UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

School of Chemistry

Total Synthesis of Chrysophaentin F and Approaches to Related Natural Products

by

Rebecca Frances Matters

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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TOTAL SYNTHESIS OF CHRYSOPHAENTIN F AND APPROACHES TO RELATED NATURAL PRODUCTS

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The chrysophaentins are a new family of natural products first isolated from the marine algae *Chrysophaeum taylori* in 2010.[1,2] They have been found to have strong antibiotic activity, particularly against methicillin resistant *Staphylococcus aureus* (MRSA), multiple drug resistant SA (MDRSA) and vancomycin resistant *Enterococcus faecium* (VREF). Chrysophaentin A was identified as the most active member of the family with MIC_{50} values of 1.5 ± 0.7 and 1.3 ± 0.4 μg/mL against MRSA and MDRSA and 2.9 ± 0.8 μg/mL towards VREF, closely followed by chrysophaentins F and H.

This thesis describes the total synthesis of chrysophaentin F and progress towards the synthesis of chrysophaentins A and E. The synthetic strategy described herein is designed to give access to all chrysophaentins with minimal modification. It takes advantage of common building blocks and symmetry elements present throughout the chrysophaentin family and uses these to proceed *via* related intermediates. It uses a variety of transition metal catalysed C-C and C-O bond forming reactions to conjoin these building blocks, including Cu-catalysed Chan-Evans-Lam couplings, Pd- and Ni-catalysed sp-sp^3 couplings and a Mo-catalysed RCAM. Furthermore, a late-stage hydrozirconation is used to install the (*E*)-vinyl chloride groups present in the natural products. This has resulted in the total synthesis of chrysophaentin F as a 2:1 mixture with a regioisomer and the preparation of a protected derivative of chrysophaentin E. Significant progress towards chrysophaentin A is also described.

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Academic Thesis: Declaration Of Authorship

I, ...

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

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2. 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;
3. Where I have consulted the published work of others, this is always clearly attributed;
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To my mum, dad, sister and extended family who haven't had a clue what I've been doing for the last three years but encourage me all the same. Your unwavering support and belief in me has been a source of constant strength and has kept me going. And thanks for the "interested" faces and polite nodding when I talk about my day.

Definitions and Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetate
ACM	alkyne cross metathesis
ADIMET	acyclic diyne metathesis polymerisation
AIBN	azobisisobutyronitrile
App.	apparent
Aq.	aqueous
Ar	aryl
Atm.	atmosphere
B. subtilis	*Bacillus subtilis*
Bn	benzyl
Brsm	based on recovered starting material(s)
^{i}Bu	*iso*-butyl
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
ca.	circa
COD	1,5-cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CuTC	copper(I)-thiophene-2-carboxylate

Cy	cyclohexyl
d	doublet
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMF	dimethyl formamide
DMP	Dess–Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOM	directed ortho metalation
dppf	1,1’-bis(diphenylphosphino)ferrocene
dtbpy	4,4’-di-*tert*-butyl-2,2’-dipyridyl
E. coli	*Escherichia coli*
EI	electron ionisation, electron impact
EOM	ethoxymethyl
equiv.	equivalents
ESI	electrospray
Et	ethyl
FT	Fourier transformation
Fts	Filamenting temperature-sensitive mutant
GTP	Guanosine-5'-triphosphate
h	hours
^{n}Hex	*n*-hexyl

HMBC	heteronuclear multiple bond correlation
HMTA	Hexamethylenetetramine
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration
IR	infra red
K	*inhibitory* constant
LC	liquid chromatography
Lit.	literature
LRMS	low resolution mass spectrometry
M. tuberculosis	*Mycobacterium tuberculosis*
M	molar
m	multiplet
MDRSA	multi drug resistant *Staphylococcus aureus*
Me	methyl
Mes	mesityl
mg	milligram
MHz	megahertz
MIC	minimum inhibitory concentration
min	minutes
mL	millilitre
MMPP	magnesium monoperoxyphthalate
mmol	millimole

MOM	methoxymethyl
MP	melting point
MRSA	methicillin resistant *Staphylococcus aureus*
MS	molecular sieves
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
ND	Not determined
nm	nanometre
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl
Phen	phenanthroline
Pin	pinacolato
Piv	pivaloyl
PG	protecting group
ppm	parts per million
^{i}Pr	*iso*-propyl
Py	pyridine
RCAM	ring closing alkyne metathesis
RCM	ring closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminum dihydride
ROAMP	ring opening alkyne metathesis polymerisation
RT	room temperature
s	singlet

