 20 min TMSCl (6.8 mL, 53.4 mmol) was added and the reaction mixture was allowed to warm to RT over 20 min. 2 M HCl (40 mL) was added and after 3 days the aqueous phase was separated and extracted with Et_2O (2 × 30 mL). The organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 40 to 65% DCM in petroleum ether) to give the title compound **7.3** (1.27 g, 9.90 mmol, 55%) as a pale yellow oil.

The physical and spectroscopic data were in agreement with reported values. [84]

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 4.27 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 1.75 (3H, t, *J* = 6.04 Hz, O**H**), 0.18 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 103.8 (**C**), 90.7 (**C**), 51.6 (**C**H$_2$), −0.2 (**C**H$_3$).

<u>3-(Trimethylsilyl)propiolaldehyde (2.37)</u>



Adapted from the protocol of Schmalz *et al.*[42] To a solution of propargyl alcohol **7.3** (600 mg, 4.68 mmol) in DCM (40 mL) at RT was added silica (2.50 g) then PDC (2.11 g, 5.61 mmol). After 16 h, the solution was filtered through a plug of silica and concentrated *in vacuo* to give the aldehyde **2.37** as a pale yellow oil (444 mg, 3.50 mmol, 75%), which was used without further purification.

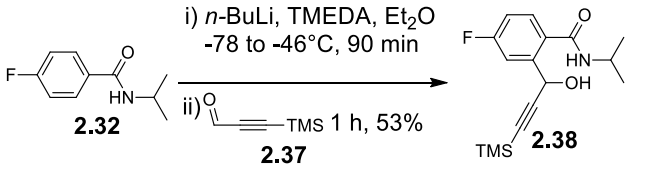
Experimental

The physical and spectroscopic data were in agreement with reported values.[85]

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 9.17 (1H, s, C**H**O), 0.27 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 176.7 (C**H**O), 103.0 (**C**), 102.1 (**C**), -1.0 (**C**H$_3$).

4-Fluoro-2-(1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)-*N*-isopropylbenzamide (2.38)



$C_{10H12F}NO$	$C_6H_{10}OSi$	$C_{16}H_{22}FNO_2Si$
MW: 181.21	MW: 126.23	MW: 307.44

To a solution of amide **2.32** (272 mg, 1.50 mmol) and TMEDA (0.5 mL, 3.30 mmol) in Et_2O (10 mL) at -78 °C was added *n*-BuLi (2.3 M in hexane,1.60 mL, 3.75 mmol) dropwise over 5 min. After 45 min the temperature was raised to -46 °C and after a further 45 min a solution of aldehyde **2.37** (0.284 mg, 2.25 mmol) in THF (2 mL) was added dropwise over 5 min. After 1 h sat. NH_4Cl (5 mL) was added, the aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The organic phases were then combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 30% EtOAc in petroleum ether) to afford the title compound **2.38** (244 mg, 0.79 mmol, 53%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 3272 br, 2964 m, 2924 m, 2853 m, 1631 s, 1549 s, 1489 m, 1459 m, 1251 s, 844 s.

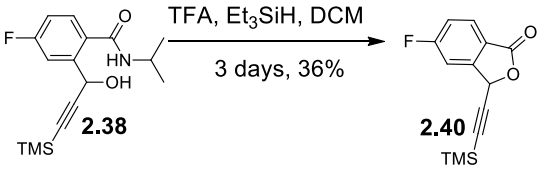
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.51 – 7.43 (2H, m, 2 × Ar**H**), 7.04 (1H, td, J = 8.2, 2.6 Hz, Ar**H**), 6.08 (1H, d, J = 7.3 Hz, N**H**), 5.53 (1H, s, C**H**), 4.24 (1H, app. oct, J = 6.6 Hz, C**H**), 1.32 – 1.26 (6H, m, 2 × C**H**$_3$), 0.20 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 168.7 (**C**O), 163.8 (d, J = 250 Hz, **C**F), 143.0 (**C**), 131.2 (**C**), 129.8 (d, J = 9 Hz, **C**H), 116.4 (d, J = 23 Hz, **C**H), 115.1 (d, J = 21 Hz, **C**H), 103.4 (**C**), 91.8 (**C**), 63.7 (**C**H), 42.5 (**C**H), 22.7 (**C**H$_3$), 22.6 (**C**H$_3$), -0.2 (**C**H$_3$).

LRMS (HPLC-MS; ES$^+$): 371 ([M+Na+MeCN]$^+$, 100%), 330 ([M+Na]$^+$, 25%).

HRMS (ES$^+$) Calcd. for $C_{16}H_{22}FNNaO_2Si^+$ [M+Na]$^+$: 330.1296, found: 330.1298.

5-Fluoro-3-((trimethylsilyl)ethynyl)isobenzofuran-1(3*H*)-one (2.40)



$C_{16}H_{22}FNO_2Si$
MW: 307.44

$C_{13}H_{13}FO_2Si$
MW: 248.33

Adapted from the protocol of Saito *et al.*[44] A solution of benzyl alcohol **2.38** (170 mg, 0.55 mmol) and triethylsilane (0.13 mL, 0.83 mmol) in DCM (3 mL) was stirred for 3 d then sat. $NaHCO_3$ (2 mL) was added. The aqueous phase was

separated and extracted with DCM (2 × 2 mL), then the organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 0 to 15% Et_2O in petroleum ether) to give the title compound **2.40** (48.0 mg, 0.20 mmol, 36%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 2961 m, 1770 s, 1607 m, 1483 m, 1288 s, 1038 s, 837 s.

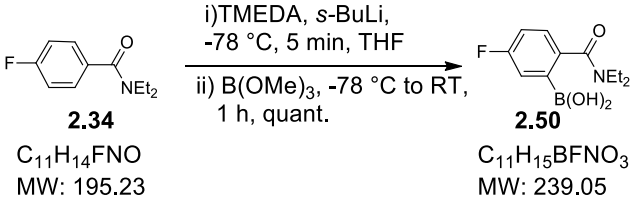
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.89 (1H, dd, J = 9.2, 4.8 Hz, Ar**H**), 7.31–7.23 (2H, m, 2 × Ar**H**), 6.03 (1H, s, C**H**), 0.19 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 168.5 (**C**O), 166.6 (d, J = 228 Hz, **C**F), 149.6 (d, J = 11 Hz, **C**), 128.1 (d, J = 10 Hz, **C**H), 121.2 (**C**), 118.2 (d, J = 24 Hz, **C**H), 110.1 (d, J = 24 Hz, **C**H), 96.8 (**C**), 95.02 (**C**), 69.6 (**C**H), –0.56 (**C**H$_3$).

LRMS (GC–MS; EI): 248 ($[M]^{+\cdot}$, 43%), 233 ($[M-CH_3]^+$, 100%).

HRMS (ES^+): Calcd. for $C_{13}H_{13}FNaO_2Si^+$ $[M+Na]^+$: 271.0561, found: 271.0557.

(2-(Diethylcarbamoyl)-5-fluorophenyl)boronic acid (2.50)



2.34
$C_{11}H_{14}FNO$
MW: 195.23

2.50
$C_{11}H_{15}BFNO_3$
MW: 239.05

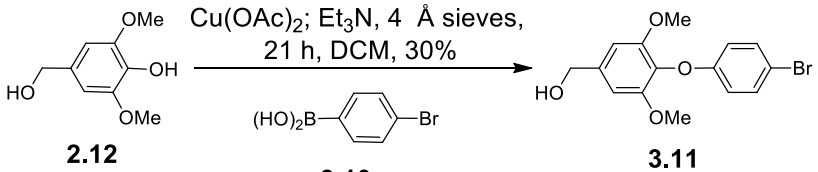
To a solution of TMEDA (0.45 mL, 3.00 mmol) in THF (10 mL) at −78 °C was added *s*-BuLi (1.30 M in cyclohexane, 2.3 mL, 3.00 mmol) over 5 min. After 5 min benzamide **2.34** (388 mg, 2.00 mmol) in THF (2 mL) was added over 5 min followed by trimethylborate (0.67 mL, 6.00 mmol). After 15 min then reaction mixture was allowed to warm to RT over 1 h then sat. NH_4Cl (10 mL), 2 M HCl (10 mL) and DCM (10 mL) were added. The aqueous phase was separated and extracted with DCM (3 × 15 mL) then the organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give boronic acid **2.50** (500 mg, 2.00 mmol, quant.) as a white solid which was used without further purification.

The physical and spectroscopic data were in agreement with reported values.[86]

^{1}H NMR (300 MHz; CD_3OD):δ ppm: 7.96 (1H, dd, *J* = 8.7, 4.1 Hz, Ar**H**), 7.27 (1H, dd, *J* = 7.9, 2.6 Hz, Ar**H**), 7.17 (1H, td, *J* = 8.7, 2.6 Hz, Ar**H**), 4.00 (2H, q, *J* = 7.2 Hz, **C**H_2), 3.77 (2H, q, *J* = 7.2 Hz, **C**H_2), 1.46 (3H, t, *J* = 7.2 Hz, **C**H_3), 1.40 – 1.31 (3H, m, **C**H_3).

7.3 Experimental Chapter 3

(4-(4-Bromophenoxy)-3,5-dimethoxyphenyl)methanol (3.11)



2.12 **3.10** **3.11**

$C_9H_{12}O_4$ MW: 184.19 | $C_6H_6BBrO_2$ MW: 200.83 | $C_{15}H_{15}BrO_4$ MW: 339.18

Adapted from a protocol by Evans *et al.*[50] Phenol **2.12** (184 mg, 1.00 mmol), $Cu(OAc)_2$ (182 mg, 1.00 mmol), boronic acid **3.10** (201 mg, 1.00 mmol) and 4 Å sieves were suspended in DCM (10 mL) and after 5 min Et_3N (0.7 mL, 5.00 mmol) was added. After 21 h the reaction mixture was filtered through a plug of silica, washed with EtOAc (3 × 10 mL), concentrated *in vacuo* and purified by column chromatography (silica, 20 to 50% EtOAc in petroleum ether) to afford the title compound **3.11** (100 mg, 0.29 mmol, 30%) as a pale yellow solid.

MP: 122 – 130 °C (EtOAc).

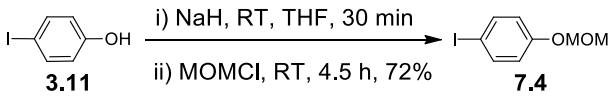
IR ν_{max} ($CDCl_3$, cm^{-1}) 3383 br, 2939 m, 2361m, 2029 m, 1599 m, 1482 s, 1462 m, 1234 s, 1068 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.33 (2H, d, J = 9.0 Hz, 2 × Ar**H**), 6.75 (2H, d, J = 9.0 Hz, 2 × **H**), 6.68(2H, s, 2 × Ar**H**), 4.71 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 157.6 (**C**), 153.3 (**C**), 138.8 (**C**), 132.1 (**C**H), 130.9 (**C**), 116.6 (**C**H), 113.7 (**C**), 103.7 (**C**H), 65.3 (**C**H_2) 56.2 (**C**H_3).

HRMS (ES^+) Calcd. for $C_{15}H_{15}BrNaO_4^+$ $[M(^{79}Br)+Na]^+$: 361.0046, found: 361.0056.

1-Iodo-4-(methoxymethoxy)benzene (7.4)



3.11 **7.4**

C_6H_5IO MW: 220.01 $C_8H_9IO_2$ MW: 264.06

Following a protocol from van Heerden *et al.*[51] To a solution of 4-iodophenol **3.11** (5.15 g, 23.4 mmol) in THF (38 mL) was added NaH (1.42 g, 35.5 mmol, 60% dispersion in oil). After 30 min MOMCl (2.57 mL, 33.8 mmol) was added over 30 min. After 4 h MeOH (20 mL) and water (30 mL) were added then the aqueous phase was separated and extracted with Et_2O (3 $\times$ 30 mL). The organic phases were combined, washed with 1 M NaOH (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* and purified by column chromatography (silica, 10% Et_2O in petroleum ether) to give the title compound **7.4** (6.18 g, 23.4 mmol, quant.) as a colourless liquid.

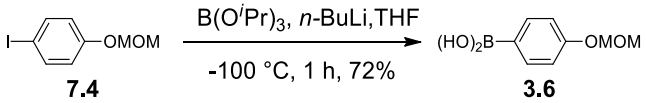
The physical and spectroscopic data were in agreement with reported values.[51,87]

IR ν_{max} ($CDCl_3$, cm^{-1}) 2953 m, 2901m, 2825 m, 1585 m, 1483 s, 1232 m, 1152 s, 993 s, 821s.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.57 (2H, d, J = 9.2 Hz, 2 × Ar**H**), 6.83 (2H, d, J = 9.2 Hz, 2 × Ar**H**), 5.15 (2H, s, C**H$_2$**), 3.47 (3H, s, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 157.1 (**C**), 138.3 (**C**H), 118.6 (**C**H), 94.3 (**C**), 84.3 (**C**H_2), 56.0 (**C**H_3).

4-(Methoxymethoxy)phenylboronic acid (3.6)



7.4 $C_8H_9IO_2$ MW: 264.06

3.6 $C_8H_{11}BO_4$ MW: 181.98

Following a protocol by van Heerden *et al.*[51] To a solution of iodoarene **7.4** (500 mg, 1.90 mmol) in THF (10 mL) and Et_2O (20 mL) was added triisopropyl borate (1.1 mL, 4.75 mmol). The reaction mixture was cooled to -100 °C and *n*-BuLi (1.8 M in hexane, 1.6 mL, 2.85 mmol) was added over 5 min. After 1 h at -90 °C sat. NH_4Cl (10 mL) was added and biphasic mixture was allowed to warm to RT over 1.5 h. The aqueous phase was separated and extracted with Et_2O (3 × 15 mL) then the organics phases were combined and extracted with 1 M NaOH (2 × 15 mL). Sat. NH_4Cl (20 mL) was then added to the combined aqueous phases, which were then extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **3.6** (250 mg, 1.37 mmol, 72%) as a white powder which was used without further purification.

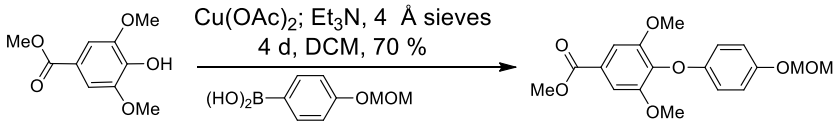
The physical and spectroscopic data were in agreement with reported values.[51]

MP 60 – 65 °C (DCM) [Lit. 65 °C].[86]

IR ν_{max} ($CDCl_3$, cm^{-1}) 3337 br, 2901 m, 2361 m, 1603 m, 1532 s, 1233 m, 1009 m, 746 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 8.17 (2H, d, J = 8.7 Hz, 2 × Ar**H**), 7.16 (2H, d, J = 8.7 Hz, 2 × Ar**H**), 5.28 (2H, s, C**H$_2$**), 3.53 (3H, s, C**H$_3$**).

Methyl 3,5-dimethoxy-4-(4-(methoxymethoxy)phenoxy)benzoate (3.12)



2.21 **3.6** **3.12**

$C_{10}H_{12}O_5$ MW: 212.20 | $C_8H_{11}BO_4$ MW: 181.98 | $C_{18}H_{20}O_7$ MW: 348.35

Adapted from a protocol of Evans *et al.*[50] To a suspension of phenol **2.21** (220 mg, 1.04 mmol), $Cu(OAc)_2$ (226 mg, 1.24 mmol), boronic acid **3.6** (300 mg, 1.64 mmol) and 4 Å molecular sieves in DCM (10 mL) were added after 5 min Et_3N (0.7 mL, 5.00 mmol) and pyridine (0.4 mL, 5.00 mmol). Daily, further $Cu(OAc)_2$ (100 mg, 0.55 mmol) and boronic acid **3.6** (100 mg, 0.55 mmol) were added over 4 days, then the reaction mixture was filtered through a pad of silica, washed with EtOAc (3 × 10 mL), concentrated *in vacuo* and purified by column chromatography (silica, 10 to 20% EtOAc in petroleum ether) to afford the title compound **3.12** (243 mg, 0.70 mmol, 70%) as a white solid.

MP 134 – 138°C (EtOAc).

IR ν_{max} ($CDCl_3$, cm^{-1}) 2950 m, 2843 m, 1719 m, 1595 m, 1498 s, 1462 m, 1220 s, 1129 s.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.37 (2H, s, 2 × Ar**H**), 6.93 (2H, d, *J* = 9.2 Hz, 2 × Ar**H**), 6.78 (2H, d, *J* = 9.2 Hz, 2 × Ar**H**), 5.10 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.83 (6H, s, 2 × C**H$_3$**), 3.47 (3H, s, C**H$_3$**).

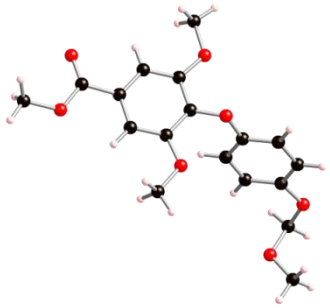
^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.5 (**C**O), 153.2 (**C**), 153.0 (**C**), 152.1 (**C**), 136.5 (**C**), 126.9 (**C**), 177.3 (**C**H), 115.6 (**C**H), 106.8 (**C**H), 95.1 ($\mathbf{C}H_2$), 56.3 ($\mathbf{C}H_3$), 55.8 ($\mathbf{C}H_3$), 52.3 ($\mathbf{C}H_3$).

LRMS (GC–MS; EI): 348 ($[M]^+$, 100%).

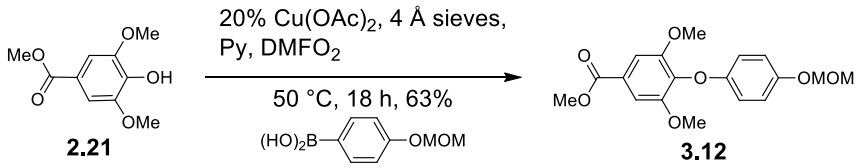
HRMS (ES^+) Calcd. for $C_{18}H_{20}NaO_7^+$ $[M+Na]^+$: 371.1101, found: 371.1103.

CHN calcd C: 62.06% H: 5.79% found C: 62.20% H: 5.71%.

Xray:



Methyl 3,5-dimethoxy-4-(4-(methoxymethoxy)phenoxy)benzoate (3.12)



$C_{10}H_{12}O_5$
MW: 212.20

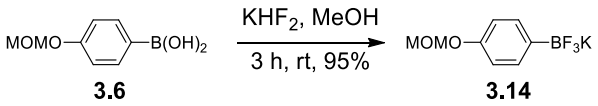
$C_8H_{11}BO_4$
MW: 181.98

$C_{18}H_{20}O_7$
MW: 348.35

Adapted from a protocol of Lam *et al.*[51] To a solution of phenol **2.21** (832 mg, 3.90 mmol), boronic acid **3.6** (1.35 g, 7.40 mmol) and $CuOAc_2$ (158 mg, 0.87 mmol) in DMF (50 mL) containing 4 Å molecular sieves and under a slight positive pressure of oxygen was added pyridine (2.5 mL, 30.9 mmol). After heating at 50 °C for 18 h the reaction mixture was cooled to RT, filtered through a pad of silica, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 40% EtOAc in petroleum ether with 0.1 % Et_3N) to afford the title compound **3.12** (861 mg, 2.47 mmol, 63%) as a white solid.

The physical and spectroscopic data were in agreement with that reported above.

Potassium (4-(methoxymethoxy)phenyl)trifluoroborate (3.14)



3.6

$C_8H_{11}BO_4$
MW: 181.98

3.14

$C_8H_9BF_3KO_2$
MW: 244.06

Adapted from a procedure of Genêt *et al.*[89] To a solution of boronic acid **3.6** (500 mg, 2.58 mmol) in methanol (30 mL) was added a solution of KHF_2 (805 mg, 10.3 mmol) in water (3 mL). After 3 h the reaction mixture was concentrated *in vacuo* then extracted with warm acetone (3 × 20 mL). The organic phases were combined, concentrated *in vacuo* to give a white solid then redissolved in

acetone (10 mL). Addition of diethyl ether (50 mL) induced precipitation of the title compound **3.14** (600 mg, 2.46 mmol, 95%) as a white solid which was collected by filtration and used without further purification.

MP >300°C (acetone).

IR ν_{max} (acetone, cm^{-1}) 3624 m, 2923 m, 2361 m, 1692 m, 1603 m, 1508 m, 920 s.

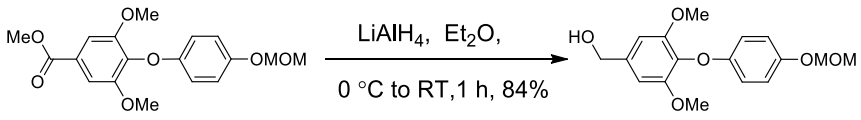
^{1}H NMR (300 MHz; acetone-d_6): δ ppm 7.39 (2H, d, J = 8.2 Hz, 2 × Ar**H**), 6.80 (2H, d, J = 8.2 Hz, 2 × Ar**H**), 5.10 (2H, s, C**H$_2$**), 3.39 (3H, s, C**H$_3$**).

^{13}C NMR (75 MHz; acetone-d_6): δ ppm 156.6 (**C**), 133.4 (**C**H), 115.4 (**C**H), 95.2 (**C**H_2), 55.7 (**C**H_3), with one **C** not observed (likely due to coupling with ^{10}B, ^{11}B and ^{19}F).

LRMS (HPLC-MS; ES^-): 205 ($[M-K]^-$, 100%).

HRMS (ES^-) Calcd. for $C_8H_9BF_3O_2^-$ $[M-K]^-$: 205.0655, found: 205.0660.

(3,5-Dimethoxy-4-(4-(methoxymethoxy)phenoxy)phenyl)methanol (3.15)



3.12

$C_{18}H_{20}O_7$
MW: 348.3472

3.15

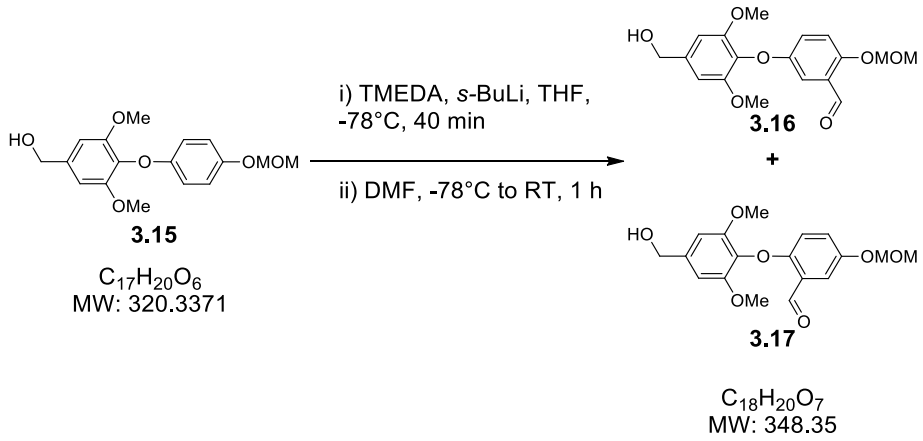
$C_{17}H_{20}O_6$
MW: 320.34

To a solution of benzyl ester **3.12** (451 mg, 1.29 mmol) in Et_2O (5 mL) at 0 °C was added a solution of $LiAlH_4$ (1.00 M in THF, 1.2 mL, 1.20 mmol) over 5 min.

After 1 h at RT, MeOH (3 mL) and sat. Rochelle's salts (10 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 30 to 60% EtOAc in petroleum ether with 0.1 % Et_3N) to afford the title compound **3.15** (359 mg, 1.10 mmol, 84%) as an off-white solid.

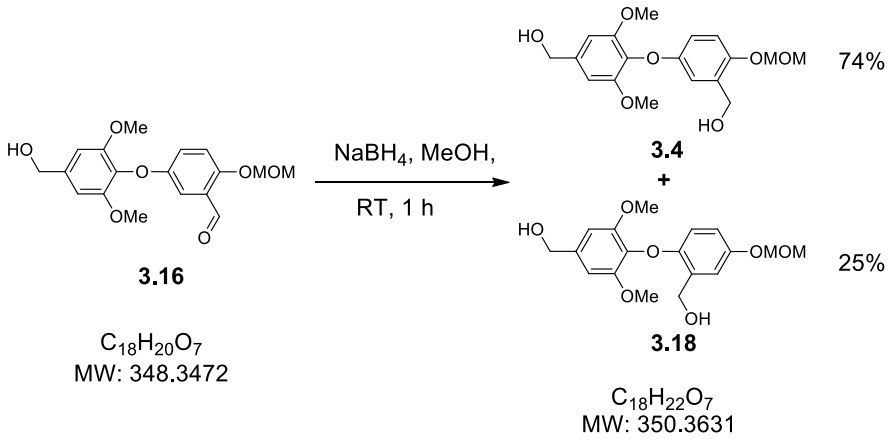
MP	85–87 °C (EtOAc).
IR ν_{max} (neat, cm^{-1})	3424 br., 2939 w, 1498 s, 1461 m, 1421 m, 1334 w, 1222 s, 1189 m, 1149 m, 1127 s, 1077 m, 1008 m, 830 m.
^{1}H NMR (300 MHz; $CDCl_3$):	δ ppm 6.92 (2H, d, J = 9.2 Hz, 2 × Ar**H**), 6.79 (2H, d, J = 9.2 Hz, 2 × Ar**H**), 6.66 (2H, s, 2 × Ar**H**), 5.10 (2H, s, C**H$_2$**), 4.68 (2H, s, C**H$_2$**), 3.78 (6H, s, 2 × C**H$_3$**), 3.47 (3H, s, C**H$_3$**).
^{13}C NMR (75 MHz; $CDCl_3$):	δ ppm 153.5 (**C**), 153.5 (**C**), 151.9 (**C**), 138.3 (**C**), 131.8 (**C**), 117.3 (**C**H), 115.5 (**C**H), 103.9 (**C**H), 95.2 (**C**H_2), 65.4 (**C**H_2), 56.2 (**C**H_3), 55.8 (**C**H_3).
LRMS (HPLC–MS; ES^+):	384 ($[M+Na+MeCN]^+$, 100%).
HRMS (ES^+)	Calcd. for $C_{17}H_{20}NaO_6^+$ $[M+Na]^+$: 343.1152, found: 343.1150.

5-(4-(Hydroxymethyl)-2,6-dimethoxyphenoxy)-2-(methoxymethoxy)benzaldehyde (3.16)



To a solution of TMEDA (0.18 ml, 1.22 mmol) and *s*-BuLi (1.10 M in cyclohexane, 1.2 mL, 1.30 mmol) in THF (4 mL) at −78 °C was added a solution of benzyl alcohol **3.15** (165 mg, 0.51 mmol) in THF (1 mL) over 5 min. After 40 min, DMF (0.18 mL, 2.26 mmol) was added and after a further 1 h the reaction was allowed to warm to RT then partitioned between sat. NH_4Cl (5 mL) and EtOAc (5 mL). The aqueous phase was separated and extracted with EtOAc (3 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a 3 : 1 mixture of aldehydes **3.16** and **3.17** (215 mg, 0.51 mmol, 100%) which was used without further purification.

(5-(4-(hydroxymethyl)-2,6-dimethoxyphenoxy)-2-(methoxymethoxy)phenyl)methanol (3.4)



To a solution of benzaldehydes **3.16** and **3.17** (215 mg, 0.51 mmol) in MeOH (3 mL) was added $NaBH_4$ (38.0 mg, 1.00 mmol). After 1 h water (3 mL) was added, the reaction mixture was concentrated *in vacuo* then EtOAc (5 mL) and water (5 mL) were added. The aqueous phase was separated and extracted with EtOAc (2 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 30 % EtOAc in petroleum ether with 0.1% of Et_3N) to afford first diol **3.18** as colourless oil (55 mg, 0.13 mmol, 25%) then the desired regioisomer **3.4** as a colourless oil (133 mg, 0.38 mmol, 74%).

Data for diol **3.4**

IR ν_{max} ($CDCl_3$, cm^{-1}) 3359 br, 2937 m, 1596 m, 1490 s, 1460 m, 1422 m, 1334 m, 1124 s, 1002 s.

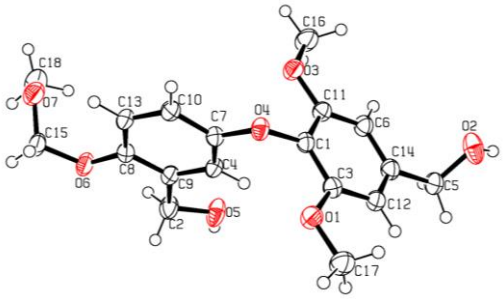
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.96 (1H, d, J = 8.6 Hz, Ar**H**), 6.84 (1H, d, J = 3.0 Hz, Ar**H**), 6.73 (1H, dd, J = 8.6, 3.0 Hz, Ar**H**), 6.67 (2H, s, 2 × Ar**H**), 5.14 (2H, s, C**H$_2$**), 4.68 (2H, s,

CH_2), 4.61 (2H, s, CH_2), 3.77 (6H, s, 2 × CH_3), 3.48 (3H, s, CH_3).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 153.4 (**C**), 149.8 (**C**), 138.5 (**C**), 131.5 (**C**), 131.2 (**C**), 115.7 (**C**H), 115.1 (**C**H), 114.4 (**C**H), 103.9 (**C**H), 95.5 (CH_2), 65.3 (CH_2), 61.6 (CH_2), 56.2 (CH_3), 56.2 (CH_3).

HRMS (ES^+) Calcd. for $C_{18}H_{22}NaO7^+$ $[M+Na]^+$: 373.1258, found: 373.1264.

Xray:



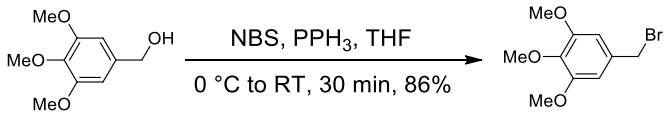
Data for diol **3.18**

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.03 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.79 (1H, dd, *J* = 9.0, 2.9 Hz, Ar**H**), 6.68 (2H, s, 2 × Ar**H**), 6.47 (1H, d, *J* = 9.0 Hz, Ar**H**), 5.10 (2H, s, CH_2), 4.80 (2H, s, CH_2), 4.70 (2H, s, CH_2), 3.81 (6H, s, 2 × CH_3), 3.46 (3 H, s, CH_3).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.4 (**C**), 152.0 (**C**), 151.6 (**C**), 138.8 (**C**), 132.0 (**C**), 130.4 (**C**), 117.8 (**C**H), 116.3 (**C**H), 114.5

(**C**H), 103.6 (**C**H), 95.1 (**C**H_2), 65.3 (**C**H_2), 62.3 (**C**H_2), 56.1 (**C**H_3), 55.9 (**C**H_3).

5-(Bromomethyl)-1,2,3-trimethoxybenzene (3.27)



3.26 $C_{10}H_{14}O_4$ MW: 198.22

3.27 $C_{10}H_{13}BrO_3$ MW: 261.11

To a solution of benzyl alcohol **3.26** (0.991, 5.00 mmol) in THF (20 mL) at 0 °C were added PPh_3 (1.57 g, 6.00 mmol) then NBS (1.07 g, 6.00 mmol). The reaction mixture was allowed to warm to RT over 25 min then sat. $NaHCO_3$ (10 mL) and sat. $Na_2S_2O_3$ (10 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 15 mL), then the organic phases were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether) to give the title compound **3.27** (1.12g, 4.29 mmol, 86%) as an off-white solid.

The physical and spectroscopic data were in agreement with reported values.[90]

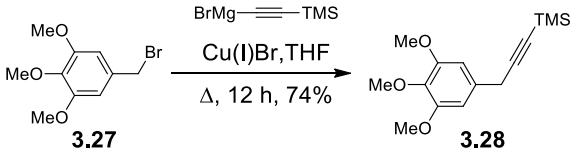
IR ν_{max} ($CDCl_3$, cm^{-1}) 2938 m, 2836 m, 1590 s, 1504 s, 1459 s, 1420 s, 1333 s, 1185 s, 1005 s.

^{1}H NMR (300 MHz; $CDCl_3$):δ ppm 6.62 (2H, s, Ar**H**), 4.47 (2H, s, C**H$_2$**), 3.88 (6H, s, 2 × C**H$_3$**), 3.85 (3H, s, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.3 (**C**), 138.2 (**C**), 133.1 (**C**), 106.1 (**C**H), 60.8 (**C**H_3), 56.1 (**C**H_3), 34.2 (**C**H_2).

LRMS (GC-MS; EI): 262 ([M(^{81}Br)]$^+$14%), 260 ([M(^{79}Br)]$^+$, 14%), 181 ([M-Br]$^+$, 100%).

Trimethyl(3-(3,4,5-trimethoxyphenyl)prop-1-yn-1-yl)silane (3.28)



3.27
$C_{10}H_{13}BrO_3$
MW 261.1124

3.28
$C_{15}H_{22}O_3Si$
MW: 278.4189

Adapted from a procedure of Tron *et al.*[90] To a solution of trimethylsilylacetylene (0.28 mL, 2.00 mmol) in THF (2 mL) at 0 °C was added a solution of MeMgBr (3.0 M in Et_2O, 0.66 mL, 2.00 mmol) over 5 min. The mixture was allowed to warm to RT over 30 min then CuBr (15.0 mg, 0.10 mmol) was added, followed after 30 min by benzyl bromide **3.27** (131 mg, 0.50 mmol). The reaction was heated at reflux for 16 h then cooled to RT and sat. NH_4Cl (5 mL) added. The aqueous phase was separated and extracted with Et_2O (3 $\times$ 5 mL), then the organic phases were combined, washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 25% Et_2O in petroleum ether) to give the title compound **3.28** as a pale yellow oil (104 mg, 0.37 mmol, 75%).

The physical and spectroscopic data were in agreement with reported values.[90]

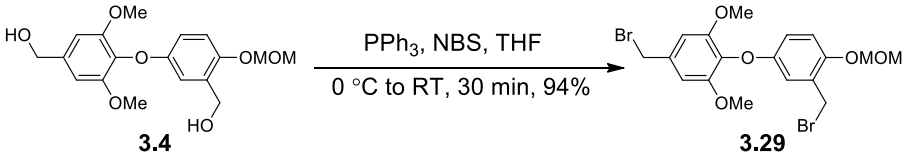
IR ν_{max} ($CDCl_3$, cm^{-1}) 2957 m, 2836 m, 2175 m, 1591 m, 1504 m, 1458 m, 1332 s, 1133 s, 840 s.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 6.60 (2H, s, Ar**H**), 3.87 (6H, s, 2 × C**H$_3$**), 3.84 (3H, s, C**H$_3$**), 3.61 (2H, s, C**H$_2$**), 0.20 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.2 (**C**), 136.6 (**C**), 131.9 (**C**), 104.8 (**C**H), 104.2 (**C**), 87.3 (**C**), 60.8 (**C**H$_3$), 56.0 (**C**H$_3$), 26.3 (**C**H$_2$), 0.0 (**C**H$_3$).

LRMS (HPLC–MS; ES$^+$): 342 ([M+Na+MeCN]$^+$, 100%).

5-(Bromomethyl)-2-(3-(bromomethyl)-4-(methoxymethoxy)phenoxy)-1,3-dimethoxybenzene (3.29)



3.4
$C_{18}H_{22}O_7$
MW: 350.3631

3.29
$C_{18}H_{20}Br_2O_5$
MW: 476.1564

To a solution of bisbenzyl alcohol **3.4** (451 mg, 1.30 mmol) in THF (10 mL) was added PPh_3 (846 g, 3.23 mmol). Recrystallized NBS (588 mg, 3.30 mmol) was then added at 0 °C. After 30 min a sat. $NaHCO_3$ (10 mL) and sat. $Na_2S_2O_3$ (10 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 25 mL), then the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo and then* purified by column chromatography (silica, 10 to 30% Et_2O in petroleum ether with 0.1% Et_3N) to afford the title compound **3.29** as an off-white solid (582 mg, 1.22 mmol, 94%).

MP 119 – 120 °C (Et_2O).

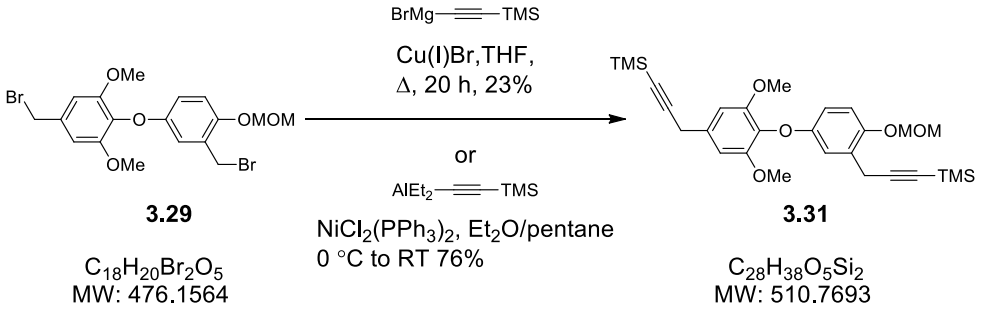
IR ν_{max} (neat, cm^{-1}) 2937 w, 2842 w, 1596 m, 1493 s, 1462 m, 1221 s, 1131 s, 999 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 6.98 (1H, d, J = 8.9 Hz, Ar**H**), 6.87 (1H, d, J = 3.0 Hz, Ar**H**), 6.75 (1H, dd, J = 8.9, 3.0 Hz, Ar**H**), 6.70 (2H, s, 2 × Ar**H**), 5.20 (2H, s, C**H$_2$**), 4.51 (2H, s, C**H$_2$**), 4.50 (2H, s, C**H$_2$**) 3.80 (6H, s, 2 × C**H$_3$**) 3.51 (3H, s, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.3 (**C**), 152.6 (**C**), 149.9 (**C**), 135.0 (**C**), 132.3 (**C**), 127.5 (**C**), 117.1 (**C**H), 116.0 (**C**H), 115.6 (**C**H), 106.2 (**C**H), 94.9 (**C**H$_2$), 56.3 (**C**H$_3$), 56.2 (**C**H$_3$), 33.9 (**C**H$_2$), 28.8 (**C**H$_2$).

HRMS (ES^+) Calcd. for $C_{18}H_{20}Br_2NaO_5^+$ [M(^{79}Br)+Na]$^+$: 496.9572, found: 496.9570.

(3-(5-(2,6-Dimethoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-2-(methoxymethoxy)phenyl)prop-1-yn-1-yl)trimethylsilane (3.31)



Adapted from a procedure of Tron *et al.*[90] To a solution of **trimethylsilylacetylene** (0.35 mL, 2.50 mmol) in THF (3 mL) at 0 °C was added a

solution of MeMgBr (3.0 M in Et_2O, 0.67 mL, 2.00 mmol) over 5 min. The reaction was warmed to RT and after 1 h CuBr (15.0 mg, 0.10 mmol) was added followed after 30 min by bisbenzyl bromide **3.29** (118 mg, 0.25 mmol). The reaction was then heated at reflux for 20 h, cooled to RT and partitioned between Et_2O (5 mL) and sat. NH_4Cl (5mL). The aqueous phase was separated and extracted with Et_2O (3 × 5 mL) then the organic phases were combined, washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 15 to 30% Et_2O in petroleum ether with 1% Et_3N) to afford the title compound **3.31** (27.0 mg, 0.06 mmol, 23%) as a yellow oil.

Alternatively

Adapted from a procedure of Gau *et al.*[58] To a solution of trimethylsilylacetylene (0.14 mL, 1.00 mmol) in pentane (2 mL) at 0 °C was added a solution of *n*-BuLi (2.25 M in hexane, 0.44 mL, 1.0 mmol) over 2 min. After 20 min a solution of Et_2AlCl (1.0 M in hexane, 1.0 mL, 1.0 mmol) was added over 5 min. After a further 20 min the reaction was allowed to warm to RT and after 2 h Et_2O (2 mL) was added followed by $NiCl_2(PPh_3)_2$ (23.0 mg, 0.035 mmol). After 10 min benzyl bromide **3.29** (119 mg, 0.25 mmol) was added. After 90 min the reaction was partitioned between sat. NH_4Cl (5 mL) and Et_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (2 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo and* purified by chromatography column (silica, 10% Et_2O in petroleum

ether) to afford the title compound **3.31** (96.0 mg, 0.19 mmol, 76%) as a yellow oil.

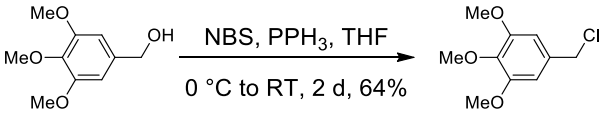
IR ν_{max} (neat, cm^{-1}) 2957 m, 2176 m, 1596 m, 1492 m, 1461 m, 1423 m, 1246 m, 1220 m, 1128 s, 839 s.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.04 (1H, d, J = 3.1 Hz, Ar**H**), 6.94 (1H, d, J = 9.0 Hz, Ar**H**), 6.73 (1H, dd, J = 9.0, 3.1 Hz, Ar**H**), 6.69 (2H, s, 2 × Ar**H**), 5.12 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.67 (2H, s, C**H$_2$**), 3.59 (2H, s, C**H$_2$**), 3.47 (3H, s, C**H$_3$**), 0.22 (9H, s, 3 × C**H$_3$**), 0.12 (9 H, s, 3 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.3 (**C**), 149.1(**C**), 133.5 (**C**), 130.9 (**C**), 126.5 (**C**), 115.1 (**C**H), 114.9 (**C**H), 113.5 (**C**H), 105.0 (**C**H), 104.0 (**C**), 103.9 (**C**), 95.2 (**C**H$_2$), 87.7 (**C**), 86.8 (**C**), 56.2 (**C**H$_3$), 56.0 (**C**H$_3$), 26.4 (**C**H$_2$), 21.0 (**C**H$_2$), 0.05 (**C**H$_3$) with one **C** not observed (likely due to the slow relaxation time proper to alkynes).

HRMS (ES^+) Calcd. for $C_{28}H_{38}NaO_5Si_2^+$ $[M+Na]^+$: 533.2150, found: 533.2154.

5-(Chloromethyl)-1,2,3-trimethoxybenzene (3.42)



3.26
$C_{10}H_{14}O_4$
MW: 198.22

3.42
$C_{10}H_{13}ClO_3$
MW: 216.66

To a solution of benzyl alcohol **3.26** (1.98, 10.0 mmol) in THF (40 mL) at 0 °C was added PPh_3 (3.14 g, 12.0 mmol) and NCS (1.60 g, 12.0 mmol). The reaction was warmed to RT and after 2 d sat. $NaHCO_3$ (20 mL) and sat. $Na_2S_2O_3$ (20 mL) were added. The aqueous phase was then separated and extracted with Et_2O (3 × 20 mL). The organic phases were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10% Et_2O in petroleum ether) to give the title compound **3.42** (1.38 g, 6.37 mmol, 64%) as an off-white solid.

MP 57 – 59 °C (Et_2O) [Lit : 58 – 60 °C].[91]

IR ν_{max} (neat, cm^{-1}) 2943 w, 2840 w, 1589 s, 1508 m, 1466 m, 1423 s, 1326 s, 1242 s, 1118 s, 992 m, 836 m.

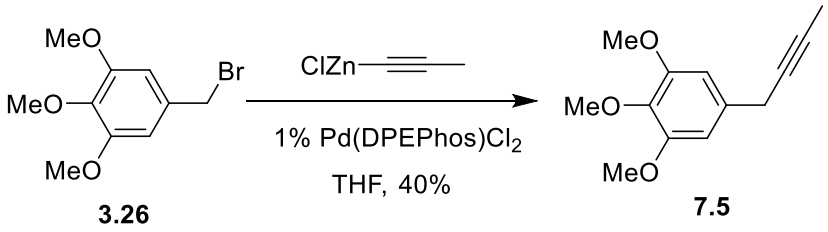
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 6.62 (2H, s, Ar**H**), 4.55 (2H, s, C**H$_2$**), 3.88 (6H, s, C**H$_3$**), 3.85 (3H, s, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.3 (**C**), 138.0 (**C**), 132.9 (**C**), 105.6 (**C**H), 60.8 (**C**H$_3$), 56.1 (**C**H$_3$), 46.8 (**C**H$_2$).

LRMS (GC-MS; EI): 216 ($[M]^+$, 41%), 201 ($[M-CH_3]^+$, 17%), 181 ($[M-Cl]^+$, 100%).

HRMS (ES^+) Calcd. for $C_{10}H_{13}ClNaO_3^+$ [M(^{35}Cl)+Na]$^+$: 239.0445, found: 239.0448.

5-(But-2-yn-1-yl)-1,2,3-trimethoxybenzene (7.5)



3.26 **7.5**

$C_{23}H_{29}BrO_6$
MW: 481.38

$C_{13}H_{16}O_3$
MW: 220.26

Adapted from a protocol of Negishi *et al.*[56] To a solution of *n*-BuLi (2.3 M in hexane, 1.10 mL, 2.50 mmol) in THF (4 mL) at −78 °C was added propyne by condensation. After 30 min, a solution of $ZnCl_2$ (1.0 M in Et_2O, 2.4 mL, 2.4 mmol) was added and after 5 min reaction was allowed to warm to RT over 30 min. Benzyl bromide **3.26** (262 mg, 1 mmol) and $PdCl_2$(DPEPhos) (20 mg, 0.03 mmol) were then added and after 22 h the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (silica, 10 to 15% Et_2O in petroleum ether, 0.5% Et_3N) gave the title compound **7.5** (86 mg, 40% of yield) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 2939 w, 1507 m, 1459 m, 1422 m, 1334 m, 1238 s, 1127 s, 1010 m, 779 w.

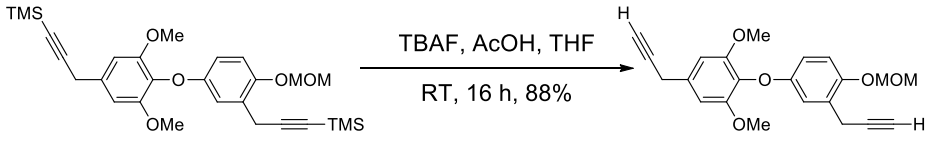
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 6.56 (2H, s, C**H**), 3.86 (6H, s, 2 × C**H$_3$**), 3.82 (3H, s, C**H$_3$**), 3.49 (2H, d, J = 2.5 Hz, C**H$_2$**), 1.85 (3H, t, J = 2.8 Hz, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.2 (**C**), 136.5 (**C**), 133.2 (**C**), 104.9 (**C**H), 77.9 (**C**), 77.2 (**C**), 60.8 (**C**H_3), 56.0 (**C**H_3), 25.4 (**C**H_2), 3.6 (**C**H_3).

LRMS (GC-MS; EI): 220 ([M]$^+$, 100%), 205 ([M-CH_3]$^+$, 93%).

HRMS (ES$^+$) Calcd. for $C_{13}H_{16}NaO_3^+$ [M+Na]$^+$: 243.0992, found: 243.0995.

1,3-Dimethoxy-2-(4-(methoxymethoxy)-3-(prop-2-yn-1-yl)phenoxy)-5-(prop-2-yn-1-yl)benzene (3.45)



3.31
$C_{28}H_{38}O_5Si_2$
MW: 510.7693

3.45
$C_{22}H_{22}O_5$
MW: 366.4071

To a solution of alkyne **3.31** (142 mg, 0.28 mmol) in THF (1.5 mL) was added AcOH (0.07mL, mmol) and TBAF (1.0 M, 1.1 mL, 1.1 mmol). After 16 h TBAF (1.0 M in THF, 1 mL, 1 mmol) was added. After 10 h the reaction mixture was partitioned between Et_2O (5 mL) and brine (5 mL). The organic phase was separated, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by chromatography column (silica, 20% in Et_2O in petroleum ether with 0.2% Et_3N) to afford alkyne **3.45** (90.0 mg, 0.25 mmol, 88%) as a yellow oil.

Experimental

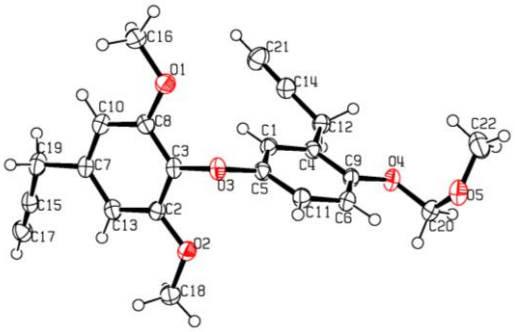
IR ν_{max} (neat, cm^{-1}) 3285 m, 2932 w, 1595 m, 1490 m, 1460 m, 1422 m, 1210 m, 1124 s, 999 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.15 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.91 (1H, d, *J* = 9.0 Hz, Ar**H**), 6.66 (2H, s, 2 × Ar**H**), 6.60 (1H, dd, *J* = 9.0, 2.9 Hz, Ar**H**), 5.12 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.63 (2H, d, *J* = 2.9 Hz, C**H$_2$**), 3.55 (2H, d, *J* = 2.8 Hz, C**H$_2$**), 3.47 (3H, s, C**H$_3$**), 2.25 (1H, t, *J* = 2.8 Hz, C**H**), 2.11 (1H, t, *J* = 2.6 Hz, C**H**).

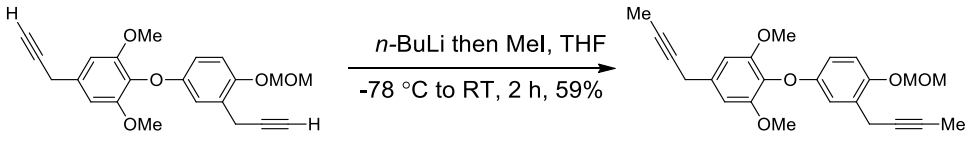
^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.4 (**C**), 153.2 (**C**), 149.2 (**C**), 133.4 (**C**), 131.0 (**C**), 126.4 (**C**), 116.1 (**C**H), 114.8 (**C**H), 112.9 (**C**H), 105.0 (**C**H), 95.1 (**C**H_2), 81.6 (**C**), 70.8 (**C**H), 70.2 (**C**H), 56.2 (**C**H_3), 55.9 (**C**H_3), 25.1 (**C**H_2), 19.6 (**C**H_2).

HRMS (ES^+) Calcd. for $C_{22}H_{22}NaO_5^+$ $[M+Na]^+$: 389.1359, found: 389.1366

Xray:



5-(But-2-yn-1-yl)-2-(3-(but-2-yn-1-yl)-4-(methoxymethoxy)phenoxy)-1,3-dimethoxybenzene (3.3)



3.45

$C_{22}H_{22}O_5$
MW: 366.4071

3.3

$C_{24}H_{26}O_5$
MW: 394.4602

To a solution of alkyne **3.45** (35 mg, 0.095mmol) in THF (1 mL) at 0 °C was added *n*–BuLi (2.3 M in hexanes, 0.16 mL, 0.36 mmol). After 1 h MeI (0.03 mL, 0.48 mmol) was added and the solution was warmed to RT. After 2 h a solution of sat. NH_4Cl (1 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 3 mL) then the organic phases were combined, washed with brine (3 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by chromatography column (silica, 20 to 30% Et_2O in petroleum ether) to afford the title compound **3.3** (22 mg, 0.056, 59%) as a colourless oil.

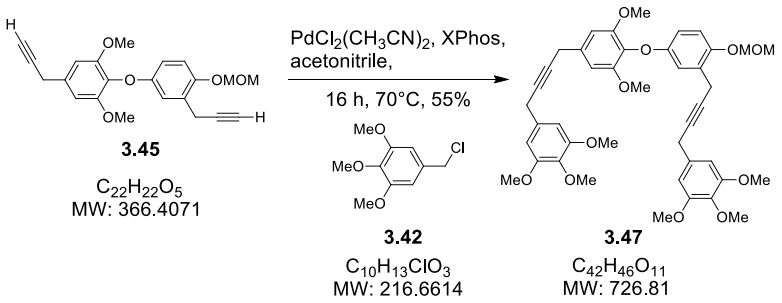
IR ν_{max} (neat, cm^{-1}) 2918 w, 2848 w, 1492 s, 1462 m, 1423 m, 1338 m, 1221 s, 1186m, 1127 s, 1005 m, 910 s, 731 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.16 (1H, d, *J* = 3.1 Hz, C**H**), 6.88 (1H, d, *J* = 8.9 Hz, C**H**), 6.64 (2H, s, C**H**), 6.56 (1H, dd, *J* = 8.9, 3.2 Hz, C**H**), 5.11 (2H, s, OC**H$_2$**), 3.79 (6 H, s, 2 × OC**H$_3$**), 3.55 (2H, q, *J* = 2.6 Hz, C**H$_2$**), 3.47 (2H, q, *J* = 2.7 Hz, C**H$_2$**), 3.46 (3H, s, C**H$_3$**), 1.88 (3H, t, *J* = 2.6 Hz, C**H$_3$**), 1.80 (3H, t, *J* = 2.6 Hz, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 153.4 (**C**), 149.3 (**C**), 135.04 (**C**), 131.04 (**C**), 128.0 (**C**), 116.3 (**C**H), 114.9 (**C**H), 112.6 (**C**H), 105.2 (**C**H), 95.3 ($\mathbf{C}H_2$), 78.3(**C**), 78.10 (**C**), 76.7 (**C**), 76.4 (**C**), 56.4 ($\mathbf{C}H_3$), 56.1 ($\mathbf{C}H_3$), 25.7 ($\mathbf{C}H_2$), 20.0 ($\mathbf{C}H_2$), 3.8 ($\mathbf{C}H_3$), 3.7 ($\mathbf{C}H_3$).

HRMS (ES^+) Calcd. for $C_{24}H_{27}O_5^+$ $[M+H]^+$: 395.1866, found: 395.1853.

5-(4-(5-(2,6-Dimethoxy-4-(4-(3,4,5-trimethoxyphenyl)but-2-yn-1-yl)phenoxy)-2-(methoxymethoxy)phenyl)but-2-yn-1-yl)-1,2,3-trimethoxybenzene (3.47)



Adapted from a procedure of Buchwald *et al.*[57] To an oven dried flask under argon was added alkyne **3.45** (26.0 mg, 0.07 mmol), benzyl chloride **3.42** (37.0 mg, 0.14 mmol), $PdCl_2(CH_3CN)_2$ (1.5 mg, 0.006 mmol), XPhos (71 mg, 0.016 mmol) and Cs_2CO_3 (48 mg, 0.14 mmol). The flask was then evacuated and back-filled with argon three times and MeCN (2.5 mL) was added. The reaction was heated at 70 °C for 16 h then filtered through a pad of silica, concentrated *in vacuo* and purified by column chromatography (silica, 30 to 50% EtOAc in

petroleum ether) to afford the title compound **3.47** as a pale yellow oil (28.0 mg, 0.039 mmol, 55%).

IR ν_{max} (neat, cm^{-1}) 2928 w, 2850 w, 1505 m, 1494 m, 1462, 1422 m, 1333 m, 1238 m, 1127 s, 1005 m.

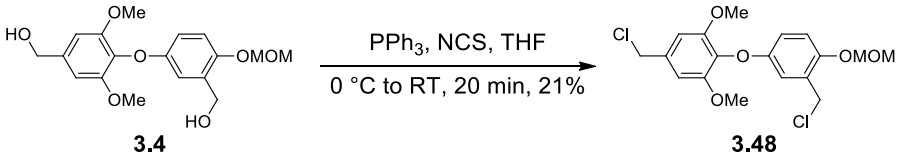
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.27 (1H, d, J = 3.1 Hz, Ar**H**), 6.88 (1H, d, J = 8.9 Hz, Ar**H**), 6.64 (2H, s, 2 × Ar**H**), 6.60 (2H, s, 2 × Ar**H**), 6.59 (2H, s, 2 × Ar**H**), 6.48 (1H, dd, J = 8.9, 3.2 Hz, Ar**H**), 5.11 (2H, s, C**H$_2$**), 3.83 (6H, s, C**H$_3$**), 3.83 (6H, s, 2 × C**H$_3$**), 3.82 (6H, s, 2 × C**H$_3$**), 3.72 (6H, s, 2 × C**H$_3$**), 3.64 (2H, t, J = 2.2 Hz, C**H$_2$**), 3.60 (4H, t, J = 2.2 Hz, 2 × C**H$_2$**), 3.57 (2H, t, J = 2.2 Hz, C**H$_2$**), 3.45 (3H, s, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.6 (**C**), 153.5 (**C**), 153.5 (**C**), 153.4 (**C**), 149.4 (**C**), 136.9 (**C**), 136.7 (**C**), 134.8 (**C**), 133.1 (**C**), 133.0 (**C**), 131.2 (**C**), 128.0 (**C**), 116.7 (**C**H), 115.0 (**C**H), 112.3 (**C**H), 105.3 (**C**H), 105.3 (**C**H), 105.0 (**C**H), 104.1 (**C**), 95.4 (**C**H$_2$), 80.66 (**C**), 80.14 (**C**), 80.08 (**C**), 61.00 (**C**H$_3$), 60.98 (**C**H$_3$), 56.36 (**C**H$_3$), 56.30 (**C**H$_3$), 56.26 (**C**H$_3$), 56.14 (**C**H$_3$), 29.84 (**C**H$_2$), 25.77 (**C**H$_2$), 25.68 (**C**H$_2$), 25.58 (**C**H$_2$).

LRMS (MS; ESI$^+$): 749 ([M+Na]$^{+\cdot}$, 100%), 695 ([M−OCH_3]$^{+\cdot}$, 15%)

HRMS (ES^+) Calcd. for $C_{42}H_{46}NaO_{11}^+$ $[M+Na]^+$: 749.2932, found: 749.2948.

5-(Chloromethyl)-2-(3-(chloromethyl)-4-(methoxymethoxy)phenoxy)-1,3-dimethoxybenzene (3.48)



3.4
$C_{18}H_{22}O_7$
MW: 350.36

3.48
$C_{18}H_{20}Cl_2O_5$
MW: 387.25

To a solution of bisbenzyl alcohol **3.4** (299 mg, 0.86 mmol) in THF (6 mL) was added PPh_3 (538 g, 2.06 mmol) and NCS (286 mg, 2.06 mmol). After 20 min sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL), then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo and* purified by column chromatography (silica, 10 to 20% Et_2O in petroleum ether with 0.1% Et_3N) to afford the title compound **3.48** as an off-white solid (69.0 mg, 0.18 mmol, 21%).

MP 102.0 – 103.4 °C ($CHCl_3$).

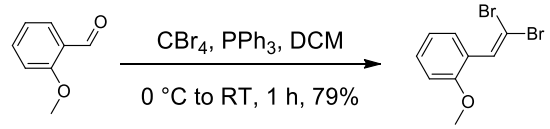
IR ν_{max} (neat, cm^{-1}) 2927 w, 2360 w, 1494 s, 1461 m, 1421 m, 1339 m, 1242 m, 1221 s, 1124 s, 1075 s, 997 s, 921 m, 808 s, 753 s, 707 m, 636 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.99 (1H, d, J = 9.0 Hz, C**H**), 6.90 (1H d, J = 3.1 Hz, C**H**), 6.75 (1H dd, J = 9.0, 3.1 Hz, C**H**), 6.69 (2H s, C**H**), 5.17 (2H s, C**H$_2$**), 4.59 (2H s, C**H$_2$**), 4.59 (2H s, C**H$_2$**), 3.80 (6H s, C**H$_3$**), 3.50 (3H s, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.64 (**C**), 153.07 (**C**), 150.03 (**C**), 134.97 (**C**), 132.52 (**C**), 127.64 (**C**), 117.09 (**C**H), 115.97 (**C**H), 115.85 (**C**H), 106.03 (**C**H), 95.35 (**C**H$_2$), 56.47 (**C**H$_3$), 56.28 (**C**H$_3$), 46.73 (**C**H$_2$).

HRMS (EI): Calcd. for $C_{18}H_{20}Cl_2O_5$ [M(^{35}Cl)]$^{+\bullet}$: 386.0688, found: 386.0681.

1-(2,2-Dibromovinyl)-2-methoxybenzene (3.71)



3.70

$C_8H_8O_2$
MW: 136.1479

3.71

$C_9H_8Br_2O$
MW: 291.9672

Following a protocol from Barton *et al.*[63] To a solution of CBr_4 (1.71 g, 5.16 mmol) in DCM (10 mL) at 0 °C was added PPh_3 (2.70 g, 10.3 mmol). After 15 min a solution of 2-methoxybenzaldehyde **3.70** (714 mg, 5.24 mmol) in DCM (5 mL) was added. After 15 min the reaction was warmed to RT and after 1 h was poured into petroleum ether (200 mL). The precipitated solid was removed by filtration then the filtrate was concentrated *in vacuo* and purified by column

chromatography (silica, petroleum ether) to afford the title compound **3.71** (1.21 g, 4.20 mmol, 79%) as a white solid.

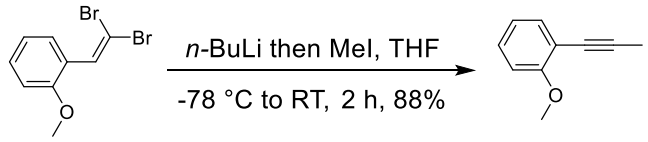
The physical and spectroscopic data were in agreement with reported values.[93]

IR ν_{max} (neat, cm^{-1}) 3027 w, 2836 w, 1486 s, 1463 s, 1435 m, 1290 m, 1248 s, 1111 s, 1027 m, 843 m, 809 s, 752 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.72 – 7.65 (1H, m, C**H**), 7.60 (1H, s, C**H**), 7.36 – 7.29 (1H, m, C**H**), 7.00 – 6.94 (1H, m, C**H**), 6.87 (1H, dd, J = 8.3, 0.9 Hz, C**H**), 3.84 (3H, s, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 156.7 (**C**), 133.1 (**C**H), 130.1 (**C**H), 129.3 (**C**H), 124.6 (**C**), 120.3 (**C**H), 110.7 (**C**H), 89.8 (**C**), 55.7 (**C**H$_3$).

1-Methoxy-2-(prop-1-yn-1-yl)benzene (3.72)



3.71

$C_9H_8Br_2O$
MWt: 291.97

3.72

$C_{10}H_{10}O$
MW: 146.19

Adapted from a protocol described by Barton *et al.*[63] To a solution of dibromide **3.71** (314 mg, 1.08 mmol) in THF at –78 °C was added *n*–BuLi (2.3 M in hexane, 1.19 mL, 2.69 mmol), dropwise over 5 min. After 1 h the reaction mixture was warmed to RT and after a further 1 h MeI (0.17 mL, 2.69 mmol) was added. After 16 h sat. NH_4Cl (5 mL) was added, the phases were separated and the aqueous

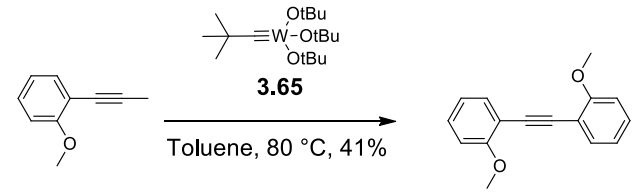
phase was extracted with Et_2O (3 × 5 mL). The organic phases were then combined, washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 5 to 15% Et_2O in petroleum ether) to afford the title compound **3.72** (139 mg, 0.95 mmol, 88%).as a pale yellow oil

The physical and spectroscopic data were in agreement with reported values.[63]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (1H, dd, *J* = 7.5, 1.7 Hz, C**H**), 7.27 – 7.22 (1H, m, C**H**), 6.93 – 6.83 (1H, m, C**H**), 3.88 (1H, s, C**H$_3$**), 2.12 (1H, s, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 160.0 (**C**), 133.8 (**C**H), 129.0 (**C**), 120.6 (**C**H), 113.0 (**C**), 110.7 (**C**H), 90.2 (**C**), 56.0 (**C**H$_3$), 4.9 (**C**H$_3$).

1,2-Bis(2-methoxyphenyl)ethyne (3.73)



3.72
$C_{10}H_{10}O$
MW: 146.1858

3.73
$C_{16}H_{14}O_2$
MW: 238.2812

To a solution of alkyne **3.72** (49.0 mg, 0.34 mmol) in toluene (5 mL) in a glove box was added the Schrock catalyst **3.65** (16.0 mg, 0.03 mmol). The reaction was heated at 80 °C for 16 h then filtered through a plug of silica and

concentrated *in vacuo*. Purification by column chromatography (silica, 5% Et_2O in petroleum ether) afforded the title compound **24** (16.0 mg, 0.07 mmol, 41%) as a yellow oil.

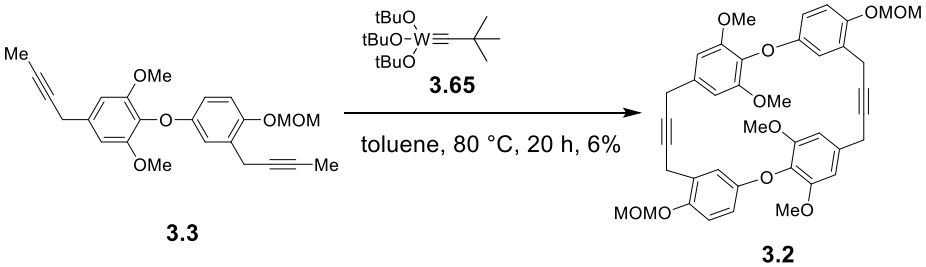
The physical and spectroscopic data were in agreement with reported values.[94]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.53 (2H, dd, J = 7.6, 1.8 Hz, 2 × Ar**H**), 7.29 (2H, ddd, J = 8.3, 7.5, 1.8 Hz, 2 × Ar**H**), 6.93 (2H, td, J = 7.6, 1.0 Hz, 2 × Ar**H**), 6.90 (2H, d, J = 8.4 Hz, 2 × Ar**H**), 3.93 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 160.1 (**C**), 133.7 (**C**H), 129.7 (**C**H), 120.6 (**C**H), 113.1 (**C**), 110.9 (**C**H), 90 0 (**C**), 56.1 (**C**H$_3$).

LRMS (GC–MS; EI): 238 ([M–CH_3]$^+$, 100%).

Macrocycle 3.2



3.3

$C_{24}H_{26}O_5$
MW : 394.46

3.2

$C_{40}H_{40}O_{10}$
MW : 680.74

To a solution of alkyne **3.3** (37.0 mg, 0.09 mmol) in toluene (12 mL) in a glove box was added the Schrock catalyst **3.65** (7.0 mg, 0.03 mmol). The reaction was heated at 80 °C for 20 h then filtered through a plug of silica and concentrated *in vacuo*. Purification by HPLC (C-18, Luna, 60 to 90% MeCN in water + 0.01%

TFA, 9 min) afforded the title compound **3.2** (2.0 mg, 0.003 mmol, 6%) as a white solid.

IR ν_{max} (neat, cm^{-1}) 2935 w, 2853 w, 1579 w, 1495 m, 1401m, 1341 m, 1263 s, 1190 m, 1110 s, 1019 s, 914 m, 812 m, 738 m.

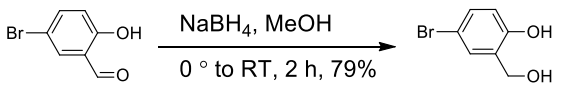
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.08 – 7.05 (6H, m, 6 × Ar**H**), 6.93 (2H, d, J = 0.9 Hz, 2 × Ar**H**), 6.91 – 6.88 (2H, m, 2 × Ar**H**), 5.16 (4H, s, 2 × C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.61 (2H, s, C**H$_2$**), 3.59 (6H, s, 2 × C**H$_3$**), 3.54 (2H, d, J = 0.8 Hz, C**H$_2$**), 3.49 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 152.9 (**C**), 152.0 (**C**), 150.1 (**C**), 149.7 (**C**), 136.3 (**C**), 132.0 (**C**), 127.1 (**C**), 118.9 (**C**), 115.3 (**C**H), 115.2 (**C**H), 113.5 (**C**H), 108.0 (**C**H), 95.3 (**C**H$_2$), 81.8 (**C**), 79.8 (**C**), 61.1 (**C**H$_3$), 56.6 (**C**H$_3$), 56.2 (**C**H$_3$), 29.9 (**C**H$_2$), 23.5(**C**H$_2$), 20.2(**C**H$_2$).

HRMS (ES^+) Calcd. for $C_{40}H_{40}NaO_{10}^+$ $[M+Na]^+$: 703.2514, found: 703.2547.

7.4 Experimental Chapter 4

4-Bromo-2-(hydroxymethyl)phenol (7.6)



4.1
$C_7H_5BrO_2$
MW: 201.02

7.6
$C_7H_7BrO_2$
MW: 203.03

Following a procedure by Gisch *et al.*[95] To a solution of 5-bromosalicylaldehyde **4.1** (2.02 g, 10.0 mmol) in MeOH (60 mL) at 0 °C was added protionwise $NaBH_4$ (770 mg, 20.1 mmol) over 5 min. After 2 h water (10 mL) was added then the reaction mixture was filtered through a pad of silica, concentrated *in vacuo and purified by* column chromatography (silica, 50–65% EtOAc in petroleum ether) to give the title compound **7.6** (1.61 g, 7.93 mmol, 79%) as a white solid.

Physical and spectroscopic characteristic consistent with reported values.[95,96]

MP: 107–109 °C (EtOAc) [Lit. 109 °C].[96]

IR ν_{max} (neat, cm^{-1}) 3401 br., 3130 br., 2908 w, 1604 m, 1479 m, 1403 s, 1353 m, 1260 s, 1175 s, 1121 s, 998 s, 817 s.

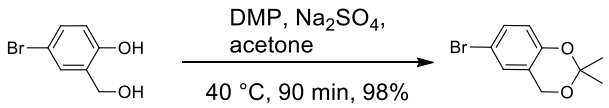
^{1}H NMR (300 MHz; DMSO-d_6): δ ppm 9.67 (1H, s, O**H**), 7.39 (1H, d, J = 2.6 Hz, Ar**H**), 7.19 (1H, dd, J = 8.4, 2.6 Hz, Ar**H**), 6.72 (1 H, d, J = 8.8 Hz, Ar**H**), 4.45 (2 H, s, C**H$_2$**), with one O**H** not observed.

^{13}C NMR (75 MHz; DMSO-d_6): δ ppm 153.3 (**C**), 131.6 (**C**), 129.6 (**C**H), 129.4 (**C**H), 116.6 (**C**H), 110.0 (**C**), 57.6 (**C**H$_2$).

LRMS (HPLC-MS; ES$^-$): 203 ([M(^{81}Br)-H]$^-$, 84%), 201 ([M(^{79}Br)-H]$^-$, 100%).

HRMS (ES$^-$) Calcd. for $C_7H_6BrO_2^+$ [M(^{79}Br)-H]$^-$: 200.9557, found: 200.9557.

6-Bromo-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxine (4.2)



7.6 $C_7H_7BrO_2$ MW: 203.03

4.2 $C_{10}H_{11}BrO_2$ MW: 243.10

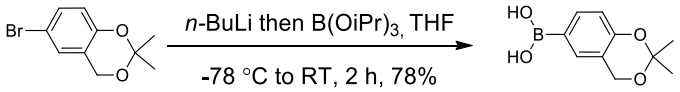
Following a procedure by Gisch *et al.*[95] To a solution of benzyl alcohol **7.6** (1.55 g, 7.63 mmol) in acetone (25 mL) was added 2,2-dimethoxypropane (4.8 mL, 39.0 mmol), Na_2SO_4 (4.00 g, 28.2 mmol) and *p*-TSA (177 mg, 0.93 mmol). The reaction mixture was heated at 40 °C for 90 min then concentrated *in vacuo* and partitioned between EtOAc (20 mL) and water (20 mL). The aqueous phase was separated and extracted with EtOAc (3 $\times$ 15 mL) then the organic phases were combined, washed with brine (15 mL), dried over $MgSO_4$, concentrated *in vacuo and purified* by column chromatography (silica, 100% petroleum ether) to give the title compound **4.2** (1.81 g, 7.45 mmol, 98%) as a colourless oil.

Physical and spectroscopic characteristic consistent with reported values.[97]

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.29–7.22 (1H, m, Ar**H**), 7.11 (1H, d, J = 2.0 Hz, Ar**H**), 6.71 (1H, d, J = 8.8 Hz, Ar**H**), 4.81 (2H, s, C**H$_2$**), 1.54 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 150.3 (**C**), 131.0 (**C**H), 127.4 (**C**H), 121.4 (**C**), 118.9 (**C**H), 112.4 (**C**), 99.8 (**C**), 60.4 (**C**H_2), 24.6 (**C**H_3).

(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)boronic acid (4.3)



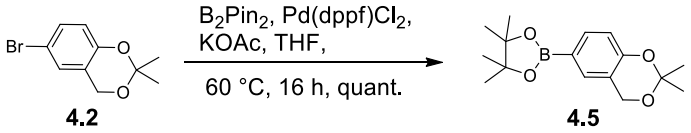
4.2
$C_{10}H_{11}BrO_2$
MW: 243.10

4.3
$C_{10}H_{13}BO_4$
MW: 208.02

To a solution of *n*–BuLi (2.25 M in hexane, 4.3 mL, 9.55 mmol) in THF (60 mL) at –78 °C was added a solution of bromobenzene **4.2** (1.55 g, 4.37 mmol) in THF (5 mL) over 5 min. After 25 min $B(OiPr)_3$ (2.9 mL, 12.7 mmol) was added over 5 min and after a futher 2 h the reaction was allowed to warm at RT then sat. NH_4Cl (40 mL) was added. After 1 h the aqueous phase was separated and extracted with Et_2O (3 × 50 mL). The combined organic phases were then extracted with 1M NaOH (3 × 50 mL). The aqueous phases were combined then acidified with conc. HCl and extracted with ethyl acetate (3 × 50 mL). The organic phases were then combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **4.3** (1.04 g, 4.99 mmol, 78%) as a white powder which was used without further purification.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 8.0 (1H, d, J = 8.3 Hz, Ar**H**), 7.8 (1 H, s, Ar**H**), 6.9 (1H, d, J = 8.3 Hz, Ar**H**), 5.0 (2H, s, C**H$_2$**), 1.6 (6H, s, 2 × C**H$_3$**).

2-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.5)



4.2 $C_{10}H_{11}BrO_2$ MW: 243.10

4.5 $C_{16}H_{23}BO_4$ MW: 290.17

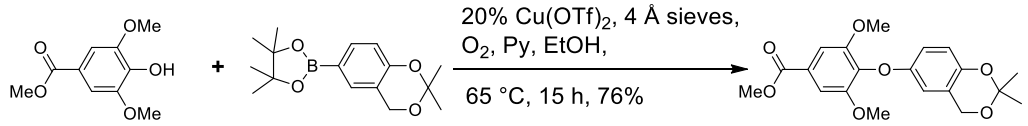
A flask charged with bromoarene **4.2** (734 mg, 3.00 mmol), bispinacolatodiboron (660 mg, 2.60 mmol) and KOAc (629 mg, 6.40 mmol) was evacuated then filled with Ar in three cycles. THF (7 mL) was added followed by $PdCl_2(dppf).CH_2Cl_2$ (165 mg, 0.22 mmol). The reaction was degassed with argon for 5 min, heated at 65 °C for 20 h then cooled to RT and filtered through a plug of silica. Concentration *in vacuo* and purification by column chromatography (silica, 0 to 10% Et_2O in petroleum ether) yielded the title compound **4.5** (870 mg, 3.00 mmol, 100%) as a pale yellow oil.

Physical and spectroscopic characteristics were consistent with reported values.[98]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.61 (1H, d, J = 8.2 Hz, Ar**H**), 7.45 (1H, s, Ar**H**), 6.81 (1H, d, J = 8.2 Hz, Ar**H**), 4.85 (2H, s, C**H$_2$**), 1.54 (6H, s, 2 × C**H$_3$**), 1.33 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 154.2 (**C**), 135.0 (**C**H), 131.8 (**C**H), 119.0 (**C**), 116.7 (**C**H), 100.0 (**C**), 83.8 (**C**), 61.0 (**C**H_2), 25.0 (**C**H_3), 24.9 (**C**H_3) with one **C** not observed (likely due to coupling with ^{10}B and ^{11}B).

Methyl 4-((2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-6-yl)oxy)-3,5-dimethoxybenzoate (4.4)



2.21 **4.5** **4.4**

$C_{10}H_{12}O_5$ MW: 212.20 | $C_{16}H_{23}BO_4$ MW: 290.16 | $C_{20}H_{22}O_7$ MW: 374.38

To solution of phenol **2.21** (380 mg, 1.80 mmol), borolane **4.5** (520 mg, 1.80 mmol) and copper triflate (196 mg, 0.50 mmol) in EtOH (18 mL) containing powdered 4 Å molecular sieves and under a slight positive pressure of oxygen was added pyridine (1 mL, 12 mmol). After heating at 65 °C for 20 h the reaction mixture was cooled to RT, filtered through a pad of silica, concentrated *in vacuo* and purified by column chromatography (silica, 25% EtOAc in petroleum ether) to afford the title compound **4.4** (513 mg, 1.37 mmol, 76%) as an off-white solid.

MP: 138–140 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}) 2946 w, 1716 m, 1491 m, 1435 m, 1415 m, 1338 s, 1214 s, 1182 s, 1123 s, 729 s.

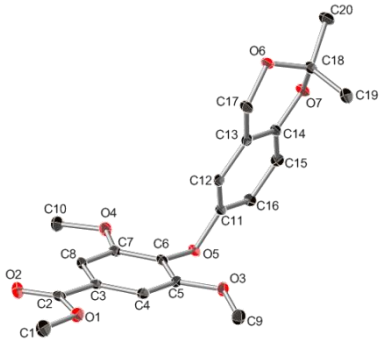
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (2H, s, 2 × Ar**H**), 6.70–6.67 (2H, m, 2 × Ar**H**), 6.48 (1H, d, J = 2.0 Hz, Ar**H**), 4.76 (2H, s, C**H$_2$**),

3.94 (3H, s, C**H**$_3$), 3.84 (6H, s, 2 × C**H**$_3$), 1.52 (6H, s, 2 × C**H**$_3$).

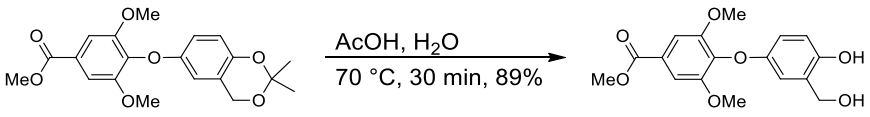
^{13}C NMR (100 MHz; $CDCl_3$):δ ppm 166.5 (**C**), 153.3 (**C**), 151.7 (**C**), 145.9 (**C**), 136.6 (**C**), 126.9 (**C**), 119.8 (**C**), 117.6 (**C**H), 114.8 (**C**H), 110.6 (**C**H), 106.9 (**C**H), 99.3 (**C**), 60.9 (**C**H$_2$), 56.4 (**C**H$_3$), 52.3 (**C**H$_3$), 24.7 (**C**H$_3$).

HRMS (ES$^+$) Calcd. for $C_{20}H_{22}NaO_7^+$ [M+Na]$^+$: 397.1258, found: 397.1261.

X-ray:



Methyl 4-(4-hydroxy-3-(hydroxymethyl)phenoxy)-3,5-dimethoxybenzoate (4.6)



4.4
$C_{20}H_{22}O_7$
MW: 374.38

4.6
$C_{17}H_{18}O_7$
MW: 334.32

A suspension of acetal **4.4** (377 mg, 1.00 mmol) in water (3 mL) and AcOH (7 mL) was heated at 70 °C for 30 min then cooled to RT and partitioned between sat. $NaHCO_3$ (20 mL) and EtOAc (10 mL). The aqueous phases was separated

and extracted with EtOAc (2 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 40% EtOAc in petroleum ether) to give the title compound **4.6** (298 mg, 0.89 mmol, 89%) as a white solid.

MP: 113–114 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}) 3376 br., 2951 w, 2849 w, 1717 m, 1497 m, 1463 m, 1436 m, 1417 m, 1341 s, 1219 s, 1185 m, 1128 s, 764 m.

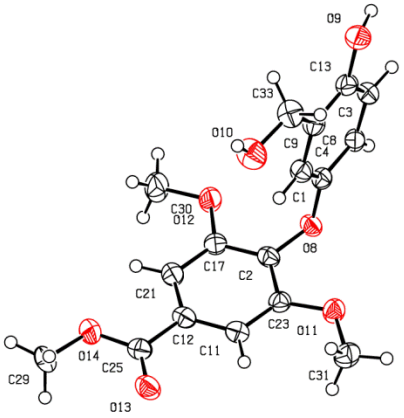
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.36 (2H, s, 2 × Ar**H**), 6.75 (1H, d, J = 8.7 Hz, Ar**H**), 6.67 (1H, dd, J = 8.8, 3.0 Hz, Ar**H**), 6.59 (1H, d, J = 3.0 Hz, Ar**H**), 4.76 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.82 (3H, s, C**H$_3$**), with one O**H** not observed..

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 166.7 (**C**), 153.5 (**C**), 151.5 (**C**), 151.0 (**C**), 136.9 (**C**), 127.1 (**C**), 125.5 (**C**), 117.1 (**C**H), 115.5 (**C**H), 114.5 (**C**H), 107.1 (**C**H), 64.6 (**C**H_2), 56.6 (**C**H_3), 52.5 (**C**H_3).

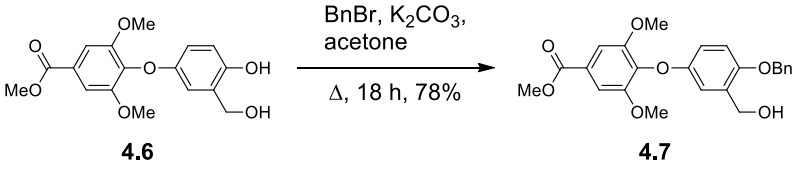
LRMS (HPLC–MS; ESI^-): 333 $[M-H]^-$.

HRMS (ES^+) Calcd. for $C_{17}H_{18}NaO_7^+$ $[M+Na]^+$: 357.0945, found: 357.0958.

X-ray:



Methyl 4-(4-(benzyloxy)-3-(hydroxymethyl)phenoxy)-3,5-dimethoxybenzoate (4.7)



4.6 **4.7**

$C_{17}H_{18}O_7$
MW 334.3206

$C_{24}H_{24}O_7$
MW: 424.4432

To a solution of biaryl ether **4.6** (287 mg, 0.86 mmol) in acetone (10 mL) was added K_2CO_3 (186 mg, 1.34 mmol) then BnBr (0.1 mL, 0.88 mmol). The reaction mixture was heated at reflux for 18 h then cooled to RT and partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was separated and extracted with EtOAc (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography column (40% EtOAc in petroleum ether) afforded the title compound **4.7** (285 mg, 0.67 mmol, 78%) as a white solid.

MP: 119–120 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}) 3454 br., 2948 w, 1718 m, 1492 s, 1462 m, 1434 m, 1416 m, 1340 s, 1217 s, 1128 s, 1025 w, 998 m, 759 m.

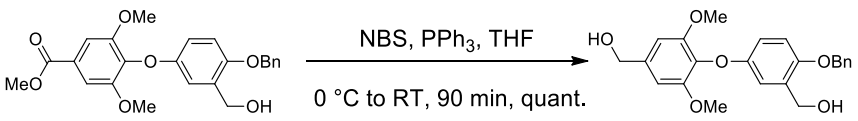
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44–7.28 (7H, m, 7 × Ar**H**), 6.85 (1H, d, J = 3.1 Hz, Ar**H**), 6.82 (1H, d, J = 8.9 Hz, Ar**H**), 6.72 (1H, dd, J = 8.8, 3.1 Hz, Ar**H**), 5.05 (2H, s, C**H$_2$**), 4.65 (2H, d, J = 6.3 Hz, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.83 (3H, s, C**H$_3$**), 2.27 (1H, t, J = 6.6 Hz, O**H**).

^{13}C NMR (100 MHz; $CDCl_3$):δ ppm 166.7 (**C**), 153.5 (**C**), 152.3 (**C**), 151.7 (**C**), 137.1 (**C**), 136.8 (**C**), 130.7 (**C**), 128.8 (**C**H), 128.2 (**C**H), 127.5 (**C**), 127.2 (**C**H), 115.7 (**C**H), 114.4 (**C**H), 112.7 (**C**H), 107.1 (**C**H), 70.9 (**C**H_2), 62.2 (**C**H_2), 56.6 (**C**H_3), 52.5 (**C**H_3).

LRMS (HPLC–MS; ESI^+): 463 $[M+K]^+$, 447 $[M+Na]^+$.

HRMS (ES^+) Calcd. for $C_{24}H_{24}NaO_7^+$ $[M+Na]^+$: 447.1414, found: 447.1435.

(4-(4-(Benzyloxy)-3-(hydroxymethyl)phenoxy)-3,5-dimethoxyphenyl)methanol (7.7)



4.7

$C_{24}H_{24}O_7$
MW: 424.44

7.7

$C_{23}H_{24}O_6$
MW: 396.43

To a solution of benzyl ester **4.7** (266 mg, 0.63 mmol) in THF (5 mL) at 0 °C was added a solution of $LiAlH_4$ (1.0 M in THF, 1.7 mL, 1.70 mmol) dropwise over 5 min. The resulting mixture was allowed to warm to RT over 90 min then MeOH (1 mL) and sat. Rochelle salt (5 mL) were added. The aqueous phase was separated and extracted with DCM (3 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **7.7** (533 mg, 1.7 mmol, quant.) as an off-white solid which was used in the next reaction without further purification.

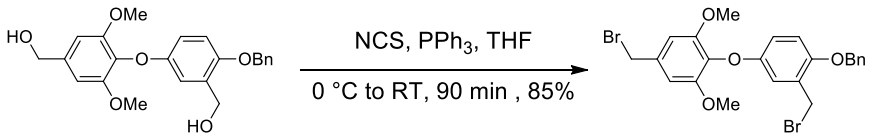
IR ν_{max} (neat, cm^{-1}) 3368 br., 2938 w, 1492 m, 1461 m, 1423 m, 1335 m, 1219 m, 1126 s, 1024 m, 736 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44 – 7.28 (5H, m, 5 × Ar**H**), 6.85 (1H, d, J = 3.0 Hz, Ar**H**), 6.82 (1H, d, J = 8.9 Hz, Ar**H**), 6.74 (1H, dd, J = 8.8, 3.1 Hz, Ar**H**), 6.67 (2H, d, J = 0.7 Hz, 2 × Ar**H**), 5.05 (2H, s, C**H$_2$**), 4.69 (2H, d, J = 5.2 Hz, C**H$_2$**), 6.64 (2H, d, J = 6.2 Hz, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.7 (**C**), 152.8 (**C**), 151.4 (**C**), 138.5 (**C**), 137.1 (**C**), 132.0 (**C**), 130.6 (**C**), 128.8 (**C**H), 128.2 (**C**H), 127.5 (**C**H), 115.6 (**C**H), 114.4 (**C**H), 112.7 (**C**H), 104.1 (**C**H), 70.9 (**C**H$_2$), 65.6 (**C**H$_2$), 62.3 (**C**H$_2$), 56.4 (**C**H$_3$).

HRMS (ES^+) Calcd. for $C_{23}H_{24}NaO_6^+$ $[M+Na]^+$: 419.1466, found: 419.1465.

2-(4-(Benzyloxy)-3-(bromomethyl)phenoxy)-5-(bromomethyl)-1,3-dimethoxybenzene (4.8)



7.7 $C_{23}H_{24}O_6$ MW 396.43

4.8 $C_{23}H_{22}Br_2O_4$ MW: 522.23

To a solution of benzyl alcohol **7.7** (222 mg, 0.56 mmol) in THF (5 mL) at 0 °C were added PPh_3 (356 mg, 1.34 mmol) and NBS (244 mg, 1.34 mmol). The reaction was warmed to RT and after 90 min sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic phases were then combined, washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 30% Et_2O in petroleum ether) to afford the title compound **4.8** (249 mg, 0.48 mmol, 85%) as an off-white solid.

MP: 107–109 °C (EtOAc).

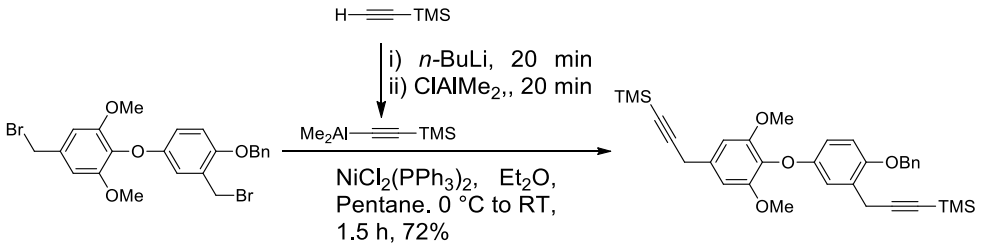
IR ν_{max} (neat, cm^{-1}) 2924 m, 2852 w, 1497 s, 1463 m, 1422 m, 1340 m, 1227 s, 1133 s, 1026 w, 913 m, 741 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.51 – 7.28 (5H, m, 5 × Ar**H**), 6.90 (1H, d, J = 3.0 Hz, Ar**H**), 6.80 (1H, d, J = 9.0 Hz, Ar**H**), 6.75 (1H, dd, J = 8.9, 3.0 Hz, Ar**H**), 6.69 (2H, s, 2 × Ar**H**), 5.09 (2H, s, C**H$_2$**), 4.53 (2H, s, C**H$_2$**), 4.50 (2H, s, C**H$_2$**), 3.79 (6H, s, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$):δ ppm 153.6 (**C**), 152.3 (**C**), 151.7 (**C**), 137.3 (**C**), 135.2 (**C**), 132.7 (**C**), 128.7 (**C**H), 128.0 (**C**H), 127.4 (**C**H), 117.6 (**C**H), 116.1 (**C**H), 113.4 (**C**H), 106.5 (**C**H), 70.9 (**C**H_2), 56.5 (**C**H_3), 34.0 (**C**H_2), 29.1(**C**H_2), with one **C** not observed (likely due to a slow relaxation time for this quaternary carbon).

HRMS (ES^+) Calcd. for $C_{23}H_{23}Br_2O_4^+$ [M(^{79}Br)+Na]$^+$: 522.9939, found: 522.9921.

(3-(4-(4-(Benzyloxy)-3-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)prop-1-yn-1-yl)trimethylsilane (4.19)



4.8
$C_{23}H_{22}Br_2O_4$
MW: 522.23

4.19
$C_{33}H_{40}O_4Si_2$
MW: 556.84

Adapted from a procedure of Gau *et al.*[58] To a solution of TMSacetylene (0.27 mL, 1.92 mmol) in pentane (4 mL) at 0 °C was added a solution of *n*–BuLi (2.4 M in hexane, 0.80 mL, 1.92 mmol) over 5 min. After 30 min a solution of Et_2AlCl (1.0 M in hexane, 1.92 mL, 1.92 mmol) was added over 5 min. After 20 min the reaction mixture was warmed RT and after 2 h Et_2O (4 mL) was added followed by $NiCl_2(PPh_3)_2$ (54.0 mg, 0.08 mmol). After a further 15 min benzyl bromide

4.8 (249 mg, 0.48 mmol) was added followed after 90 min by sat. NH_4Cl (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic phases were then combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (silica, 10% Et_2O in petroleum ether) afforded the title compound **4.19** (192 mg, 0.34 mmol, 72%) as a yellow oil.

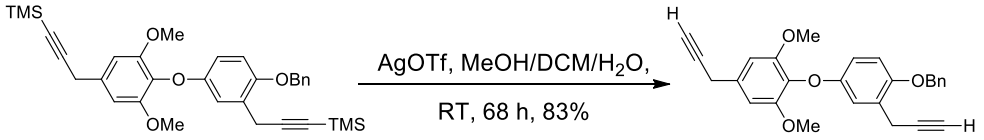
IR ν_{max} (neat, cm^{-1}) 2958 w, 2177 m, 1737 br., 1494 s, 1463 m, 1424 m, 1337 m, 1249 s, 1130 s, 842 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46 – 7.28 (5H, m, 5 × Ar**H**), 7.07 (1H, dd, J = 2.7, 0.8 Hz, Ar**H**), 6.77 (1H, d, J = 8.8 Hz, Ar**H**), 6.73 (1H, dd, J = 8.8, 2.9 Hz, Ar**H**), 6.68 (2H, t, J = 0.7 Hz, Ar**H**), 5.01 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.66 (2H, s, C**H$_2$**), 3.63 (2H, s, C**H$_2$**), 0.21 (9H, s, 3 × C**H$_3$**), 0.11 (s, 9H, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 152.8 (**C**), 150.8 (**C**), 137.6 (**C**), 133.6 (**C**), 131.3 (**C**), 128.6 (**C**H), 127.9 (**C**H), 127.3 (**C**H), 126.3 (**C**), 115.5 (**C**H), 113.5 (**C**H), 112.5 (**C**H), 105.3 (**C**H), 104.3 (**C**), 104.1 (**C**), 87.9 (**C**), 87.1 (**C**), 70.7 (**C**H_2), 56.4 (**C**H_3), 26.5 (**C**H_2), 21.2 (**C**H_2), 0.23 (**C**H_3).