SA	*Staphylococcus aureus*
sat.	saturated
SCOOPY	α-substitution plus carbonyl olefination *via* β-oxido phosphorous ylides
SM	starting material
S_NAr	nucleophilic aromatic substitution
sol.	solution
STD	saturation transfer difference
t	triplet
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMEDA	tetramethylethylenediamine
Tol	tolyl
Ts	tosyl
VREF	vancomycin resistant Enterococcus faecium

XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Chapter 1 Introduction

1.1 Chrysophaentins and Related Natural Products

The chrysophaentins (**1.1-1.10**) are a new family of natural products that were first isolated from the rare marine algae, *Chrysophaeum taylori*, in 2010 with the discovery of two further linear relatives in 2012.[1,2] The 7 macrocyclic family members possess either an asymmetric (chrysophaentins A-D, **1.1-1.4**) or a symmetric core (chrysophaentins F-H, **1.8-1.10**). However, both of these frameworks could, theoretically, be derived from each of the linear chrysophaentins (E-E2, **1.5-1.7**) *via* an oxidative coupling at one of two positions (Figure 1.1).

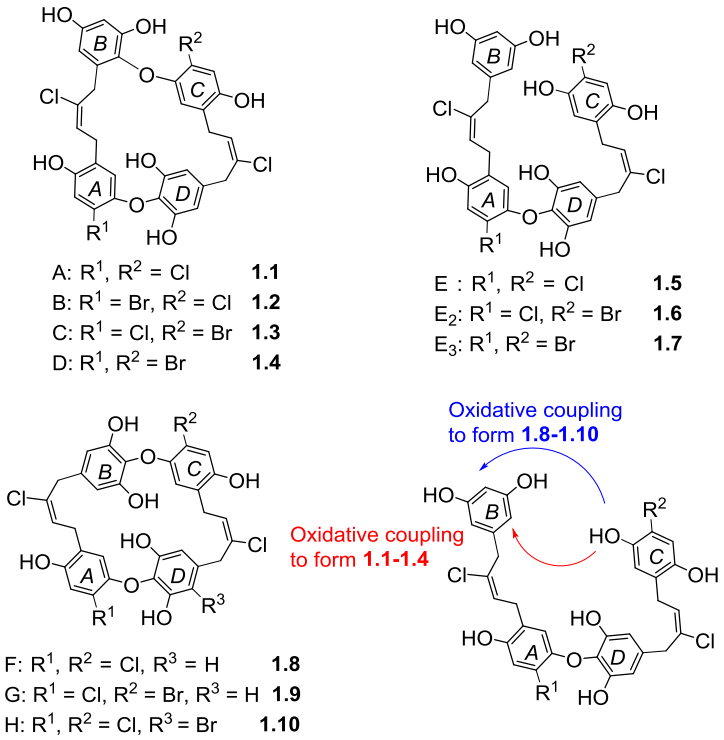


Figure 1.1. Structure of chrysophaentins A-H and possible biosynthesis.

Each of these scaffolds are architecturally unique and define the chrysophaentins as a new natural product family; the macrocyclic bisdiarylbutenes. They are structurally related to the ubiquitous macrocyclic bisbibenzyl family which are commonly found in liverwarts and other bryophytes.[3] Both the chrysophaentins and the bisbibenzyls possess a core macrocyclic structure consisting of 4 aromatic rings connected by both carbon chains and ether linkages. It is thought that, for the bisbibenzyls, this structure is derived from the oxidative coupling of 2 lunularin subunits.[4] Within the bisbibenzyl family, individual natural products are identified by

the regiochemistry of this linkage and the positions of the hydroxyl or alkoxy ring substituents (Figure 1.2).