HRMS (ES^+) Calcd. for $C_{33}H_{40}NaO_4Si^+$ $[M+Na]^+$: 579.2357, found: 579.2360

2-(4-(Benzyloxy)-3-(prop-2-yn-1-yl)phenoxy)-1,3-dimethoxy-5-(prop-2-yn-1-yl)benzene (7.8)



4.17

$C_{33}H_{40}O_4Si_2$
MW: 556.84

7.8

$C_{27}H_{24}O_4$
MW: 412.48

To diyne **4.17** (292 mg, 0.52 mmol) in MeOH/H_2O/DCM (3.4 mL/0.75 mL/5.5 mL) was added AgOTf (31.0 mg, 0.12 mmol). After 20 h further AgOTf (41.0 mg, 0.16 mmol) was added followed after 48 h by sat. NH_4Cl (4 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether) to afford the title compound **7.8** (156mg, 0.38 mmol, 73%) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44 – 7.28 (5H, m, 5 × Ar**H**), 7.19 (1H, dt, *J* = 3.0, 0.8 Hz, Ar**H**), 6.74 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.66 (2H, s, 2 × Ar**H**), 6.61 (1H, dd, *J* = 8.8, 3.1 Hz, Ar**H**), 5.02 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.62 (2H, d, *J* = 2.7 Hz, C**H$_2$**), 3.59 (2H, d, *J* = 2.8 Hz, C**H$_2$**), 2.24 (1H, t, *J* = 2.7 Hz, C**H**), 2.11 (1H, t, *J* = 2.7 Hz, C**H**).

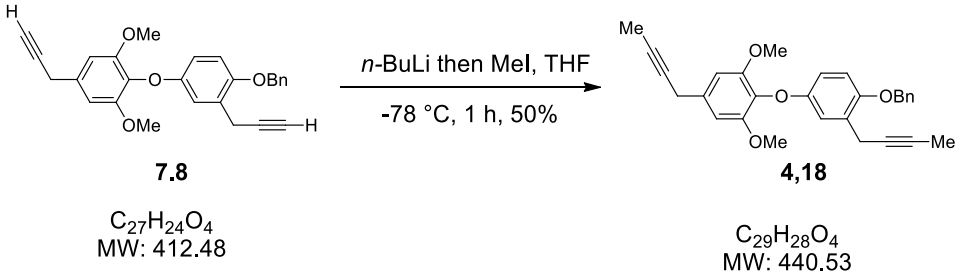
^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.6 (**C**), 152.8 (**C**), 150.9 (**C**), 137.5 (**C**), 133.5 (**C**), 131.5 (**C**), 128.6 (**C**H), 127.9 (**C**H), 127.3 (**C**H), 126.2 (**C**), 116.6 (**C**H), 112.9 (**C**H), 112.4 (**C**H),

105.4 (**C**H), 81.9 (**C**H), 81.9 (**C**H), 70.8 (**C**H_2), 56.5 (**C**H_3), 25.3 (**C**H_2), 19.8 (**C**H_2).

LRMS (HPLC–MS; ESI^+): 451 $[M+K]^+$, 435 $[M+Na]^+$.

HRMS (ES^+) Calcd. for $C_{27}H_{24}NaO_4^+$ $[M+Na]^+$: 435.1567, found: 435.1587.

2-(4-(Benzyloxy)-3-(but-2-yn-1-yl)phenoxy)-5-(but-2-yn-1-yl)-1,3-dimethoxybenzene (4.18)



7.8

$C_{27}H_{24}O_4$
MW: 412.48

4,18

$C_{29}H_{28}O_4$
MW: 440.53

To a solution of diyne **7.8** (75 mg, 0.18 mmol) in THF (4 mL) at 0 °C was added *n*–BuLi (2.2 M in hexane, 0.33 mL, 0.73 mmol). After 1 h, MeI (0.05 mL, 0.8 mmol) was added then the reaction was allowed to warm to RT. After a further 1 h sat. NH_4Cl (4 mL) was added, then the aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether) to give the title compound **4.18** (39 mg, 0.09 mmol, 50%) as a colourless oil.

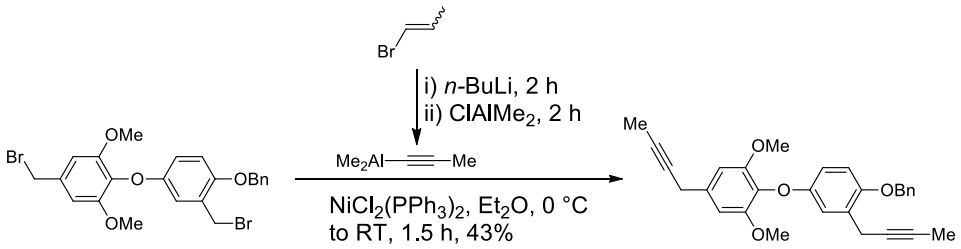
IR ν_{max} (neat, cm^{-1}) 2934 w, 1496 m, 1463 m, 1421 m, 1335 m, 1220 m, 1145 s, 701 w.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46 – 7.27 (5H, m, 5 × Ar**H**), 7.21 (1H, d, J = 3.1 Hz, Ar**H**), 6.72 (1H, d, J = 8.9 Hz, Ar**H**), 6.65 (2H, d, J = 0.9 Hz, 2 × Ar**H**), 6.58 (1H, dd, J = 8.7, 3.1 Hz, Ar**H**), 5.01 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.56 (2H, br. q, J = 2.6 Hz, C**H$_2$**), 3.53 (2H, br. q, J = 2.4 Hz, C**H$_2$**), 1.88 (3H, t, J = 2.5 Hz, C**H$_3$**), 1.81 (3H, t, J = 2.5 Hz, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.6 (**C**), 152.8 (**C**), 150.8 (**C**), 137.7 (**C**), 135.0 (**C**), 131.4 (**C**), 128.6 (**C**H), 127.8 (**C**H), 127.6 (**C**), 127.3 (**C**H), 116.6 (**C**H), 112.4 (**C**H), 112.3 (**C**H), 105.4 (**C**H), 78.3 (**C**), 78.1 (**C**), 76.7 (**C**), 76.5 (**C**), 70.7 (**C**H$_2$), 56.4 (**C**H$_3$), 25.7 (**C**H$_2$), 20.0 (**C**H$_2$), 3.8 (**C**H$_3$), 3.7 (**C**H$_3$).

HRMS (ES^+) Calcd. for $C_{29}H_{28}NaO_4^+$ $[M+Na]^+$: 463.1880, found: 463.1882.

Alternatively



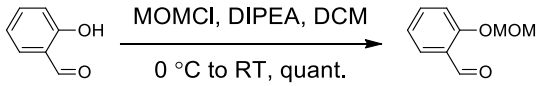
4.8
$C_{23}H_{22}Br_2O_4$
MW: 522.23

4.18
$C_{33}H_{40}O_4Si_2$
MW: 556.84

Experimental

Adapted from a procedure of Toussaint *et al.*[66] To a solution of bromopropene (0.18 mL, 2.00 mmol) in Et_2O (8 mL) at 0 °C was added a solution of *n*-BuLi (2.1 M in hexane, 1.4 mL, 3.00 mmol) over 5 min. After 30 min a solution of Et_2AlCl (1.0 M in hexane, 2.0 mL, 2.00 mmol) was added over 5 min. After 20 min the reaction mixture was warmed RT and after 2 h was added $NiCl_2(PPh_3)_2$ (54.0 mg, 0.08 mmol). After a further 15 min benzyl bromide **4.8** (258 mg, 0.50 mmol) was added followed after 90 min by sat. NH_4Cl (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic phases were then combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (silica, 20% Et_2O in petroleum ether) afforded the title compound **4.18** (94 mg, 0.21 mmol, 42%) as a yellow oil.

2-(Methoxymethoxy)benzaldehyde (4.21)



4.20
$C_7H_6O_2$
MW: 122.12

4.21
$C_9H_{10}O_3$
MW: 166.17

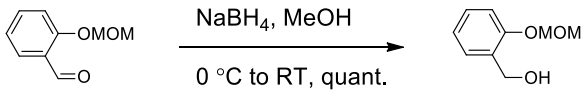
Following a protocol from Akazawa *et al.*[87] To a solution of phenol **4.20** (3.75 g, 30.0 mmol) in DCM (90 mL) at 0 °C was added MOMCl (3.0 mL, 39.0 mmol) followed by DIPEA (7.0 mL, 39.0 mmol). The reaction mixture was allowed to warm to RT and after 1 h H_2O (20 mL) was added. The aqueous phase was separated and extracted with DCM (3 × 60 mL), then the combined organic phases were washed with 1 M NaOH (60 mL) and brine (60 mL), dried over

$MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **4.21** (4.98 g, 30.0 mmol, quant.) as a pale yellow oil which was used in the next reaction without further purification.

Physical and spectroscopic characteristics were consistent with reported values.[99]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 10.52 (1H, d, J = 0.8 Hz, C**H**O), 7.85 (1H, dd, J = 7.7, 1.9 Hz, Ar**H**), 7.54 (1H, ddd, J = 8.4, 7.4, 1.9 Hz, Ar**H**), 7.23 (1H, dd, J = 8.5, 0.6 Hz, Ar**H**), 7.13 – 7.05 (1H, m, Ar**H**), 5.32 (2H, s, C**H$_2$**), 3.54 (3H, s, C**H$_3$**).

(2-(Methoxymethoxy)phenyl)methanol (4.22)



4.21
$C_9H_{10}O_3$
MW: 166.17

4.22
$C_9H_{12}O_3$
MW: 168.19

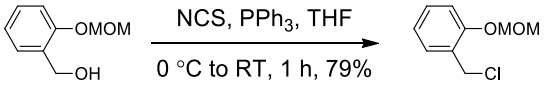
To a solution of benzaldehyde **4.21** (4.98 g, 30.0 mmol) in MeOH (150 mL) at 0 °C was added $NaBH_4$ (2.84 g, 75.0 mmol). The reaction was warmed to RT and after 1 h H_2O (30 mL) was added. The mixture was then filtered through a pad of silica and diluted with EtOAc (50 mL). The aqueous phases was separated and extracted with EtOAc (3 × 50 mL) then the organic phases were combined, concentrated *in vacuo* and purified by column chromatography (silica, 20% EtOAc in petroleum ether with 0.1% of NEt_3) to afford the title compound **4.22** (5.05 g, 30.0 mmol, quant.) as a pale yellow oil.

Experimental

Physical and spectroscopic characteristics were consistent with reported values.[100]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.35 – 7.31 (1H, m, Ar**H**), 7.29 – 7.24 (1H, m, Ar**H**), 7.11 (1H, dd, J = 8.2, 0.9 Hz, Ar**H**), 7.02 (1H, ddd, J = 7.4, 7.4, 1.0 Hz, Ar**H**), 5.25 (2H, s, C**H$_2$**), 4.72 (2H, d, J = 5.4 Hz, C**H$_2$**), 3.50 (3H, s, C**H$_3$**), (1H, s (br.), O**H**).

1-(Chloromethyl)-2-(methoxymethoxy)benzene (4.23)



4.22
$C_9H_{12}O_3$
MW: 168.19

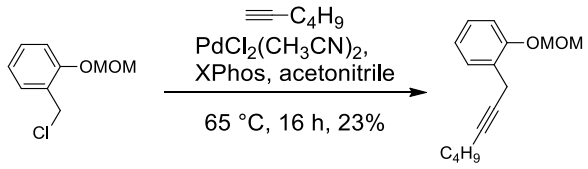
4.23
$C_9H_{11}ClO_2$
MW: 186.64

To a solution of benzyl alcohol **4.22** (5.05 g, 30.0 mmol) in THF (120 mL) at 0 °C was added PPh_3 (9.42 g, 36.0 mmol) followed by NCS (5.93 g, 44.0 mmol). The reaction mixture was warmed to RT and after 1 h sat. $NaHCO_3$ (60 mL) and sat. $Na_2S_2O_3$ (60 mL) were added. The aqueous phase was separated then extracted with Et_2O (3 × 60 mL). The organic phases were combined then washed with brine (60 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether with 0.1% NEt_3) to give the title compound **4.23** (4.41 g, 23.6 mmol, 79%) as a colourless oil.

Physical and spectroscopic characteristics were consistent with reported values.[101]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.38 (1H, dd, *J* = 7.4, 2.0 Hz, Ar**H**), 7.33 – 7.27 (1H, m, Ar**H**), 7.12 (1H, dd, *J* = 8.4, 0.9 Hz, Ar**H**), 7.01 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz, Ar**H**), 5.27 (2H, s, C**H$_2$**), 4.69 (2H, s, C**H$_2$**), 3.52 (3H, s, C**H$_3$**).

1-(Hept-2-yn-1-yl)-2-(methoxymethoxy)benzene (4.24)



4.23

$C_9H_{11}ClO_2$
MW: 186.64

4.24

$C_{15}H_{20}O_2$
MW: 232.32

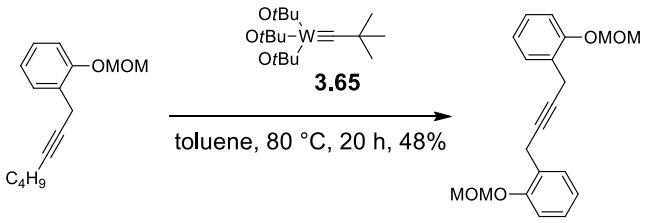
A flask charged with benzyl chloride **4.23** (95.0 mg, 0.50 mmol), $PdCl_2(CH_3CN)_2$ (7 mg, 0.03 mmol), XPhos (37.0 mg, 0.08 mmol) and Cs_2CO_3 (181 mg, 0.55 mmol) was evacuated then filled with Ar in three cycles. Hex-1-yne (0.09 mL, 0.75 mmol) and CH_3CN (2.0 mL) were then added sequentially and the reaction was heated at 65 °C for 24 h. After cooling to RT and filtration through a plug of silica, the solvent was removed *in vacuo*. Purification by column chromatography (silica, petroleum ether) afforded the title compound **4.24** (102.2 mg, 0.44 mmol, 88%) contaminated with the *ca*. 10% starting material.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.55 – 7.49 (1H, m, Ar**H**), 7.21 – 7.16 (1H, m, Ar**H**), 7.05 (1H, dd, *J* = 8.2, 1.0 Hz, Ar**H**), 7.00 (1H,

app. td, J = 7.5, 1.2 Hz, ArH), 5.20 (2H, s, CH_2), 3.57 (2H, t, J = 2.4 Hz, CH_2), 3.48 (3H, s, CH_3), 2.31 – 2.17 (2H, m, CH_2), 1.55 – 1.37 (4H, m, 2 × CH_2), 0.92 (3H, t, J = 7.3 Hz, CH_3) with additional signals attributed to **4.21.**

HRMS (EI) Calcd. for $C_{15}H_{20}O_2$ $[M]^{+\bullet}$: 232.1463, found: 232.1461.

1,4-Bis(2-(methoxymethoxy)phenyl)but-2-yne (4.25)



4.24

$C_{15}H_{20}O_2$
MW: 232.32

4.25

$C_{20}H_{22}O_4$
MW: 326.39

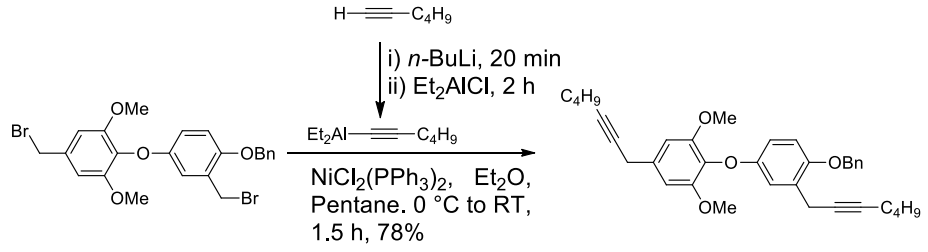
To a solution of alkyne **4.24** (30.0 mg, 0.13 mmol) in toluene (13 mL) in a glove box was added the Schrock catalyst **3.65** (10 mg, 0.02 mmol). The reaction was heated at 80 °C for 20 h then filtered through a plug of silica, concentrated *in vacuo* and purified by column chromatography (silica, 10% Et_2O in petroleum ether) to afford the title compound **4.25** (10.0 mg, 0.031 mmol, 48%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 2926 br., 1601 w, 1490 s, 1456 m, 1235 s, 1154 s, 1079 s, 1003 s, 923 m, 754 s

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.55 (2H, dd, J = 7.7, 1.7 Hz, 2 × Ar**H**), 7.23 – 7.14 (2H, m, 2 × Ar**H**), 7.06 (2H, dd, J = 8.2, 1.1 Hz, 2 × Ar**H**), 6.99 (2H, td, J = 7.4, 1.1 Hz, 2 × Ar**H**), 5.21 (4H, s, 4 × C**H$_2$**), 3.65 (4H, s, 4 × C**H$_2$**), 3.47 (6 H, s, 6 × C**H$_3$**).

HRMS (ES^+) Calcd. for $C_{20}H_{22}NaO_4^+$ $(M+Na)^+$: 349.1410, found: 349.1424.

2-(4-(Benzyloxy)-3-(hept-2-yn-1-yl)phenoxy)-5-(hept-2-yn-1-yl)-1,3-dimethoxybenzene (4.26)



4.8

$C_{23}H_{22}Br_2O_4$
MW: 522.23

4.26

$C_{35}H_{40}O_4$
MW: 524.69

Adapted from a procedure by Gau *et al.*[58] To a solution of hex-1-yne (0.23 mL, 2.00 mmol) in pentane (4 mL) at 0 °C was added *n*-BuLi (2.3 M in hexane, 0.87 mL, 2.00 mmol) over 5 min. After 30 min a solution of Et_2AlCl (1.0 M in hexane, 2.0 mL, 2.00 mmol) was added over 5 min. The solution was warmed to RT over 20 min and after a further 2 h, Et_2O (4 mL) and $NiCl_2(PPh_3)_2$ (57.0 mg, 0.07 mmol) were added. After a further 15 min benzyl bromide **4.8** (261 mg, 0.50 mmol) was added followed after 90 min by sat. NH_4Cl (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$,

concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether) to afford the title compound **4.26** (204 mg, 0.38 mmol, 78%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 2957 m, 2933 m, 2872 w, 1732 w, 1492 s, 1462 m, 1422 w, 1337 w, 1220 s, 1192 m, 1129 s, 737 w

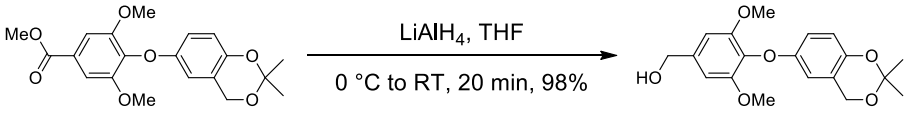
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45 – 7.27 (5H, m, 5 × Ar**H**), 7.18 (1H, d, *J* = 3.1 Hz, Ar**H**), 6.73 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.67 (2H, s, 2 × Ar**H**), 6.62 (1H, dd, *J* = 8.8, 3.1 Hz, Ar**H**), 5.01 (2H, s, C**H$_2$**), 3.78 (6H, s, 2 × C**H$_3$**), 3.59 (2H, s), 3.56 (2H, s, C**H$_2$**), 2.26 (2H, tt, *J* = 6.9, 2.4 Hz, C**H$_2$**), 2.17 (2H, tt, *J* = 7.0, 2.3 Hz, C**H$_2$**), 1.53 – 1.24 (8H, m, 4 × C**H$_2$**), 0.96 – 0.91 (3H, t, *J* = 7.2 Hz, C**H$_3$**), 0.90 (3H, t, *J* = 6.4 Hz, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.6 (**C**), 152.9 (**C**), 150.8 (**C**), 137.7 (**C**), 135.0 (**C**), 131.4 (**C**), 128.6 (**C**H), 127.8 (**C**H), 127.7 (**C**), 127.3 (**C**H), 116.3 (**C**H), 112.6 (**C**H), 112.3 (**C**H), 105.4 (**C**H), 83.3 (**C**), 82.9 (**C**), 70.7 (**C**H$_2$), 56.4 (O**C**H$_3$), 31.3 (**C**H$_2$), 31.3 (**C**H$_2$), 25.6 (**C**H$_2$), 22.1 (**C**H$_2$), 20.1 (**C**H$_2$), 18.7 (**C**H$_2$), 13.8 (**C**H$_3$) with one **C**H$_2$ not observed (likely due to a peak overlap).

HRMS (ES^+) Calcd. for $C_{29}H_{28}NaO_4^+$ $[M+H]^+$: 525.2999, found: 525.3018.

7.5 Experimental chapter 5

(4-((2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)oxy)-3,5-dimethoxyphenyl)methanol (7.9)



4.4
$C_{20}H_{22}O_7$
MW: 374.38

7.9
$C_{19}H_{22}O_6$
MW: 346.37

To a solution of benzyl ester **4.4** (577 mg, 1.54 mmol) in THF (7 mL) at 0 °C was added $LiAlH_4$ (1.0 M in THF, 1.7 mL, 1.70 mmol) over 5 min. After 20 min at RT, MeOH (1 mL) and sat. Rochelle's salts (10 mL) were added. The phases were separated and the aqueous phase was extracted with DCM (4 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound **7.9** (525 mg, 1.52 mmol, 98%) as a white solid which was used in the next step without further purification.

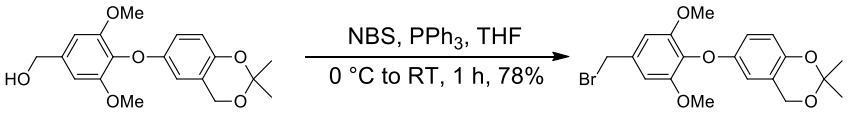
IR ν_{max} (neat, cm^{-1}) 3459 br., 2994 w, 2941 w, 1739 w, 1492 s, 1463 m, 1422 w, 1374 w, 1336 w, 1259 m, 1239 s, 1218 m, 1128 s, 1063 w, 959 m, 875 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.70 – 6.68 (2H, m, 2 × Ar**H**), 6.67 (2H, s, 2 × Ar**H**), 6.51 – 6.45 (1H, m, Ar**H**), 4.75 (2H, d, J = 0.9 Hz, C**H$_2$**), 4.69 (2H, d, J = 1.4 Hz, C**H$_2$**), 3.79 (6H, s,

2 × C**H**$_3$), 1.51 (6H, s, 2 × C**H**$_3$) with one O**H** not observed.

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.7 (**C**), 152.4 (**C**), 145.8 (**C**), 138.4 (**C**), 132.0 (**C**), 119.9 (**C**), 117.6 (**C**H), 114.9 (**C**H), 110.6 (**C**H), 104.1 (**C**H), 99.4 (**C**), 65.6 (**C**H$_2$), 61.1 (**C**H$_2$), 56.4 (**C**H$_3$), 24.8 (**C**H$_3$).

6-(4-(Bromomethyl)-2,6-dimethoxyphenoxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxine (5.6)



7.9

$C_{19}H_{22}O_6$
MW: 346.37

5.6

$C_{19}H_{21}BrO_5$
MW: 409.27

To a solution of benzyl alcohol **7.9** (525 mg, 1.25 mmol) in THF (6 mL) at 0 °C were added PPh_3 (479 mg, 1.82 mmol) and NBS (335 mg, 1.82 mmol). The reaction was warmed to RT and after 1 h sat. $NaHCO_3$ (6 mL) and sat. $Na_2S_2O_3$ (6 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 6 mL) then the organic phases were combined, washed with brine (6 mL), dried over $MgSO_4$, and concentrated *in vacuo.* Purification by column chromatography (silica, 30% Et_2O in petroleum ether) afforded the title compound **5.6** (483 mg, 1.18 mmol, 78%) as an off white solid.

MP 129.5 – 131.2 °C (EtOAc).

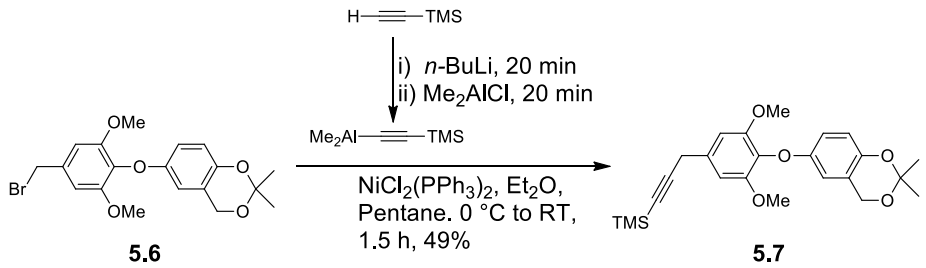
IR ν_{max} (neat, cm^{-1}) 2924 w, 2852 w, 1497 s, 1463 m, 1422 m, 1340 m, 1245 m, 1227 s, 1133 s, 1026 m, 913 m, 741 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.72 – 6.63 (4H, m, 4 × Ar**H**), 6.50 – 6.48 (1H, m, Ar**H**), 4.76 (2H, s, C**H$_2$**), 4.49 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 1.51 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.7 (**C**), 152.2 (**C**), 145.9 (**C**), 135.0 (**C**), 132.9 (**C**), 119.9 (**C**), 117.7 (**C**H), 114.9 (**C**H), 110.7 (**C**H), 106.5 (**C**H), 99.4 (**C**), 61.1 (**C**H$_2$), 56.5 (**C**H$_3$), 34.1 (**C**H$_2$), 24.9 (**C**H$_3$).

HRMS (ES^+) Calcd. for $C_{19}H_{21}BrNaO_5^+$ [M(^{79}Br)+Na]$^+$: 431.0465, found: 431.0476

(3-(4-((2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)oxy)-3,5-dimethoxyphenyl)prop-1-yn-1-yl)trimethylsilane (5.7)



5.6

$C_{19}H_{21}BrO_5$
MW: 409.27

5.7

$C_{24}H_{30}O_5Si$
MW: 426.58

Adapted from a procedure by Gau *et al.*[58] To a solution of trimethylsilylacetylene (0.33 mL, 2.36 mmol) in pentane (6 mL) at 0 °C was added *n*−BuLi (2.25 M in hexane, 1.05 mL, 2.36 mmol) over 5 min. After 30 min a solution of Et_2AlCl (1.0 M in hexane, 2.36 mL, 2.36 mmol) was added over 5 min. The solution was warmed to RT after 20 min and after a further 2 h, Et_2O (6 mL) and $NiCl_2(PPh_3)_2$

(69 mg, 0.09 mmol) were added. After a further 15 min benzyl bromide **5.6** (430 mg, 0.1.05 mmol) was added followed after 90 min by sat. NH_4Cl (6 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL) then the organic phases were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (silica, 10% Et_2O in petroleum ether) afforded the title compound **5.7** (221 mg, 0.52 mmol, 49%) as a yellow oil.

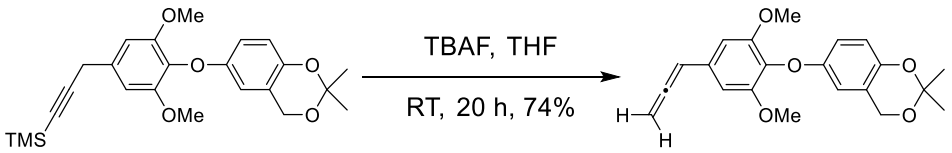
IR ν_{max} (neat, cm^{-1}) 2957 w, 2177 m, 1738 m, 1492 s, 1463 m, 1423 m, 1373 w, 1239 m, 1130 m, 958 m, 843 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.70 – 6.67 (2H, m, 2 × Ar**H**), 6.66 (2H, s, 2 × Ar**H**), 6.50 – 6.48 (1H, m, Ar**H**), 4.76 (2H, d, J = 0.9 Hz, C**H$_2$**), 3.78 (6H, s, 2 × C**H$_3$**), 3.66 (2H, s, C**H$_2$**), 1.51 (6H, s, 2 × C**H$_3$**), 0.21 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 152.4 (**C**), 145.8 (**C**), 133.8 (**C**), 131.3 (**C**), 119.9 (**C**), 117.6 (**C**H), 114.9 (**C**H), 110.6 (**C**H), 105.2 (**C**H), 104.1 (**C**), 99.4 (**C**), 87.9 (**C**), 61.2 (**C**H_2), 56.4 (**C**H_3), 26.6 (**C**H_2), 24.9 (**C**H_3), 0.23 (**C**H_3).

HRMS: (ES^+) Calcd. for $C_{24}H_{30}NaO_5Si^+$ $[M+Na]^+$: 449.1755, found: 449.1744

6-(2,6-Dimethoxy-4-(propa-1,2-dien-1-yl)phenoxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxine (5.9)



5.7

$C_{24}H_{30}O_5Si$
MW: 426.58

5.9

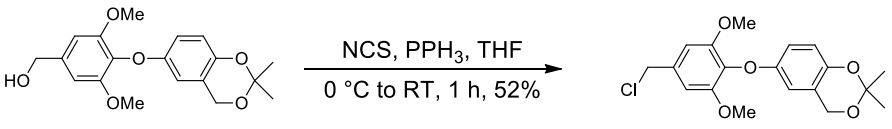
$C_{21}H_{22}O_5$
MW: 354.40

To a solution of alkyne **5.7** (209 mg, 0.50 mmol) in THF (2.5 mL) was added TBAF (1.0 M in THF, 2.5 mL, 2.50 mmol). After 20 h Et_2O (3 mL) and H_2O (3 mL) were added, then the aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 30% Et_2O in petroleum ether) to afford the title compound **5.9** (131 mg, 0.37 mmol, 74%) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.72 – 6.66 (2H, m, 2 × Ar**H**), 6.59 (2H, s, 2 × Ar**H**), 6.50 – 6.47 (1H, m, Ar**H**), 6.14 (1H, t, *J* = 6.7 Hz, =C**H**), 5.20 (2H, d, *J* = 6.7 Hz, =C**H$_2$**), 4.75 (2H, d, *J* = 0.9 Hz, C**H$_2$**), 3.78 (6H, s, 2 × C**H$_3$**), 1.51 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 209.7 (**C**), 153.6 (**C**), 152.3 (**C**), 145.6 (**C**), 131.7 (**C**), 131.2 (**C**), 119.7 (**C**), 117.5 (**C**H), 114.8 (**C**H), 110.4 (**C**H), 104.0 (**C**H), 99.2 (**C**), 94.2 (**C**H), 79.3 (=**C**H$_2$), 61.0 (**C**H$_2$), 56.3 (**C**H$_3$), 24.7 (**C**H$_3$).

6-(4-(Chloromethyl)-2,6-dimethoxyphenoxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxine (5.10)



7.9

$C_{19}H_{22}O_6$
MW: 346.37

5.10

$C_{19}H_{21}ClO_5$
MW: 364.82

To a solution of benzyl alcohol **7.9** (534 mg, 1.25 mmol) in THF (6 mL) at 0 °C were added PPh_3 (476 mg, 1.82 mmol) and NCS (257 mg, 1.85 mmol). The reaction was warmed to RT and after 1 h sat. $NaHCO_3$ (6 mL) and sat. $Na_2S_2O_3$ (6 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo.* Purification by column chromatography (silica, 20% Et_2O in petroleum ether) afforded the title compound **5.10** (295 mg, 0.81 mmol, 52%) as an off white solid.

IR ν_{max} (neat, cm^{-1}) 2994 w, 2941 w, 1492 s, 1463 m, 1340m, 1259 m, 1241 s, 1223 m, 1129 s, 876 m.

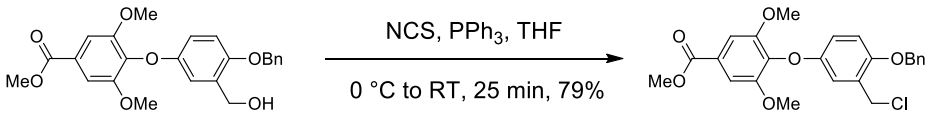
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.70 – 6.67 (4H, m, 4 × Ar**H**), 6.51 – 6.48 (1H, m, Ar**H**), 4.76 (2H, d, J = 0.9 Hz, C**H$_2$**), 4.58 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 1.51 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.7 (**C**), 152.2 (**C**), 145.9 (**C**), 134.8 (**C**), 132.8 (**C**), 119.9 (**C**), 117.7 (**C**H), 114.9 (**C**H), 110.7

(**C**H), 106.0 (**C**H), 99.4 (**C**), 61.2 (**C**H$_2$), 56.5 (**C**H$_3$), 46.8 (**C**H$_2$), 24.9 (**C**H$_3$).

HRMS (ES$^+$) Calcd. for $C_{19}H_{21}ClNaO_5^+$ [M(^{35}Cl)+Na]$^+$: 387.0970, found: 387.0971.

Methyl 4-(4-(benzyloxy)-3-(chloromethyl)phenoxy)-3,5-dimethoxybenzoate (5.14)



4.7

$C_{24}H_{24}O_7$
MW: 424.45

5.14

$C_{24}H_{23}ClO_6$
MW: 442.89

To a solution of benzyl alcohol **4.7** (412 mg, 0.97 mmol) in THF (4 mL) at 0 °C were added sequentially PPh_3 (305 mg, 1.16 mmol) and NCS (154 mg, 1.16 mmol). The reaction mixture was allowed to wart to RT and after 25 min sat. $NaHCO_3$ (4 mL) and sat. $Na_2S_2O_3$ (4 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 6 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica, 20% Et_2O in petroleum ether) gave the title compound **5.14** (340 mg, 0.77 mmol, 79%) as an off-white solid.

MP 125–126 °C (EtOAc).

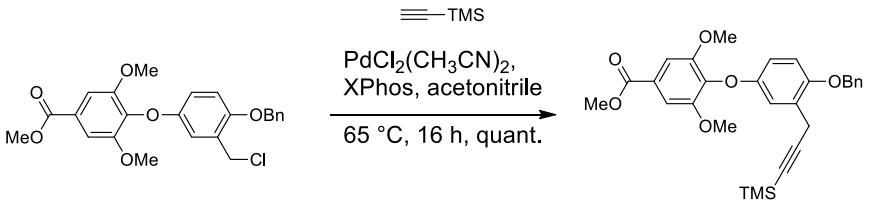
IR ν_{max} (neat, cm^{-1}) 2949 w, 1719 m, 1497 s, 1461 m, 1416 m, 1341 s, 1217 s, 1184 m, 1129 s, 999 w, 758 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.49 – 7.28 (7H, m, 7 × Ar**H**), 6.92 (1H, d, J = 3.0 Hz, Ar**H**), 6.82 (1H, d, J = 8.9 Hz, Ar**H**), 6.75 (1H, dd, J = 8.9, 3.0 Hz, Ar**H**), 5.08 (2H, s, C**H$_2$**), 4.62 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.83 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 166.5 (**C**O), 153.2 (**C**), 151.9 (**C**), 151.5 (**C**), 137.0 (**C**), 136.5 (**C**), 128.5 (**C**H), 127.9 (**C**H), 127.2 (**C**H), 127.1 (**C**), 127.1 (**C**), 117.3 (**C**H), 115.7 (**C**H), 113.2 (**C**H), 107.0 (**C**H), 70.9 (**C**H$_2$), 56.4 (**C**H$_3$), 52.4 (**C**H$_3$), 41.5 (**C**H$_2$).

HRMS (ES$^+$) Calcd. for $C_{24}H_{23}ClNaO_6^+$ [M(^{35}Cl)+Na]^1: 443.1256, found: 443.1252.

Methyl 4-(4-(benzyloxy)-3-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (5.15)



5.14

$C_{24}H_{23}ClO_6$
MW: 442.89

5.16

$C_{29}H_{32}O_6Si$
MW: 504.65

A flask charged with benzyl chloride **5.14** (750 mg, 1.70 mmol), $PdCl_2(CH_3CN)_2$ (26 mg, 0.1 mmol), XPhos (146 mg, 0.31 mmol) and Cs_2CO_3 (609 mg, 1.87 mmol) was evacuated then filled with Ar in three cycles. TMSacetylene (0.38 mL, 2.70 mmol) and CH_3CN (5 mL) were added sequentially then the reaction mixture was heated at 70 °C for 18 h, cooled to RT, filtered through a plug of silica and

concentrated *in vacuo*. Purification by column chromatography (silica, 30% Et_2O in petroleum ether) afforded the title compound **5.15** (858 mg, 1.70 mmol, quant.) as a wax.

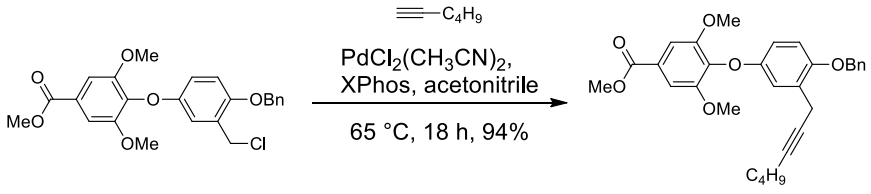
IR ν_{max} (neat, cm^{-1}) 2956 w, 2177 w, 1720 s, 1493 s, 1463 m, 1433 m, 1416 m, 1340 s, 1216 s, 1130 s, 1027 w, 999 w, 844 s, 758 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7. 45 – 7. 29 (7H, m, 7 × Ar**H**), 7.06 (1H, d, *J* = 2.8 Hz, Ar**H**), 6.78 (1H, d, *J* = 9.1 Hz, Ar**H**), 6.74 (1H, dd, *J* = 8.9, 3.0 Hz, Ar**H**), 5.03 (2H, s, C**H$_2$**), 3.95 (3H, s, C**H$_3$**), 3.85 (6H, s, 2 × C**H$_3$**), 3.64 (2H, s, C**H$_2$**), 0.10 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 166.6 (**C**O), 153.4 (**C**), 152.2 (**C**), 150.9 (**C**), 137.3 (**C**), 136.8 (**C**), 128.5 (**C**H), 127.8 (**C**H), 127.1 (**C**H), 126.9 (**C**), 126.3 (**C**), 115.5 (**C**H), 113.5 (**C**H), 112.3 (**C**H), 107.1 (**C**H), 103.9 (**C**), 87.1 (**C**), 70.6 (**C**H_2), 56.5 (**C**H_3), 52.3 (**C**H_3), 21.0 (**C**H_2), 0.00 (**C**H_3), with one alkyne resonance not observed.

HRMS (ES^+) Calcd. for $C_{29}H_{32}NaO_6Si^+$ $[M+Na]^+$: 527.1860, found: 527.1845.

Methyl 4-(4-(benzyloxy)-3-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (5.20)



5.14
$C_{24}H_{23}ClO_6$
MW: 442.89

5.20
$C_{30}H_{32}O_6$
MW: 488.57

A flask charged with benzyl chloride **5.14** (200 mg, 0.50 mmol), $PdCl_2(CH_3CN)_2$ (8 mg, 0.03 mmol), XPhos (43 mg, 0.09 mmol) and Cs_2CO_3 (163 mg, 0.50 mmol) was evacuated then filled with Ar in three cycles. Hex-1-yne (0.08 mL, 0.72 mmol) and CH_3CN (1.3 mL) were then added sequentially and the reaction was heated at 65 °C for 18 h then cooled to RT, filtered through a plug of silica and concentrated *in vacuo.* Purification by column chromatography (silica, 20% Et_2O in petroleum ether) gave the title compound **5.20** (206 mg, 0.42 mmol, 94%) as a yellow wax.

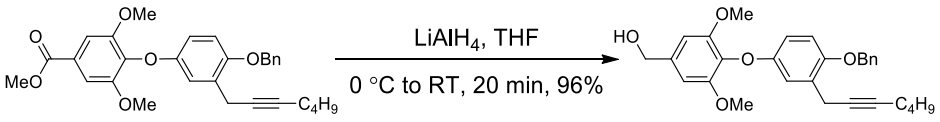
IR ν_{max} (neat, cm^{-1}) 2956 w, 2934 w, 1720 m, 1492 s, 1463 m, 1434 m, 1416 m, 1340 s, 1216 s, 1130 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45 – 7.27 (7H, m, 7 × Ar**H**), 7.15 (1H, dd, *J* = 3.1, 0.9 Hz, Ar**H**), 6.74 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.63 (1H, m, Ar**H**), 5.02 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.83 (6H, s, 2 × C**H$_3$**), 3.56 (2H, t, *J* = 2.4 Hz, C**H$_2$**), 2.15 (2H, tt, *J* = 7.1, 2.4 Hz, C**H$_2$**), 1.47 – 1.21 (4H, m, 2 × C**H$_2$**), 0.89 (3H, t, *J* = 7.5 Hz, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 166.7 (**C**O), 153.6 (**C**), 152.3 (**C**), 151.1 (**C**), 137.6 (**C**), 137.1 (**C**), 128.6 (**C**H), 127.9 (**C**), 127.8 (**C**H), 127.3 (**C**H), 127.0 (**C**), 116.3 (**C**H), 112.9 (**C**H), 112.3 (**C**H), 107.2 (**C**H), 83.1 (**C**), 70.7 (**C**H_2), 56.6 (**C**H_3), 52.4 (**C**H_3), 31.3 (**C**H_2), 22.8 (**C**H_2), 20.1 (**C**H_2), 18.7 (**C**H_2), 13.7 (**C**H_3), with one alkyne resonance not observed.

HRMS (ES^+) Calcd. for $C_{30}H_{32}NaO_6^+$ $[M+Na]^+$: 511.2091 found: 511.2100.

(4-(4-(Benzyloxy)-3-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (7.10)



5.20

$C_{30}H_{32}O_6$
MW: 488.57

7.10

$C_{29}H_{32}O_5$
MW: 460.56

To a solution of benzyl ester **5.20** (586 mg, 1.20 mmol) in THF (6 mL) at 0 °C was added a solution of $LiAlH_4$ (1.0 M in THF, 1.2 mL, 1.20 mmol) dropwise over 5 min. The resulting mixture was allowed to warm to RT over 20 min then MeOH (1 mL) and sat. Rochelle salt (10 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica, 50% EtOAc in petroleum

ether) afforded the title compound **7.10** (533 mg, 1.16 mmol, 96%) as a pale yellow oil.

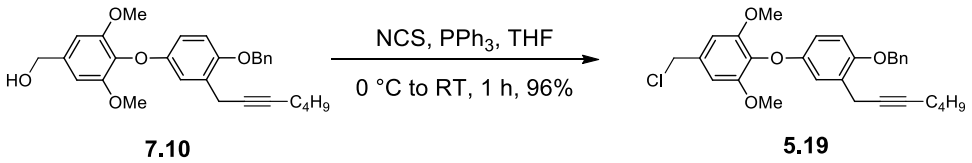
IR ν_{max} (neat, cm^{-1}) 3411 br., 2957 w, 2933 m, 1492 s, 1462 s, 1422 m, 1335 m, 1220 s, 1129 s, 1025 w, 957 w.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45 – 7.27 (5H, m, 5 × Ar**H**), 7.19 (1H, d, *J* = 3.1 Hz, Ar**H**), 6.73 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.68 (2H, s, 2 × Ar**H**), 6.60 (1H, dd, *J* = 8.8, 3.1 Hz), 5.01 (2H, s, C**H$_2$**), 4.70 (2H, d, *J* = 2.3 Hz, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.56 (2H, t, *J* = 2.4 Hz, C**H$_2$**), 2.17 (2H, tt, *J* = 7.1, 2.4 Hz, C**H$_2$**), 1.74 (1H, br. t, *J* = 2.3 Hz, O**H**), 1.51 – 1.33 (4H, m, C**H$_2$**), 0.90 (3H, t, *J* = 7.2 Hz, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.8 (**C**), 152.8 (**C**), 150.9 (**C**), 138.3 (**C**), 137.7 (**C**), 132.3 (**C**), 128.6 (**C**H), 127.9 (**C**H), 127.8 (**C**), 127.3 (**C**H), 116.4 (**C**H), 112.6 (**C**H), 112.3 (**C**H), 104.2 (**C**H), 82.9 (**C**), 70.8 (**C**H_2), 65.7 (**C**H_2), 56.5 (**C**H_3), 31.3 (**C**H_2), 22.1 (**C**H_2), 20.1 (**C**H_2), 18.7 (**C**H_2), 13.8 (**C**H_3) with one alkyne resonance not observed.

HRMS (ES^+) Calcd. for $C_{29}H_{32}NaO_5^+$ $[M+Na]^+$: 483.2142 found: 483.2128.

2-(4-(Benzyloxy)-3-(hept-2-yn-1-yl)phenoxy)-5-(chloromethyl)-1,3-dimethoxybenzene (5.19)



7.10

$C_{29}H_{32}O_5$
MW: 460.56

5.19

$C_{29}H_{31}ClO_4$
MW: 479.01

To a solution of benzyl alcohol **7.10** (125 mg, 0.27 mmol) in THF (1 mL) at 0 °C were added PPh_3 (87 mg, 0.33 mmol) and NCS (47 mg, 0.33 mmol). The reaction was warmed to RT and after 1 h sat. $NaHCO_3$ (1 mL) and sat. $Na_2S_2O_3$ (1 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 2 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether) to afford the title compound **5.19** (124 mg, 0.26 mmol, 96%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 2958 w, 2936 w, 1493 s, 1464 m, 1433 m, 1421 m, 1340 m, 1243 m, 1223 s, 1130 s.

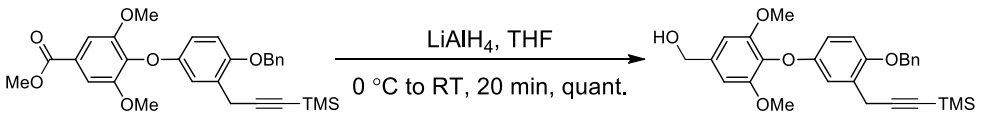
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45 – 7.28 (5H, m, 5 × Ar**H**), 7.17 (1H, d, J = 3.1 Hz, Ar**H**), 6.74 (1H, d, J = 8.9 Hz, Ar**H**), 6.69 (2H, s, 2 × Ar**H**), 6.62 (1H, dd, J = 8.8, 3.1 Hz, Ar**H**), 5.01 (2H, s, C**H$_2$**), 4.58 (2H, s, C**H$_2$**), 3.80 (6H, s, 2 × C**H$_3$**), 3.56 (2H, t, J = 2.3 Hz, C**H$_2$**), 2.17 (2H, tt, J = 7.0,

2.4 Hz, C**H**$_2$CH$_3$), 1.51 – 1.32 (4H, m, 2 × C**H**$_2$), 0.90 (3H, t, J = 7.2 Hz, C**H**$_3$).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.8 (**C**), 152.6 (**C**), 151.0 (**C**), 137.7 (**C**), 134.7 (**C**), 133.0 (**C**), 128.6 (**C**H), 127.9 (**C**H), 127.8 (**C**), 127.3 (**C**H), 116.3 (**C**H), 112.7 (**C**H), 112.3 (**C**H), 106.2 (**C**H), 83.1 (≡**C**), 70.7 (**C**H$_2$), 56.5 (**C**H$_3$), 46.8 (**C**H$_2$), 31.3 (**C**H$_2$), 22.1 (**C**H$_2$), 20.1 (**C**H$_2$), 18.7 (**C**H$_2$), 13.8 (**C**H$_3$) with one alkyne resonance not observed.

HRMS (ES$^+$) Calcd. for $C_{29}H_{31}ClNaO_4^+$ [M(^{35}Cl)+Na]$^+$: 501.1803 found: 501.1819.

(4-(4-(Benzyloxy)-3-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (7.11)



5.15

$C_{29}H_{32}O_6Si$
MW: 504.65

7.11

$C_{28}H_{32}O_5Si$
MW: 476.64

To a solution of benzyl ester **5.15** (810 mg, 1.70 mmol) in THF (9 mL) at 0 °C was added a solution of $LiAlH_4$ (1.0 M in THF, 1.7 mL, 1.70 mmol) dropwise over 5 min. The resulting mixture was allowed to warm to RT over 20 min then MeOH (1 mL) and sat. Rochelle salt (10 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in*

vacuo. Purification by column chromatography (silica, 50% EtOAc in petroleum ether) gave the title compound **7.11** (533 mg, 1.70 mmol, quant.) as a pale yellow oil

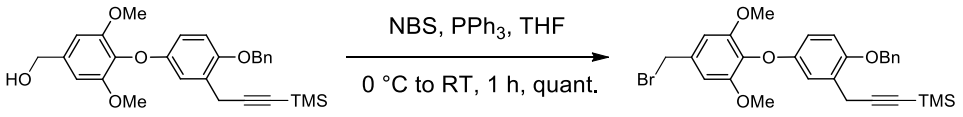
IR ν_{max} (neat, cm^{-1}) 3416 br., 2958 w, 2177 m, 1493 s, 1463 m, 1423 m, 1335 m, 1248 s, 1219 s, 1129 s, 1027 m, 955 w, 843 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.43 – 7.30 (5H, m, 5 × Ar**H**), 7.07 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.77 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.72 (1H, dd, *J* = 8.8, 3.0 Hz, Ar**H**), 6.68 (2H, s, 2 × Ar**H**), 5.01 (2H, s, C**H$_2$**), 4.69 (2H, d, *J* = 5.0 Hz, C**H$_2$**), 3.80 (6H, s, 2 × C**H$_3$**), 3.67 – 3.56 (2H, m, C**H$_2$**), 1.73 (1H, br. t, *J* = 5.9 Hz, O**H**), 0.11 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.8 (**C**), 152.8 (**C**), 150.8 (**C**), 138.4 (**C**), 137.6 (**C**), 132.2 (**C**), 128.6 (**C**H), 127.9 (**C**H), 127.3 (**C**H), 126.3 (**C**), 115.7 (**C**H), 113.5 (**C**H), 112.5 (**C**H), 104.3 (**C**H), 87.0 (**C**), 70.8 (**C**H_2), 65.7 (**C**H_2), 56.5 (**C**H_3), 21.2 (**C**H_2), 0.25 (**C**H_3) with one alkyne resonance not observed.

HRMS (ES^+) Calcd. for $C_{28}H_{32}NaO_5Si^+$ $[M+Na]^+$: 499.1911 found: 499.1887.

(3-(2-(Benzyloxy)-5-(4-(bromomethyl)-2,6-dimethoxyphenoxy)phenyl)prop-1-yn-1-yl)trimethylsilane (5.21)



7.11

$C_{28}H_{32}O_5Si$
MW: 476.64

5.21

$C_{28}H_{31}BrO_4Si$
MW: 539.53

To a solution of benzyl alcohol **7.11** (136 mg, 0.29 mmol) in THF (1 mL) at 0 °C were added PPh_3 (94.0 mg, 0.36 mmol) and NBS (70.0 mg, 0.39 mmol). The reaction was warmed to RT and after 1 h sat. $NaHCO_3$ (1 mL) and sat. $Na_2S_2O_3$ (1 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 2 mL) then the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica, 20% Et_2O in petroleum ether) afforded the title compound **5.21** (160 mg, 0.29 mmol, quant.) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 2959 w, 2177 m, 1493 s, 1463 s, 1421 m, 1339 m, 1246 s, 1212 s, 1133 s, 1027 m, 844 s.

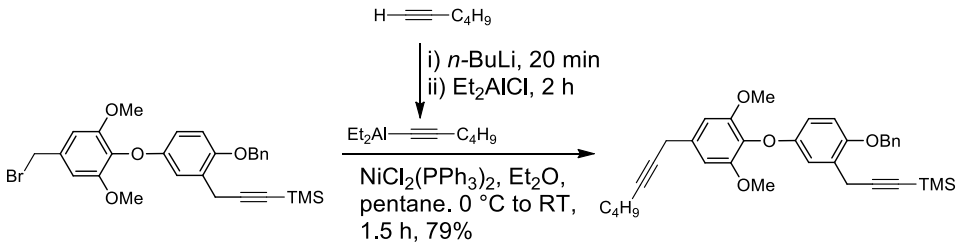
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44 – 7.29 (5H, m, 5 × Ar**H**), 7.07 (1H, d, J = 3.0 Hz, Ar**H**), 6.77 (1H, d, J = 8.8 Hz, Ar**H**), 6.74 – 6.67 (3H, m, 3 × Ar**H**), 5.02 (2H, s, C**H$_2$**), 4.49 (2H, s, C**H$_2$**), 3.80 (6H, s, 2 × C**H$_3$**), 3.64 (2H, s, C**H$_2$**), 0.12 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.7 (**C**), 152.6 (**C**), 150.9 (**C**), 137.6 (**C**), 134.9 (**C**), 133.0 (**C**), 128.6 (**C**H), 127.9 (**C**H), 127.3 (**C**), 126.4 (**C**H), 115.8 (**C**H), 113.5 (**C**H), 112.5 (**C**H),

106.7 (**C**H), 104.3 (**C**), 87.0 (**C**), 70.7 (**C**H_2), 56.6 (**C**H_3), 34.0 (**C**H_2), 21.2 (**C**H_2), 0.3 (**C**H_3).

HRMS (ES^+) Calcd. for $C_{28}H_{32}BrNaO_4Si^+$ $[M(^{79}Br)+Na]^+$: 516.1067 found: 561.1094.

(3-(2-(Benzyloxy)-5-(4-(hept-2-yn-1-yl)-2,6-dimethoxyphenoxy)phenyl)prop-1-yn-1-yl)trimethylsilane (5.22)



5.21

$C_{28}H_{31}BrO_4Si$
MW: 539.53

5.22

$C_{34}H_{40}O_4Si$
MW: 540.76

Adapted from a procedure by Gau *et al.*[58] To a solution of hex-1-yne (0.07 mL, 0.58 mmol) in pentane (2 mL) at 0 °C was added *n*-BuLi (1.98 M in hexane, 0.29 mL, 0.58 mmol) over 5 min. After 30 min Et_2AlCl (1.0 M in hexane, 0.58 mL, 0.58 mmol) was added over 5 min. The solution was warmed to RT after 20 min and after a further 2 h Et_2O (4 mL) and $NiCl_2(PPh_3)_2$ (13.0 mg, 0.02 mmol) were added. After a further 15 min benzyl bromide **5.21** (115 mg, 0.21 mmol) was added followed after 90 min by sat. NH_4Cl (1 mL). The aqueous phase was separated and extracted with Et_2O (3 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (silica, 10% Et_2O in petroleum

ether) afforded the title compound **5.22** (192 mg, 0.34 mmol, 72%) as a yellow oil.

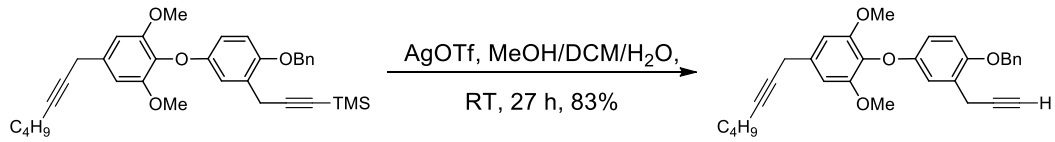
IR ν_{max} (neat, cm^{-1}) 2958 br., 2933 w, 2177 w, 1493 s, 1463 s, 1423 m, 1336 m, 1219 s, 1128 s, 1027 w, 844 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45 – 7.33 (5H, m, 5 × Ar**H**), 7.31 (1H, d, J = 6.6 Hz, Ar**H**), 7.07 (1H, d, J = 2.4 Hz, Ar**H**), 6.77 (1H, d, J = 8.7 Hz, Ar**H**), 6.67 (2H, d, J = 0.8 Hz, 2 × Ar**H**), 5.01 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.65 – 3.62 (2H, m, C**H$_2$**), 3.58 (2H, t, J = 2.5 Hz, C**H$_2$**), 2.26 (2H, tt, J = 6.9, 2.4 Hz, C**H$_2$**), 1.61 – 1.42 (4H, m, 2 × C**H$_2$**), 0.93 (3H, t, J = 7.2 Hz, C**H$_3$**), 0.11 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$) δ ppm 153.5 (**C**), 152.9 (**C**), 150.8 (**C**), 137.6 (**C**), 135.0 (**C**), 131.1 (C) 128.6 (**C**H), 127.9 (**C**H), 127.3 (**C**H), 126.3 (**C**), 115.6 (**C**H), 113.5 (**C**H), 112.5 (**C**H), 105.4 (**C**H), 87.0 (**C**), 83.3 (**C**), 70.2 (**C**H_2), 56.5 (**C**H_3), 31.3 (**C**H_2), 25.6 (**C**H_2), 22.1 (**C**H_2), 21.2 (**C**H_2), 18.7 (**C**H_2), 13.8 (**C**H_3), 0.23 (**C**H_3) with two alkyne resonance not observed.

HRMS (ES^+) Calcd. for $C_{34}H_{40}NaO_4Si^+$ $[M+Na]^+$: 563.2588 found: 563.2601.

2-(4-(Benzyloxy)-3-(prop-2-yn-1-yl)phenoxy)-5-(hept-2-yn-1-yl)-1,3-dimethoxybenzene (5.18)



5.22

$C_{34}H_{40}O_4Si$
MW: 540.76

5.18

$C_{31}H_{32}O_4$
MW: 468.58

To diyne **5.22** (379 mg, 0.70 mmol) in MeOH/H_2O/DCM (4.5 mL/1 mL/7 mL) was added AgOTf (59 mg, 0.21 mmol). After 20 h further AgOTf (18 mg, 0.07 mmol) was added followed after 7 h by sat. NH_4Cl (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica, 20% Et_2O in petroleum ether) afforded the title compound **5.18** (272 mg, 0.58 mmol, 83%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 3288 w, 2957 br., 2933 w, 1493 s, 1461 m, 1423 m, 1337 w, 1219 s, 1127 s, 1026 w, 969 w, 737 m.

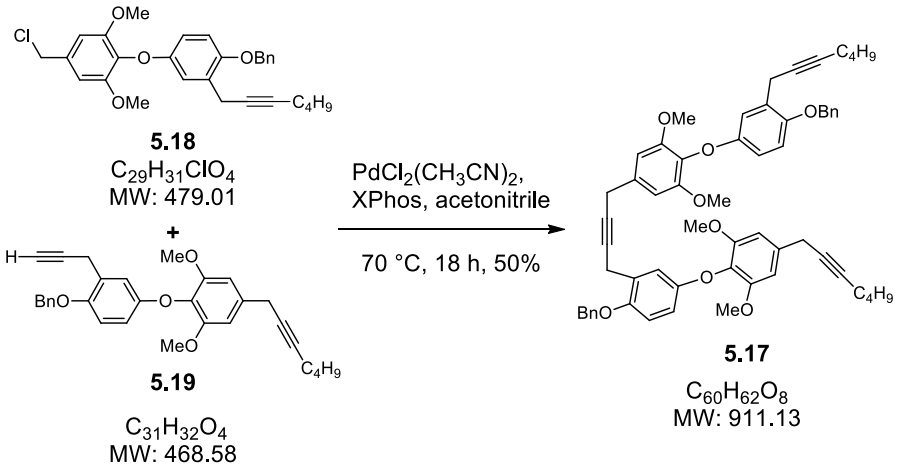
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45 – 7.28 (5H, m, 5 × Ar**H**), 7.20 (1H, d, J = 3.1 Hz, Ar**H**), 6.74 (1H, d, J = 8.9 Hz, Ar**H**), 6.66 (2H, s, 2 × Ar**H**), 6.61 (1H, dd, J = 8.8, 3.1 Hz Ar**H**), 5.02 (2H, s, C**H$_2$**), 3.78 (6H, s, 2 × C**H$_3$**), 3.59 (4H, m, 2 × C**H$_2$**), 2.26 (2H, tt, J = 7.0, 2.6 Hz, C**H$_2$**), 2.11 (1H, t,

J = 2.7 Hz, C**H**), 1.61 – 1.40 (4H, m, 2 × C**H**$_2$), 0.93 (3H, t, J = 7.2 Hz, C**H**$_3$).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 152.9 (**C**), 150.8 (**C**), 137.6 (**C**), 135.1 (**C**), 131.3 (**C**), 128.6 (**C**H), 127.9 (**C**H), 127.4 (**C**H), 126.2 (**C**), 116.7 (**C**H), 113.0 (**C**H), 112.4 (**C**H), 105.3 (**C**H), 83.3 (**C**), 82.0 (**C**), 70.8 (**C**H$_2$), 70.5 (**C**), 56.4 (**C**H$_3$), 31.3 (**C**H$_2$), 25.7 (**C**H$_2$), 22.1 (**C**H$_2$), 19.8 (**C**H$_2$), 18.7 (**C**H$_2$), 13.8 (**C**H$_3$) with one alkyne resonance not observed.

HRMS (ES$^+$) Calcd. for $C_{31}H_{32}NaO_4^+$ [M+Na]$^+$: 491.2193 found: 491.2203.

2-(4-(Benzyloxy)-3-(4-(4-(4-(benzyloxy)-3-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)but-2-yn-1-yl)phenoxy)-5-(hept-2-yn-1-yl)-1,3-dimethoxybenzene (5.17)



A flask charged with benzyl chloride **5.18** (72.0 mg, 0.140 mmol), $PdCl_2(CH_3CN)_2$ (2.0 mg, 0.008 mmol), XPhos (11.0 mg, 0.023 mmol) and Cs_2CO_3 (44.0 mg, 0.130 mmol) was evacuated then filled with Ar in three cycles. Alkyne **5.19** (0.56 mL, 0.120 mmol) and CH_3CN (1 mL) were then added sequentially. The reaction was heated at 70 °C for 18 h then cooled to RT, filtered through a plug of silica, concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether) to afford the title compound **5.17** (54.0 mg, 0.060 mmol, 50%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 2957 br., 2930 m, 1493 s, 1462 s, 1423 m, 1337 m, 1220 s, 1128 s.

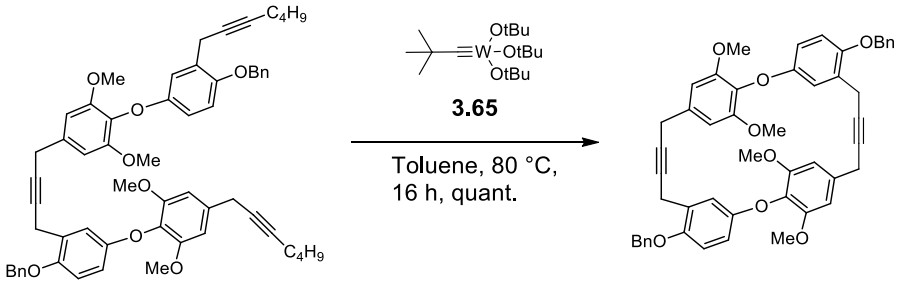
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44 – 7.28 (11H, m, 11 × Ar**H**), 7.19 (1H, d, *J* = 3.1 Hz, Ar**H**), 6.72 (1H, d, *J* = 4.4 Hz, Ar**H**), 6.70 (1H, d, *J* = 4.4 Hz, Ar**H**), 6.68 (2H, s, 2 × Ar**H**), 6.64 (2H, s, 2 × Ar**H**), 6.59 (1H, dd, *J* = 8.8, 3.1 Hz, Ar**H**), 6.51 (1H, dd, *J* = 8.8, 3.1 Hz, Ar**H**), 5.01 (2H, s, C**H$_2$**), 4.99 (2H, s, C**H$_2$**), 3.75 (6H, s, 2 × C**H$_3$**) 3.74 (6H, s, 2 × C**H$_3$**), 3.67 (2H, d, *J* = 2.4 Hz, C**H$_2$**), 3.64 (2H, d, *J* = 2.5 Hz, C**H$_2$**), 3.58 (2H, t, *J* = 2.5 Hz, C**H$_2$**), 3.56 (2H, d, *J* = 2.4 Hz, C**H$_2$**), 2.26 (2H, tt, *J* = 6.9, 2.5 Hz, C**H$_2$**), 2.17 (2H, tt, *J* = 7.0, 2.4 Hz, C**H$_2$**), 1.52 – 1.33 (8H, m, 4 × C**H$_2$**), 0.92 (3H, t, *J* = 7.5 Hz, C**H$_3$**), 0.88 (3H, t, *J* = 7.1 Hz, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.6 (**C**), 153.5 (**C**), 152.9 (**C**), 150.8 (**C**), 150.8 (**C**), 137.8 (**C**), 137.6 (**C**), 135.1 (**C**), 134.7 (**C**),

131.3 (**C**), 131.1 (**C**), 128.6 (**C**H), 128.5 (**C**H), 128.0 (**C**H), 127.8 (**C**H), 127.7 (C), 127.4 (C), 127.3 (**C**H), 127.2 (**C**H), 116.9 (**C**H), 116.5 (**C**H), 112.6 (CH), 112.3 (**C**H), 112.3 (**C**H), 112.1 (**C**H) 105.3 ($\mathbf{C}_{Ar}$H), 105.2 ($\mathbf{C}_{Ar}$H), 83.3 (**C**), 83.0 (**C**), 80.5 (**C**), 79.9 (**C**), 70.8 ($\mathbf{C}H_2$), 70.7 ($\mathbf{C}H_2$), 56.5 ($\mathbf{C}H_3$), 56.3 ($\mathbf{C}H_3$), 31.3 ($\mathbf{C}H_2$), 31.3 ($\mathbf{C}H_2$), 29.9 ($\mathbf{C}H_2$), 25.7 ($\mathbf{C}H_2$), 25.7 ($\mathbf{C}H_2$), 22.1 ($\mathbf{C}H_2$), 20.2 ($\mathbf{C}H_2$), 20.1 ($\mathbf{C}H_2$), 18.7 ($\mathbf{C}H_2$), 13.8 ($\mathbf{C}H_3$).

HRMS (ES^+) Calcd. for $C_{60}H_{62}NaO_8^+$ $[M+Na]^+$: 933.4337 found: 933.4346.

Macrocycle 4.28



5.17

$C_{60}H_{62}O_8$
MW: 911.13

4.28

$C_{50}H_{44}O_8$
MW: 772.88

To a solution of triyne **5.17** (20 mg, 0.022 mmol) in toluene (5 mL) in a glove box was added the Schrock catalyst **3.65** (2 mg, 0.008 mmol). The reaction was heated at 80 °C for 16 h then filtered through a plug of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 10 to 30% EtOAc in petroleum ether) afforded the title compound **4.28** (18 mg, 0.022 mmol, quant.) as a yellow oil, which was crystallised from EtOAc at –20 °C.

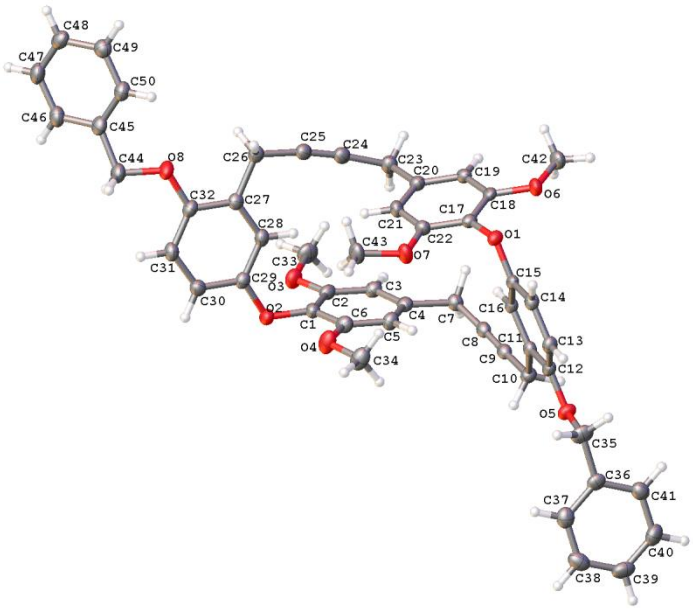
IR ν_{max} (neat, cm^{-1}) 2957 s, 2917 m, 1731br., 1496 s, 1462 m, 1423 m, 1337 w, 1239 m, 1218 s, 1195 m, 1128 s, 1026 w, 963 w, 913 w.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.47 – 7.28 (10H, m, 10 × Ar**H**), 7.10 (2H, dd, J = 8.8, 3.0 Hz, 2 × Ar**H**), 6.98 (2H, d, J = 3.0 Hz, 2 × Ar**H**), 6.89 (2H, d, J = 8.8 Hz, 2 × Ar**H**), 6.54 (4H, s, 4 × Ar**H**), 5.06 (4H, s, 2 × C**H$_2$**), 3.69 (12H, s, 4 × C**H$_3$**), 3.63 (4H, br s, 2 × C**H$_2$**), 3.51 (4H, br s, 2 × C**H$_2$**).

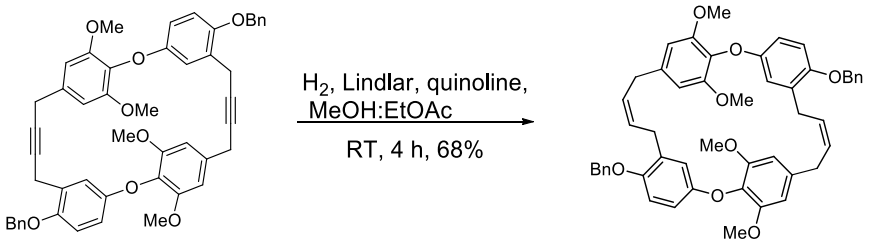
^{13}C NMR (100 MHz; $CDCl_3$):δ ppm 153.4 (**C**), 152.8 (**C**), 150.7 (**C**), 137.6 (**C**), 134.1 (**C**), 131.3 (**C**), 128.7 (**C**H), 128.0 (**C**H), 127.4 (**C**H), 126.4 (**C**), 114.9 (**C**H), 113.3 (**C**H), 112.6 (**C**H), 105.0 (**C**H), 80.9 (**C**), 80.6 (**C**), 70.7 (**C**H_2), 56.6 (**C**H_3), 25.1 (**C**H_2), 20.2 (**C**H_2).

HRMS (ES^+) Calcd. for $C_{50}H_{44}NaO_8^+$ $[M+Na]^+$: 795.2928 found: 795.2917.

X-Ray



Macrocycle 5.23



4.28

$C_{50}H_{44}O_8$
MW: 772.88

5.23

$C_{50}H_{48}O_8$
MW: 776.91

To a solution of diyne **4.28** (15.0 mg, 0.019 mmol) in MeOH (2 mL) and EtOAc (0.5 mL) was added Lindlar catalyst (1.0 mg) and quinoline (30 µL, 0.25 mmol). The reaction was placed under an atmosphere of hydrogen for 4 h then filtered through a plug of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 10 to 20% EtOAc in petroleum ether) afforded the title compound **5.23** (10.0 mg, 0.013 mmol, 68%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 2916 br., 2849 m, 1492 m, 1462 m, 1423 w, 1217 m, 1127 s, 1026 w, 805 w, 754 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.50 – 7.29 (10H, m, 10 × Ar**H**), 7.07 (2H, dd, J = 8.8, 3.1 Hz, 2 × Ar**H**), 6.92 (2H, d, J = 8.9 Hz, 2 × Ar**H**), 6.33 (2H, d, J = 3.1 Hz, 2 × Ar**H**), 6.27 (4H, s, 4 × Ar**H**), 5.79 – 5.68 (2H, m, 2 × =C**H**), 5.62 – 5.51 (2H, m, 2 × =C**H**), 5.10 (4H, s, 2 × C**H$_2$**), 3.60 (12H, s, 4 × C**H$_3$**), 3.47 (4H, d, J = 7.5 Hz, 2 × C**H$_2$**), 3.36 (4H, d, J = 7.7 Hz, 2 × C**H$_2$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.3 (**C**), 152.9 (**C**), 151.4 (**C**), 138.1 (**C**), 137.8 (**C**), 130.9 (**C**), 130.0 (**C**), 128.7 (**C**H), 128.6 (**C**H), 128.5 (**C**H), 127.9 (**C**H), 127.4 (**C**H), 115.1 (**C**H), 114.2 (**C**H), 113.1 (**C**H), 105.9 (**C**H), 70.8 (**C**H$_2$), 56.4 (**C**H$_3$), 33.8 (**C**H$_2$), 28.8 (**C**H$_2$).

HRMS (ES^+) Calcd. for $C_{50}H_{48}NaO_8^+$ $[M+Na]^+$: 799.3241 found: 799.3236.

Macrocycle 3.1

5.23

$C_{50}H_{48}O_8$
MW: 776.91

3.1

$C_{32}H_{28}O_8$
MW: 540.56

Experimental

Adapted from a protocol Coe *et al*.[68] To a solution of macrocycle **5.23** (5 mg, 0.064 mmol) and TBAI (138 mg, 0.05mmol) in DCM (1 mL) at –78 °C was added BCl_3 (0.16 mL, 0.080 mmol) dropwise. The reaction mixture was warmed to 0 °C for 3 h then ice (1.0 g) and sat. $NaHCO_3$ (2 mL) were added. The aqueous phase was separated and extracted with DCM (3 × 3 mL) then the organic phases were combined, washed with 1M HCl (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting mixture was next passed through a amberlyst 15 column twice then purified by preparative HPLC (C-18, Luna, 30 to 80% acetonitrile in water, 0.01% TFA, 22 min) to afford the chrysophaentin analogue **3.1** (3.2 mg, 0.0060 mmol, 92%) as a white solid.

IR (thin film) 3431 br., 1686 s, 1439 m, 1210 s, 1146 s, 848 w, 805 w, 726 m.

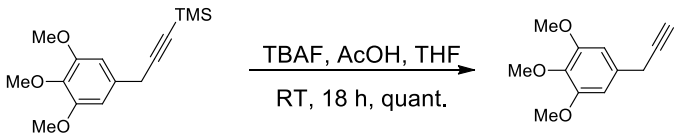
^{1}H NMR (400 MHz; CD_3OD): δ ppm 6.93 (2H, dd, *J* = 8.7, 2.9 Hz, 2 × Ar**H**), 6.77 (2H, d, *J* = 8.7 Hz, 2 × Ar**H**), 6.41 (2H, d, *J* = 3.1 Hz, 2 × Ar**H**), 6.22 (4H, s, 4 × Ar**H**), 5.56 (2H, dt, *J* = 10.8, 7.9 Hz, 2 × =C**H**), 5.37 (2H, dt, J = 10.8, 7.7 Hz, 2 × =C**H**), 3.34 (4H, br d, *J* = 7.3 Hz, 2 × C**H$_2$**), 3.22 (4H, br d, *J* = 7.3 Hz, 2 × C**H$_2$**).

^{13}C NMR (100 MHz; CD_3OD): δ ppm 153.0 (**C**), 151,6 (**C**), 150.4 (**C**), 139.9 (**C**), 130.2 (**C**H), 128.8 (**C**), 127.9 (**C**H), 119.7 (**C**), 116.8 (**C**H), 116.1 (**C**H), 114.0 (**C**H), 109.7 (**C**H), 34.5 (**C**H$_2$), 28.8 (**C**H$_2$).

HRMS (ES$^+$) Calcd. for $C_{32}H_{28}NaO_8^+$ $[M+Na]^+$: 563.1676 found: 563.1666.

7.6 Experimental Chapter 6

1,2,3-Trimethoxy-5-(prop-2-yn-1-yl)benzene (6.11)



3.28 $C_{15}H_{22}O_3Si$ MW: 278.42

6.11 $C_{12}H_{14}O_3$ MW: 206.24

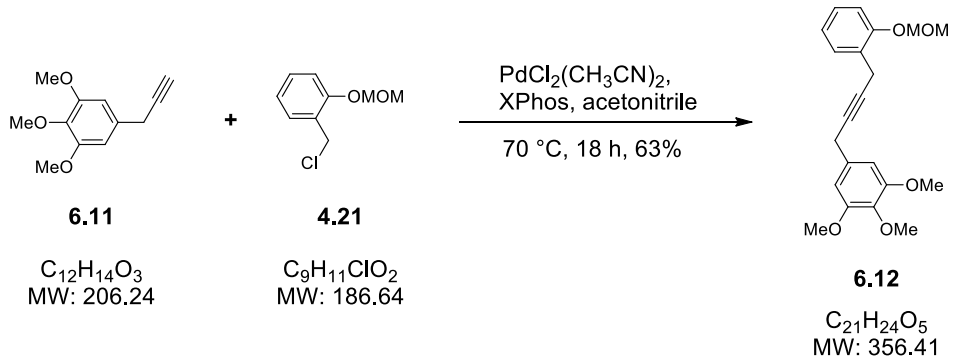
To a solution of alkyne **3.28** (2.73 g, 9.80 mmol) in THF (50 mL) was added AcOH (2.81 mL, 49.0 mmol) followed by TBAF (1.0 M, 49.0 mL, 49.0 mmol). After 18 h the reaction mixture partitioned between Et_2O (50 mL) and H_2O (50 mL) then the aqueous phase was separated and extracted with Et_2O (3 × 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 10 to 20% Et_2O in petroleum ether) afforded the title compound **6.11** (2.02 mmol, 9.8 mmol, quant.) as a yellow oil.

The physical and spectroscopic data were in agreement with reported values.[101]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.58 (2H, s br., 2 × Ar**H**), 3.86 (6H, s, 2 × C**H$_3$**), 3.83 (3H, s, C**H$_3$**), 3.56 (2H, dt, *J* = 2.7, 0.62 Hz C**H$_2$**), 2.21 (1 H, t, *J* = 2.7 Hz, C**H**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 137.0 (**C**), 131.8 (**C**), 105.1 (**C**H), 82.0 (**C**), 70.8 (**C**), 61.0 (**C**H_3), 56.3 (**C**H_3), 25.2 (**C**H_2).

1,2,3-Trimethoxy-5-(4-(2-(methoxymethoxy)phenyl)but-2-yn-1-yl)benzene (6.12)



6.11

$C_{12}H_{14}O_3$
MW: 206.24

4.21

$C_9H_{11}ClO_2$
MW: 186.64

6.12

$C_{21}H_{24}O_5$
MW: 356.41

A flask charged with $PdCl_2(CH_3CN)_2$ (40.0 mg, 0.15 mmol), XPhos (219 mg, 0.45 mmol) and Cs_2CO_3 (1.06 g, 3.00 mmol) was evacuated then filled with Ar in three cycles. Alkyne **6.11** (625 mg, 3.00 mmol), benzyl chloride **4.21** (562 mg, 3.00 mmol) and CH_3CN (10 mL) were added sequentially then the reaction mixture was heated at 70 °C for 18 h. After cooling to RT and filtration through a plug of silica, the solvent was removed *in vacuo*. Purification by column chromatography (silica, 20 to 30% Et_2O in petroleum ether) afforded the title compound **6.12** (731 mg, 1.89 mmol, 63%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 2939 w, 1506 m, 1492 m, 1457 m, 1422 m, 1333 m, 1235 s, 1126 s, 1079 m, 1002 s, 756 m.

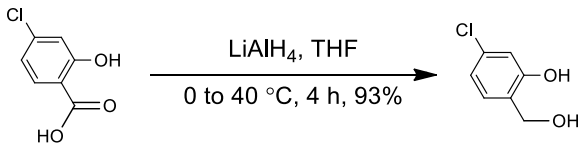
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.56 (1H, d, J = 7.9 Hz, Ar**H**), 7.20 (1H, td, J = 8.3, 1.9 Hz, Ar**H**), 7.06 (1H, dd, J = 8.3, 1.0 Hz,

Ar**H**), 6.99 (1H, td, *J* = 7.4, 1.1 Hz, Ar**H**), 6.61 (2H, s, 2 × Ar**H**), 5.21 (2H, s, C**H**$_2$), 3.83 (9H, s, 3 × C**H**$_3$), 3.66 (2H, t, *J* = 2.3 Hz, C**H**$_2$), 3.61 (2H, d, *J* = 2.5 Hz, C**H**$_2$), 3.47 (3H, s, C**H**$_3$).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 154.6 (**C**), 153.3 (**C**), 136.7 (**C**), 133.1 (**C**), 129.2 (**C**H), 127.9 (**C**H), 126.6 (**C**), 121.8 (**C**H), 113.8 (**C**H), 105.0 (**C**H), 94.6 (**C**H_2), 80.3 (**C**), 79.9 (**C**), 61.0 (**C**H_3), 56.2 (**C**H_3), 25.6 (**C**H_2), 19.9 (**C**H_2).

HRMS (ES^-) Calcd. for $C_{21}H_{24}NaO_5^+$ $[M+Na]^+$: 379.1516, found: 379.1524.

5-Chloro-2-(hydroxymethyl)phenol (6.8)



6.7

$C_7H_5ClO_3$
MW: 172.56

6.8

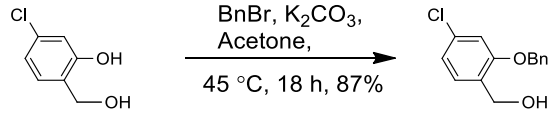
$C_7H_7ClO_2$
MW: 158.58

To a solution of acid **6.7** (17.3 g, 100 mmol) in THF (360 mL) at 0 °C was added a solution of $LiAlH_4$ (1.0 M in THF, 150 mL, 150 mmol) dropwise over 15 min. After heating at 40 °C for 4 h, MeOH (40 mL) and sat. Rochelle's salt (300 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 500 mL) then the organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, EtOAc) afforded benzyl alcohol **6.8** (14.8 g, 93 mmol, 93%) as an off-white solid.

The physical and spectroscopic data were in agreement with reported values. [103]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.49 (1H, s, O**H**), 6.95 (1H, d, J = 8.1 Hz, Ar**H**), 6.91 (1H, d, J = 2.0 Hz, Ar**H**), 6.83 (1H, dd, J = 8.0, 2.0 Hz, Ar**H**), 4.85 (2H, d, J = 5.1 Hz, C**H$_2$**), 2.22 (1H, t, J = 5.6 Hz, O**H**).

(2-(Benzyloxy)-4-chlorophenyl)methanol (6.9)



6.8
$C_7H_7ClO_2$
MW: 158.58

6.9
$C_{14}H_{13}ClO_2$
MW: 248.70

To a solution of phenol **6.8** (9.32 g, 58.7 mmol) in acetone (400 mL) was added K_2CO_3 (23.4 mg, 170 mmol) and BnBr (7.60 mL, 64.6 mmol). The reaction mixture was heated at 45 °C for 18 h then cooled and partitioned between EtOAc (200 mL) and water (200 mL). The aqueous phase was separated and extracted with EtOAc (3 × 200 mL) then the organic phases were combined, washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 40 % EtOAc in petroleum ether) gave the title compound **6.9** (12.7 mg, 51.0 mmol, 87%) as a white solid.

MP 57.5 – 59 °C (EtOAc).

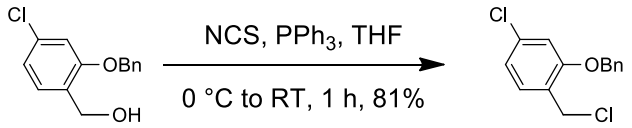
IR ν_{max} (neat, cm^{-1}) 3357 br., 2923 w, 1583 m, 1490 s, 1455 m, 1407 s, 1382 m, 1241 s, 1093 m, 1040 m, 1011s, 898 s, 836m, 737s, 697 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46 – 7.31 (5H, m, 5 × Ar**H**), 7.28 – 7.23 (1H, m, Ar**H**), 6.99 – 6.93 (2H, m, 2 × Ar**H**), 5.09 (2H, s, C**H**$_2$), 4.69 (2H, s, C**H**$_2$).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 157.2 (**C**) 136.2 (**C**) 134.3 (**C**) 129.6 (**C**H) 128.93 (**C**H) 128.5 (**C**H) 128.3 (**C**H) 127.5 (**C**) 121.2 (**C**H) 112.6 (**C**H) 70.6 (**C**H$_2$) 61.4 (**C**H$_2$).

HRMS (ES^+) Calcd. for $C_{14}H_{13}ClNaO_2^+$ [M(^{35}Cl)+Na]$^+$: 271.0496, found: 271.0486.

2-(Benzyloxy)-4-chloro-1-(chloromethyl)benzene (6.10)



6.9

$C_{14}H_{13}ClO_2$
MW: 248.70

6.10

$C_{14}H_{12}Cl_2O$
MW: 267.15

To a solution of benzyl alcohol **6.9** (1.12 g, 4.47 mmol) in THF (18 mL) at 0 °C were added PPh_3 (1.40 g, 5.36 mmol) and NCS (774 mg, 5.80 mmol). The reaction was warmed to RT and after 1 h sat. $NaHCO_3$ (20 mL) and sat. $Na_2S_2O_3$ (20 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 20 mL) then the organic phases were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 5 to 10% Et_2O in petroleum ether) afforded the title compound **6.10** (966 mg, 3.62 mmol, 81%) as a colourless oil.

Experimental

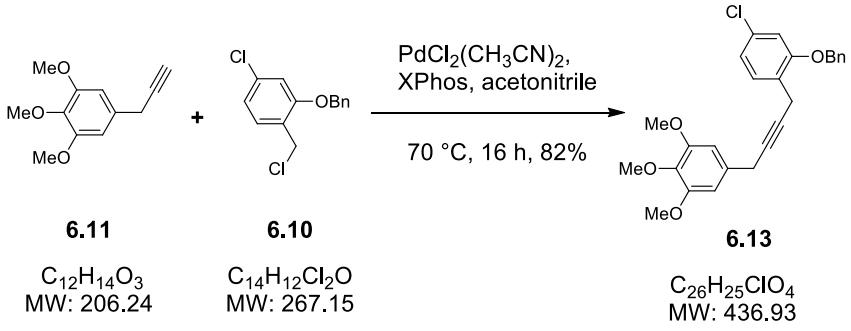
IR ν_{max} (neat, cm^{-1}) 3034 w, 1490 s, 1409 m, 1383 m, 1250 s, 1114 m, 1095 m, 1025 m, 917 m, 839 m, 739 s, 696 s

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.51 – 7.28 (6H, m, 6 × Ar**H**), 7.02 – 6.91 (2H, m, 2 × Ar**H**), 5.12 (2H, s, C**H$_2$**), 4.65 (2H, s, C**H$_2$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 157.1 (**C**), 136.3 (**C**), 135.5 (**C**), 131.5 (**C**H), 128.8 (**C**H), 128.3 (**C**H), 127.4 (**C**H), 125.1 (**C**), 121.2 (**C**H), 113.1 (**C**H), 70.6 (**C**H_2), 41.1 (**C**H_2).

HRMS (EI) Calcd. for $C_{14}H_{12}Cl_2O_2$ $[M(^{35}Cl)]^{+\bullet}$: 266.0265, found: 266.0266.

5-(4-(2-(Benzyloxy)-4-chlorophenyl)but-2-yn-1-yl)-1,2,3-trimethoxybenzene (6.13)



6.11 $C_{12}H_{14}O_3$ MW: 206.24

6.10 $C_{14}H_{12}Cl_2O$ MW: 267.15

6.13 $C_{26}H_{25}ClO_4$ MW: 436.93

A flask charged with $PdCl_2(CH_3CN)_2$ (40.0 mg, 0.15 mmol), XPhos (219 mg, 0.45 mmol) and Cs_2CO_3 (1.06 g, 3.00 mmol) was evacuated then filled with Ar in three cycles. Alkyne **6.11** (618 mg, 3.00 mmol), benzyl chloride **6.10** (801 mg, 3.00 mmol) and CH_3CN (10 mL) were added sequentially then the reaction mixture was heated at 70 °C for 16 h. After cooling to RT and filtration through a plug of silica, the solvent was removed *in vacuo*. Purification by column

chromatography (silica, 30% Et_2O in petroleum ether) afforded the title compound **6.13** (1.08 g, 2.46 mmol, 82%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 2936 w, 2836 w, 2380 w, 1505 m, 1489 m, 1456 m, 1420 m, 1333 m, 1238 s, 1127 s, 1009 m, 739 m.

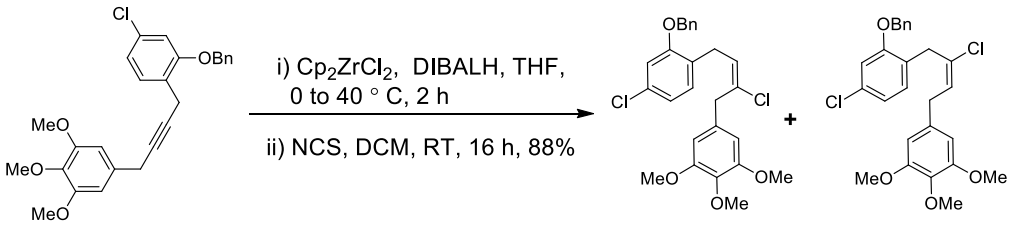
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.48 (1H, d, J = 8.0 Hz, Ar**H**), 7. 45 – 7. 31 (5H, m, 5 × Ar**H**), 6.99 – 6.88 (2H, m, 2 × Ar**H**), 6.59 (2H, s, 2 × Ar**H**), 5.07 (2H, s, C**H$_2$**), 3.83 (3H, s, C**H$_2$**), 3.82 (6H, s, 2 × C**H$_3$**), 3.63 (2H, d, J = 2.3 Hz, C**H$_2$**), 3.61 (2H, d, J = 2.2 Hz, C**H$_2$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 156.6 (**C**), 153.4 (**C**), 136.9 (**C**), 136.6 (**C**), 133.2 (**C**), 133.1 (**C**), 129.9 (**C**H), 128.8 (**C**H), 128.3 (**C**H), 127.3 (**C**H), 125.0 (**C**), 120.9 (**C**H), 112.3 (**C**H), 105.1 (**C**H), 80.4 (**C**), 79.8 (**C**), 70.4 (**C**H_2), 61.0 (**C**H_3), 56.2 (**C**H_3), 25.6 (**C**H_2), 19.7 (**C**H_2).

LRMS (HPLC–MS; ES^+): 437 ($[M+H]^+$, 100%).

HRMS (ES^+) Calcd. for $C_{26}H_{25}ClNaO_4^+$ ($M(^{35}Cl)+Na)^+$: 459.1334, found: 459.1340.

(*E*)-5-(4-(2-(Benzyloxy)-4-chlorophenyl)-2-chlorobut-2-en-1-yl)-1,2,3-trimethoxybenzene (6.17)



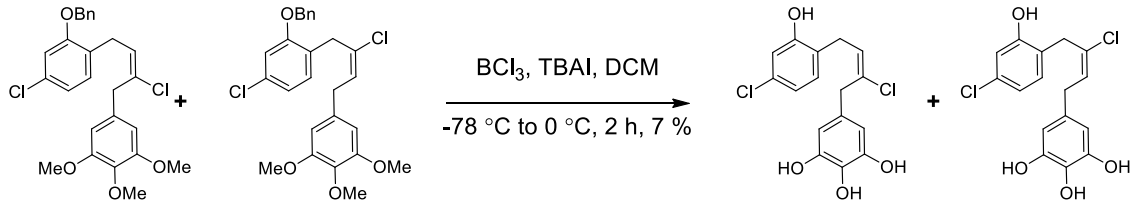
6.13 **6.17** **6.18**

$C_{26}H_{25}ClO_4$
MW: 436.93

$C_{26}H_{26}Cl_2O_4$
MW: 473.39

To a solution of Cp_2ZrCl_2 (304 mg, 1.00 mmoL) in THF (8 mL) at 0 °C was added DIBALH (1.0 M in hexane, 1.0 mL, 1.00 mmol) over 5 min. After 1 h the solution was warmed to RT, then alkyne **6.13** (233 mg, 0.50 mmol) was added. The reaction was heated at 40 °C for 2 h then cooled to RT and a solution of NCS (67.0 mg, 0.5 mmol) in DCM (4 mL) was added, followed after 16 h by MeOH (4 mL). Filtration through a plug of silica, concentrated *in vacuo* and purification by column chromatography (silica, 20% Et_2O in petroleum ether) afforded the title compound **6.17** as an inseparable 2 : 1 mixture with its regioisomer **6.18** (210 mg, 0.44 mmol, 88%) as a yellow oil which was use in the next reaction without further purification.

(*E*)-5-(2-Chloro-4-(4-chloro-2-hydroxyphenyl)but-2-en-1-yl)benzene-1,2,3-triol (6.19)



6.17 **6.18** **6.19** **6.20**

$C_{26}H_{26}Cl_2O_4$
MW: 473.39

$C_{16}H_{14}Cl_2O_4$
MW: 341.19

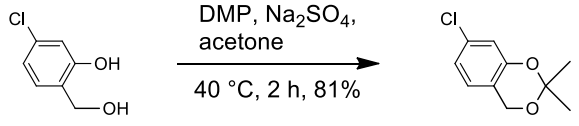
Adapted from a protocol by Coe *et al.*[68] To a solution of alkenes **X** and **X** (210 mg, 0.44 mmol) and TBAI (813 mg, 2.20 mmol) in DCM (15 mL) at –78 °C was added BCl_3 (1.0 M in DCM, 3.5 mL, 3.50 mmol) dropwise. The reaction mixture was warmed to 0 °C for 2 h then ice (3.0 g) and sat. $NaHCO_3$ (10 mL) were added. The aqueous phase was separated and extracted with DCM (3 × 10 mL) then the organic phases were combined, washed with 1 M HCl (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was first purified through through a column of amberlyst 15® twice then injected in a preparative HPLC (C-18, Luna, 40-90% acetonitrile in water, 0.01% TFA, 8 min) to afford an inseparable 3 : 1 mixture of vinyl chloride **6.19** and its regioisomer **6.20** (11 mg, 0.032 mmol, 7%) as a white solid.

^{1}H NMR (400 MHz; CD_3OD):δ ppm mixture of regioisomers (†major isomer) 7.01† (1H, d, *J* = 8.0 Hz, Ar**H**), 7.09 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.80 – 6.78† (2H, m, Ar**H**), 6.77 – 6.74 (2H, m, 2 × Ar**H**), 6.28† (2H, s, 2 × ArH), 6.21 (2H, s, 2 × Ar**H**), 5.82† (1H, t, *J* = 7.8 Hz, =C**H**), 5.81 (1H, t, *J* =

7.8 Hz, =C**H**), 3.70 (2H, s, C**H$_2$**), 3.60† (2H, s, C**H$_2$**), 3.43† (2H, d, *J* = 7.8 Hz, C**H$_2$**), 3.32 (2H, d, *J* = 7.8 Hz, C**H$_2$**).