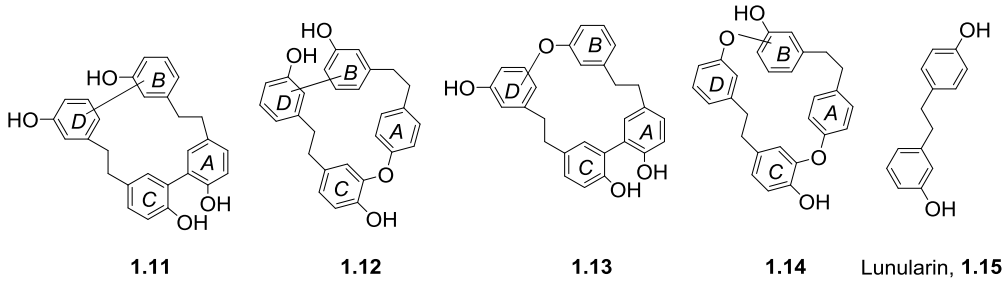
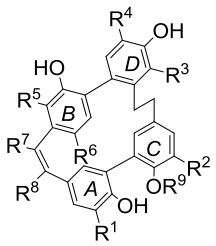


Figure 1.2. General bisbibenzyl family structures (**1.11-1.14**) and their biosynthetic subunit, lunularin (**1.15**).

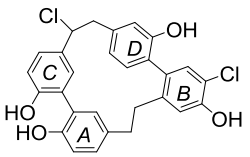
To aid identification, Asakawa formulated a labelling system for the four aromatic rings based on the lunularin subunits themselves. Rings derived from the paraphenol ring are labelled *A* and *C* and those from the metaphenol are labelled *B* and *D* (Figure 1.2). Thus, the carbon bridges always link arene *A* to *B* and *C* to *D* respectively. Due to the similarities between the bisbibenzyls and the chrysophaentins, an analogous identification system will be applied to the chrysophaentins which maintains this pattern of linkages. Thus, rings possessing both halogen and oxy substituents are labelled *A* and *C* and those possessing only oxy substituents are labelled *B* and *D*.

The key variance between the bisbibenzyls and the chrysophaentins lies in the carbon linker chain; the bisbibenzyls contain a 2 carbon linker which is typically fully saturated, whereas the chrysophaentins possess a longer, 4 carbon unsaturated chain. The chrysophaentins are also polyhalogenated with chlorine or bromine atoms present on the aromatic rings as well as in the carbon linker chain. Although halogenation is not consistent throughout the bisbibenzyl family, the bazzanin sub-class in particular shows extensive chlorination with the presence of up to 8 chlorine atoms (Figure 1.3). Interestingly, bazzanins B-I and R contain an (*E*)-chloroalkene or dichloroalkene moiety respectively showing further commonality with the chrysophaentins. Chlorinated derivatives of the plagiochins have also been isolated.[5–8]



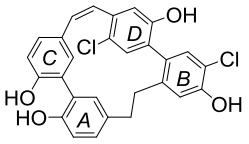
Bazzanins A-R

		R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
A	**1.16**	Cl	H	H	H	H	H	H	H	H
B	**1.17**	Cl	H	H	H	H	H	Cl	H	H
C	**1.18**	Cl	H	H	Cl	H	H	Cl	H	H
D	**1.19**	Cl	H	H	H	Cl	H	Cl	H	H
E	**1.20**	Cl	H	H	Cl	Cl	H	Cl	H	H
F	**1.21**	Cl	H	Cl	H	H	Cl	Cl	H	H
G	**1.22**	Cl	Cl	Cl	H	Cl	H	Cl	H	H
H	**1.23**	Cl	H	Cl	H	Cl	Cl	Cl	H	H
I	**1.24**	Cl	Cl	H	Cl	Cl	Cl	Cl	H	H
L	**1.25**	H	H	Cl	Cl	Cl	H	H	H	Me
M	**1.26**	H	H	Cl	Cl	Cl	H	H	H	H
N	**1.27**	H	Cl	Cl	Cl	Cl	H	H	H	H
O	**1.28**	Cl	H	Cl	Cl	Cl	Cl	H	H	Me
P	**1.29**	Cl	Cl	Cl	Cl	Cl	H	H	H	H
Q	**1.30**	Cl	Cl	Cl	Cl	Cl	Cl	H	H	H
R	**1.31**	Cl	Cl	Cl	Cl	Cl	Cl	Cl	Cl	H



1.32

12,7'-dichloroisoplagiochin D



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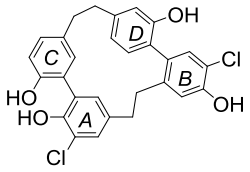
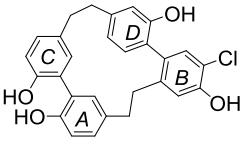
12,10'-dichloroisoplagiochin C



1.34

2,12-dichloroisoplagiochin D

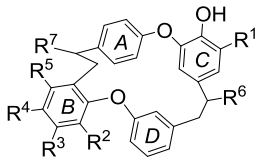


1.35

12-dichloroisoplagiochin D

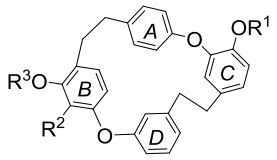
Figure 1.3. Bazzanin and isoplagiochin natural products.