^{13}C NMR (75 MHz; CD_3OD):δ ppm mixture of regioisomers (†major isomer) 157.5 & 157.2† (**C**), 147.1 & 147.0† (**C**), 134.7† (**C**), 133.7 (**C**), 133.4† (**C**), 132.8† (**C**), 132.5 (**C**), 132.1 (**C**), 132.0 (**C**H), 131.6† (**C**H), 130.0 (**C**H) 129.9† (**C**), 127.8† (**C**H), 126.3† (**C**), 123.9 (**C**), 120.5† & 120.2 (**C**H), 115.9† & 115.8 (**C**H), 108.8† & 108.3 (**C**H), 40.2† (**C**H_2), 35.2 (**C**H_2), 34.2 (**C**H_2), 29.8† (**C**H_2) with one **C** not observed for the minor isomer (likely due to the slow relaxation time of this quaternary carbon and the low concentration of the minor isomer in the sample)

7-Chloro-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxine (6.26)



6.8 **6.26**

$C_7H_7ClO_2$
MW: 158.58

$C_{10}H_{11}ClO_2$
MW:198.64

To a solution of benzyl alcohol **6.8** (500 mg, 3.15 mmol) in acetone (10 mL) was added 2,2-dimethoxypropane (2.1 mL, 17.0 mmol), Na_2SO_4 (1.70 g, 11.8 mmol) and *p*-TSA (126 mg, 0.66 mmol). The reaction mixture was heated at 40 °C for

2 h then concentrated *in vacuo* and partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was separated and extracted with EtOAc (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by chromatography column (silica, petroleum ether) gave the title compound **6.26** (966 mg, 3.62 mmol, 81%) as a white solid.

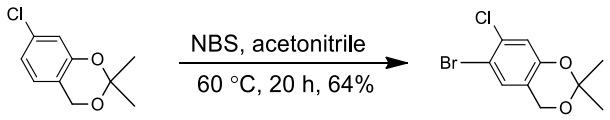
MP 64.5 – 65.2 °C ($CHCl_3$).

IR ν_{max} (neat, cm^{-1}) 2996 w, 2943 w, 2860w, 168 m, 1582 m, 1489 s, 1422 m, 1386 m, 1375 m, 1356 w, 1282 s, 1245, 1207 w, 1138 m, 1080 s, 1058 m, 963 s, 916 s, 812 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.88 (2H, t, *J* = 1.2 Hz, 2 × Ar**H**), 6.84 (1H, s, Ar**H**), 4.80 (2H, d, *J* = 0.6 Hz, C**H$_2$**), 1.53 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 152.1 (**C**), 133.4 (**C**), 125.7 (**C**H), 120.7 (**C**H), 118.0 (**C**H), 117.5 (**C**), 100.0 (**C**), 60.7 (**C**H$_2$), 24.9 (2 × C**H$_3$**).

6-Bromo-7-chloro-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxine (6.27)



6.26
$C_{10}H_{11}ClO_2$
MW: 198.65

6.27
$C_{10}H_{10}BrClO_2$
MW: 277.54

Experimental

To a solution of **6.26** (517 mg, 2.60 mmol) in acetonitrile (10 mL) was added NBS (618 mg, 3.47 mmol). The reaction was heated at 60 °C for 6 h then water (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL), then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 10% Et_2O in petroleum ether) afforded the title compound **6.27** (462 mg, 1.66 mmol, 64%) as an off-white solid.

MP 44.5 – 46 °C ($CHCl_3$).

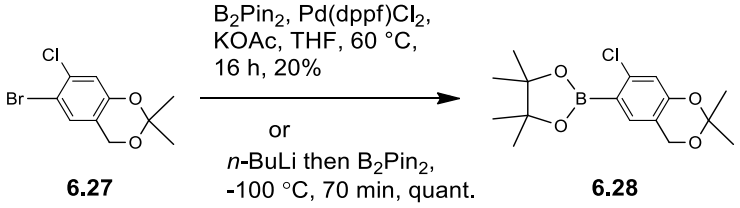
IR ν_{max} (neat, cm^{-1}) 2995 w, 2944 w, 2860 w, 1601 m, 1568 m, 1477 m, 1458 s, 1396 s, 1386 s, 1376 m, 1338 s, 1286 s, 1232 m, 1204 m, 1134 s, 1113 s, 964 s, 854 m, 760 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.21 (1H, s, Ar**H**), 6.95 (1H, s, Ar**H**), 4.78 (2H, s, C**H$_2$**), 1.52 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 151.3 (**C**), 133.5 (**C**), 129.3 (**C**H), 120.0 (**C**), 119.1 (**C**H), 112.6 (**C**), 100.4 (**C**), 60.2 (**C**H_2), 24.8 (**C**H_3).

HRMS (EI) Calcd. for $C_{10}H_{10}ClBrO_2$ $[M(^{35}Cl, ^{79}Br)]^{+\bullet}$: 275.9553, found: 275.9552.

2-(7-chloro-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.28)



$C_{10}H_{10}BrClO_2$
MW: 277.54

$C_{16}H_{22}BClO_4$
MW: 324.61

A flask charged with bromoarene **6.27** (150 mg, 0.55 mmol), bispinacolatodiboron (140 mg, 0.55 mmol) and KOAc (128 mg, 1.20 mmol) was evacuated then filled with Ar in three cycles. THF (1 mL) was added followed by $PdCl_2(dppf).CH_2Cl_2$ (25.0 mg, 0.04 mmol). The reaction was degassed with argon for 5 min, heated at 60 °C for 20 h then cooled to RT, filtered through a plug of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 5 to 10% Et_2O in petroleum ether) afforded the title compound **6.28** (36.0 mg, 0.11 mmol, 20%) as pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 3334 br, 2980 m, 2925 m, 1607 m, 1572 m, 1412 m, 1372 s, 1354 s, 1330 s, 1287 m, 1142 s, 1107 s, 974 m, 961 m, 870 m, 856 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.36 (1H, d, J = 1.0 Hz, Ar**H**), 6.84 (1H, s, Ar**H**), 4.80 (2H, d, J = 1.0 Hz, C**H$_2$**), 1.52 (6H, s, 2 × C**H$_3$**), 1.35 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 154.3 (**C**), 139.3 (**C**), 133.4 (**C**H), 118.2 (**C**H), 117.5 (**C**), 100.4 (**C**), 84.1 (**C**), 60.7 (**C**H$_2$), 25.0

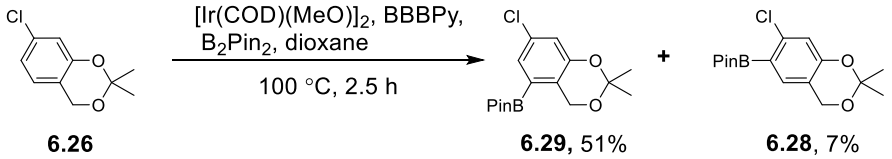
(**C**H_3), 24.9 (**C**H_3), with one **C** not observed (likely due to coupling with ^{10}B and ^{11}B).

HRMS (ES^+) Calcd. for $C_{16}H_{22}BClNaO_4^+$ $[M(^{35}Cl)+Na]^+$: 347.1195, found: 347.1200.

Alternatively

To a solution of bromoarene **6.27** (275 mg, 1.00 mmol) in THF (6 mL) and Et_2O (8 mL) at −100 °C was added *n*-BuLi (2.3 M in hexane, 0.65 mL, 1.50 mmol) was added over 5 min. After 30 min bispinacolatodiboron (508 mg, 2.00 mmol) in THF (4 mL) was added over 5 min. After a further 40 min sat. NH_4Cl (10 mL) was added and biphasic mixture was allowed to warm to RT. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL) then the organics phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 5 to 10% Et_2O in petroleum ether) gave the title compound **6.28** (324 mg, 1.00 mmol, quant.) as a pale yellow oil.

2-(7-Chloro-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.29)



6.26

$C_{10}H_{11}ClO_2$
MW: 198.65

6.29, 51%

6.28, 7%

$C_{10}H_{10}ClO_2$
MW: 197.64

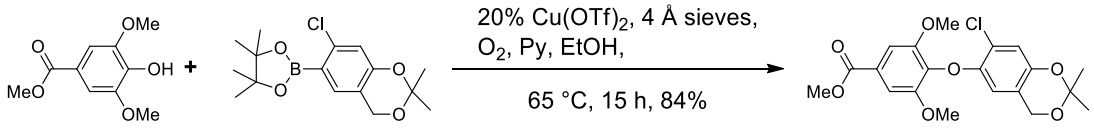
To a flask charged with bromoarene **6.26** (734 mg, 3.00 mmol), bispinacolatodiboron (660 mg, 2.60 mmol) and BBBPy (3 mg, 0.01mmol) in a glove box was added $[Ir(COD)(MeO)]_2$ (4 mg, 0.006 mmol). Dioxane (2 mL) was

added and the reaction heated at 100 °C for 2.5 h then cooled to RT, filtered through a plug of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 20% Et_2O in petroleum ether) gave the title compound **6.29** (29.0 mg, 0.15 mmol, 51%) as a mixture with the starting material **6.26** then the regioisomer **6.28** (4.00 mg, 0.02 mmol, 7%).

Data for **6.29**:

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.36 (1H, d, J = 2.2 Hz, Ar**H**), 6.90 (1H, d, J = 2.2 Hz, Ar**H**), 5.02 (2H, s, C**H$_2$**), 1.52 (6H, s, 2 × C**H$_3$**).

Methyl 4-((7-chloro-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)oxy)-3,5-dimethoxybenzoate (6.30)



2.21 **6.28** **6.30**

$C_{10}H_{12}O_5$ MW: 212.20

$C_{16}H_{22}BClO_4$ MW: 324.61

$C_{20}H_{21}ClO_7$ MW: 408.83

A solution of phenol **2.21** (50 mg, 0.23 mmol), borolane **6.28** (76 mg, 0.23 mmol) and copper triflate (21 mg, 0.06 mmol) in EtOH (2.6 mL) and pyridine (0.15 mL, 1.8 mmol) containing powdered 4 Å molecular sieves was heated at 65 °C under a slight positive pressure of oxygen for 15 h. The reaction mixture was then cooled to RT, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 20% EtOAc in petroleum ether) afforded the title compound **6.30** (80 mg, 0.20 mmol, 84%) as an off-white solid.

MP 97.2–98 °C ($CHCl_3$).

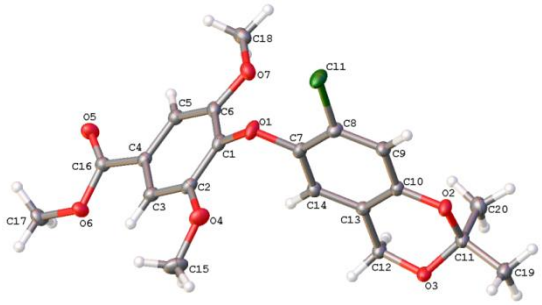
IR ν_{max} (neat, cm^{-1}) 2995 w, 2923 w, 2851 w, 1720 m, 1491 m, 1415 s, 1344 s, 1282 w, 1215 s, 1129 s, 1044 m, 882 m, 829 m, 767 m, 732 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.35 (2H, s, 2 × Ar**H**), 6.89 (1H, s, Ar**H**), 6.12 (1H, s, Ar**H**), 4.61 (2H, s, C**H$_2$**), 3.92 (3H, s, C**H$_3$**), 3.81 (6H, s, 2 × C**H$_3$**), 1.47 (6H, s, 2 × C**H$_3$**).

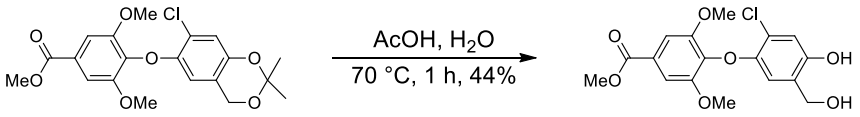
^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 166.5 (**C**O), 153.1 (**C**), 147.7 (**C**), 146.2 (**C**), 136.9 (**C**), 127.3 (**C**), 121.9 (**C**), 118.7 (**C**H), 118.3 (**C**), 110.4 (**C**H), 107.2 (**C**H), 99.7 (**C**), 60.6 (**C**H_2), 56.6 (**C**H_3), 52.4 (**C**H_3), 24.7 (**C**H_3).

HRMS (ES^+) Calcd. for $C_{20}H_{22}ClO_7^+$ $[M(^{35}Cl)+Na]^+$: 409.1049, found: 409.1050.

Xray



Methyl 4-(2-chloro-4-hydroxy-5-(hydroxymethyl)phenoxy)-3,5-dimethoxybenzoate (6.31)



6.30

$C_{20}H_{21}ClO_7$
MW: 408.83

6.31

$C_{17}H_{17}ClO_7$
MW: 368.77

A suspension of acetal **6.30** (80.0 mg, 0.20 mmol) in water (0.6 mL) and AcOH (1.4 mL) was heated at 70 °C for 1 h then cooled to RT and partitioned between sat. $NaHCO_3$ (10 mL) and EtOAc (10 mL). The aqueous phases was separated and extracted with DCM (2 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 50% EtOAc in petroleum ether) afforded the title compound **6.31** (32 mg, 0.09 mmol, 44%) as a white solid.

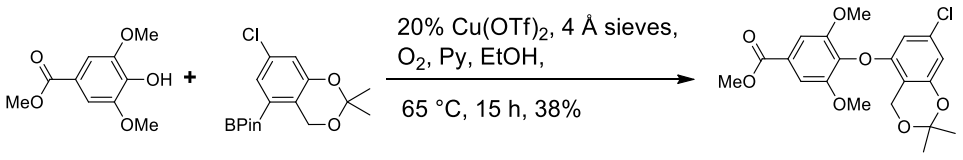
IR ν_{max} (neat, cm^{-1}) 3404 br, 2926 m, 2854 w, 1718 m, 1498 m, 1464 s, 1417 s, 1342 s, 1216 s, 1185 s, 1130 s, 997 m, 763 s

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.36 (2H, s, 2 × Ar**H**), 6.96 (1H, s, Ar**H**), 6.22 (1H, s, Ar**H**), 4.65 (s, 2H, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.83 (6H, s, 2 × OC**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.7 (**C**O), 153.2 (**C**), 151.1 (**C**), 147.3 (**C**), 137.2 (**C**), 127.4 (**C**), 123.7 (**C**), 122.8 (**C**), 118.5 (**C**H), 113.9 (**C**H), 107.3 (**C**H), 64.2 (**C**H$_2$), 56.7 (**C**H$_3$), 52.5 (**C**H$_3$).

HRMS (ES$^-$) Calcd. for $C_{17}H_{17}ClNaO_7^-$ [M(^{35}Cl)+Na]$^+$: 391.0555, found: 391.0538.

Methyl 4-((7-chloro-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-5-yl)oxy)-3,5-dimethoxybenzoate (6.32)



2.21 $C_{10}H_{12}O_5$ MW: 212.20

5.29 $C_{10}H_{10}ClO_2$ MW: 197.64

6.32 $C_{20}H_{21}ClO_7$ MW: 408.83

To solution of phenol **2.21** (20 mg, 0.09 mmol), borolane **6.29** (29 mg, 0.15 mmol) and copper triflate (8 mg, 0.02 mmol) in EtOH (2 mL) containing powdered 4 Å molecular sieves and under a slight positive pressure of oxygen was added pyridine (0.06 mL, 0.74 mmol). After heating at 65 °C for 20 h, the reaction mixture was cooled to RT, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 10 to 20% EtOAc in petroleum ether) afforded the title compound **6.32** (14 mg, 0.034 mmol, 38%) as a white solid.

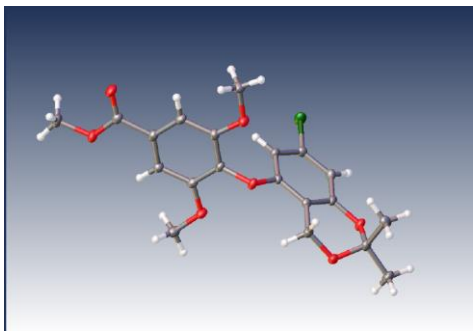
IR ν_{max} (neat, cm^{-1}) 2995 w, 2918 w, 2850 w, 1723 m, 1501 w, 1464 m, 1418 m, 1362 w, 1341 s, 1232 s, 1214 s, 1130 s, 1057 s, 909 m, 763 w.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.36 (2H, s, 2 × Ar**H**), 6.53 (1H, d, J = 1.9 Hz, Ar**H**), 6.01 (1H, d, J = 1.9 Hz, Ar**H**), 4.99 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.84 (6H, s, 2 × C**H$_3$**), 1.58 (6H, s, 2 × C**H$_3$**).

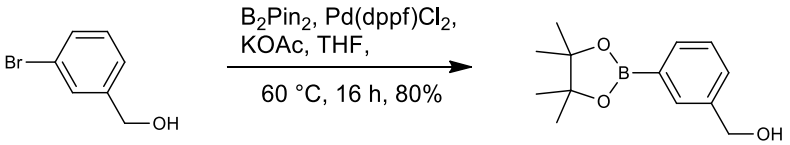
^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.6 (**C**O), 154.9 (**C**), 153.1 (**C**), 152.7 (**C**), 136.4 (**C**), 133.2 (**C**), 127.7 (C), 111.4 (**C**H), 108.0 (**C**), 106.9 (**C**H), 106.2 (**C**H), 100.1 (**C**), 58.1 (**C**H_2), 56.5 (**C**H_3), 52.6 (**C**H_3), 24.8 (**C**H_3).

HRMS (ES^+) Calcd. for $C_{20}H_{22}ClO_7^+$ $[M(^{35}Cl)+H]^+$: 409.1049, found: 409.1067.

Xray



(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanolm (6.34)



6.33

C_7H_7BrO
MW: 187.03

6.34

$C_{13}H_{19}BO_3$
MWt: 234.10

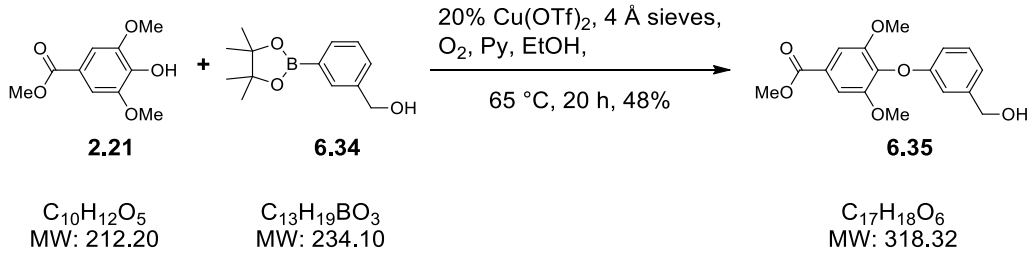
A flask charged with bromoarene **6.33** (94.0 mg, 0.50 mmol), bispinacolatodiboron (140 mg, 0.55 mmol) and KOAc (118 mg, 1.20 mmol) was evacuated then filled with Ar in three cycles. THF (1 mL) was added followed by $PdCl_2$(dppf).CH_2Cl_2 (25.0 mg, 0.04 mmol). The reaction was then degassed with argon for 5 min, heated at 60 °C for 16 h, cooled to RT and filtered through a plug of silica. Concentration *in vacuo* and purification by column

chromatography (silica, 40–60% Et_2O in petroleum ether) yielded the title compound **6.34** (113 mg, 0.40 mmol, 80%) as mixture with the starting material (*ca.* 20% by NMR).

The physical and spectroscopic data were in agreement with reported values.[104]

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.80 (1H, s, Ar**H**), 7.74 (1H, d, J = 7.3 Hz, Ar**H**), 7.51 (1H, d, J = 15.9 Hz, Ar**H**), 7.37 (1H, t, J = 7.4 Hz, Ar**H**), 4.70 (2H, s, C**H$_2$**), 1.35 (12H, s, 4 × C**H$_3$**).

Methyl 4-(3-(hydroxymethyl)phenoxy)-3,5-dimethoxybenzoate (6.35)



2.21 **6.34** **6.35**

$C_{10}H_{12}O_5$ MW: 212.20 | $C_{13}H_{19}BO_3$ MW: 234.10 | $C_{17}H_{18}O_6$ MW: 318.32

To solution of phenol **2.21** (135 mg, 0.63 mmol), borolane **6.34** (150 mg, 0.64 mmol) and copper triflate (46 mg, 0.09 mmol) in EtOH (6 mL) containing powdered 4 Å molecular sieves and under a slight positive pressure of oxygen was added pyridine (0.40 mL, 4.94 mmol). After heating at 65 °C for 20 h, the reaction mixture was cooled, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 40% EtOAc in petroleum ether) afforded the title compound **6.35** (96.0 mg, 0.30 mmol, 48%) as an off-white solid.

MP 135 – 137 °C ($CHCl_3$).

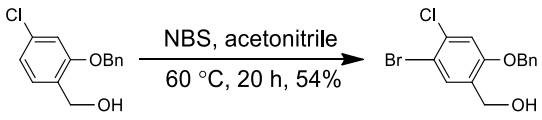
IR ν_{max} (neat, cm^{-1}) 3416 br., 2952 w, 2849 w, 1719 m, 1463 m, 1417 m, 1340 s, 1235 m, 1218 s, 1184 w, 1128 s, 998 s, 764 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.30 (2H, s, 2 × Ar**H**), 7.15 (1H, t, J = 7.9 Hz, Ar**H**), 6.92 (1H, dd, J = 7.5, 0.8 Hz, Ar**H**), 6.79 (1H, d, J = 0.9 Hz, Ar**H**), 6.68 (1H, dd, J = 8.7, 2.2 Hz, Ar**H**), 4.55 (2H, s, C**H$_2$**), 3.87 (3H, s, C**H$_3$**), 3.75 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.7 (**C**O), 158.4 (**C**), 153.4 (**C**), 142.7 (**C**), 136.2 (**C**), 129.6 (**C**H), 127.4 (**C**), 120.5 (**C**H), 114.1 (**C**H), 113.5 (**C**H), 107.1 (**C**H), 65.2 (**C**H$_2$), 56.5 (**C**H$_3$), 52.5 (**C**H$_3$).

HRMS (ES^-) Calcd. for $C_{17}H_{18}NaO_6^+$ $[M+Na]^+$: 341.0996, found: 341.1009.

(2-(Benzyloxy)-5-bromo-4-chlorophenyl)methanol (6.36)



6.9 **6.36**

$C_{14}H_{13}ClO_2$ MW: 248.70 $C_{14}H_{12}BrClO_2$ MW: 327.60

To a solution of **6.9** (8.70 g, 35.0 mmol) in acetonitrile (300 mL) was added NBS (8.15 g, 45.60 mmol). The reaction was heated at 60 °C for 6 h then water (300 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 ×

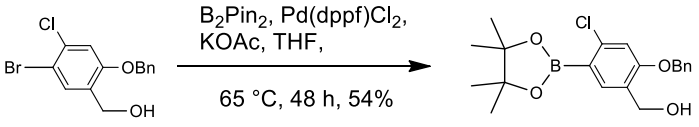
200 mL) then the organic phases were combined, washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 10% EtOAc in petroleum ether) afforded the title compound **6.36** (6.20 g, 18.9 mmol 54%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 3455 br., 3028 w, 2971 w, 1739 s, 1481 m, 1454 m, 1366 s, 1230 s, 1217 s, 1012 m, 835 w, 737 m, 697 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.57 (1H, d, J = 0.8 Hz, Ar**H**), 7.39 (5H, s, 5 × Ar**H**), 7.04 (1H, s, Ar**H**), 5.07 (2H, s, C**H$_2$**), 4.67 (2H, d, J = 0.8 Hz, C**H$_2$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 155.9 (**C**), 135.9 (**C**), 133.9 (**C**), 132.9 (**C**H), 130.4 (**C**), 129.0 (**C**H), 128.6 (**C**H), 127.5 (**C**H), 114.0 (**C**), 113.4 (**C**H), 70.9 (**C**H_2), 60.7 (**C**H_2).

(2-(Benzyloxy)-4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-methanol (6.37)



6.36 **6.37**

$C_{14}H_{12}BrClO_2$
MW: 327.60

$C_{20}H_{24}BClO_4$
MW: 374.67

A flask charged with bromoarene **6.36** (5.00 g, 15.3 mmol), bispinacolatodiboron (4.66 g, 18.4 mmol) and KOAc (4.20 g, 42.8 mmol) was evacuated then filled with Ar in three cycles. THF (100 mL) was added followed by $PdCl_2(dppf).CH_2Cl_2$ (2.50 g, 3.06 mmol). The reaction was degassed with

argon for 5 min, heated at 65 °C for 48 h then cooled to RT. Filtration through a plug of silica, concentration *in vacuo* and purification by column chromatography (silica, 10% EtOAc in petroleum ether) gave the title compound **6.37** (3.40 g, 9.00 mmol, 59%) as an off-white solid.

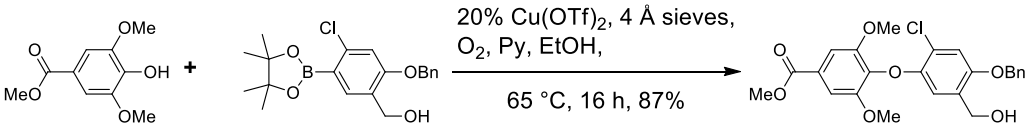
IR ν_{max} (neat, cm^{-1}) 3420 br., 2979 w, 2932 w, 1600 m, 1564 w, 1455 s, 1400 m, 1327 s, 1233 m, 1141 s, 1120 m, 1024 m, 969 m, 859 m, 738 m, 670 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.67 (1H, s, Ar**H**), 7.43 – 7.31 (5H, m, 5 × Ar**H**), 6.96 (1H, s, Ar**H**), 5.11 (2H, s, C**H$_2$**), 4.68 (2H, d, J = 0.6 Hz, C**H$_2$**), 1.35 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 159.0 (**C**), 140.7 (**C**), 137.0 (**C**H), 136.1 (**C**), 128.9 (**C**H), 128.5 (**C**H), 127.5 (**C**H), 113.4 (**C**H), 84.1 (**C**), 70.5 (**C**H$_2$), 61.4 (**C**H$_2$), 25.0 (**C**H$_3$).

HRMS (ES^+) Calcd. for $C_{20}H_{24}BClNaO_4^+$ $[M(^{35}Cl)+Na]^+$: 397.1352, found: 397.1362.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(hydroxymethyl)phenoxy)-3,5-dimethoxy-benzoate (6.38)



2.21 $C_{10}H_{12}O_5$ MW: 212.1993

6.37 $C_{20}H_{24}BClO_4$ MW: 374.6662

6.38 $C_{20}H_{21}ClO_7$ MW: 408.83

Experimental

To solution of phenol **2.21** (27.0 mg, 0.13 mmol), borolane **6.37** (47.0 mg, 0.13 mmol) and copper triflate (9.20 mg, 0.03 mmol) in EtOH (2 mL) containing powdered 4 Å molecular sieves and under a slight positive pressure of oxygen was added pyridine (0.08 mL, 1.00 mmol). After heating at 65 °C for 16 h, the reaction mixture was cooled, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica, 30% EtOAc in petroleum ether) afforded the title compound **6.38** (57.0 mg, 0.11 mmol, 87%) as an off-white solid.

MP 146 – 147 °C (EtOAc).

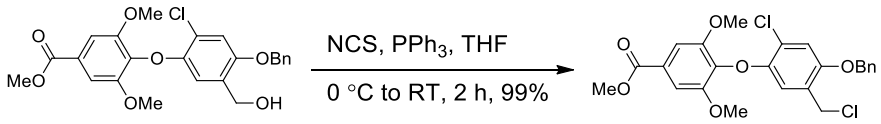
IR ν_{max} (neat, cm^{-1}) 3499 br., 2952 w, 2850 w, 1717 m, 1493 m, 1463 m, 1340 s, 1215 s, 1190 s, 1129 s, 997 m, 867 w, 765 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.42 – 7.31 (5H, m, 7 × Ar**H**), 7.02 (1H, s, Ar**H**), 6.53 (1H, s, Ar**H**), 5.05 (2H, s, C**H$_2$**), 4.53 (2H, s, C**H$_2$**), 3.93 (3H, s, C**H$_3$**), 3.82 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.6 (**C**O), 153.2 (**C**), 151.4 (**C**), 148.1 (**C**), 136.9 (**C**), 136.5 (**C**), 129.2 (**C**), 128.9 (**C**H), 128.4 (**C**H), 127.53 , (**C**H) 127.4 (**C**), 121.6 (**C**), 115.1 (**C**H), 114.2 (**C**H), 107.2 (**C**H), 71.1 (**C**H$_2$), 61.3 (**C**H$_2$), 56.7 (**C**H$_3$), 52.5 (**C**H$_3$).

HRMS (ES^+) Calcd. for $C_{24}H_{23}ClNaO_7^+$ [M(^{35}Cl)+Na]$^+$: 481.1025, found: 481.1034.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(chloromethyl)phenoxy)-3,5-dimethoxy-benzoate (6.25)



6.38
$C_{24}H_{23}ClO_7$
MW: 458.89

6.25
$C_{24}H_{22}Cl_2O_6$
MW: 477.33

To a solution of **6.38** (689 mg, 1.5 mmol) in THF (8 mL) at 0 °C was added PPh_3 (472 mg, 1.8 mmol) and NBS (246 mg, 1.8 mmol). After 2h at RT, sat. $NaHCO_3$ (8 mL) and sat. $Na_2S_2O_3$ (8 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 10 mL) then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by chromatography column (10 to 30% EtOAc in petroleum ether) to afford the titled compound **6.25** (710 mg, 1.48 mmol, 99%)as an off white solid.

MP: 174-176 °C (EtOAc).

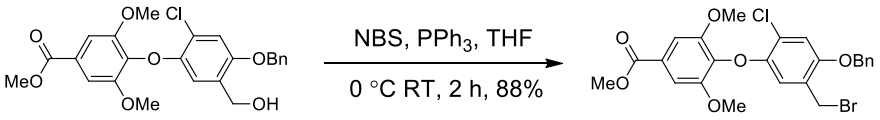
IR ν_{max} (neat, cm^{-1}) 3008 w, 2949 w, 1719 m, 1496 s, 1463 m, 1416 m, 1397 m, 1341 s, 1216 s, 1130 s, 1000 m, 759 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.49 – 7.30 (5H, m, 5 × Ar**H**), 7.03 (1H, s, Ar**H**), 6.56 (1H, s, Ar**H**), 5.09 (2H, s, C**H$_2$**), 4.49 (2H, s, C**H$_2$**), 3.95 (3H, s, C**H$_3$**), 3.83 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.6 (**C**O), 153.1 (**C**), 151.5 (**C**), 147.9 (**C**), 136.7 (**C**), 136.6 (**C**), 128.8 (**C**H), 128.3 (**C**H), 127.5 (**C**H), 127.5 (**C**), 125.7 (**C**), 123.2 (**C**), 116.8 (**C**H),

	114.9 (**C**H), 107.3 (**C**H), 71.3 (**C**H_2), 56.7 (**C**H_3), 52.5 (**C**H_3), 41.0 (**C**H_2).
HRMS (ES^+)	Calcd. for $C_{24}H_{22}Cl_2NaO_6^+$ $[M(^{35}Cl)+Na]^+$: 499.0686, found: 499.0690.

Methyl 4-(4-(benzyloxy)-5-(bromomethyl)-2-chlorophenoxy)-3,5-dimethoxy-benzoate (6.42)



6.38

$C_{24}H_{23}ClO_7$
MW: 458.89

6.42

$C_{24}H_{22}BrClO_6$
MW: 521.79

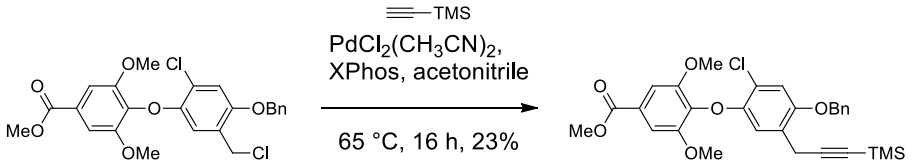
To a solution of **6.38** (230 mg, 0.50 mmol) in THF (4 mL) at 0 °C was added PPh_3 (157 mg, 0.6 mmol) and NBS (106 mg, 0.6 mmol). After 2h at RT, sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 40% Et_2O in petroleum ether) to afford the title compound **6.42** (230 mg, 0.44 mmol, 88%) as an off white solid.

MP	158-160 °C (Et_2O).
IR ν_{max} (neat, cm^{-1})	2925 w, 2852 w, 1710 s, 1492 m, 1434 m, 1417 m, 1396 m, 1342 s, 1216 s, 1184 s, 1129 s, 760 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.62 – 7.31 (5H, m, 5 × Ar**H**), 7.01 (1H, s, Ar**H**), 6.53 (1H, s, Ar**H**), 5.11 (2H, s, C**H$_2$**), 4.39 (2H, s, C**H$_2$**), 3.95 (3H, s, C**H$_3$**), 3.84 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.6 (**C**), 153.1 (**C**), 151.6 (**C**), 147.8 (**C**), 136.7 (**C**), 136.6 (**C**), 128.8 (**C**H), 128.3 (**C**H), 127.5 (**C**H), 127.5 (**C**), 125.9 (**C**), 123.3 (**C**), 116.9 (**C**H), 114.9 (**C**H), 107.3 (**C**H), 71.2 (**C**H$_2$), 56.7 (2 × C**H$_3$**), 52.5 (**C**H$_3$), 28.2 (**C**H$_2$).

Methyl 4-(4-(benzyloxy)-2-chloro-5-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (6.39)



6.25
$C_{24}H_{22}Cl_2O_6$
MW: 477.33

6.39
$C_{29}H_{31}ClO_6Si$
MW: 539.09

A flask charged with benzyl chloride **6.25** (119 mg, 0.25 mmol), $PdCl_2(CH_3CN)_2$ (4.0 mg, 0.015 mmol), XPhos (21.0 mg, 0.045 mmol) and Cs_2CO_3 (93.0 mg, 0.28 mmol) was evacuated then filled with Ar in three cycles. TMSacetylene (0.6 mL, 0.40 mmol) and CH_3CN (2 mL) were added sequentially then the reaction was heated at 65 °C for 16 h. On cooling to RT the reaction was filtered through a plug of silica, concentrated *in vacuo* and purified by column chromatography (silica, 10% EtOAc in petroleum ether) to give the title compound **6.39** (31.0 mg, 0.06 mmol, 23%) as an off-white solid.

MP: 130 – 131.5 °C (EtOAc).

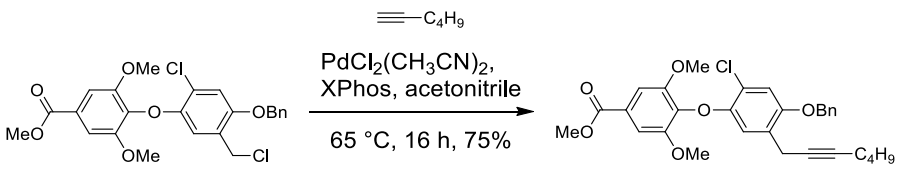
IR ν_{max} (neat, cm^{-1}) 2956 w, 2849 w, 2179 w, 1721 m, 1493 s, 1463 m, 1416 m, 1392 m, 1248 s, 1215 s, 1189 s, 1130 s, 1028 w, 997 w, 843 m, 759 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.47 – 7.29 (7H, m, 7 × Ar**H**), 6.96 (1H, s, Ar**H**), 6.78 (1H, d, J = 0.9 Hz, Ar**H**), 5.02 (2H, s, C**H$_2$**), 3.93 (3H, s, C**H$_3$**), 3.83 (6H, s, 2 × C**H$_3$**), 3.52 (2H, d, J = 0.9 Hz, C**H$_2$**), 0.01 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.6 (**C**O), 153.2 (**C**), 150.8 (**C**), 148.0 (**C**), 136.9 (**C**), 136.8 (**C**), 128.7 (**C**H), 128.2 (**C**H), 127.4 (**C**H), 127.3 (**C**), 124.8 (**C**), 120.3 (**C**), 115.2 (**C**H), 113.8 (**C**H), 107.4 (**C**H), 103.4 (**C**) , 87.7 (**C**), 70.9 (**C**H_2), 56.7 (2 × C**H$_3$**), 52.4 (**C**H_3), 20.8 (**C**H_2), 0.01(**C**H_3).

HRMS (ES^+) Calcd. for $C_{29}H_{31}ClNaO_6Si^+$ $[M(^{35}Cl)+Na]^+$: 561.1461, found: 561.1471.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxy-benzoate (6.40)



6.25

$C_{24}H_{22}Cl_2O_6$
MW: 477.33

6.40

$C_{30}H_{31}ClO_6$
MW: 523.02

A flask charged with benzyl chloride **6.25** (570 mg, 1.20 mmol), $PdCl_2(CH_3CN)_2$ (19 mg, 0.07 mmol), XPhos (103 mg, 0.22 mmol) and Cs_2CO_3 (430 mg, 1.3 mmol) was evacuated then filled with Ar in three cycles. Hex-1-yne (0.22 mL, 1.92 mmol) and CH_3CN (3 mL) were then added sequentially and the reaction was heated at 65 °C for 16 h. After cooling to RT, filtration through a plug of silica, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 20% EtOAc in petroleum ether) gave the title compound **6.40** (472 mg, 0.90 mmol, 75%) as an off-white solid.

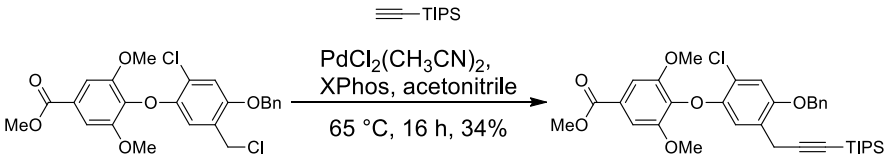
MP 138–139 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}) 2957 w, 1721 m, 1498 s, 1464 m, 1416 m, 1393 w, 1342 s, 1216 s, 1189 s, 1131 s, 999 m, 865 m, 760 m.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.45 – 7.29 (7H, m, 7 × Ar**H**), 6.95 (1H, s, Ar**H**), 6.79 (1H, s, Ar**H**), 5.03 (2H, s, C**H$_2$**), 3.93 (3H, s, C**H$_3$**), 3.83 (6H, s, 2 × C**H$_3$**), 3.43 (2H, s, C**H$_2$**), 2.07 – 1.98 (2H, m, C**H$_2$**), 1.35 – 1.21 (4H, m, 2 × C**H$_2$**), 0.84 (3H, t, J = 7.2 Hz, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 166.6 (**C**), 153.3 (**C**), 150.9 (**C**), 147.9 (**C**), 137.1 (**C**), 136.9 (**C**), 128.7 (**C**H), 128.1 (**C**H), 127.4 (**C**H), 127.2 (**C**), 126.1 (**C**), 120.1 (**C**), 115.6 (**C**H), 113.7 (**C**H), 107.3 (**C**H), 83.4 (**C**), 70.9 (**C**H$_2$), 56.7 (**C**H$_3$), 52.4 (**C**H$_3$), 31.2 (**C**H$_2$), 22.0 (**C**H$_2$), 19.7 (**C**H$_2$), 18.4 (**C**H$_2$), 13.6 (**C**H$_3$).

Methyl 4-(4-(benzyloxy)-2-chloro-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (6.41)



A flask charged with benzyl chloride **6.25** (119 mg, 0.25 mmol), $PdCl_2(CH_3CN)_2$ (4.0 mg, 0.015 mmol), XPhos (21.0 mg, 0.045 mmol) and Cs_2CO_3 (93.0 mg, 0.28 mmol) was evacuated then filled with Ar in three cycles. TIPS-acetylene (73.0 mg, 0.40 mmol) and CH_3CN (2 mL) were then added sequentially and the reaction was heated at 65 °C for 16 h. After cooling to RT, filtration through a plug of silica, concentration *in vacuo* and purification by column chromatography (silica, 10 to 10% EtOAc in petroleum ether) gave the title compound **6.41** (53.0 mg, 0.085 mmol, 34%) as an off-white solid.

MP: 83 – 84 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}) 2942 w, 2865 w, 2177 w, 1722 m, 1493 s, 1463 m, 1416 m, 1391 m, 1341 s, 1216 s, 1189 s, 1131 s, 1027 w, 997 w, 760 w.

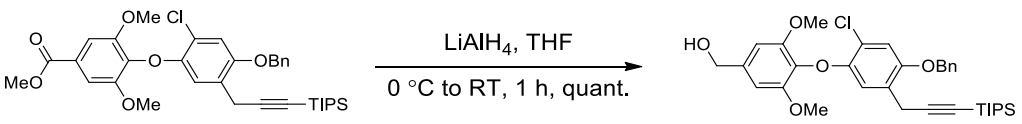
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm, 2 : 1 mixture of rotamers (†major rotamer) 7.45 – 7.30 (7H, m, 7 × Ar**H**), 6.98 (1H, br. s, Ar**H**) 6.87† & 6.85 (1H, 2 × s, Ar**H**), 5.03 (2 H, s, C**H$_2$**) 3.94 (3H, s, C**H$_3$**) 3.82 & 3.81† (6H, 2 × s, 2 × C**H$_3$**), 3.61†

& 3.59 (2H, 2 × s, C**H**$_2$), 1.08 – 0.84 (21H, m, 6 × C**H**$_3$ and 3 × C**H**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm, mixture of rotamers (†major rotamer) 166.6 (**C**O), 153.1 & 153.0† (**C**), 150.8 & 150.7† (**C**), 148.1† & 148.0 (**C**), 136.9† & 136.8 (**C**), 128.7 (**C**H), 128.2 (**C**H), 127.4† & 127.1 (**C**H), 125.2† & 125.1 (**C**), 120.4 & 120.3† (**C**), 115.0 & 114.9† (**C**H), 113.6 & 113.5† (**C**H), 107.3 (**C**H), 104.6† & 104.5 (**C**), 84.1 & 83.8† (**C**), 70.9 (**C**H$_2$), 56.7 & 56.6† (**C**H$_3$), 52.4 (**C**H$_3$), 20.9 (**C**H$_2$), 18.7† & 18.3 (**C**H$_3$) 11.8 & 11.3† (CH).

HRMS (ES^+) Calcd. for $C_{35}H_{44}ClO_6^+$ [M(^{35}Cl)+Na]$^+$: 623.2590, found: 623.2582.

(4-(4-(Benzyloxy)-2-chloro-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (6.44)



6.41

$C_{35}H_{43}ClO_6Si$
MW: 623.25

6.44

$C_{34}H_{43}ClO_5Si$
MW: 595.24

Experimental

To a solution of benzyl ester **6.41** (40.0 mg, 0.06 mmol) in THF (1 mL) at 0 °C was added $LiAlH_4$ (1.0 M in THF, 0.2 mL, 0.20 mmol) dropwise over 5 min. After 1 h at RT, MeOH (1 mL) and sat. Rochelle salt (1 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 40% EtOAc in petroleum ether) afforded the title compound **6.44** (39.0 mg, 0.06 mmol, quant.) as a pale yellow oil.

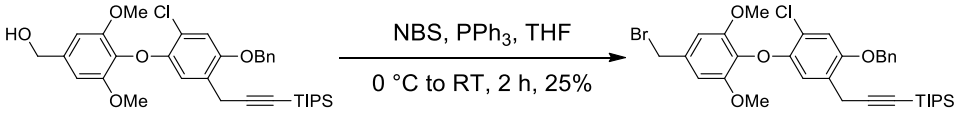
IR ν_{max} (neat, cm^{-1}) 3417 br., 2941 m, 2864m, 2177 w, 1492 s, 1463 s, 1420 m, 1392 m, 1335 w, 1219 s, 1189 m, 1130 s, 1027 m, 736 m, 679 s

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 2 : 1 mixture of rotamers (†major rotamer) 7.45 – 7.29 (5H, m, 5 × Ar**H**), 6.97 (1H, s, Ar**H**), 6.85† & 6.83 (1H, 2 × s, Ar**H**), 6.65 & 6.64† (2H, 2 × s, 2 × Ar**H**), 5.01 (2H, s, C**H$_2$**), 4.68 (2H, s, C**H$_2$**), 3.77 & 3.76† (6H, 2 × s, 2 × C**H$_3$**), 3.60 & 3.58 (2H, m, C**H$_2$**), 1.11 – 0.83 (21 H, m, 6 × C**H$_3$** and 3 × C**H**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm mixture of rotamers (†major rotamer) 153.4 (**C**), 150.6 & 150.5† (**C**), 148.6† & 148.5 (**C**), 138.5 (**C**), 132.1 & 132.0† (**C**), 128.7 (**C**H), 128.1 (**C**H), 127.4† & 127.3 (**C**H), 125.1† & 125.0 (**C**), 120.2 & 120.1† (**C**) , 115.1 & 115.0† (**C**H), 113.7 & 113.6† (**C**H), 105.0† & 104.9 (**C**), 104.2 & 104.1† (**C**H), 83.5

& 83.2† (**C**), 70.9 (**C**H_2), 65.6 (**C**H_2), 56.5 & 56.5† (**C**H_3), 20.8 (**C**H_2), 18.7† & 18.4 (**C**H_3) , 11.8 & 11.3† (**C**H).

(3-(2-(Benzyloxy)-5-(4-(bromomethyl)-2,6-dimethoxyphenoxy)-4-chlorophenyl)prop-1-yn-1-yl)triisopropylsilane (6.45)



6.44

$C_{34}H_{43}ClO_5Si$
MW: 595.24

6.45

$C_{34}H_{42}BrClO_4Si$
MW: 658.14

To a solution of benzyl alcohol **6.44** (34.0 mg, 0.06 mmol) in THF (1 mL) at 0 °C was added PPh_3 (19.0 mg, 0.07 mmol) and NBS (11 mg, 0.07 mmol). After 2 h at RT, sat. $NaHCO_3$ (1 mL) and sat. $Na_2S_2O_3$ (1 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 2 mL), then the organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 10% EtOAc in petroleum ether) to afford the title compound **6.45** (10.0 mg, 0.015 mmol, 25%) as an off white solid.

MP: 100.6 – 102 °C ($CHCl_3$).

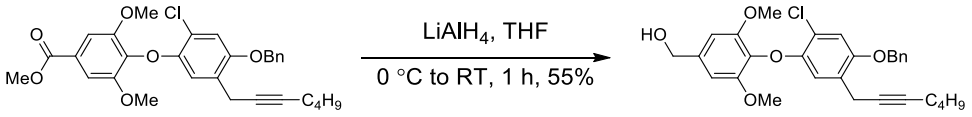
^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 2 : 1 mixture of rotamers (†major rotamer) 7.44 – 7.31 (5 H, m, 5 × Ar**H**), 6.96 (1H, s, Ar**H**), 6.86† & 6.83 (1H, 2 × s, Ar**H**), 6.67 & 6.66† (2H, 2 × s, Ar**H**), 5.01 (2H, s, C**H$_2$**), 4.47 (2H, s, C**H$_2$**), 3.77 &

3.76† (6H, 2 × s, 2 × C**H**$_3$), 3.60† & 3.59 (2H, 2 × s, C**H**$_2$), 1.00 – 0.89 (21H, m, 3 × C**H**$_3$ and 3 × C**H**).

^{13}C NMR ($CDCl_3$): δ ppm mixture of rotamers (†major rotamer) 153.3 (**C**), 150.7 (**C**), 148.4 (**C**), 134.9 (**C**), 132.3 & 132.2† (**C**), 128.7 (**C**H), 128.2 (**C**H), 127.4† & 127.3 (**C**H), 125.1 (**C**), 120.4 (**C**), 115.3 & 115.2† (**C**H),113.8 & 113.6† (**C**H), 106.8 & 106.7† (**C**H), 105.0† & 104.9 (**C**), 83.3 (**C**), 70.9 (**C**H_2), 65.5 (**C**H_2), 56.6 & 56.5 (**C**H_3), 20.8 (**C**H_2), 18.7† & 18.4 (**C**H_3), 11.8 & 11.3† (**C**H), with one **C** resonance not observed (likely due to the slow relaxation time of this particular quaternary carbon).

HRMS (ES^+) Calcd. for $C_{34}H_{42}BrClNaO_4Si^+$ [M(^{35}Cl, ^{79}Br)+Na]$^+$:679.1616, found: 679.1601

(4-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)-methanol (6.43)



6.40
$C_{30}H_{31}ClO_6$
MW: 523.02

6.43
$C_{29}H_{31}ClO_5$
MW: 495.01

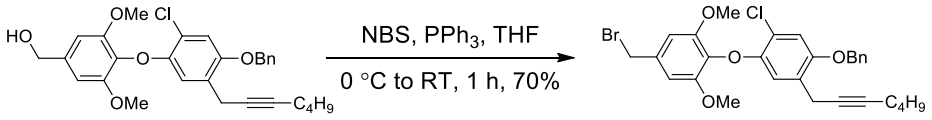
To a solution of benzyl ester **6.40** (470 mg, 0.90 mmol) in THF (7 mL) at 0 °C was added a solution of $LiAlH_4$ (1.0 M in THF, 0.90 mL, 0.90 mmol) over 5 min.

After 1 h at RT, MeOH (1 mL) and sat. Rochelle salt (2 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 50% EtOAc in petroleum ether) to afford the title compound **6.43** (248 mg, 0.5 mmol, 55%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 3388 br., 2934 w, 1493 s, 1462 m, 1421 m, 1393 m, 1335 w, 1218 s, 1190 m, 1130 s, 1027 w, 866 w, 739 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46 – 7.29 (5H, m, 5 × Ar**H**), 6.95 (1H, s, Ar**H**), 6.78 (1H, s, Ar**H**), 6.67 (2H, s, 2 × Ar**H**), 5.02 (2H, s, C**H$_2$**), 4.69 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.43 (2H, t, *J* = 2.1 Hz, C**H$_2$**), 1.37 – 1.29 (4H, m, 2 × C**H$_2$**), 0.93 – 0.83 (3 H, m, C**H$_3$**).

2-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-5-(bromomethyl)-1,3-dimethoxybenzene (6.49)



6.43

$C_{29}H_{31}ClO_5$
MW: 495.01

6.49

$C_{29}H_{30}BrClO_4$
MW: 557.90

To a solution of benzyl alcohol **6.43** (248 mg, 0.50 mmol) in THF (4 mL) at 0 °C was added PPh_3 (157 mg, 0.6 mmol) and NBS (106 mg, 0.6 mmol). After 1 h at

RT, sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 × 5 mL), then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 10 to 40% Et_2O in petroleum ether) to afford the title compound **6.49** (195 mg, 0.35 mmol, 70%) as an off white solid.

MP 96 – 97 °C ($CHCl_3$)

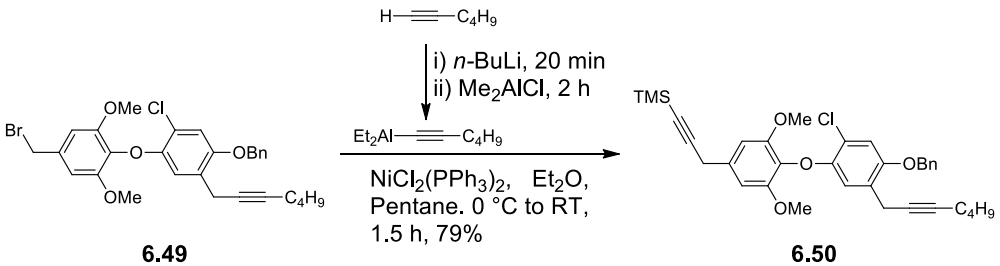
IR ν_{max} (neat, cm^{-1}) 2957 w, 2923 m, 2852 w, 1493 s, 1463 s, 1421 m, 1393 m, 1339 m, 1244 m, 1210 s, 1190 s, 1210 s, 1190 s, 1133 s, 1120 s, 998 m, 865 m, 739 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.47 – 7.28 (5H, m, 5 × Ar**H**), 6.95 (1H, s, Ar**H**), 6.80 (1H, s, Ar**H**), 6.69 (2H, s,2 × Ar$_r$**H**), 5.02 (2H, s, C**H$_2$**), 4.49 (2H, s, C**H$_2$**), 3.80 (6H, s, 2 × C**H$_3$**), 3.44 (2H, d, J = 0.9 Hz, C**H$_2$**), 2.06 (2H, dd, J = 9.0, 2.1 Hz, C**H$_2$**), 1.38 – 1.21 (4H, m, 2 × C**H$_2$**), 0.87 (3H, t, J = 7.1 Hz, C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 150.8 (**C**), 148.1 (**C**), 137.0 (**C**), 135.2 (**C**), 133.1 (**C**), 128.7 (**C**H), 128.1 (**C**H), 127.3 (**C**H), 126.1 (**C**), 119.9 (**C**), 115.5 (**C**H), 113.7 (**C**H), 106.7 (**C**H), 83.3 (**C**), 70.9 (**C**H$_2$), 56.6 (**C**H$_3$), 34.0 (**C**H$_2$), 31.2 (**C**H$_2$), 22.0 (**C**H$_2$), 19.8 (**C**H$_2$), 18.5 (**C**H$_2$), 13.8 (**C**H$_3$), with one **C** not observed (likely due to the slow relaxation time of this quaternary carbon).

HRMS (ES^+) Calcd. for $C_{29}H_{30}BrClNaO_4^+$ [M(^{35}Cl, ^{79}Br)+Na]$^+$: 579.0908, found: 579.0905

(3-(4-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)-prop-1-yn-1-yl)trimethylsilane (6.50)



6.49

$C_{29}H_{30}BrClO_4$
MW: 557.90

6.50

$C_{34}H_{39}ClO_4Si$
MW: 575.21

Adapted from a procedure by Gau *et al.*[58] To a solution of trimethylsilylacetylene (0.1 mL, 0.70 mmol) in pentane (3 mL) at 0 °C was added *n*−BuLi (2.45 M in hexane, 0.29 mL, 0.70 mmol) over 5 min. After 30 min a solution of Me_2AlCl (0.9 M in hexane, 0.78 mL, 0.70 mmol) was added over 5 min. The solution was warmed to RT after 20 min and after a further 2 h, Et_2O (3 mL) and $NiCl_2(PPh_3)_2$ (16.0 mg, 0.024 mmol) were added. After a further 15 min benzyl bromide **6.49** (195 mg, 0.35 mmol) was added followed after 90 min by sat. NH_4Cl (3 mL). The aqueous phase was separated and extracted with Et_2O (3 × 5 mL) then the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 10% EtOAc in petroleum ether) to afford the title compound **6.50** (159 mg, 0.28 mmol, 79%) as a yellow oil.

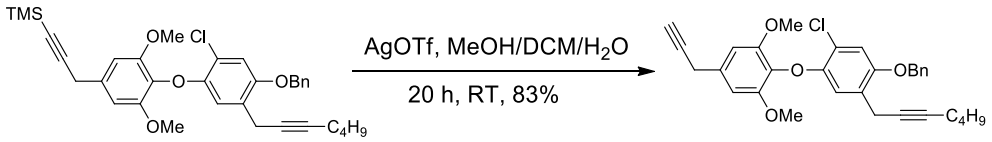
IR ν_{max} (neat, cm^{-1}) 2958 w, 2934 w, 2178 w, 1493 s, 1463 m, 1422 m, 1393 m, 1337 m, 1240 m, 1218 s, 1131 s, 843 s, 698 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46 – 7.29 (5H, m, 5 × Ar**H**), 6.94 (1H, s, Ar**H**), 6.79 (1H, s, Ar**H**), 6.67 (2H, s, 2 × Ar**H**), 5.02 (2H, s, C**H$_2$**), 3.78 (3H, s, C**H$_3$**), 3.66 (1H, s, C**H$_2$**), 3.43 (2H, s, C**H$_2$**), 2.10 – 1.99 (2H, m, C**H$_2$**), 1.37 – 1.27 (4H, m, C**H$_2$**), 0.94 – 0.80 (3H, m, C**H$_3$**), 0.21 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.4 (**C**), 150.6 (**C**), 148.4 (**C**), 137.1 (**C**), 133.9 (**C**), 131.6 (**C**), 128.7 (**C**H), 128.1 (**C**H), 127.3 (**C**H), 115.5 (**C**H), 113.8 (**C**H), 105.4 (**C**H), 104.0 (**C**), 83.1 (**C**), 71.0 (**C**H_2), 56.5 (**C**H_3), 31.1 (**C**H_2), 26.5 (**C**H_2), 22.0 (**C**H_2), 19.8 (**C**H_2), 18.5 (**C**H_2), 13.7 (**C**H_3), 0.2 (**C**H_3).

HRMS (ES^+) Calcd. for $C_{34}H_{39}ClNaO_4Si^+$ $[M(^{35}Cl)+Na]^+$: 597.2198, found: 597.2197.

2-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-1,3-dimethoxy-5-(prop-2-yn-1-yl)benzene (6.48)



6.50

$C_{34}H_{39}ClO_4Si$
MW: 575.21

6.48

$C_{31}H_{31}ClO_4$
MW: 503.03

To diyne **6.50** (159 mg, 0.28 mmol) in MeOH/H_2O/DCM (1,7 mL/0.4 mL/2.9 mL) was added AgOTf (24 mg, 0.09 mmol). After 20 h, sat. NH_4Cl (10 mL) was added then the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 20% Et_2O in petroleum ether) to give the title compound **6.48** (107 mg, 0.21 mmol, 77%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 3292 w, 2958 w, 2930 w, 2856 w, 1493 s, 1463 s, 1422 m, 1393 m, 1337 m, 1241 m, 1218 s, 1190 m, 1130 s, 998 w, 866 m, 697 w.

^{1}H NMR (300 MHz; $CDCl_3$): δ ppm 7.48 – 7.29 (5H, m, 5 × Ar**H**), 6.94 (1H, s, Ar**H**), 6.79 (1H, s, Ar**H**), 6.66 (2H, s, 2 × Ar**H**), 5.02 (2H, s, C**H$_2$**), 3.79 (6H, s, 2 × C**H$_3$**), 3.61 (2H, d, *J* = 2.8 Hz, C**H$_2$**), 3.43 (2H, d, *J* = 0.8 Hz, C**H$_2$**), 2.09 – 2.00 (2H, m, C**H$_2$**), 1.39 – 1.22 (4H, m, 2 × C**H$_2$**), 0.87 (3H, t, *J* = 7.1 Hz, C**H$_3$**).

^{13}C NMR (75 MHz; $CDCl_3$): δ ppm 153.5 (**C**), 150.6 (**C**), 148.3 (**C**), 137.1 (**C**), 133.7 (**C**), 131.7 (**C**), 128.7 (**C**H), 128.1 (**C**H), 127.3 (**C**H), 126.0 (**C**), 119.8 (**C**), 115.5 (**C**H), 113.8 (**C**H), 105.5 (**C**H), 83.2 (**C**), 81.7 (**C**), 70.9 (**C**H_2), 56.6 (**C**H_3), 31.1 (**C**H_2), 25.3 (**C**H_2), 22.0 (**C**H_2), 19.8 (**C**H_2), 18.5 (**C**H_2), 13.7 (**C**H_3).

HRMS (ES^+) Calcd. for $C_{31}H_{32}ClO_4^+$ $[M(^{35}Cl)+H]^+$: 503.1984, found: 503.1961.

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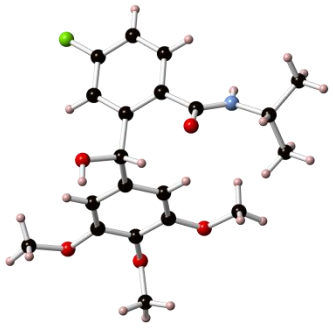
Appendix

Crystallography data:

Table 1. Crystal data and structure refinement details.



Identification code	**2011sot0779** (JBV6661/13/13)
Empirical formula	$C_{20}H_{24}FNO_5$
Formula weight	377.40
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	*C*2/*c*
Unit cell dimensions	*a* = 14.568(11) Å
	b = 19.918(13) Å β = 118.552(8)°
	c = 15.177(11) Å
Volume	3868(5) Å^3
Z	8
Density (calculated)	1.296 Mg / m^3
Absorption coefficient	0.099 mm^{-1}
F(000)	1600
Crystal	Fragment; Colourless
Crystal size	0.12 × 0.08 × 0.02 mm^3

θ range for data collection	3.06 – 25.03°
Index ranges	$-15 \le h \le 17$, $-16 \le k \le 23$, $-18 \le l \le 12$
Reflections collected	7151
Independent reflections	3410 [R_{int} = 0.0426]
Completeness to θ = 25.03°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9980 and 0.9882
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3410 / 0 / 257
Goodness-of-fit on F^2	1.160
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0761, $wR2$ = 0.1172
R indices (all data)	$R1$ = 0.1090, $wR2$ = 0.1294
Largest diff. peak and hole	0.206 and –0.221 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with VHF *Varimax* optics (70µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except those of the hetero atoms which were located in the difference map and freely refined.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
F1	8661(1)	2708(1)	1009(1)	35(1)	1
O1	11528(2)	2067(1)	−968(2)	27(1)	1
O2	8471(2)	2351(1)	−2294(2)	22(1)	1
O3	6171(2)	295(1)	−2934(2)	34(1)	1
O4	7445(2)	−756(1)	−2238(2)	28(1)	1
O5	9512(2)	−624(1)	−1383(2)	32(1)	1
N1	12265(2)	1393(1)	393(2)	22(1)	1
C1	14162(2)	1228(2)	1239(2)	36(1)	1
C2	13150(2)	1177(2)	250(2)	24(1)	1
C3	12961(3)	462(2)	−160(3)	34(1)	1
C4	11542(2)	1825(2)	−208(2)	20(1)	1
C5	10730(2)	2020(2)	92(2)	19(1)	1
C6	11069(2)	2185(2)	1097(2)	21(1)	1
C7	10379(2)	2411(2)	1416(2)	23(1)	1
C8	9346(2)	2471(2)	709(2)	22(1)	1
C9	8968(2)	2301(2)	−283(2)	22(1)	1
C10	9666(2)	2071(2)	−603(2)	18(1)	1
C11	9214(2)	1855(2)	−1697(2)	18(1)	1

C12	8724(2)	1159(2)	−1852(2)	17(1)	1
C13	7645(2)	1082(2)	−2319(2)	23(1)	1
C14	7223(2)	439(2)	−2455(2)	25(1)	1
C15	7874(2)	−119(2)	−2131(2)	24(1)	1
C16	8953(2)	−39(2)	−1665(2)	23(1)	1
C17	9380(2)	600(2)	−1536(2)	24(1)	1
C18	5471(2)	846(2)	−3392(3)	41(1)	1
C19	7209(3)	−1079(2)	−3165(2)	35(1)	1
C20	10627(2)	−567(2)	−936(3)	33(1)	1

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

F1–C8	1.365(3)	N1–C4	1.329(4)
O1–C4	1.242(4)	N1–C2	1.471(4)
O2–C11	1.426(3)	C1–C2	1.524(4)
O3–C14	1.377(4)	C2–C3	1.525(4)
O3–C18	1.433(4)	C4–C5	1.508(4)
O4–C15	1.391(4)	C5–C6	1.399(4)
O4–C19	1.431(4)	C5–C10	1.401(4)
O5–C16	1.368(4)	C6–C7	1.383(4)
O5–C20	1.434(4)	C7–C8	1.373(4)

C8–C9	1.375(4)	C12–C17	1.395(4)
C9–C10	1.397(4)	C13–C14	1.391(4)
C10–C11	1.526(4)	C14–C15	1.389(4)
C11–C12	1.526(4)	C15–C16	1.390(4)
C12–C13	1.390(4)	C16–C17	1.389(4)

C14–O3–C18	116.8(3)	C7–C8–C9	123.4(3)
C15–O4–C19	114.0(2)	C8–C9–C10	119.0(3)
C16–O5–C20	116.8(2)	C9–C10–C5	119.2(3)
C4–N1–C2	123.5(3)	C9–C10–C11	117.7(3)
N1–C2–C1	109.8(3)	C5–C10–C11	123.0(3)
N1–C2–C3	109.4(3)	O2–C11–C12	112.0(2)
C1–C2–C3	111.4(3)	O2–C11–C10	107.3(2)
O1–C4–N1	123.0(3)	C12–C11–C10	110.5(2)
O1–C4–C5	121.0(3)	C13–C12–C17	120.6(3)
N1–C4–C5	116.0(3)	C13–C12–C11	120.7(3)
C6–C5–C10	119.4(3)	C17–C12–C11	118.7(3)
C6–C5–C4	118.0(3)	C12–C13–C14	119.3(3)
C10–C5–C4	122.4(3)	O3–C14–C15	114.8(3)
C7–C6–C5	121.4(3)	O3–C14–C13	124.9(3)
C8–C7–C6	117.6(3)	C15–C14–C13	120.3(3)
F1–C8–C7	118.2(3)	C14–C15–C16	120.2(3)
F1–C8–C9	118.4(3)	C14–C15–O4	119.7(3)

C16–C15–O4	120.0(3)
O5–C16–C17	125.2(3)
O5–C16–C15	114.9(3)
C17–C16–C15	119.9(3)
C16–C17–C12	119.7(3)

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F1	28(1)	57(1)	24(1)	−5(1)	15(1)	10(1)
O1	23(1)	41(2)	18(1)	6(1)	10(1)	3(1)
O2	25(1)	21(1)	16(1)	3(1)	8(1)	6(1)
O3	22(1)	27(1)	47(2)	−2(1)	12(1)	−6(1)
O4	36(1)	25(1)	24(1)	−1(1)	15(1)	−8(1)
O5	30(1)	20(1)	40(1)	2(1)	12(1)	1(1)
N1	23(2)	28(2)	18(2)	2(1)	12(1)	3(1)
C1	20(2)	48(3)	37(2)	−7(2)	11(2)	2(2)
C2	19(2)	31(2)	23(2)	4(2)	12(1)	2(1)
C3	33(2)	34(2)	40(2)	−7(2)	20(2)	−2(2)
C4	17(2)	24(2)	15(2)	−4(1)	5(1)	−2(1)
C5	19(2)	17(2)	22(2)	−1(1)	10(1)	0(1)
C6	20(2)	22(2)	16(2)	−1(1)	6(1)	−2(1)
C7	28(2)	27(2)	14(2)	−6(1)	10(2)	1(1)
C8	26(2)	25(2)	23(2)	−2(2)	18(2)	0(1)
C9	19(2)	26(2)	17(2)	0(1)	6(1)	1(1)
C10	22(2)	13(2)	18(2)	4(1)	10(1)	0(1)
C11	19(2)	16(2)	17(2)	2(1)	7(1)	4(1)

C12	23(2)	16(2)	16(2)	0(1)	12(1)	−2(1)
C13	19(2)	25(2)	25(2)	−2(2)	10(1)	3(1)
C14	23(2)	27(2)	24(2)	−3(2)	11(2)	−5(1)
C15	32(2)	19(2)	22(2)	−1(2)	13(2)	−9(2)
C16	30(2)	17(2)	18(2)	−2(1)	10(2)	2(1)
C17	22(2)	24(2)	22(2)	−3(2)	9(1)	−1(1)
C18	20(2)	37(2)	57(3)	−5(2)	13(2)	0(2)
C19	41(2)	30(2)	30(2)	−4(2)	14(2)	−10(2)
C20	29(2)	27(2)	39(2)	3(2)	13(2)	8(2)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H902	8350(30)	2300(20)	−2890(30)	58(14)	1
H901	12240(20)	1235(15)	930(20)	24(9)	1
H1A	14274	1695	1471	53	1
H1B	14748	1079	1142	53	1
H1C	14114	942	1741	53	1
H2	13200	1481	−250	29	1
H3A	12907	160	323	52	1
H3B	13543	321	−268	52	1
H3C	12309	447	−797	52	1

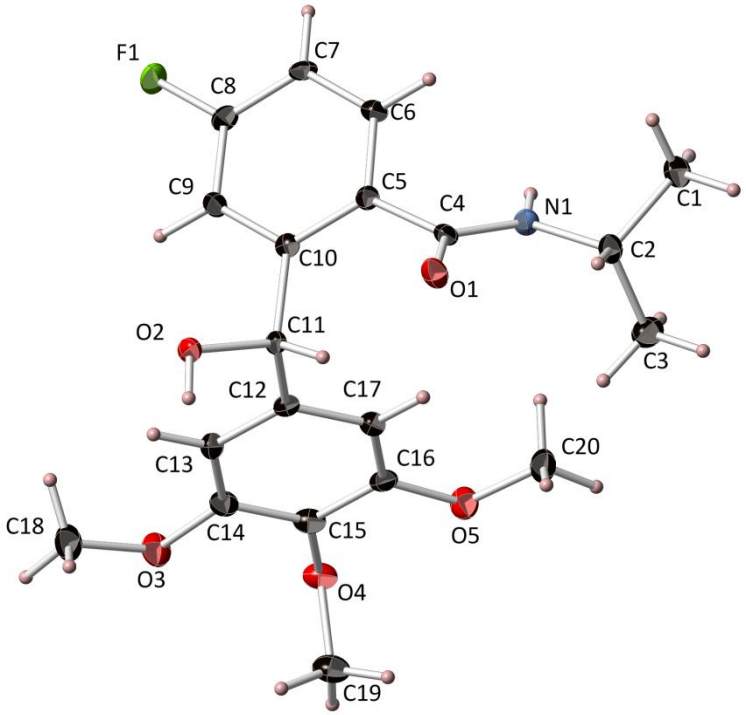
H6	11789	2142	1570	25	1
H7	10611	2520	2099	28	1
H9	8244	2340	−743	26	1
H11	9789	1842	−1879	21	1
H13	7200	1463	−2544	28	1
H17	10116	656	−1233	28	1
H18A	5583	1185	−2882	61	1
H18B	4748	686	−3696	61	1
H18C	5603	1046	−3911	61	1
H19A	6760	−785	−3725	52	1
H19B	6846	−1503	−3218	52	1
H19C	7859	−1168	−3187	52	1
H20A	10811	−350	−1410	49	1
H20B	10941	−1015	−769	49	1
H20C	10890	−297	−323	49	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H902···O1^{i}	0.83(4)	1.89(4)	2.698(4)	163(4)
N1–H901···O4^{ii}	0.89(3)	2.04(3)	2.914(4)	164(3)

Symmetry transformations used to generate equivalent atoms:

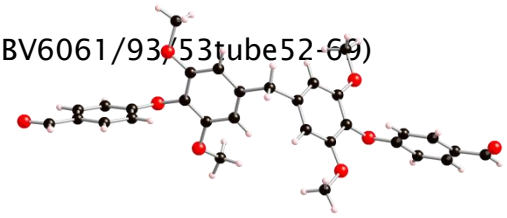
(i) −x+2,y,−z−1/2 (ii) −x+2,−y,−z



Thermal ellipsoids drawn at the 35% probability level.

4,4'-((methylenebis(2,6-dimethoxy-4,1-phenylene))bis(oxy))dibenzaldehyde (24)

Table 1. Crystal data and structure refinement details.



Identification code	**2011SOT0539** (JBV6061/93/53tube52-69)	
Empirical formula	$C_{31}H_{28}O_8$	
Formula weight	528.53	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	*a* = 9.9546(9) Å	α = 90.122(6)°
	b = 11.7249(13) Å	β = 110.086(6)°
	c = 13.1149(8) Å	γ = 113.958(3)°
Volume	1295.8(2) Å^3	
Z	2	
Density (calculated)	1.355 Mg / m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	556	

Crystal	Block; Colourless
Crystal size	$0.18 \times 0.10 \times 0.05$ mm^3
θ range for data collection	$3.21 - 25.02^\circ$
Index ranges	$-11 \le h \le 11$, $-13 \le k \le 13$, $-15 \le l \le 15$
Reflections collected	19331
Independent reflections	4543 [R_{int} = 0.2142]
Completeness to $\theta = 25.02^\circ$	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9951 and 0.9826
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4543 / 0 / 356
Goodness-of-fit on F^2	0.944
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0813, $wR2$ = 0.1865
R indices (all data)	$R1$ = 0.2180, $wR2$ = 0.2566
Largest diff. peak and hole	0.329 and –0.365 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	548(5)	1758(4)	6228(3)	55(1)	1
O2	4234(4)	2350(3)	2980(3)	33(1)	1
O3	6002(4)	1197(4)	4095(3)	40(1)	1
O4	5567(4)	4568(4)	2308(3)	41(1)	1
O5	11780(4)	4373(4)	315(3)	39(1)	1
O6	12385(4)	8215(4)	1856(3)	38(1)	1
O7	12251(4)	6775(4)	214(3)	35(1)	1
O8	19555(5)	10248(4)	1064(3)	60(1)	1
C1	1908(7)	2421(6)	6302(4)	38(2)	1
C2	2515(6)	2414(5)	5430(4)	28(1)	1
C3	1553(6)	1610(5)	4422(4)	34(1)	1
C4	2140(6)	1630(5)	3614(4)	30(1)	1
C5	3721(6)	2418(5)	3815(4)	28(1)	1
C6	4700(6)	3242(5)	4815(4)	34(1)	1
C7	4072(6)	3223(5)	5623(4)	35(1)	1
C8	6725(7)	335(6)	4308(5)	44(2)	1
C9	5606(7)	4870(6)	1264(4)	46(2)	1
C10	5878(6)	2928(5)	3229(4)	28(1)	1

C11	6550(6)	4000(5)	2838(4)	30(1)	1
C12	8141(6)	4528(5)	2996(4)	28(1)	1
C13	9076(6)	3947(5)	3555(4)	29(1)	1
C14	8399(6)	2827(5)	3929(4)	32(1)	1
C15	6789(6)	2295(5)	3766(4)	31(1)	1
C16	10846(6)	4548(5)	3793(4)	36(1)	1
C17	11335(6)	5169(5)	2878(4)	30(1)	1
C18	11363(6)	4458(6)	2051(4)	35(1)	1
C19	11714(6)	4987(6)	1172(4)	35(1)	1
C20	12043(6)	6258(5)	1136(4)	31(1)	1
C21	12014(6)	6967(6)	1977(4)	37(1)	1
C22	11665(6)	6422(5)	2850(4)	30(1)	1
C23	11381(7)	3040(5)	301(5)	46(2)	1
C24	12314(7)	8970(6)	2668(5)	44(2)	1
C25	13750(6)	7568(5)	294(4)	33(1)	1
C26	15103(7)	7887(5)	1253(4)	37(1)	1
C27	16582(7)	8662(5)	1238(4)	36(1)	1
C28	16729(6)	9145(5)	293(4)	35(1)	1
C29	15369(6)	8846(5)	–633(4)	35(1)	1
C30	13879(6)	8066(5)	–647(4)	33(1)	1
C31	18295(7)	9935(6)	293(5)	51(2)	1

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

O1–C1	1.226(6)	C10–C11	1.359(7)
O2–C5	1.372(6)	C10–C15	1.407(7)
O2–C10	1.405(6)	C11–C12	1.383(7)
O3–C15	1.368(6)	C12–C13	1.383(7)
O3–C8	1.440(6)	C13–C14	1.390(7)
O4–C11	1.396(6)	C13–C16	1.520(7)
O4–C9	1.425(6)	C14–C15	1.399(7)
O5–C19	1.369(6)	C16–C17	1.525(7)
O5–C23	1.446(6)	C17–C22	1.372(7)
O6–C21	1.381(7)	C17–C18	1.381(7)
O6–C24	1.421(6)	C18–C19	1.392(7)
O7–C25	1.367(6)	C19–C20	1.395(8)
O7–C20	1.395(6)	C20–C21	1.395(7)
O8–C31	1.218(7)	C21–C22	1.392(7)
C1–C2	1.467(7)	C25–C30	1.389(7)
C2–C7	1.379(7)	C25–C26	1.401(7)
C2–C3	1.395(7)	C26–C27	1.389(7)
C3–C4	1.370(7)	C27–C28	1.392(7)
C4–C5	1.391(7)	C28–C29	1.383(7)
C5–C6	1.398(7)	C28–C31	1.454(8)
C6–C7	1.400(7)	C29–C30	1.384(7)

C5–O2–C10	117.7(4)	C12–C11–O4	121.8(5)
C15–O3–C8	116.6(4)	C13–C12–C11	119.5(5)
C11–O4–C9	114.7(4)	C12–C13–C14	119.7(5)
C19–O5–C23	116.6(4)	C12–C13–C16	120.5(5)
C21–O6–C24	116.3(4)	C14–C13–C16	119.8(5)
C25–O7–C20	118.7(4)	C13–C14–C15	120.6(5)
O1–C1–C2	124.9(5)	O3–C15–C14	125.5(5)
C7–C2–C3	120.0(5)	O3–C15–C10	116.0(5)
C7–C2–C1	118.7(5)	C14–C15–C10	118.5(5)
C3–C2–C1	121.4(5)	C13–C16–C17	115.8(4)
C4–C3–C2	120.4(5)	C22–C17–C18	120.3(5)
C3–C4–C5	119.9(5)	C22–C17–C16	119.5(5)
O2–C5–C4	116.4(4)	C18–C17–C16	120.1(5)
O2–C5–C6	123.0(5)	C17–C18–C19	121.1(5)
C4–C5–C6	120.6(5)	O5–C19–C18	126.0(5)
C5–C6–C7	118.6(5)	O5–C19–C20	115.1(5)
C2–C7–C6	120.5(5)	C18–C19–C20	118.9(5)
C11–C10–O2	120.6(5)	O7–C20–C21	120.5(5)
C11–C10–C15	119.9(5)	O7–C20–C19	119.8(4)
O2–C10–C15	118.9(5)	C21–C20–C19	119.4(5)
C10–C11–C12	121.6(5)	O6–C21–C22	125.3(5)
C10–C11–O4	116.6(4)	O6–C21–C20	113.8(5)

C22–C21–C20	120.8(5)
C17–C22–C21	119.4(5)
O7–C25–C30	116.0(5)
O7–C25–C26	123.5(5)
C30–C25–C26	120.4(5)
C27–C26–C25	119.1(5)
C26–C27–C28	120.9(5)
C29–C28–C27	118.7(5)
C29–C28–C31	121.5(5)
C27–C28–C31	119.7(5)
C28–C29–C30	121.7(5)
C29–C30–C25	119.0(5)
O8–C31–C28	126.3(6)

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

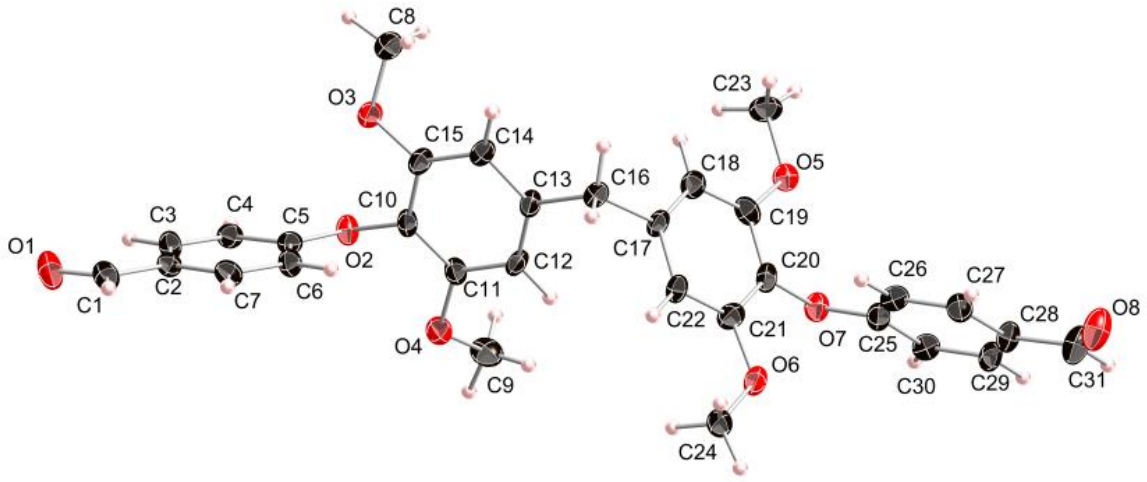
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	41(3)	79(4)	52(3)	17(2)	26(2)	27(3)
O2	31(2)	40(3)	30(2)	7(2)	16(2)	13(2)
O3	35(2)	34(3)	59(2)	24(2)	24(2)	18(2)
O4	38(2)	48(3)	46(2)	18(2)	22(2)	23(2)
O5	44(3)	37(3)	45(2)	11(2)	25(2)	19(2)
O6	44(2)	32(3)	45(2)	12(2)	29(2)	14(2)
O7	36(2)	40(3)	32(2)	9(2)	16(2)	16(2)
O8	42(3)	76(4)	41(2)	13(2)	12(2)	9(3)
C1	36(4)	50(4)	35(3)	10(3)	15(3)	24(3)
C2	25(3)	32(3)	30(3)	8(2)	9(2)	15(3)
C3	27(3)	38(4)	40(3)	8(3)	17(3)	13(3)
C4	27(3)	27(3)	33(3)	3(2)	9(2)	11(3)
C5	28(3)	25(3)	31(3)	7(2)	11(2)	13(3)
C6	26(3)	38(4)	41(3)	10(3)	15(3)	13(3)
C7	31(4)	37(4)	35(3)	2(3)	9(3)	17(3)
C8	40(4)	37(4)	57(4)	14(3)	22(3)	15(3)

C9	58(4)	61(5)	33(3)	17(3)	16(3)	39(4)
C10	22(3)	31(4)	33(3)	6(2)	15(2)	9(3)
C11	25(3)	37(4)	32(3)	10(3)	14(2)	14(3)
C12	34(3)	23(3)	34(3)	13(2)	20(2)	11(3)
C13	27(3)	29(3)	31(3)	9(2)	15(2)	9(3)
C14	35(3)	29(4)	33(3)	10(2)	16(3)	11(3)
C15	28(3)	25(3)	35(3)	12(2)	12(2)	9(3)
C16	33(3)	30(4)	44(3)	12(3)	19(3)	11(3)
C17	24(3)	23(4)	38(3)	9(2)	14(2)	4(3)
C18	28(3)	38(4)	39(3)	13(3)	13(3)	13(3)
C19	27(3)	42(4)	37(3)	2(3)	10(2)	17(3)
C20	25(3)	34(4)	33(3)	9(3)	15(2)	8(3)
C21	33(3)	31(4)	45(3)	12(3)	13(3)	13(3)
C22	23(3)	27(4)	34(3)	5(2)	13(2)	4(3)
C23	50(4)	30(4)	56(4)	3(3)	18(3)	17(3)
C24	55(4)	34(4)	58(4)	7(3)	39(3)	18(3)
C25	30(3)	34(4)	35(3)	6(3)	16(3)	12(3)
C26	40(4)	32(4)	39(3)	9(3)	15(3)	15(3)
C27	33(4)	43(4)	33(3)	12(3)	13(3)	16(3)
C28	35(4)	37(4)	33(3)	8(3)	18(3)	10(3)
C29	43(4)	37(4)	30(3)	11(3)	23(3)	16(3)
C30	35(4)	32(4)	28(3)	2(2)	8(2)	14(3)
C31	44(4)	51(5)	39(4)	10(3)	15(3)	4(4)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	2623	2981	6974	46	1
H3	486	1044	4295	41	1
H4	1467	1106	2918	36	1
H6	5770	3804	4943	41	1
H7	4723	3771	6310	42	1
H8A	6856	96	3644	66	1
H8B	6045	–424	4514	66	1
H8C	7765	745	4911	66	1
H9A	6659	5529	1364	69	1
H9B	4804	5176	914	69	1
H9C	5383	4111	796	69	1
H12	8590	5284	2723	34	1
H14	9036	2419	4299	39	1
H16A	11233	3887	3957	43	1
H16B	11390	5194	4465	43	1
H18	11140	3593	2083	42	1
H22	11654	6913	3422	36	1
H23A	12150	2929	950	69	1

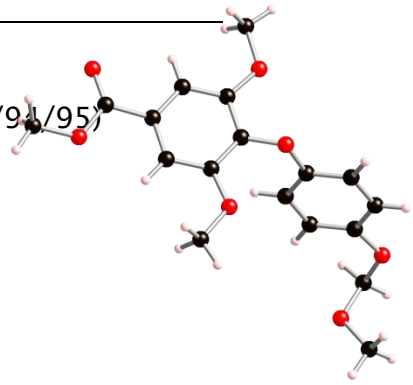
H23B	11410	2692	−367	69	1
H23C	10314	2596	311	69	1
H24A	11242	8598	2677	66	1
H24B	12572	9828	2494	66	1
H24C	13079	9006	3392	66	1
H26	15009	7577	1906	45	1
H27	17507	8865	1881	44	1
H29	15460	9185	−1277	42	1
H30	12958	7875	−1290	39	1
H31	18339	10236	−372	61	1



Thermal ellipsoids drawn at the 35% probability level.

Methyl 3,5-dimethoxy-4-(4-(methoxymethoxy)phenoxy)benzoate (68)

Table 1. Crystal data and structure refinement details.



Identification code	**2011sot0719** (JBV6061/94/95)
Empirical formula	$C_{18}H_{20}O_7$
Formula weight	348.34
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*–1
Unit cell dimensions	*a* = 7.1100(3) Å α = 104.444(2)°

	b = 10.3038(6) Å β = 94.2380(10)°
	c = 12.5087(6) Å γ = 107.774(2)°
Volume	833.80(7) Å^3
Z	2
Density (calculated)	1.387 Mg / m^3
Absorption coefficient	0.107 mm^{-1}
F(000)	368
Crystal	Prism; Colourless
Crystal size	0.46 × 0.35 × 0.19 mm^3
θ range for data collection	3.05 – 27.48°
Index ranges	$-9 \le h \le 9$, $-11 \le k \le 13$, $-16 \le l \le 15$
Reflections collected	7557
Independent reflections	3784 [R_{int} = 0.0181]
Completeness to θ = 27.48°	98.9 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9799 and 0.9523
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3784 / 0 / 230
Goodness-of-fit on F^2	1.058
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0386, *wR2* = 0.1079
R indices (all data)	*R1* = 0.0399, *wR2* = 0.1093
Largest diff. peak and hole	0.260 and –0.259 e Å^{-3}

Diffractometer: *Rigaku R-Axis Spider* including curved Fujifilm image plate and a graphite monochromated sealed tube Mo generator. **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	2888(1)	12225(1)	5752(1)	24(1)	1
O2	2258(1)	10661(1)	4049(1)	26(1)	1
O3	3288(1)	9330(1)	8443(1)	25(1)	1
O4	2354(1)	6104(1)	4936(1)	22(1)	1
O5	2691(1)	6698(1)	7135(1)	21(1)	1
O6	9011(1)	5970(1)	9483(1)	26(1)	1
O7	11166(1)	8202(1)	10584(1)	29(1)	1
C1	2756(2)	13289(1)	5207(1)	26(1)	1
C2	2595(1)	10934(1)	5053(1)	18(1)	1
C3	3405(2)	10678(1)	9169(1)	29(1)	1
C4	2009(2)	5724(1)	3740(1)	26(1)	1
C5	2573(1)	7470(1)	5493(1)	17(1)	1
C6	2513(1)	8518(1)	4988(1)	17(1)	1

C7	2727(1)	9874(1)	5654(1)	17(1)	1
C8	3015(1)	10215(1)	6817(1)	19(1)	1
C9	3063(1)	9161(1)	7322(1)	19(1)	1
C10	2848(1)	7794(1)	6658(1)	18(1)	1
C11	4391(2)	6627(1)	7704(1)	18(1)	1
C12	6299(2)	7592(1)	7845(1)	19(1)	1
C13	7895(2)	7421(1)	8451(1)	21(1)	1
C14	7559(2)	6270(1)	8891(1)	20(1)	1
C15	5640(2)	5296(1)	8724(1)	23(1)	1
C16	4053(2)	5473(1)	8138(1)	22(1)	1
C17	10991(2)	6965(1)	9754(1)	25(1)	1
C18	10974(2)	7967(2)	11650(1)	41(1)	1

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

O1–C2	1.3422(12)	C2–C7	1.4925(13)
O1–C1	1.4492(12)	C5–C6	1.3904(13)
O2–C2	1.2052(13)	C5–C10	1.3965(14)
O3–C9	1.3607(12)	C6–C7	1.3930(13)
O3–C3	1.4322(13)	C7–C8	1.3921(14)
O4–C5	1.3603(11)	C8–C9	1.3934(14)
O4–C4	1.4298(12)	C9–C10	1.4007(14)
O5–C10	1.3825(11)	C11–C12	1.3836(14)
O5–C11	1.3876(12)	C11–C16	1.3910(14)
O6–C14	1.3811(12)	C12–C13	1.3979(14)
O6–C17	1.4222(13)	C13–C14	1.3918(14)
O7–C17	1.3928(13)	C14–C15	1.3900(15)
O7–C18	1.4231(15)	C15–C16	1.3831(14)

C2–O1–C1	114.77(8)
C9–O3–C3	117.89(8)
C5–O4–C4	117.08(8)
C10–O5–C11	119.69(7)
C14–O6–C17	118.23(8)
C17–O7–C18	112.52(9)
O2–C2–O1	123.54(9)
O2–C2–C7	123.75(9)
O1–C2–C7	112.71(8)
O4–C5–C6	124.93(9)
O4–C5–C10	115.59(9)
C6–C5–C10	119.47(9)
C5–C6–C7	119.37(9)
C8–C7–C6	121.79(9)
C8–C7–C2	121.84(9)
C6–C7–C2	116.36(9)
C7–C8–C9	118.78(9)
O3–C9–C8	125.30(9)
O3–C9–C10	114.86(9)
C8–C9–C10	119.84(9)
O5–C10–C5	118.19(9)
O5–C10–C9	120.70(9)

C5–C10–C9	120.76(9)
C12–C11–O5	124.81(9)
C12–C11–C16	120.63(9)
O5–C11–C16	114.56(9)
C11–C12–C13	119.62(9)
C14–C13–C12	119.85(9)
O6–C14–C15	114.77(9)
O6–C14–C13	125.37(9)
C15–C14–C13	119.85(9)
C16–C15–C14	120.43(9)
C15–C16–C11	119.60(9)
O7–C17–O6	112.67(9)

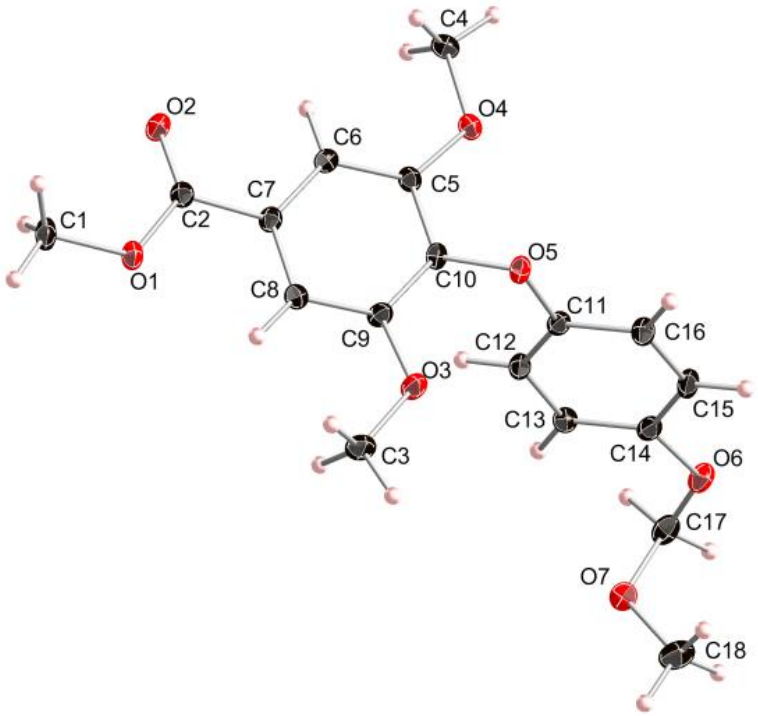
Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	35(1)	17(1)	23(1)	8(1)	3(1)	11(1)
O2	35(1)	23(1)	20(1)	10(1)	2(1)	10(1)
O3	40(1)	24(1)	15(1)	6(1)	4(1)	14(1)
O4	30(1)	16(1)	20(1)	4(1)	2(1)	9(1)
O5	22(1)	19(1)	23(1)	11(1)	1(1)	5(1)

O6	30(1)	24(1)	28(1)	11(1)	−2(1)	11(1)
O7	33(1)	26(1)	26(1)	9(1)	1(1)	8(1)
C1	31(1)	20(1)	31(1)	13(1)	5(1)	12(1)
C2	17(1)	18(1)	21(1)	7(1)	2(1)	6(1)
C3	43(1)	29(1)	17(1)	2(1)	3(1)	17(1)
C4	36(1)	20(1)	20(1)	1(1)	1(1)	9(1)
C5	16(1)	15(1)	20(1)	5(1)	2(1)	6(1)
C6	18(1)	18(1)	16(1)	6(1)	2(1)	6(1)
C7	16(1)	18(1)	20(1)	7(1)	3(1)	6(1)
C8	21(1)	17(1)	19(1)	5(1)	2(1)	8(1)
C9	21(1)	21(1)	16(1)	6(1)	3(1)	7(1)
C10	17(1)	18(1)	20(1)	9(1)	2(1)	6(1)
C11	24(1)	18(1)	14(1)	5(1)	3(1)	10(1)
C12	26(1)	16(1)	18(1)	7(1)	4(1)	8(1)
C13	24(1)	19(1)	20(1)	6(1)	2(1)	7(1)
C14	29(1)	20(1)	15(1)	4(1)	2(1)	13(1)
C15	33(1)	20(1)	21(1)	11(1)	7(1)	12(1)
C16	25(1)	20(1)	23(1)	10(1)	5(1)	7(1)
C17	26(1)	31(1)	25(1)	12(1)	5(1)	15(1)
C18	56(1)	45(1)	23(1)	8(1)	2(1)	18(1)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	3861	13489	4782	38	1
H1B	2838	14163	5773	38	1
H1C	1478	12933	4698	38	1
H3A	4567	11423	9071	44	1
H3B	3546	10650	9948	44	1
H3C	2183	10884	8985	44	1
H4A	775	5871	3482	39	1
H4B	1878	4721	3437	39	1
H4C	3138	6319	3482	39	1
H6	2328	8312	4196	21	1
H8	3177	11150	7258	23	1
H12	6524	8366	7532	23	1
H13	9205	8090	8563	25	1
H15	5416	4503	9015	27	1
H16	2741	4810	8033	26	1
H17A	11916	6515	10010	30	1
H17B	11396	7218	9072	30	1
H18A	9611	7344	11631	62	1
H18B	11243	8879	12217	62	1
H18C	11934	7517	11837	62	1



Thermal ellipsoids drawn at the 35% probability level

Data for JBVICES088

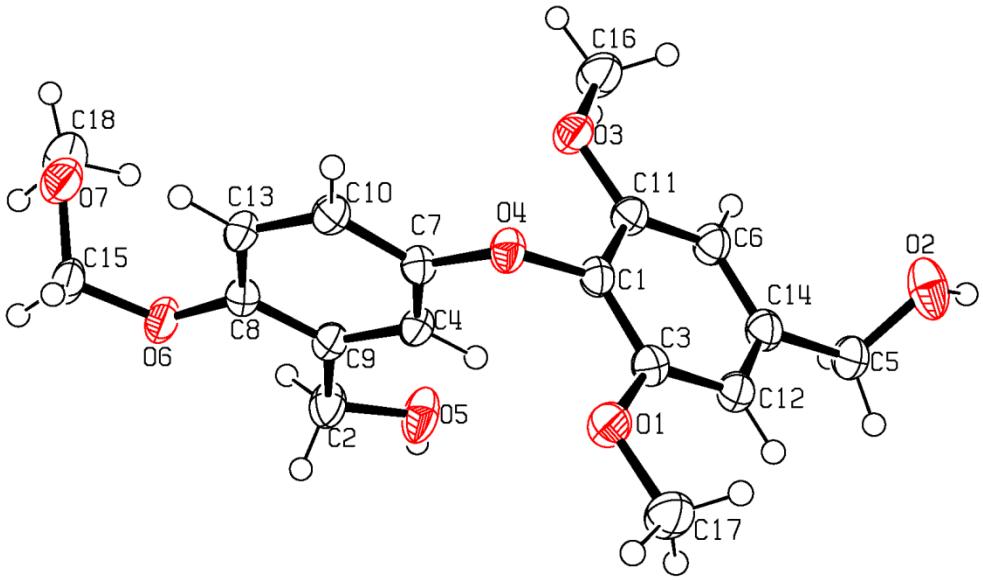


Table 1. Crystal data and structure refinement for jbvices088.