The bisdiaryl ether connectivity in the macrocyclic chrysophaentins is, again, present but not consistent amongst the bisbibenzyl family. However, this is more prevalent than polyhalogenation, with the marchantins, isomarchantins, neomarchantins, pakyonols,[9,10] riccardin B,[11] and ptychantols[12] all containing this structural motif (Figure 1.4). The ptychantols also contain an unsaturated 2 carbon linker chain providing further similarity. For the asterelins, one diaryl ether bond is a constituent in a unique dibenzofuran moiety.[13]

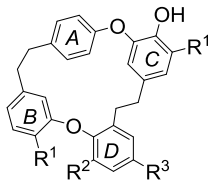


Marchantins A-O

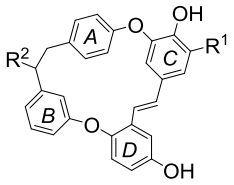
		R^1	R^2	R^3	R^4	R^5	R^6	R^7
A	**1.36**	OH	OH	H	H	H	H	H
B	**1.37**	OH	OH	OH	H	H	H	H
C	**1.38**	H	OH	H	H	H	H	H
D	**1.39**	OH	OH	H	H	H	OH	H
E	**1.40**	OH	OH	H	H	H	OMe	H
F	**1.41**	OH	OH	OH	H	H	OH	H
G	**1.42**	OH	OH	H	H	H	=O	H
H	**1.43**	H	OH	OH	H	H	H	H
I	**1.44**	H	H	H	OMe	H	H	H
J	**1.45**	OH	OH	H	H	H	OEt	H
K	**1.46**	OH	OH	OH	H	OMe	H	H
L	**1.47**	OH	OH	H	H	H	H	OH
M	**1.48**	H	OMe	H	H	OH	H	H
O	**1.49**	H	OMe	H	H	H	H	H



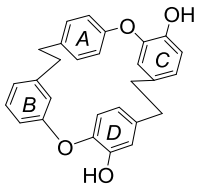
		R^1	R^2	R^3
Pakyonol	**1.50**	Me	H	H
Neomarchantin A	**1.51**	H	H	H
Neomarchantin B	**1.52**	H	OH	H



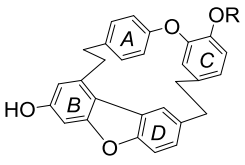
		R^1	R^2	R^3
Isomarchantin B	**1.53**	OH	OH	H
Isomarchantin C	**1.54**	H	OH	H
Dihydroptychantol	**1.55**	H	H	OH



		R^1	R^2
Ptychantol A	**1.56**	H	H
Ptychantol B	**1.57**	OH	H
Ptychantol C	**1.58**	OH	OH



Riccardin B **1.59**



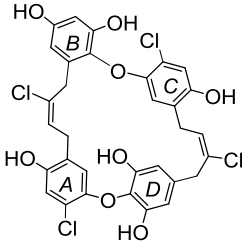
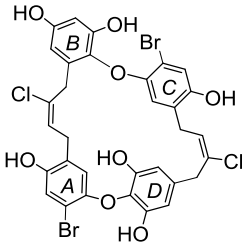
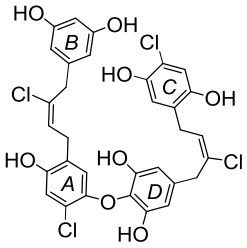
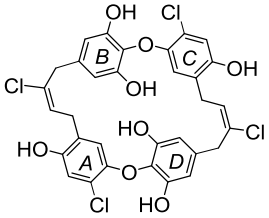
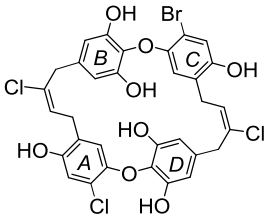
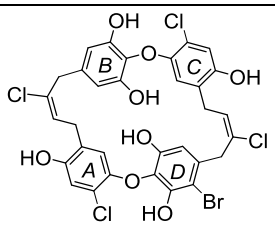
		R
Asterelin A	**1.60**	H
Asterelin B	**1.61**	Me

Figure 1.4. Bisdiaryl ethers from the bisbibenzyl family.