Identification code	shelxs
Empirical formula	C18 H22 O7
Formula weight	350.36
Temperature	110(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.5707(17) A alpha = 84.63(3) deg.
	b = 8.9167(18) A beta = 80.51(3) deg.
	c = 12.589(3) A gamma = 65.10(3) deg.

Volume	860.4(3) A^3
Z, Calculated density	2, 1.352 Mg/m^3
Absorption coefficient	0.104 mm^-1
F(000)	372
Crystal size	0.40 x 0.22 x 0.22 mm
Theta range for data collection	2.52 to 28.28 deg.
Limiting indices	-11<=h<=11, -9<=k<=11, -16<=l<=16
Reflections collected / unique	12435 / 4221 [R(int) = 0.0299]
Completeness to theta = 28.28	98.7 %
Max. and min. transmission	0.9774 and 0.9599
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4221 / 0 / 232
Goodness-of-fit on F^2	1.157
Final R indices [I>2sigma(I)]	R1 = 0.0751, wR2 = 0.1987
R indices (all data)	R1 = 0.0853, wR2 = 0.2088
Extinction coefficient	0.000(4)
Largest diff. peak and hole	0.586 and -0.263 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for jbvices088.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(4)	1698(2)	7017(2)	2568(1)	29(1)
O(3)	4611(2)	6466(2)	1235(1)	33(1)
O(6)	1903(2)	947(2)	1728(1)	38(1)
O(1)	1418(2)	7530(2)	4658(1)	34(1)
C(1)	3130(2)	6984(2)	2973(2)	26(1)
O(7)	1041(2)	1144(2)	32(1)	41(1)
O(5)	5639(2)	1118(2)	3276(2)	44(1)
C(3)	3010(2)	7242(2)	4059(2)	27(1)
C(4)	2996(2)	4004(2)	2732(2)	28(1)
C(6)	6127(2)	6564(2)	2701(2)	30(1)
C(7)	1831(2)	5470(2)	2316(2)	26(1)
C(8)	1836(2)	2490(2)	1868(2)	28(1)
C(9)	3005(3)	2511(2)	2507(2)	29(1)
C(10)	713(2)	5463(2)	1643(2)	28(1)
C(11)	4677(2)	6668(2)	2286(2)	28(1)
C(12)	4451(2)	7172(2)	4473(2)	29(1)
C(13)	714(2)	3963(2)	1415(2)	29(1)
C(14)	6015(3)	6818(2)	3791(2)	31(1)
C(15)	706(3)	823(3)	1127(2)	38(1)
C(2)	4241(3)	902(3)	2960(2)	37(1)
C(5)	7602(3)	6704(3)	4231(2)	36(1)
C(16)	6170(3)	6055(3)	501(2)	42(1)
C(17)	1178(3)	7970(3)	5754(2)	41(1)
C(18)	2600(3)	-113(3)	-476(2)	53(1)
O(2)	8035(2)	8039(2)	3795(2)	46(1)

Table 3. Bond lengths [A] and angles [deg] for jbvices088.

O(4)-C(1)	1.393(2)
O(4)-C(7)	1.398(2)
O(3)-C(11)	1.365(2)
O(3)-C(16)	1.420(3)
O(6)-C(8)	1.379(2)
O(6)-C(15)	1.416(2)
O(1)-C(3)	1.378(2)
O(1)-C(17)	1.429(3)
C(1)-C(3)	1.387(3)
C(1)-C(11)	1.392(3)
O(7)-C(15)	1.389(3)
O(7)-C(18)	1.429(3)
O(5)-C(2)	1.413(2)
O(5)-H(5)	0.8400
C(3)-C(12)	1.394(3)
C(4)-C(9)	1.383(3)
C(4)-C(7)	1.387(3)
C(4)-H(4)	0.9500
C(6)-C(11)	1.391(3)
C(6)-C(14)	1.393(3)
C(6)-H(6)	0.9500
C(7)-C(10)	1.382(3)
C(8)-C(9)	1.392(3)
C(8)-C(13)	1.397(3)
C(9)-C(2)	1.507(3)
C(10)-C(13)	1.393(3)
C(10)-H(10)	0.9500
C(12)-C(14)	1.396(3)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(14)-C(5)	1.512(3)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(5)-O(2)	1.428(3)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
O(2)-H(2)	0.8400

C(1)-O(4)-C(7)	114.78(14)
C(11)-O(3)-C(16)	117.61(16)
C(8)-O(6)-C(15)	118.74(15)
C(3)-O(1)-C(17)	117.15(16)
C(3)-C(1)-C(11)	120.64(17)
C(3)-C(1)-O(4)	119.77(16)
C(11)-C(1)-O(4)	119.58(17)

C(15)-O(7)-C(18)	112.59(19)
C(2)-O(5)-H(5)	109.5
O(1)-C(3)-C(1)	115.23(16)
O(1)-C(3)-C(12)	124.80(18)
C(1)-C(3)-C(12)	119.97(17)
C(9)-C(4)-C(7)	120.01(17)
C(9)-C(4)-H(4)	120.0
C(7)-C(4)-H(4)	120.0
C(11)-C(6)-C(14)	120.07(18)
C(11)-C(6)-H(6)	120.0
C(14)-C(6)-H(6)	120.0
C(10)-C(7)-C(4)	120.97(18)
C(10)-C(7)-O(4)	116.72(16)
C(4)-C(7)-O(4)	122.30(16)
O(6)-C(8)-C(9)	115.10(16)
O(6)-C(8)-C(13)	124.80(17)
C(9)-C(8)-C(13)	120.09(18)
C(4)-C(9)-C(8)	119.63(17)
C(4)-C(9)-C(2)	121.11(17)
C(8)-C(9)-C(2)	119.26(18)
C(7)-C(10)-C(13)	119.26(17)
C(7)-C(10)-H(10)	120.4
C(13)-C(10)-H(10)	120.4
O(3)-C(11)-C(6)	125.75(17)
O(3)-C(11)-C(1)	114.73(16)
C(6)-C(11)-C(1)	119.52(18)
C(3)-C(12)-C(14)	119.54(18)
C(3)-C(12)-H(12)	120.2
C(14)-C(12)-H(12)	120.2
C(10)-C(13)-C(8)	119.93(17)
C(10)-C(13)-H(13)	120.0
C(8)-C(13)-H(13)	120.0
C(6)-C(14)-C(12)	120.24(18)
C(6)-C(14)-C(5)	119.51(18)
C(12)-C(14)-C(5)	120.25(18)
O(7)-C(15)-O(6)	113.05(18)
O(7)-C(15)-H(15A)	109.0
O(6)-C(15)-H(15A)	109.0
O(7)-C(15)-H(15B)	109.0
O(6)-C(15)-H(15B)	109.0
H(15A)-C(15)-H(15B)	107.8
O(5)-C(2)-C(9)	109.80(16)
O(5)-C(2)-H(2A)	109.7
C(9)-C(2)-H(2A)	109.7
O(5)-C(2)-H(2B)	109.7
C(9)-C(2)-H(2B)	109.7
H(2A)-C(2)-H(2B)	108.2
O(2)-C(5)-C(14)	109.61(17)
O(2)-C(5)-H(5A)	109.7
C(14)-C(5)-H(5A)	109.7
O(2)-C(5)-H(5B)	109.7
C(14)-C(5)-H(5B)	109.7
H(5A)-C(5)-H(5B)	108.2
O(3)-C(16)-H(16A)	109.5
O(3)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(3)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5

O(1)-C(17)-H(17A)	109.5
O(1)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(1)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
O(7)-C(18)-H(18A)	109.5
O(7)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(7)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(5)-O(2)-H(2)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for jbvices088.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(4)	25(1)	28(1)	35(1)	-1(1)	-10(1)	-12(1)
O(3)	30(1)	47(1)	27(1)	-4(1)	-4(1)	-19(1)
O(6)	49(1)	34(1)	43(1)	5(1)	-25(1)	-23(1)
O(1)	28(1)	44(1)	31(1)	-5(1)	-2(1)	-17(1)
C(1)	24(1)	25(1)	30(1)	0(1)	-7(1)	-12(1)
O(7)	47(1)	40(1)	41(1)	2(1)	-19(1)	-19(1)
O(5)	44(1)	32(1)	62(1)	-1(1)	-33(1)	-12(1)
C(3)	26(1)	28(1)	30(1)	-2(1)	-3(1)	-12(1)
C(4)	29(1)	35(1)	26(1)	-1(1)	-8(1)	-16(1)
C(6)	26(1)	33(1)	32(1)	-1(1)	-6(1)	-14(1)
C(7)	25(1)	28(1)	27(1)	-1(1)	-5(1)	-13(1)
C(8)	31(1)	30(1)	29(1)	1(1)	-8(1)	-17(1)
C(9)	32(1)	31(1)	28(1)	1(1)	-10(1)	-16(1)
C(10)	27(1)	31(1)	30(1)	2(1)	-9(1)	-12(1)
C(11)	28(1)	29(1)	28(1)	0(1)	-6(1)	-13(1)
C(12)	31(1)	30(1)	30(1)	0(1)	-8(1)	-14(1)
C(13)	28(1)	36(1)	28(1)	-1(1)	-10(1)	-16(1)
C(14)	30(1)	32(1)	35(1)	2(1)	-9(1)	-16(1)
C(15)	46(1)	39(1)	41(1)	3(1)	-21(1)	-26(1)
C(2)	41(1)	31(1)	47(1)	6(1)	-23(1)	-16(1)
C(5)	35(1)	44(1)	38(1)	3(1)	-13(1)	-23(1)
C(16)	36(1)	64(2)	32(1)	-7(1)	0(1)	-25(1)
C(17)	39(1)	55(1)	32(1)	-8(1)	2(1)	-22(1)
C(18)	46(1)	60(2)	57(2)	-12(1)	-12(1)	-23(1)
O(2)	27(1)	36(1)	81(1)	1(1)	-18(1)	-15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for jbvices088.

	x	y	z	U(eq)
H(5)	6378	199	3464	67
H(4)	3787	4026	3171	34
H(6)	7195	6320	2240	36
H(10)	-47	6469	1338	34
H(12)	4370	7365	5214	35
H(13)	-47	3942	953	35
H(15A)	742	-305	1232	45
H(15B)	-481	1614	1407	45
H(2A)	3622	530	3589	45
H(2B)	4689	43	2408	45
H(5A)	7364	6754	5026	43
H(5B)	8590	5637	4035	43
H(16A)	6624	6891	521	64
H(16B)	5931	6019	-229	64
H(16C)	7030	4970	705	64
H(17A)	2007	7064	6147	62
H(17B)	-9	8174	6086	62
H(17C)	1371	8973	5781	62
H(18A)	3605	-76	-223	79
H(18B)	2683	75	-1259	79
H(18C)	2581	-1199	-294	79
H(2)	9057	7829	3886	69

Data for JBVICES115

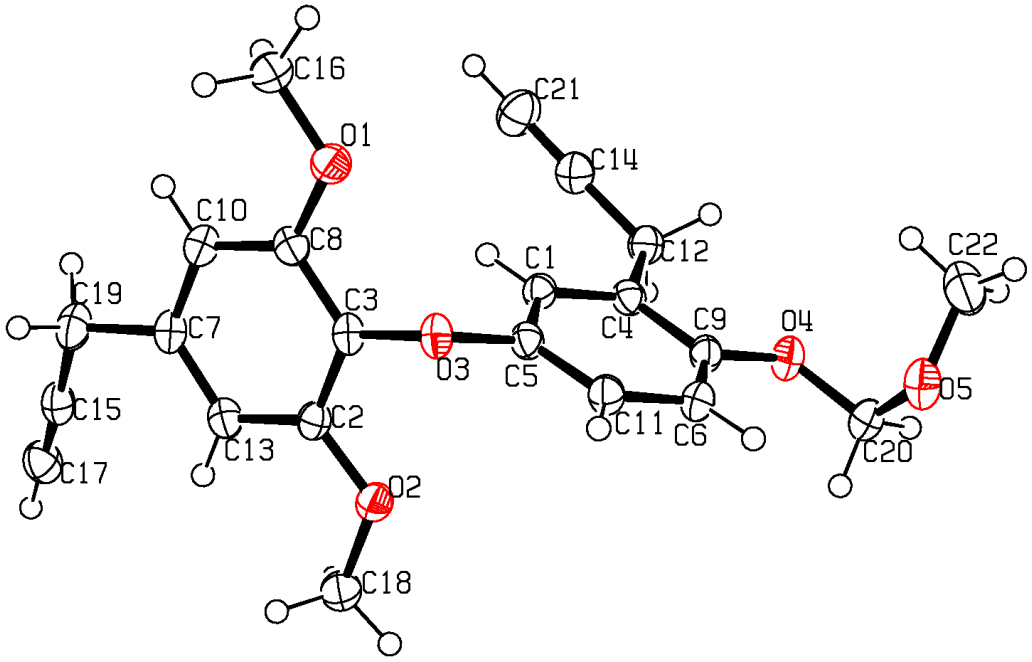


Table 1. Crystal data and structure refinement for shelx1.

Identification code	shelx1
Empirical formula	C22 H22 O5
Formula weight	366.40
Temperature	110(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P -1
Unit cell dimensions	a = 8.5211(17) A alpha = 104.60(3) deg. b = 10.160(2) A beta = 98.53(3) deg. c = 12.900(3) A gamma = 114.60(3) deg.
Volume	941.0(3) A^3
Z, Calculated density	2, 1.293 Mg/m^3
Absorption coefficient	0.091 mm^-1
F(000)	388
Crystal size	0.44 x 0.44 x 0.44 mm

Theta range for data collection	2.37 to 28.28 deg.
Limiting indices	-11<=h<=11, -13<=k<=13, -17<=l<=17
Reflections collected / unique	13419 / 4598 [R(int) = 0.0194]
Completeness to theta = 28.28	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9610 and 0.9610
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4598 / 0 / 247
Goodness-of-fit on F^2	1.154
Final R indices [I>2sigma(I)]	R1 = 0.0585, wR2 = 0.1598
R indices (all data)	R1 = 0.0600, wR2 = 0.1615
Largest diff. peak and hole	0.379 and -0.292 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for shelx1.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(3)	7607(1)	6304(1)	2716(1)	26(1)
O(4)	7314(1)	2052(1)	-1071(1)	30(1)
O(2)	8841(1)	8508(1)	1814(1)	30(1)
O(1)	9417(1)	6612(1)	4697(1)	32(1)
O(5)	4286(1)	201(1)	-1909(1)	37(1)
C(1)	9011(2)	4941(1)	1709(1)	24(1)
C(2)	9870(2)	8813(2)	2845(1)	24(1)
C(3)	9239(2)	7629(1)	3283(1)	24(1)
C(4)	8874(2)	3841(1)	752(1)	24(1)
C(5)	7572(2)	5243(1)	1772(1)	24(1)
C(6)	5841(2)	3340(2)	-55(1)	28(1)
C(7)	12369(2)	10366(2)	4516(1)	27(1)
C(8)	10169(2)	7826(1)	4342(1)	26(1)
C(9)	7296(2)	3075(1)	-139(1)	25(1)
C(10)	11741(2)	9198(2)	4960(1)	28(1)
C(11)	5984(2)	4432(2)	910(1)	26(1)
C(12)	10365(2)	3411(2)	646(1)	28(1)
C(13)	11446(2)	10186(2)	3464(1)	27(1)
C(14)	11730(2)	3968(2)	1701(1)	31(1)
C(15)	14974(2)	12880(2)	4669(1)	30(1)
C(16)	10257(2)	6793(2)	5803(1)	34(1)
C(17)	15772(2)	13746(2)	4239(1)	35(1)
C(18)	9397(2)	9703(2)	1348(1)	34(1)
C(19)	14056(2)	11858(2)	5246(1)	34(1)
C(20)	5813(2)	1322(2)	-2029(1)	32(1)
C(21)	12805(2)	4392(2)	2568(1)	41(1)
C(22)	4568(3)	-1000(2)	-1679(2)	45(1)

Table 3. Bond lengths [A] and angles [deg] for shelx1.

O(3)-C(3)	1.3869(17)
O(3)-C(5)	1.3947(15)
O(4)-C(9)	1.3833(15)
O(4)-C(20)	1.4117(18)
O(2)-C(2)	1.3616(16)
O(2)-C(18)	1.4253(17)
O(1)-C(8)	1.3619(16)
O(1)-C(16)	1.4265(17)
O(5)-C(20)	1.3891(19)
O(5)-C(22)	1.428(2)
C(1)-C(5)	1.3912(18)
C(1)-C(4)	1.3924(18)
C(1)-H(1)	0.9500
C(2)-C(13)	1.396(2)
C(2)-C(3)	1.3965(18)
C(3)-C(8)	1.3944(19)
C(4)-C(9)	1.3975(19)
C(4)-C(12)	1.5192(18)
C(5)-C(11)	1.3823(19)
C(6)-C(9)	1.3873(19)
C(6)-C(11)	1.3936(18)
C(6)-H(6)	0.9500
C(7)-C(10)	1.3884(19)
C(7)-C(13)	1.3902(19)
C(7)-C(19)	1.521(2)
C(8)-C(10)	1.393(2)
C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
C(12)-C(14)	1.455(2)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-H(13)	0.9500
C(14)-C(21)	1.184(2)
C(15)-C(17)	1.186(2)
C(15)-C(19)	1.459(2)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17)	0.9500
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-H(21)	0.9500
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800

C(3)-O(3)-C(5)	116.96(10)
C(9)-O(4)-C(20)	117.94(11)
C(2)-O(2)-C(18)	117.19(11)
C(8)-O(1)-C(16)	117.36(11)
C(20)-O(5)-C(22)	112.53(12)

C(5)-C(1)-C(4)	119.71(12)
C(5)-C(1)-H(1)	120.1
C(4)-C(1)-H(1)	120.1
O(2)-C(2)-C(13)	125.04(13)
O(2)-C(2)-C(3)	115.15(12)
C(13)-C(2)-C(3)	119.81(12)
O(3)-C(3)-C(8)	119.18(12)
O(3)-C(3)-C(2)	120.50(12)
C(8)-C(3)-C(2)	120.09(12)
C(1)-C(4)-C(9)	119.24(12)
C(1)-C(4)-C(12)	122.39(12)
C(9)-C(4)-C(12)	118.35(11)
C(11)-C(5)-C(1)	120.84(12)
C(11)-C(5)-O(3)	116.47(12)
C(1)-C(5)-O(3)	122.60(11)
C(9)-C(6)-C(11)	119.57(12)
C(9)-C(6)-H(6)	120.2
C(11)-C(6)-H(6)	120.2
C(10)-C(7)-C(13)	120.83(12)
C(10)-C(7)-C(19)	117.22(12)
C(13)-C(7)-C(19)	121.91(13)
O(1)-C(8)-C(10)	124.74(12)
O(1)-C(8)-C(3)	115.24(12)
C(10)-C(8)-C(3)	120.02(13)
O(4)-C(9)-C(6)	124.18(12)
O(4)-C(9)-C(4)	115.05(12)
C(6)-C(9)-C(4)	120.76(12)
C(7)-C(10)-C(8)	119.62(12)
C(7)-C(10)-H(10)	120.2
C(8)-C(10)-H(10)	120.2
C(5)-C(11)-C(6)	119.77(12)
C(5)-C(11)-H(11)	120.1
C(6)-C(11)-H(11)	120.1
C(14)-C(12)-C(4)	113.84(11)
C(14)-C(12)-H(12A)	108.8
C(4)-C(12)-H(12A)	108.8
C(14)-C(12)-H(12B)	108.8
C(4)-C(12)-H(12B)	108.8
H(12A)-C(12)-H(12B)	107.7
C(7)-C(13)-C(2)	119.62(13)
C(7)-C(13)-H(13)	120.2
C(2)-C(13)-H(13)	120.2
C(21)-C(14)-C(12)	178.11(16)
C(17)-C(15)-C(19)	177.44(15)
O(1)-C(16)-H(16A)	109.5
O(1)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(1)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(15)-C(17)-H(17)	180.0
O(2)-C(18)-H(18A)	109.5
O(2)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(2)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(15)-C(19)-C(7)	115.92(12)
C(15)-C(19)-H(19A)	108.3

C(7)-C(19)-H(19A)	108.3
C(15)-C(19)-H(19B)	108.3
C(7)-C(19)-H(19B)	108.3
H(19A)-C(19)-H(19B)	107.4
O(5)-C(20)-O(4)	113.24(12)
O(5)-C(20)-H(20A)	108.9
O(4)-C(20)-H(20A)	108.9
O(5)-C(20)-H(20B)	108.9
O(4)-C(20)-H(20B)	108.9
H(20A)-C(20)-H(20B)	107.7
C(14)-C(21)-H(21)	180.0
O(5)-C(22)-H(22A)	109.5
O(5)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
O(5)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for shelx1.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(3)	23(1)	21(1)	26(1)	2(1)	8(1)	6(1)
O(4)	29(1)	28(1)	24(1)	1(1)	4(1)	11(1)
O(2)	31(1)	27(1)	26(1)	8(1)	4(1)	10(1)
O(1)	34(1)	27(1)	29(1)	12(1)	7(1)	8(1)
O(5)	31(1)	30(1)	36(1)	2(1)	5(1)	10(1)
C(1)	23(1)	22(1)	23(1)	7(1)	5(1)	7(1)
C(2)	25(1)	24(1)	22(1)	5(1)	7(1)	12(1)
C(3)	22(1)	21(1)	24(1)	3(1)	7(1)	7(1)
C(4)	24(1)	22(1)	25(1)	8(1)	7(1)	9(1)
C(5)	24(1)	20(1)	23(1)	7(1)	7(1)	8(1)
C(6)	25(1)	24(1)	25(1)	5(1)	2(1)	8(1)
C(7)	24(1)	24(1)	25(1)	2(1)	7(1)	8(1)
C(8)	27(1)	23(1)	26(1)	8(1)	11(1)	11(1)
C(9)	29(1)	21(1)	21(1)	5(1)	6(1)	9(1)
C(10)	26(1)	28(1)	23(1)	5(1)	6(1)	11(1)
C(11)	25(1)	24(1)	27(1)	7(1)	6(1)	11(1)
C(12)	29(1)	28(1)	26(1)	7(1)	9(1)	13(1)
C(13)	27(1)	22(1)	27(1)	7(1)	10(1)	10(1)
C(14)	29(1)	31(1)	32(1)	9(1)	10(1)	15(1)
C(15)	25(1)	24(1)	30(1)	2(1)	4(1)	8(1)
C(16)	41(1)	35(1)	28(1)	13(1)	10(1)	18(1)
C(17)	29(1)	28(1)	39(1)	10(1)	7(1)	9(1)
C(18)	40(1)	31(1)	28(1)	12(1)	10(1)	15(1)
C(19)	32(1)	29(1)	26(1)	4(1)	7(1)	4(1)
C(20)	36(1)	30(1)	22(1)	4(1)	3(1)	13(1)
C(21)	34(1)	47(1)	37(1)	9(1)	4(1)	21(1)
C(22)	53(1)	30(1)	44(1)	9(1)	18(1)	13(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for shelx1.

	x	y	z	U(eq)
H(1)	10084	5483	2316	29
H(6)	4754	2780	-651	33
H(10)	12379	9333	5681	33
H(11)	4993	4619	975	32
H(12A)	9821	2272	327	34
H(12B)	10955	3836	115	34
H(13)	11886	10993	3168	32
H(16A)	11492	6964	5863	51
H(16B)	9573	5858	5965	51
H(16C)	10283	7682	6341	51
H(17)	16412	14440	3894	41
H(18A)	9427	10623	1847	50
H(18B)	8544	9352	615	50
H(18C)	10602	9955	1263	50
H(19A)	13723	12436	5835	41
H(19B)	14919	11589	5624	41
H(20A)	5535	2114	-2195	39
H(20B)	6131	838	-2675	39
H(21)	13668	4732	3264	49
H(22A)	5101	-1386	-2225	68
H(22B)	3411	-1845	-1730	68
H(22C)	5385	-592	-924	68

Table 1. Crystal data and structure refinement details.

Identification code	**2013ncs0884a**
Empirical formula	$C_{50}H_{44}O_8$
Formula weight	772.89
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Triclinic

Space group	$P\bar{1}$	
Unit cell dimensions	a = **8.8734(5) Å**	α = **107.646(6)°**
	b = **14.4831(10) Å**	β = **103.245(6)°**
	c = **16.6971(11) Å**	γ = **96.196(5)°**
Volume	1953.7(2) Å^3	
Z	2	
Density (calculated)	1.314 Mg / m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	816	
Crystal	Fragment; Colourless	
Crystal size	0.11 × 0.09 × 0.05 mm^3	
θ range for data collection	2.322 – 25.087°	
Index ranges	$-10 \le h \le 10$, $-17 \le k \le 17$, $-19 \le l \le 19$	
Reflections collected	21028	
Independent reflections	6875 [R_{int} = 0.0395]	
Completeness to θ = 25.000°	99.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	1.000 and 0.829	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6875 / 0 / 527	
Goodness-of-fit on F^2	1.012	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0415, *wR2* = 0.0931	
R indices (all data)	*R1* = 0.0659, *wR2* = 0.1044	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.180 and –0.173 e Å^{-3}	

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with VHF *Varimax* optics (70µm focus). **Cell determination and data collection**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Data reduction, cell refinement and absorption correction**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Structure solution**: *SUPERFLIP* (Palatinus, L. & Chapuis, G. (2007). J. Appl. Cryst. 40, 786-790). **Structure refinement**: *SHELXL-2012* (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122). **Graphics:** *OLEX2* (Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). J. Appl. Cryst. 42, 339-341).

Special details:

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	3158(1)	2484(1)	−7(1)	24(1)	1
O2	11775(2)	6380(1)	2626(1)	31(1)	1
O3	13223(2)	5090(1)	3236(1)	35(1)	1
O4	9349(2)	5748(1)	1178(1)	39(1)	1
O5	4638(2)	1839(1)	−3159(1)	28(1)	1
O6	3836(2)	966(1)	522(1)	29(1)	1
O7	4717(2)	4334(1)	924(1)	32(1)	1
O8	9746(2)	8044(1)	5536(1)	34(1)	1
C1	11272(2)	5372(1)	2180(1)	26(1)	1
C2	12044(2)	4693(1)	2466(1)	26(1)	1
C3	11617(2)	3699(1)	1978(1)	26(1)	1
C4	10407(2)	3373(1)	1205(1)	25(1)	1
C5	9607(2)	4040(1)	934(1)	28(1)	1
C6	10039(2)	5040(1)	1416(1)	29(1)	1
C7	9975(2)	2283(1)	660(1)	26(1)	1
C8	8991(2)	2078(1)	−232(1)	24(1)	1
C9	8156(2)	1970(1)	−935(1)	24(1)	1
C10	7024(2)	1867(1)	−1762(1)	26(1)	1
C11	5395(2)	2018(1)	−1665(1)	22(1)	1
C12	4216(2)	2010(1)	−2386(1)	24(1)	1
C13	2732(2)	2163(1)	−2303(1)	26(1)	1
C14	2401(2)	2319(1)	−1503(1)	25(1)	1

C15	3569(2)	2331(1)	−791(1)	22(1)	1
C16	5052(2)	2186(1)	−870(1)	21(1)	1
C17	4371(2)	2654(1)	744(1)	22(1)	1
C18	4727(2)	1878(1)	1031(1)	23(1)	1
C19	5916(2)	2050(1)	1795(1)	26(1)	1
C20	6709(2)	3006(1)	2285(1)	25(1)	1
C21	6322(2)	3788(1)	2015(1)	27(1)	1
C22	5159(2)	3612(1)	1243(1)	25(1)	1
C23	8035(2)	3192(1)	3107(1)	30(1)	1
C24	8236(2)	4181(1)	3755(1)	28(1)	1
C25	8383(2)	5013(1)	4216(1)	27(1)	1
C26	8689(2)	6071(1)	4704(1)	27(1)	1
C27	9729(2)	6669(1)	4356(1)	24(1)	1
C28	10218(2)	6235(1)	3624(1)	26(1)	1
C29	11167(2)	6792(1)	3322(1)	25(1)	1
C30	11583(2)	7804(1)	3725(1)	28(1)	1
C31	11095(2)	8249(1)	4458(1)	28(1)	1
C32	10206(2)	7682(1)	4782(1)	27(1)	1
C33	13866(3)	4406(2)	3616(1)	40(1)	1
C34	8129(3)	5412(2)	364(1)	40(1)	1
C35	3504(2)	1938(2)	−3877(1)	36(1)	1
C36	4210(2)	1817(1)	−4632(1)	28(1)	1
C37	5000(2)	2635(2)	−4740(1)	34(1)	1
C38	5595(2)	2527(2)	−5448(1)	38(1)	1
C39	5434(2)	1593(2)	−6050(1)	40(1)	1
C40	4694(2)	775(2)	−5941(1)	38(1)	1

C41	4069(2)	894(2)	−5234(1)	33(1)	1
C42	4181(3)	147(1)	797(1)	35(1)	1
C43	5242(3)	5341(1)	1511(1)	37(1)	1
C44	10418(2)	9035(1)	6092(1)	33(1)	1
C45	10077(2)	9178(1)	6956(1)	30(1)	1
C46	11137(3)	9834(1)	7716(1)	35(1)	1
C47	10787(3)	10030(1)	8517(1)	37(1)	1
C48	9381(3)	9571(1)	8555(1)	36(1)	1
C49	8328(2)	8896(1)	7801(1)	33(1)	1
C50	8676(2)	8704(1)	7008(1)	32(1)	1

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

O1–C15	1.3994(19)	C5–H5	0.9500
O1–C17	1.388(2)	C5–C6	1.388(3)
O2–C1	1.390(2)	C7–H7A	0.9900
O2–C29	1.391(2)	C7–H7B	0.9900
O3–C2	1.373(2)	C7–C8	1.465(2)
O3–C33	1.429(2)	C8–C9	1.191(2)
O4–C6	1.362(2)	C9–C10	1.464(2)
O4–C34	1.438(2)	C10–H10A	0.9900
O5–C12	1.383(2)	C10–H10B	0.9900
O5–C35	1.433(2)	C10–C11	1.523(2)
O6–C18	1.370(2)	C11–C12	1.398(2)
O6–C42	1.434(2)	C11–C16	1.387(2)
O7–C22	1.364(2)	C12–C13	1.389(3)
O7–C43	1.443(2)	C13–H13	0.9500
O8–C32	1.381(2)	C13–C14	1.390(2)
O8–C44	1.425(2)	C14–H14	0.9500
C1–C2	1.395(3)	C14–C15	1.381(2)
C1–C6	1.389(3)	C15–C16	1.383(2)
C2–C3	1.382(3)	C16–H16	0.9500
C3–H3	0.9500	C17–C18	1.389(2)
C3–C4	1.387(2)	C17–C22	1.389(2)
C4–C5	1.381(2)	C18–C19	1.391(2)
C4–C7	1.519(2)	C19–H19	0.9500

C19–C20	1.386(2)	C34–H34B	0.9800
C20–C21	1.387(2)	C34–H34C	0.9800
C20–C23	1.519(2)	C35–H35A	0.9900
C21–H21	0.9500	C35–H35B	0.9900
C21–C22	1.388(2)	C35–C36	1.505(3)
C23–H23A	0.9900	C36–C37	1.392(3)
C23–H23B	0.9900	C36–C41	1.380(3)
C23–C24	1.473(3)	C37–H37	0.9500
C24–C25	1.191(3)	C37–C38	1.375(3)
C25–C26	1.463(3)	C38–H38	0.9500
C26–H26A	0.9900	C38–C39	1.390(3)
C26–H26B	0.9900	C39–H39	0.9500
C26–C27	1.522(2)	C39–C40	1.373(3)
C27–C28	1.383(2)	C40–H40	0.9500
C27–C32	1.392(2)	C40–C41	1.388(3)
C28–H28	0.9500	C41–H41	0.9500
C28–C29	1.382(3)	C42–H42A	0.9800
C29–C30	1.382(2)	C42–H42B	0.9800
C30–H30	0.9500	C42–H42C	0.9800
C30–C31	1.389(3)	C43–H43A	0.9800
C31–H31	0.9500	C43–H43B	0.9800
C31–C32	1.383(3)	C43–H43C	0.9800
C33–H33A	0.9800	C44–H44A	0.9900
C33–H33B	0.9800	C44–H44B	0.9900
C33–H33C	0.9800	C44–C45	1.499(3)
C34–H34A	0.9800	C45–C46	1.389(3)

C45–C50	1.388(3)	C2–C3–C4	120.10(17)
C46–H46	0.9500	C4–C3–H3	120.0
C46–C47	1.394(3)	C3–C4–C7	119.74(16)
C47–H47	0.9500	C5–C4–C3	119.95(17)
C47–C48	1.373(3)	C5–C4–C7	120.31(16)
C48–H48	0.9500	C4–C5–H5	119.8
C48–C49	1.390(3)	C4–C5–C6	120.31(17)
C49–H49	0.9500	C6–C5–H5	119.8
C49–C50	1.381(3)	O4–C6–C1	116.13(16)
C50–H50	0.9500	O4–C6–C5	123.97(17)
		C5–C6–C1	119.88(16)
C17–O1–C15	117.18(13)	C4–C7–H7A	108.8
C1–O2–C29	117.00(14)	C4–C7–H7B	108.8
C2–O3–C33	116.49(15)	H7A–C7–H7B	107.7
C6–O4–C34	116.23(15)	C8–C7–C4	113.59(14)
C12–O5–C35	116.16(14)	C8–C7–H7A	108.8
C18–O6–C42	117.16(14)	C8–C7–H7B	108.8
C22–O7–C43	117.25(14)	C9–C8–C7	175.58(18)
C32–O8–C44	118.08(14)	C8–C9–C10	174.92(19)
O2–C1–C2	120.67(16)	C9–C10–H10A	108.9
C6–C1–O2	119.62(16)	C9–C10–H10B	108.9
C6–C1–C2	119.62(17)	C9–C10–C11	113.18(14)
O3–C2–C1	115.31(16)	H10A–C10–H10B	107.8
O3–C2–C3	124.59(16)	C11–C10–H10A	108.9
C3–C2–C1	120.10(16)	C11–C10–H10B	108.9
C2–C3–H3	120.0	C12–C11–C10	119.87(15)

C16–C11–C10	121.49(15)	C19–C20–C21	120.21(16)
C16–C11–C12	118.63(16)	C19–C20–C23	119.71(16)
O5–C12–C11	115.59(16)	C21–C20–C23	120.05(16)
O5–C12–C13	124.04(16)	C20–C21–H21	120.0
C13–C12–C11	120.37(15)	C20–C21–C22	120.00(17)
C12–C13–H13	119.8	C22–C21–H21	120.0
C12–C13–C14	120.33(16)	O7–C22–C17	116.04(15)
C14–C13–H13	119.8	O7–C22–C21	123.89(16)
C13–C14–H14	120.4	C21–C22–C17	120.08(16)
C15–C14–C13	119.17(17)	C20–C23–H23A	109.1
C15–C14–H14	120.4	C20–C23–H23B	109.1
C14–C15–O1	116.40(16)	H23A–C23–H23B	107.8
C14–C15–C16	120.72(15)	C24–C23–C20	112.66(15)
C16–C15–O1	122.87(15)	C24–C23–H23A	109.1
C11–C16–H16	119.6	C24–C23–H23B	109.1
C15–C16–C11	120.77(16)	C25–C24–C23	173.90(19)
C15–C16–H16	119.6	C24–C25–C26	172.0(2)
O1–C17–C18	120.15(15)	C25–C26–H26A	109.1
O1–C17–C22	120.01(15)	C25–C26–H26B	109.1
C18–C17–C22	119.69(16)	C25–C26–C27	112.30(15)
O6–C18–C17	115.75(15)	H26A–C26–H26B	107.9
O6–C18–C19	123.97(15)	C27–C26–H26A	109.1
C17–C18–C19	120.28(16)	C27–C26–H26B	109.1
C18–C19–H19	120.2	C28–C27–C26	121.97(16)
C20–C19–C18	119.68(16)	C28–C27–C32	118.63(17)
C20–C19–H19	120.2	C32–C27–C26	119.40(16)

C27–C28–H28	119.5	H34B–C34–H34C	109.5
C29–C28–C27	120.91(17)	O5–C35–H35A	109.9
C29–C28–H28	119.5	O5–C35–H35B	109.9
C28–C29–O2	122.92(16)	O5–C35–C36	108.95(15)
C30–C29–O2	116.78(16)	H35A–C35–H35B	108.3
C30–C29–C28	120.29(17)	C36–C35–H35A	109.9
C29–C30–H30	120.4	C36–C35–H35B	109.9
C29–C30–C31	119.27(17)	C37–C36–C35	120.55(18)
C31–C30–H30	120.4	C41–C36–C35	120.58(18)
C30–C31–H31	119.9	C41–C36–C37	118.87(17)
C32–C31–C30	120.19(17)	C36–C37–H37	119.8
C32–C31–H31	119.9	C38–C37–C36	120.48(19)
O8–C32–C27	114.73(16)	C38–C37–H37	119.8
O8–C32–C31	124.68(16)	C37–C38–H38	120.1
C31–C32–C27	120.58(16)	C37–C38–C39	119.83(19)
O3–C33–H33A	109.5	C39–C38–H38	120.1
O3–C33–H33B	109.5	C38–C39–H39	119.8
O3–C33–H33C	109.5	C40–C39–C38	120.44(19)
H33A–C33–H33B	109.5	C40–C39–H39	119.8
H33A–C33–H33C	109.5	C39–C40–H40	120.4
H33B–C33–H33C	109.5	C39–C40–C41	119.26(19)
O4–C34–H34A	109.5	C41–C40–H40	120.4
O4–C34–H34B	109.5	C36–C41–C40	121.10(19)
O4–C34–H34C	109.5	C36–C41–H41	119.5
H34A–C34–H34B	109.5	C40–C41–H41	119.5
H34A–C34–H34C	109.5	O6–C42–H42A	109.5

O6–C42–H42B	109.5	C47–C48–H48	120.0
O6–C42–H42C	109.5	C47–C48–C49	120.04(18)
H42A–C42–H42B	109.5	C49–C48–H48	120.0
H42A–C42–H42C	109.5	C48–C49–H49	119.9
H42B–C42–H42C	109.5	C50–C49–C48	120.1(2)
O7–C43–H43A	109.5	C50–C49–H49	119.9
O7–C43–H43B	109.5	C45–C50–H50	119.8
O7–C43–H43C	109.5	C49–C50–C45	120.49(18)
H43A–C43–H43B	109.5	C49–C50–H50	119.8
H43A–C43–H43C	109.5		
H43B–C43–H43C	109.5		
O8–C44–H44A	110.0		
O8–C44–H44B	110.0		
O8–C44–C45	108.34(15)		
H44A–C44–H44B	108.4		
C45–C44–H44A	110.0		
C45–C44–H44B	110.0		
C46–C45–C44	119.83(19)		
C50–C45–C44	121.13(17)		
C50–C45–C46	118.96(18)		
C45–C46–H46	119.7		
C45–C46–C47	120.6(2)		
C47–C46–H46	119.7		
C46–C47–H47	120.1		
C48–C47–C46	119.76(19)		
C48–C47–H47	120.1		

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	24(1)	26(1)	20(1)	5(1)	7(1)	4(1)
O2	43(1)	22(1)	26(1)	3(1)	15(1)	1(1)
O3	38(1)	34(1)	25(1)	6(1)	0(1)	3(1)
O4	52(1)	27(1)	32(1)	7(1)	2(1)	16(1)
O5	31(1)	34(1)	19(1)	10(1)	6(1)	10(1)
O6	39(1)	16(1)	28(1)	4(1)	7(1)	0(1)
O7	43(1)	18(1)	31(1)	9(1)	2(1)	2(1)
O8	39(1)	25(1)	32(1)	−2(1)	15(1)	0(1)
C1	32(1)	22(1)	23(1)	5(1)	10(1)	1(1)
C2	26(1)	31(1)	20(1)	6(1)	6(1)	2(1)
C3	28(1)	28(1)	24(1)	9(1)	8(1)	8(1)
C4	26(1)	25(1)	24(1)	8(1)	10(1)	5(1)
C5	27(1)	28(1)	23(1)	6(1)	3(1)	6(1)
C6	35(1)	26(1)	28(1)	10(1)	10(1)	11(1)
C7	26(1)	23(1)	27(1)	8(1)	6(1)	4(1)
C8	27(1)	18(1)	27(1)	6(1)	11(1)	5(1)
C9	26(1)	19(1)	28(1)	6(1)	12(1)	5(1)
C10	28(1)	27(1)	21(1)	7(1)	8(1)	6(1)
C11	25(1)	16(1)	23(1)	6(1)	6(1)	4(1)
C12	33(1)	19(1)	19(1)	5(1)	7(1)	4(1)
C13	28(1)	23(1)	22(1)	7(1)	2(1)	4(1)
C14	24(1)	21(1)	27(1)	4(1)	6(1)	4(1)
C15	30(1)	15(1)	20(1)	4(1)	9(1)	2(1)

C16	26(1)	16(1)	19(1)	5(1)	4(1)	4(1)
C17	22(1)	25(1)	19(1)	7(1)	7(1)	3(1)
C18	30(1)	20(1)	20(1)	3(1)	12(1)	2(1)
C19	36(1)	21(1)	23(1)	9(1)	13(1)	6(1)
C20	31(1)	24(1)	22(1)	7(1)	9(1)	4(1)
C21	33(1)	19(1)	26(1)	5(1)	7(1)	0(1)
C22	31(1)	22(1)	24(1)	10(1)	9(1)	4(1)
C23	36(1)	26(1)	27(1)	10(1)	5(1)	4(1)
C24	29(1)	29(1)	24(1)	10(1)	3(1)	1(1)
C25	26(1)	29(1)	24(1)	9(1)	4(1)	1(1)
C26	28(1)	26(1)	24(1)	7(1)	6(1)	4(1)
C27	22(1)	25(1)	24(1)	7(1)	3(1)	4(1)
C28	28(1)	21(1)	23(1)	4(1)	3(1)	3(1)
C29	27(1)	24(1)	21(1)	5(1)	4(1)	5(1)
C30	30(1)	26(1)	26(1)	9(1)	6(1)	2(1)
C31	30(1)	20(1)	30(1)	4(1)	6(1)	4(1)
C32	29(1)	25(1)	22(1)	3(1)	7(1)	7(1)
C33	44(1)	45(1)	26(1)	14(1)	−1(1)	8(1)
C34	50(1)	36(1)	32(1)	10(1)	5(1)	19(1)
C35	34(1)	51(1)	26(1)	18(1)	4(1)	15(1)
C36	29(1)	36(1)	21(1)	12(1)	3(1)	9(1)
C37	32(1)	31(1)	34(1)	10(1)	2(1)	7(1)
C38	33(1)	42(1)	43(1)	25(1)	8(1)	5(1)
C39	40(1)	57(2)	25(1)	19(1)	9(1)	9(1)
C40	41(1)	37(1)	26(1)	2(1)	2(1)	5(1)
C41	34(1)	32(1)	31(1)	14(1)	5(1)	2(1)
C42	51(1)	18(1)	35(1)	9(1)	14(1)	4(1)

C43	50(1)	18(1)	38(1)	9(1)	7(1)	5(1)
C44	39(1)	22(1)	32(1)	2(1)	11(1)	3(1)
C45	36(1)	21(1)	30(1)	4(1)	9(1)	9(1)
C46	39(1)	24(1)	37(1)	4(1)	8(1)	3(1)
C47	46(1)	25(1)	31(1)	1(1)	5(1)	2(1)
C48	53(1)	28(1)	28(1)	8(1)	14(1)	12(1)
C49	37(1)	29(1)	33(1)	10(1)	10(1)	6(1)
C50	36(1)	27(1)	29(1)	4(1)	6(1)	5(1)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3	12152	3239	2170	32	1
H5	8758	3813	414	33	1
H7A	10956	2024	630	31	1
H7B	9406	1925	955	31	1
H10A	6930	1200	−2184	31	1
H10B	7434	2354	−2005	31	1
H13	1939	2160	−2795	31	1
H14	1383	2416	−1447	30	1
H16	5844	2201	−372	25	1
H19	6183	1515	1980	31	1
H21	6854	4444	2359	33	1
H23A	7812	2688	3375	36	1
H23B	9033	3120	2946	36	1
H26A	9209	6188	5327	32	1
H26B	7672	6301	4670	32	1
H28	9897	5544	3325	31	1
H30	12196	8192	3502	33	1
H31	11371	8945	4738	34	1
H33A	14366	3983	3219	60	1
H33B	13019	3998	3714	60	1
H33C	14654	4770	4175	60	1
H34A	8545	5044	−107	59	1
H34B	7767	5981	237	59	1

H34C	7242	4981	407	59	1
H35A	3211	2596	−3701	43	1
H35B	2539	1429	−4052	43	1
H37	5128	3273	−4323	41	1
H38	6115	3090	−5524	45	1
H39	5840	1519	−6541	47	1
H40	4610	135	−6345	46	1
H41	3536	331	−5164	39	1
H42A	3478	−460	379	52	1
H42B	4020	255	1378	52	1
H42C	5279	88	823	52	1
H43A	4802	5785	1218	55	1
H43B	6396	5507	1676	55	1
H43C	4884	5416	2036	55	1
H44A	9956	9501	5826	39	1
H44B	11571	9162	6174	39	1
H46	12109	10153	7691	42	1
H47	11519	10479	9034	45	1
H48	9127	9715	9097	43	1
H49	7367	8567	7831	40	1
H50	7950	8243	6494	39	1

Table 6. Torsion angles [°].

O1–C15–C16–C11	178.80(15)
O1–C17–C18–O6	1.2(2)
O1–C17–C18–C19	–178.40(15)
O1–C17–C22–O7	–3.2(2)
O1–C17–C22–C21	177.02(16)
O2–C1–C2–O3	4.6(2)
O2–C1–C2–C3	–174.67(16)
O2–C1–C6–O4	–3.1(3)
O2–C1–C6–C5	175.33(16)
O2–C29–C30–C31	–175.82(16)
O3–C2–C3–C4	–179.91(16)
O5–C12–C13–C14	179.24(16)
O5–C35–C36–C37	–92.1(2)
O5–C35–C36–C41	88.7(2)
O6–C18–C19–C20	–177.36(16)
O8–C44–C45–C46	148.79(18)
O8–C44–C45–C50	–34.6(2)
C1–O2–C29–C28	5.8(2)
C1–O2–C29–C30	–175.59(16)
C1–C2–C3–C4	–0.7(3)
C2–C1–C6–O4	–179.76(16)
C2–C1–C6–C5	–1.4(3)
C2–C3–C4–C5	–1.3(3)
C2–C3–C4–C7	178.32(16)

C3–C4–C5–C6	1.9(3)
C3–C4–C7–C8	–164.77(16)
C4–C5–C6–O4	177.68(17)
C4–C5–C6–C1	–0.6(3)
C5–C4–C7–C8	14.8(2)
C6–C1–C2–O3	–178.70(16)
C6–C1–C2–C3	2.0(3)
C7–C4–C5–C6	–177.69(17)
C9–C10–C11–C12	175.64(15)
C9–C10–C11–C16	–3.0(2)
C10–C11–C12–O5	1.3(2)
C10–C11–C12–C13	–179.04(16)
C10–C11–C16–C15	179.43(15)
C11–C12–C13–C14	–0.4(3)
C12–O5–C35–C36	174.96(15)
C12–C11–C16–C15	0.7(2)
C12–C13–C14–C15	0.7(3)
C13–C14–C15–O1	–179.54(15)
C13–C14–C15–C16	–0.2(3)
C14–C15–C16–C11	–0.5(3)
C15–O1–C17–C18	–94.82(18)
C15–O1–C17–C22	89.71(19)
C16–C11–C12–O5	–179.96(15)
C16–C11–C12–C13	–0.3(2)
C17–O1–C15–C14	–170.05(14)
C17–O1–C15–C16	10.7(2)

C17–C18–C19–C20	2.2(3)
C18–C17–C22–O7	–178.67(15)
C18–C17–C22–C21	1.5(3)
C18–C19–C20–C21	–0.1(3)
C18–C19–C20–C23	–178.48(16)
C19–C20–C21–C22	–1.3(3)
C19–C20–C23–C24	–152.47(17)
C20–C21–C22–O7	–179.24(16)
C20–C21–C22–C17	0.6(3)
C21–C20–C23–C24	29.2(2)
C22–C17–C18–O6	176.69(15)
C22–C17–C18–C19	–2.9(3)
C23–C20–C21–C22	177.10(17)
C25–C26–C27–C28	3.8(2)
C25–C26–C27–C32	–176.20(16)
C26–C27–C28–C29	–179.76(16)
C26–C27–C32–O8	3.8(2)
C26–C27–C32–C31	–177.21(16)
C27–C28–C29–O2	175.48(16)
C27–C28–C29–C30	–3.0(3)
C28–C27–C32–O8	–176.18(16)
C28–C27–C32–C31	2.8(3)
C28–C29–C30–C31	2.8(3)
C29–O2–C1–C2	–86.9(2)
C29–O2–C1–C6	96.5(2)
C29–C30–C31–C32	0.2(3)

C30–C31–C32–O8	175.82(17)
C30–C31–C32–C27	–3.0(3)
C32–O8–C44–C45	–165.90(15)
C32–C27–C28–C29	0.2(3)
C33–O3–C2–C1	170.51(16)
C33–O3–C2–C3	–10.2(3)
C34–O4–C6–C1	176.86(17)
C34–O4–C6–C5	–1.5(3)
C35–O5–C12–C11	–173.26(16)
C35–O5–C12–C13	7.1(2)
C35–C36–C37–C38	–177.64(18)
C35–C36–C41–C40	178.95(18)
C36–C37–C38–C39	–1.2(3)
C37–C36–C41–C40	–0.2(3)
C37–C38–C39–C40	–0.4(3)
C38–C39–C40–C41	1.7(3)
C39–C40–C41–C36	–1.4(3)
C41–C36–C37–C38	1.5(3)
C42–O6–C18–C17	179.61(15)
C42–O6–C18–C19	–0.8(2)
C43–O7–C22–C17	166.41(16)
C43–O7–C22–C21	–13.8(3)
C44–O8–C32–C27	169.03(16)
C44–O8–C32–C31	–9.9(3)
C44–C45–C46–C47	175.39(18)
C44–C45–C50–C49	–175.38(17)

C45–C46–C47–C48	–0.1(3)
C46–C45–C50–C49	1.3(3)
C46–C47–C48–C49	1.6(3)
C47–C48–C49–C50	–1.6(3)
C48–C49–C50–C45	0.1(3)
C50–C45–C46–C47	–1.3(3)

Symmetry transformations used to generate equivalent atoms:

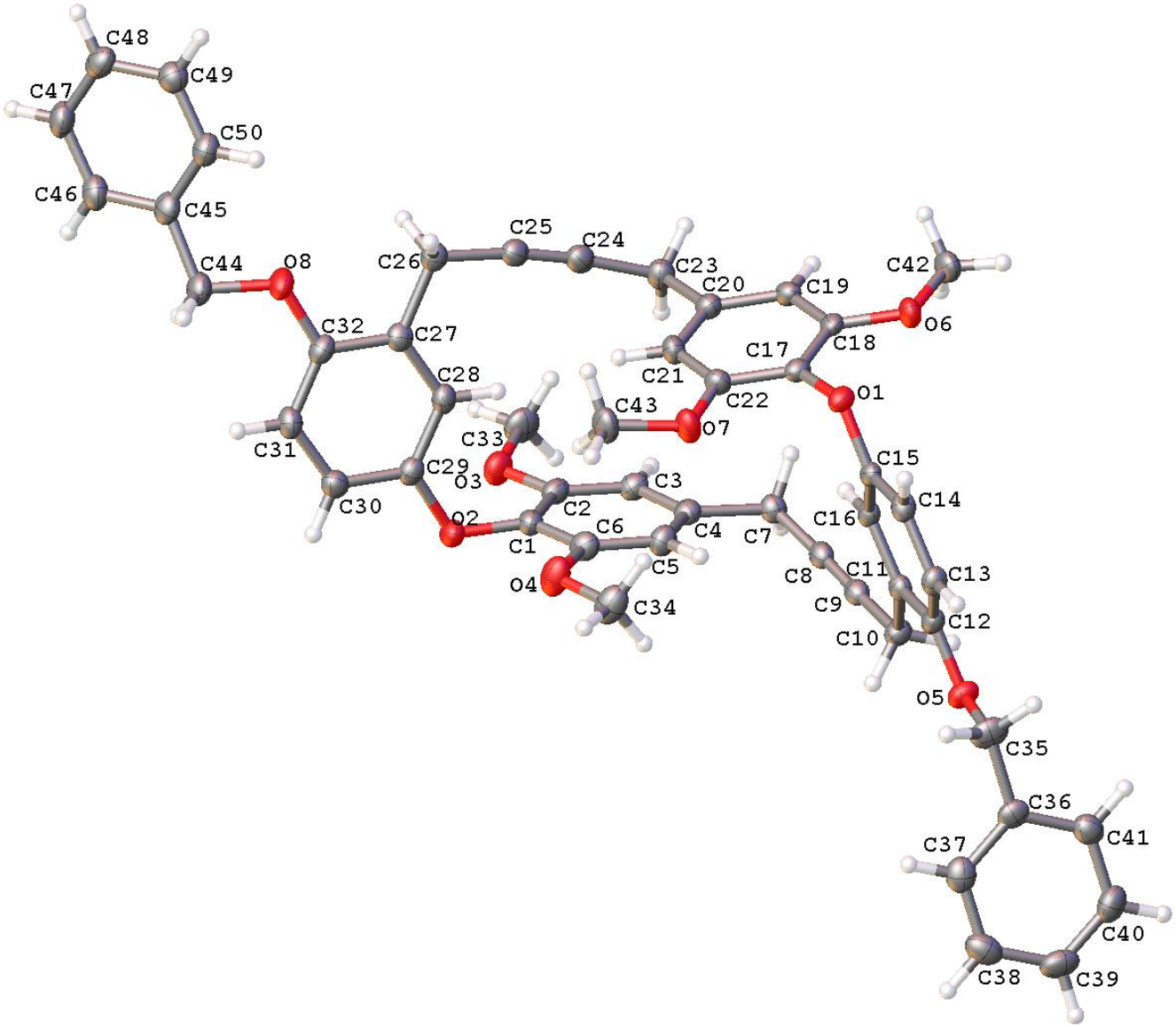

C48
C49
C47
C50
C46
C45
C44
O8
C25
C24
C26
C23
C20
C19
C42
O6
C32
C27
C18
C17
C21
C28
C22
O1
C43
O7
C33
C15
C31
C29
O3
C3
C14
C30
C2
C16
O2
C6
C4
C7
C1
C5
C8
C11
C13
O4
C34
C9
C12
C10
O5
C35
C36
C37
C41
C40
C38
C39

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Table 1. Crystal data and structure refinement details.

Identification code	**2013ncs0883a**	
Empirical formula	$C_{20}H_{21}Cl_1O_7$	
Formula weight	408.83	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	*P*121/*c*1	
Unit cell dimensions	a = **8.0412(5) Å**	α = **90°**
	b = **13.1949(9) Å**	β = **94.469(2)°**
	c = **18.0575(13) Å**	γ = **90°**
Volume	1910.1(2) Å^3	
Z	4	
Density (calculated)	1.422 Mg / m^3	
Absorption coefficient	0.241 mm^{-1}	
F(000)	856	
Crystal	Block; Colorless	
Crystal size	0.09 × 0.07 × 0.06 mm^3	
θ range for data collection	2.263 – 27.456°	
Index ranges	$-10 \le h \le 6$, $-17 \le k \le 17$, $-22 \le l \le 23$	
Reflections collected	13239	
Independent reflections	4358 [R_{int} = 0.0245]	
Completeness to θ = 27.500°	99.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	1.000 and 0.703	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4358 / 0 / 258	
Goodness-of-fit on F^2	1.066	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0607, *wR2* = 0.1600	
R indices (all data)	*R1* = 0.0669, *wR2* = 0.1646	
Extinction coefficient	n/a	
Largest diff. peak and hole	3.023 and –0.526 e Å^{-3}	

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with VHF *Varimax* optics (70µm focus). **Cell determination and data collection**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Data reduction, cell refinement and absorption correction**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Structure solution**: *SUPERFLIP* (Palatinus, L. & Chapuis, G. (2007). J. Appl. Cryst. 40, 786-790). **Structure refinement**: *SHELXL-2014* (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122). **Graphics:** *OLEX2* (Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). J. Appl. Cryst. 42, 339-341).

Special details:
Large residual density (3.02 eÅ^{-3}) 1.133Å distance from C19 suggests small amount of unidentified side product maybe present in this crystal

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Cl1	1576(1)	6934(1)	1267(1)	28(1)	1
O1	1842(2)	5840(1)	2666(1)	23(1)	1
O2	–3158(2)	4484(1)	624(1)	21(1)	1
O3	–3793(2)	3133(1)	1395(1)	21(1)	1
O4	3201(2)	4043(1)	3092(1)	26(1)	1
O5	2576(2)	5658(1)	6178(1)	24(1)	1
O6	3356(2)	4078(1)	5894(1)	20(1)	1
O7	402(2)	7024(1)	3622(1)	23(1)	1
C1	1916(3)	5554(2)	3406(1)	20(1)	1
C2	2712(3)	4658(2)	3641(1)	20(1)	1
C3	2979(3)	4452(2)	4400(1)	19(1)	1
C4	2429(3)	5152(2)	4905(1)	17(1)	1
C5	1567(3)	6027(2)	4675(1)	18(1)	1
C6	1285(3)	6222(2)	3917(1)	19(1)	1
C7	531(3)	5486(2)	2195(1)	18(1)	1
C8	319(3)	5926(2)	1492(1)	20(1)	1
C9	–928(3)	5595(2)	974(1)	20(1)	1
C10	–1991(3)	4822(2)	1168(1)	17(1)	1
C11	–4483(3)	3864(2)	888(1)	21(1)	1
C12	–2980(3)	3554(2)	2061(1)	20(1)	1
C13	–1815(3)	4387(2)	1872(1)	17(1)	1
C14	–537(3)	4719(2)	2378(1)	18(1)	1
C15	3735(4)	3040(2)	3312(2)	31(1)	1
C16	2778(3)	5007(2)	5722(1)	17(1)	1
C17	3745(3)	3886(2)	6678(1)	22(1)	1
C18	–225(3)	7719(2)	4144(2)	25(1)	1
C19	–5191(3)	3271(2)	212(1)	24(1)	1
C20	–5741(3)	4550(2)	1221(2)	27(1)	1

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

Cl1–C8	1.737(2)	O1–C1–C6	118.3(2)
O1–C1	1.386(3)	C2–C1–C6	121.0(2)
O1–C7	1.383(3)	O4–C2–C1	115.8(2)
O2–C10	1.379(3)	O4–C2–C3	124.5(2)
O2–C11	1.453(3)	C1–C2–C3	119.7(2)
O3–C11	1.414(3)	C2–C3–H3	120.7
O3–C12	1.435(3)	C4–C3–C2	118.6(2)
O4–C2	1.364(3)	C4–C3–H3	120.7
O4–C15	1.437(3)	C3–C4–C16	121.1(2)
O5–C16	1.209(3)	C5–C4–C3	122.1(2)
O6–C16	1.340(3)	C5–C4–C16	116.8(2)
O6–C17	1.449(3)	C4–C5–H5	120.5
O7–C6	1.360(3)	C4–C5–C6	119.0(2)
O7–C18	1.434(3)	C6–C5–H5	120.5
C1–C2	1.394(4)	O7–C6–C1	115.9(2)
C1–C6	1.400(3)	O7–C6–C5	124.6(2)
C2–C3	1.397(3)	C5–C6–C1	119.4(2)
C3–H3	0.9500	O1–C7–C8	116.9(2)
C3–C4	1.394(3)	O1–C7–C14	123.9(2)
C4–C5	1.393(3)	C14–C7–C8	119.2(2)
C4–C16	1.493(3)	C7–C8–Cl1	119.92(18)
C5–H5	0.9500	C9–C8–Cl1	119.19(18)
C5–C6	1.393(3)	C9–C8–C7	120.8(2)
C7–C8	1.395(3)	C8–C9–H9	120.4
C7–C14	1.385(3)	C8–C9–C10	119.2(2)
C8–C9	1.386(3)	C10–C9–H9	120.4
C9–H9	0.9500	O2–C10–C9	117.0(2)
C9–C10	1.393(3)	O2–C10–C13	122.2(2)
C10–C13	1.392(3)	C13–C10–C9	120.7(2)
C11–C19	1.523(3)	O2–C11–C19	105.28(19)
C11–C20	1.517(4)	O2–C11–C20	108.9(2)
C12–H12A	0.9900	O3–C11–O2	109.61(18)
C12–H12B	0.9900	O3–C11–C19	105.8(2)
C12–C13	1.501(3)	O3–C11–C20	113.0(2)
C13–C14	1.392(3)	C20–C11–C19	113.9(2)
C14–H14	0.9500	O3–C12–H12A	109.6
C15–H15A	0.9800	O3–C12–H12B	109.6
C15–H15B	0.9800	O3–C12–C13	110.11(18)
C15–H15C	0.9800	H12A–C12–H12B	108.2
C17–H17A	0.9800	C13–C12–H12A	109.6
C17–H17B	0.9800	C13–C12–H12B	109.6
C17–H17C	0.9800	C10–C13–C12	119.3(2)
C18–H18A	0.9800	C10–C13–C14	119.2(2)
C18–H18B	0.9800	C14–C13–C12	121.5(2)
C18–H18C	0.9800	C7–C14–C13	120.9(2)
C19–H19A	0.9800	C7–C14–H14	119.6
C19–H19B	0.9800	C13–C14–H14	119.6
C19–H19C	0.9800	O4–C15–H15A	109.5
C20–H20A	0.9800	O4–C15–H15B	109.5
C20–H20B	0.9800	O4–C15–H15C	109.5
C20–H20C	0.9800	H15A–C15–H15B	109.5
		H15A–C15–H15C	109.5
C7–O1–C1	118.33(18)	H15B–C15–H15C	109.5
C10–O2–C11	115.05(17)	O5–C16–O6	123.7(2)
C11–O3–C12	114.14(18)	O5–C16–C4	123.9(2)
C2–O4–C15	116.37(19)	O6–C16–C4	112.42(19)
C16–O6–C17	115.55(18)	O6–C17–H17A	109.5
C6–O7–C18	116.12(19)	O6–C17–H17B	109.5
O1–C1–C2	120.6(2)	O6–C17–H17C	109.5

H17A–C17–H17B	109.5	C11–C19–H19C	109.5
H17A–C17–H17C	109.5	H19A–C19–H19B	109.5
H17B–C17–H17C	109.5	H19A–C19–H19C	109.5
O7–C18–H18A	109.5	H19B–C19–H19C	109.5
O7–C18–H18B	109.5	C11–C20–H20A	109.5
O7–C18–H18C	109.5	C11–C20–H20B	109.5
H18A–C18–H18B	109.5	C11–C20–H20C	109.5
H18A–C18–H18C	109.5	H20A–C20–H20B	109.5
H18B–C18–H18C	109.5	H20A–C20–H20C	109.5
C11–C19–H19A	109.5	H20B–C20–H20C	109.5
C11–C19–H19B	109.5		

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	34(1)	29(1)	21(1)	6(1)	−4(1)	−17(1)
O1	25(1)	31(1)	13(1)	2(1)	−2(1)	−12(1)
O2	20(1)	23(1)	18(1)	4(1)	−4(1)	−6(1)
O3	24(1)	18(1)	20(1)	3(1)	−5(1)	−4(1)
O4	34(1)	26(1)	18(1)	−6(1)	6(1)	−3(1)
O5	34(1)	21(1)	17(1)	−2(1)	1(1)	4(1)
O6	29(1)	18(1)	15(1)	1(1)	1(1)	3(1)
O7	22(1)	25(1)	22(1)	5(1)	−2(1)	2(1)
C1	20(1)	24(1)	14(1)	1(1)	−1(1)	−7(1)
C2	20(1)	22(1)	17(1)	−5(1)	3(1)	−6(1)
C3	21(1)	17(1)	18(1)	−1(1)	2(1)	−2(1)
C4	17(1)	18(1)	16(1)	−1(1)	1(1)	−4(1)
C5	18(1)	19(1)	17(1)	−1(1)	2(1)	−2(1)
C6	17(1)	20(1)	20(1)	3(1)	−1(1)	−3(1)
C7	18(1)	20(1)	15(1)	−3(1)	0(1)	−2(1)
C8	22(1)	18(1)	18(1)	1(1)	2(1)	−5(1)
C9	23(1)	18(1)	17(1)	3(1)	−2(1)	−2(1)
C10	17(1)	18(1)	17(1)	0(1)	−1(1)	−1(1)
C11	20(1)	22(1)	22(1)	5(1)	−3(1)	−4(1)
C12	20(1)	20(1)	18(1)	3(1)	−2(1)	−4(1)
C13	18(1)	15(1)	17(1)	1(1)	1(1)	0(1)
C14	19(1)	19(1)	15(1)	1(1)	1(1)	0(1)
C15	45(2)	21(1)	28(1)	−9(1)	13(1)	−4(1)
C16	18(1)	17(1)	17(1)	0(1)	2(1)	−1(1)
C17	28(1)	23(1)	16(1)	5(1)	1(1)	5(1)
C18	23(1)	22(1)	31(1)	6(1)	2(1)	3(1)
C19	24(1)	25(1)	23(1)	1(1)	−4(1)	−5(1)
C20	23(1)	29(1)	29(1)	3(1)	0(1)	2(1)

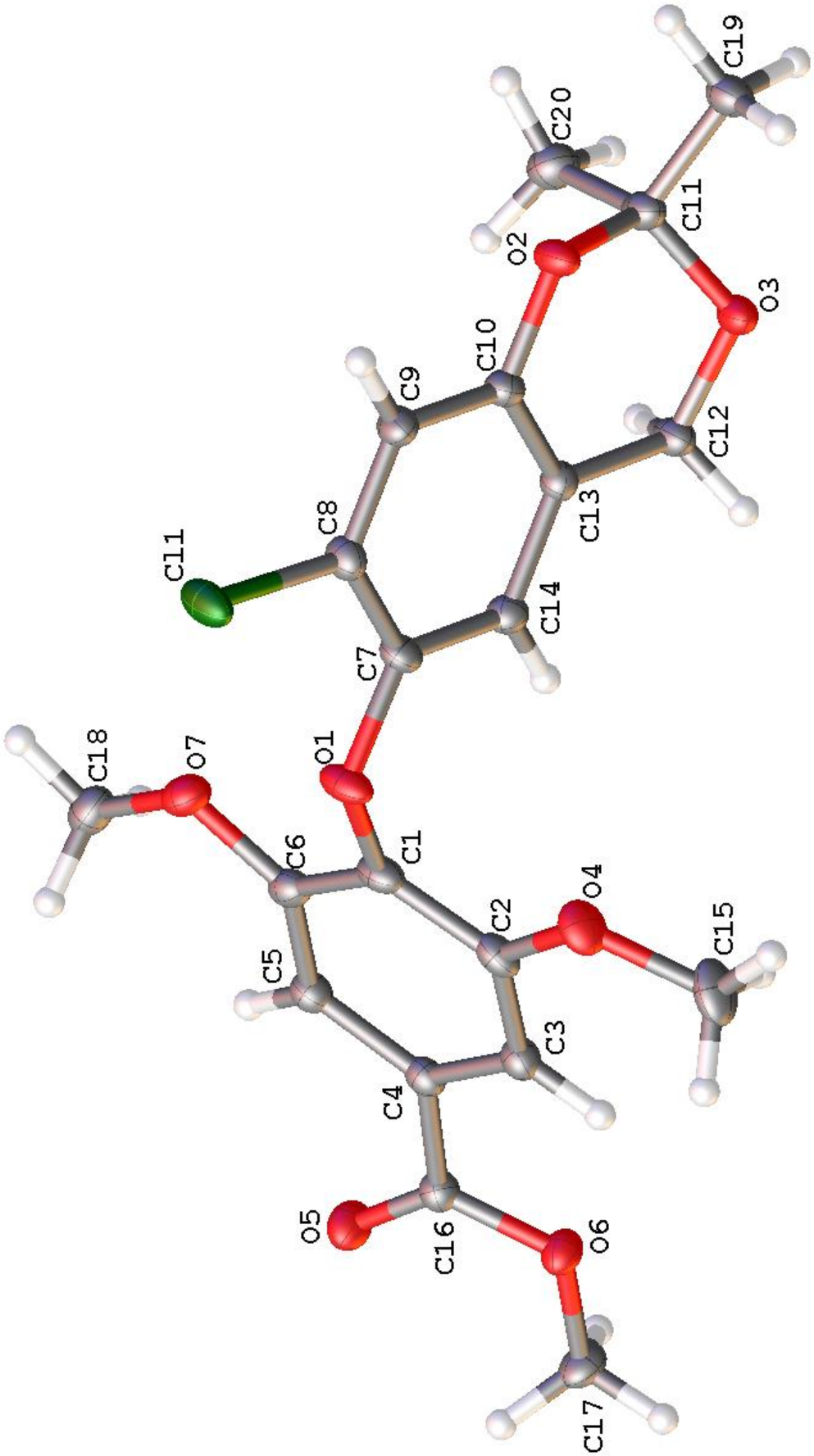
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3	3525	3846	4569	22	1
H5	1177	6483	5029	22	1
H9	–1055	5892	494	23	1
H12A	–2347	3016	2343	23	1
H12B	–3827	3825	2378	23	1
H14	–397	4416	2856	21	1
H15A	3910	2637	2869	46	1
H15B	2877	2718	3589	46	1
H15C	4781	3082	3627	46	1
H17A	4430	3273	6741	34	1
H17B	2708	3790	6921	34	1
H17C	4360	4464	6904	34	1
H18A	–818	8272	3875	38	1
H18B	707	7996	4463	38	1
H18C	–993	7363	4450	38	1
H19A	–5678	3743	–164	36	1
H19B	–6055	2805	359	36	1
H19C	–4296	2884	5	36	1
H20A	–5157	5021	1571	41	1
H20B	–6522	4138	1483	41	1
H20C	–6358	4934	824	41	1

Table 6. Torsion angles [°].

Cl1–C8–C9–C10	–176.74(18)
O1–C1–C2–O4	–8.0(3)
O1–C1–C2–C3	171.1(2)
O1–C1–C6–O7	10.5(3)
O1–C1–C6–C5	–170.4(2)
O1–C7–C8–Cl1	–4.6(3)
O1–C7–C8–C9	177.8(2)
O1–C7–C14–C13	–178.8(2)
O2–C10–C13–C12	–2.9(3)
O2–C10–C13–C14	175.7(2)
O3–C12–C13–C10	17.4(3)
O3–C12–C13–C14	–161.1(2)
O4–C2–C3–C4	179.4(2)
C1–O1–C7–C8	168.8(2)
C1–O1–C7–C14	–12.5(3)
C1–C2–C3–C4	0.3(3)
C2–C1–C6–O7	–174.3(2)
C2–C1–C6–C5	4.9(3)
C2–C3–C4–C5	2.6(3)
C2–C3–C4–C16	–175.9(2)
C3–C4–C5–C6	–1.8(3)
C3–C4–C16–O5	167.6(2)
C3–C4–C16–O6	–11.8(3)
C4–C5–C6–O7	177.1(2)
C4–C5–C6–C1	–2.0(3)
C5–C4–C16–O5	–11.1(3)
C5–C4–C16–O6	169.6(2)
C6–C1–C2–O4	176.8(2)
C6–C1–C2–C3	–4.1(3)
C7–O1–C1–C2	87.7(3)
C7–O1–C1–C6	–97.0(3)
C7–C8–C9–C10	0.9(4)
C8–C7–C14–C13	–0.1(3)
C8–C9–C10–O2	–176.9(2)
C8–C9–C10–C13	0.3(4)
C9–C10–C13–C12	–179.9(2)
C9–C10–C13–C14	–1.4(3)
C10–O2–C11–O3	–45.9(3)
C10–O2–C11–C19	–159.23(19)
C10–O2–C11–C20	78.2(2)
C10–C13–C14–C7	1.3(3)
C11–O2–C10–C9	–165.8(2)
C11–O2–C10–C13	17.1(3)
C11–O3–C12–C13	–48.5(3)
C12–O3–C11–O2	64.0(2)
C12–O3–C11–C19	177.01(19)
C12–O3–C11–C20	–57.7(3)
C12–C13–C14–C7	179.8(2)
C14–C7–C8–Cl1	176.65(18)
C14–C7–C8–C9	–1.0(4)
C15–O4–C2–C1	–168.8(2)
C15–O4–C2–C3	12.1(3)
C16–C4–C5–C6	176.8(2)
C17–O6–C16–O5	–0.2(3)
C17–O6–C16–C4	179.18(19)
C18–O7–C6–C1	–179.1(2)
C18–O7–C6–C5	1.8(3)

Symmetry transformations used to generate equivalent atoms: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C20
C11
O2
O3
C10
C9
C12
C8
C13
Cl1
C14
C7
O1
C18
O7
C6
C1
O4
C2
C15
C5
C3
C4
O5
C16
O6
C17

2014sot0012

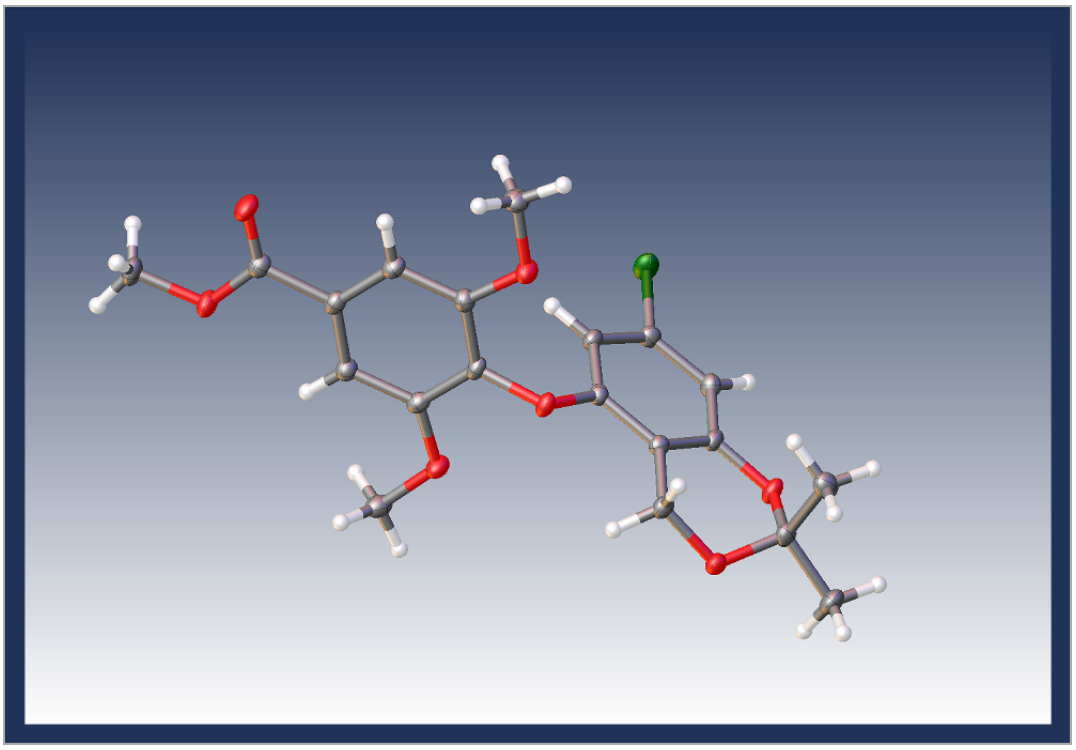

Table 1 Crystal data and structure refinement for 2014sot0012.

Identification code	2014sot0012
Empirical formula	$C_{20}H_{21}ClO_7$
Formula weight	408.82
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	8.0250(5)
b/Å	16.8467(10)
c/Å	14.6221(10)
α/°	90
β/°	102.9800(10)
γ/°	90
Volume/Å^3	1926.3(2)
Z	4
ρ_{calc}mg/mm^3	1.410
m/mm^{-1}	0.239
F(000)	856.0
Crystal size/mm^3	0.22 × 0.18 × 0.06

Radiation	MoKα (λ = 0.71075)
2Θ range for data collection	4.836 to 55.068°
Index ranges	$-10 \leq h \leq 10$, $-21 \leq k \leq 20$, $-15 \leq l \leq 18$
Reflections collected	17565
Independent reflections	4424 [R_{int} = 0.0291, R_{sigma} = 0.0230]
Data/restraints/parameters	4424/0/258
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0295, wR_2 = 0.0813
Final R indexes [all data]	R_1 = 0.0346, wR_2 = 0.0838
Largest diff. peak/hole / e Å^{-3}	0.32/-0.20

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters (Å$^2 \times 10^3$) for 2014sot0012. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
Cl1	1983.7(3)	2183.0(2)	2951.0(2)	24.92(9)
O1	-3551.1(11)	6109.1(5)	4366.5(6)	22.58(18)
O2	-1662.1(11)	6024.7(5)	5751.0(6)	25.80(19)
O3	-738.4(10)	3013.9(5)	6118.8(6)	21.77(18)
O4	-2926.2(10)	2385.1(4)	4660.6(5)	17.93(16)
O5	-4658.3(10)	3282.0(5)	3256.0(6)	21.43(18)
O6	-2113.4(10)	-34.8(4)	3169.0(6)	19.96(17)
O7	-4585.7(10)	132.6(4)	3747.5(6)	19.90(17)
C1	-3543.6(16)	6962.4(7)	4478.0(9)	25.0(3)
C2	-2539.2(14)	5707.8(7)	5069.9(8)	19.1(2)
C3	-2623.0(13)	4831.6(6)	4914.8(8)	18.0(2)
C4	-1612.9(14)	4361.4(7)	5606.6(8)	18.8(2)
C5	-1670.7(13)	3541.2(6)	5501.1(8)	17.8(2)
C6	-2741.7(13)	3204.7(6)	4709.9(8)	16.7(2)
C7	-3716.2(13)	3680.0(7)	4006.3(8)	17.9(2)
C8	-3665.4(13)	4503.0(7)	4111.8(8)	18.3(2)
C9	406.9(15)	3349.4(7)	6921.4(8)	22.5(2)
C10	-5749.5(15)	3745.3(7)	2538.7(8)	23.0(2)
C11	-1963.5(13)	1966.3(6)	4152.1(7)	15.4(2)

C12	-603.4(13)	2294.4(6)	3843.3(8)	17.0(2)
C13	232.7(13)	1803.8(6)	3326.0(8)	17.9(2)
C14	-235.1(14)	1027.3(6)	3107.7(8)	18.2(2)
C15	-1611.5(13)	724.6(6)	3431.9(7)	16.4(2)
C16	-2484.8(13)	1179.2(6)	3964.9(7)	16.0(2)
C17	-4012.8(14)	842.8(6)	4264.3(8)	18.8(2)
C18	-3253.5(14)	-403.6(6)	3687.3(8)	20.1(2)
C19	-2209.4(15)	-660.0(7)	4639.4(9)	25.1(3)
C20	-4078.7(16)	-1085.2(7)	3084.3(10)	27.4(3)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 2014sot0012. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
Cl1	22.19(14)	20.06(15)	36.17(17)	0.81(11)	14.29(12)	-2.99(10)
O1	29.9(4)	12.9(4)	23.9(4)	0.3(3)	3.7(3)	0.2(3)
O2	32.0(4)	15.7(4)	27.0(4)	-4.3(3)	1.1(4)	-2.3(3)
O3	26.2(4)	16.1(4)	20.3(4)	0.5(3)	-0.5(3)	0.9(3)
O4	21.1(4)	11.8(4)	22.4(4)	-2.1(3)	8.2(3)	-1.2(3)
O5	25.3(4)	15.9(4)	20.2(4)	-2.1(3)	-1.0(3)	-2.6(3)
O6	25.3(4)	11.6(4)	24.2(4)	-2.4(3)	8.0(3)	-3.3(3)
O7	17.9(4)	13.6(4)	27.1(4)	-0.8(3)	2.8(3)	-1.7(3)
C1	31.4(6)	12.3(5)	30.9(6)	1.4(5)	6.2(5)	0.8(4)
C2	21.2(5)	16.8(5)	20.0(5)	-0.4(4)	6.5(4)	-1.1(4)
C3	19.8(5)	15.0(5)	20.4(5)	-1.4(4)	7.2(4)	-1.4(4)
C4	20.5(5)	17.8(5)	18.1(5)	-3.2(4)	3.9(4)	-2.0(4)
C5	18.8(5)	16.3(5)	18.7(5)	1.1(4)	4.8(4)	1.0(4)
C6	19.4(5)	11.8(5)	19.9(5)	-1.8(4)	6.8(4)	-1.3(4)
C7	18.5(5)	17.5(5)	18.1(5)	-2.8(4)	4.9(4)	-2.5(4)
C8	19.8(5)	16.4(5)	18.4(5)	0.8(4)	3.5(4)	-0.2(4)
C9	23.8(5)	22.7(6)	18.5(5)	0.8(5)	-0.3(4)	-1.1(4)
C10	24.5(5)	21.9(6)	20.3(5)	0.9(5)	0.1(4)	-5.0(4)
C11	16.8(5)	14.0(5)	14.7(5)	0.0(4)	2.1(4)	1.5(4)
C12	17.6(5)	13.0(5)	19.3(5)	-0.7(4)	1.9(4)	-1.5(4)
C13	15.9(5)	17.5(5)	20.5(5)	2.8(4)	4.4(4)	-1.0(4)
C14	20.1(5)	16.3(5)	18.8(5)	-0.7(4)	5.4(4)	1.9(4)
C15	19.7(5)	11.3(5)	16.8(5)	0.7(4)	1.3(4)	-0.6(4)

C16	16.5(5)	14.6(5)	16.0(5)	1.5(4)	1.9(4)	-0.4(4)
C17	19.9(5)	14.3(5)	22.4(5)	-0.7(4)	5.4(4)	-2.0(4)
C18	19.9(5)	13.6(5)	27.2(6)	1.9(4)	5.8(4)	-1.0(4)
C19	22.5(5)	22.1(6)	30.4(6)	6.7(5)	5.4(5)	0.6(4)
C20	27.8(6)	15.6(6)	37.3(7)	-3.5(5)	4.2(5)	-4.5(5)

Table 4 Bond Lengths for 2014sot0012.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Cl1	C13	1.7405(11)	C3	C4	1.3927(16)
O1	C1	1.4465(13)	C3	C8	1.3940(15)
O1	C2	1.3412(14)	C4	C5	1.3900(15)
O2	C2	1.2072(14)	C5	C6	1.3971(15)
O3	C5	1.3641(13)	C6	C7	1.3964(15)
O3	C9	1.4342(13)	C7	C8	1.3946(16)
O4	C6	1.3887(13)	C11	C12	1.3865(14)
O4	C11	1.3804(12)	C11	C16	1.3988(15)
O5	C7	1.3609(13)	C12	C13	1.3905(15)
O5	C10	1.4365(14)	C13	C14	1.3786(15)
O6	C15	1.3702(13)	C14	C15	1.3929(14)
O6	C18	1.4522(13)	C15	C16	1.3893(15)
O7	C17	1.4344(13)	C16	C17	1.5026(14)
O7	C18	1.4174(13)	C18	C19	1.5176(16)
C2	C3	1.4928(15)	C18	C20	1.5074(16)

Table 5 Bond Angles for 2014sot0012.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C2	O1	C1	115.34(9)	C3	C8	C7	119.02(10)
C5	O3	C9	116.13(9)	O4	C11	C12	123.26(9)
C11	O4	C6	118.04(8)	O4	C11	C16	114.27(9)
C7	O5	C10	117.26(9)	C12	C11	C16	122.48(10)
C15	O6	C18	115.65(8)	C11	C12	C13	116.84(10)
C18	O7	C17	114.03(8)	C12	C13	Cl1	118.40(8)
O1	C2	C3	112.53(9)	C14	C13	Cl1	118.19(8)
O2	C2	O1	123.38(10)	C14	C13	C12	123.40(10)
O2	C2	C3	124.10(10)	C13	C14	C15	117.65(10)
C4	C3	C2	116.94(10)	O6	C15	C14	116.86(9)

C4	C3	C8	121.81(10)	O6	C15	C16	121.24(9)
C8	C3	C2	121.24(10)	C16	C15	C14	121.85(10)
C5	C4	C3	119.04(10)	C11	C16	C17	121.89(9)
O3	C5	C4	125.04(10)	C15	C16	C11	117.77(10)
O3	C5	C6	115.33(9)	C15	C16	C17	120.20(9)
C4	C5	C6	119.62(10)	O7	C17	C16	110.31(9)
O4	C6	C5	119.02(9)	O6	C18	C19	108.53(9)
O4	C6	C7	119.76(9)	O6	C18	C20	105.43(9)
C7	C6	C5	121.06(10)	O7	C18	O6	109.40(8)
O5	C7	C6	115.42(10)	O7	C18	C19	113.16(10)
O5	C7	C8	125.18(10)	O7	C18	C20	106.47(9)
C8	C7	C6	119.40(10)	C20	C18	C19	113.53(10)

Table 6 Torsion Angles for 2014sot0012.

A	**B**	**C**	**D**	**Angle/°**	**A**	**B**	**C**	**D**	**Angle/°**
Cl1	C13	C14	C15	178.42(8)	C8	C3	C4	C5	-1.22(16)
O1	C2	C3	C4	179.87(9)	C9	O3	C5	C4	-1.47(15)
O1	C2	C3	C8	-0.03(14)	C9	O3	C5	C6	178.19(9)
O2	C2	C3	C4	-0.16(16)	C10	O5	C7	C6	176.80(9)
O2	C2	C3	C8	179.93(11)	C10	O5	C7	C8	-3.23(15)
O3	C5	C6	O4	7.11(14)	C11	O4	C6	C5	-98.25(11)
O3	C5	C6	C7	-177.58(9)	C11	O4	C6	C7	86.38(12)
O4	C6	C7	O5	-7.07(14)	C11	C12	C13	Cl1	-178.30(8)
O4	C6	C7	C8	172.95(9)	C11	C12	C13	C14	0.55(16)
O4	C11	C12	C13	-179.05(9)	C11	C16	C17	O7	161.86(9)
O4	C11	C16	C15	178.12(9)	C12	C11	C16	C15	-1.35(16)
O4	C11	C16	C17	2.44(15)	C12	C11	C16	C17	-177.03(10)
O5	C7	C8	C3	-179.20(10)	C12	C13	C14	C15	-0.44(17)
O6	C15	C16	C11	-175.85(9)	C13	C14	C15	O6	176.81(9)
O6	C15	C16	C17	-0.09(16)	C13	C14	C15	C16	-0.62(16)
C1	O1	C2	O2	-0.60(15)	C14	C15	C16	C11	1.47(16)
C1	O1	C2	C3	179.37(9)	C14	C15	C16	C17	177.23(10)
C2	C3	C4	C5	178.88(10)	C15	O6	C18	O7	47.16(12)
C2	C3	C8	C7	-179.11(10)	C15	O6	C18	C19	-76.74(11)
C3	C4	C5	O3	179.32(10)	C15	O6	C18	C20	161.30(9)
C3	C4	C5	C6	-0.33(16)	C15	C16	C17	O7	-13.72(14)
C4	C3	C8	C7	0.99(16)	C16	C11	C12	C13	0.37(16)

C4	C5	C6	O4	-173.21(9)	C17	O7	C18	O6	-63.67(11)
C4	C5	C6	C7	2.10(16)	C17	O7	C18	C19	57.47(12)
C5	C6	C7	O5	177.66(9)	C17	O7	C18	C20	-177.14(9)
C5	C6	C7	C8	-2.32(15)	C18	O6	C15	C14	165.73(9)
C6	O4	C11	C12	12.75(14)	C18	O6	C15	C16	-16.82(14)
C6	O4	C11	C16	-166.72(9)	C18	O7	C17	C16	45.97(12)
C6	C7	C8	C3	0.78(15)					

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 2014sot0012.

Atom	***x***	***y***	***z***	**U(eq)**
H1A	-4404	7193	3986	37
H1B	-2442	7168	4447	37
H1C	-3780	7093	5075	37
H4	-910	4593	6132	23
H8	-4317	4828	3653	22
H9A	1215	3688	6717	34
H9B	1006	2931	7305	34
H9C	-234	3654	7279	34
H10A	-6307	3403	2038	35
H10B	-5076	4131	2299	35
H10C	-6594	4012	2799	35
H12	-266	2818	3976	20
H14	348	716	2756	22
H17A	-3713	724	4930	23
H17B	-4928	1231	4156	23
H19A	-1355	-1035	4556	38
H19B	-2948	-903	4992	38
H19C	-1665	-205	4973	38
H20A	-4707	-885	2492	41
H20B	-4844	-1359	3395	41
H20C	-3211	-1445	2982	41

Experimental

Single crystals of $C_{20}H_{21}ClO_7$ [2014sot0012] were []. A suitable crystal was selected and [] on a Rigaku Saturn724+ (2x2 bin mode) diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [1], the structure was solved with

the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122

Crystal structure determination of [2014sot0012]

Crystal Data for $C_{20}H_{21}ClO_7$ (M =408.82): monoclinic, space group $P2_1/n$ (no. 14), a = 8.0250(5) Å, b = 16.8467(10) Å, c = 14.6221(10) Å, β = 102.9800(10)°, V = 1926.3(2) Å^3, Z = 4, T = 100(2) K, μ(MoKα) = 0.239 mm^{-1}, $Dcalc$ = 1.410 g/mm^3, 17565 reflections measured (4.836 ≤ 2Θ ≤ 55.068), 4424 unique (R_{int} = 0.0291, R_{sigma} = 0.0230) which were used in all calculations. The final R_1 was 0.0295 (I > 2σ(I)) and wR_2 was 0.0838 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups
2.a Secondary CH2 refined with riding coordinates:
 C17(H17A,H17B)
2.b Aromatic/amide H refined with riding coordinates:
 C4(H4), C8(H8), C12(H12), C14(H14)
2.c Idealised Me refined as rotating group:
 C1(H1A,H1B,H1C), C9(H9A,H9B,H9C), C10(H10A,H10B,H10C), C19(H19A,H19B,H19C),
 C20(H20A,H20B,H20C)
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