1.2 Therapeutic Potential of the Chrysophaentins

The chrysophaentins have strong antibiotic activity, particularly against Gram-positive bacteria. Importantly, this also includes methicillin resistant *Staphylococcus aureus* (MRSA), multiple drug resistant SA (MDRSA) and vancomycin resistant *Enterococcus faecium* (VREF). Chrysophaentin A (**1.1**) was found to be the most active with MIC_{50} values of 1.5 ± 0.7 and 1.3 ± 0.4 μg/mL against MRSA and MDRSA and 2.9 ± 0.8 μg/mL towards VREF.[1] Chrysophaentins F and H were the next most potent compounds in the series, both possessing a MIC_{50} value of 4.2-4.7 μg/mL and 9.5 μg/mL against MRSA and VREF respectively. Structurally, chrysophaentins F and H differ only in the addition of a bromine atom on ring *D*, suggesting that this ring is either particularly amenable to substitution or is not essential for activity.

Table 1.1. Biological activity of chrysophaentins A (**1.1**), D and E (**1.4**-**1.5**) and F-H (**1.8**-**1.10**).

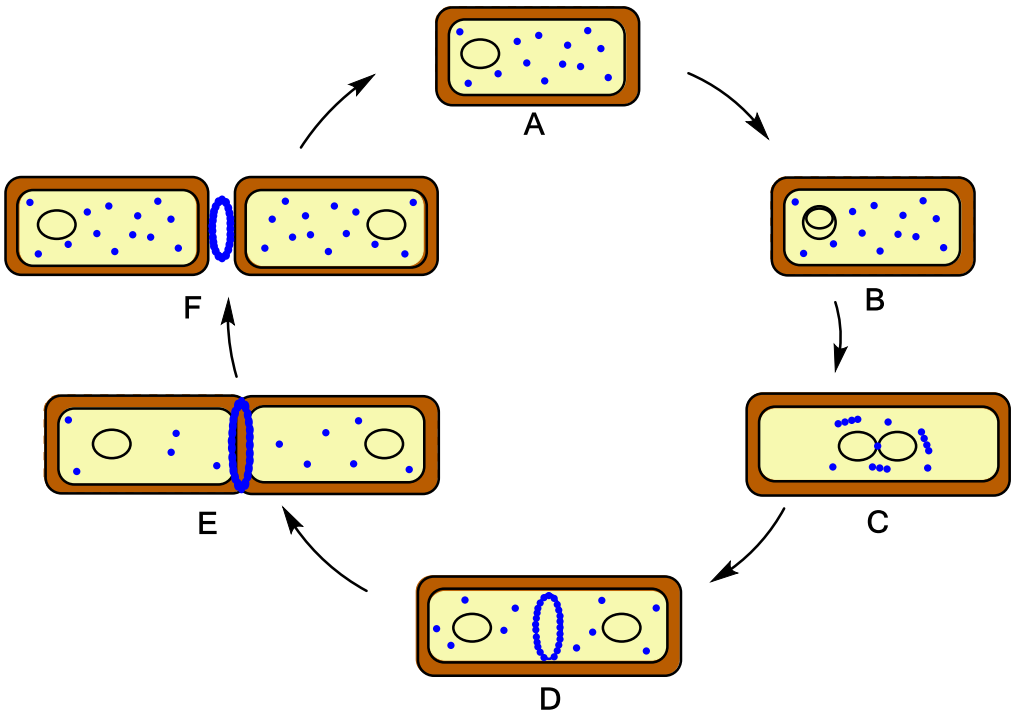
Molecule	Structure	MIC_{50} (μg/mL)			
		S. aureus	**MRSA**	***E. faecium***	**VREF**
chrysophaentin A **1.1**		1.8 ± 0.6	1.5 ± 0.7	3.8 ± 1.9	2.9 ± 0.8
chrysophaentin D **1.4**		>25	20 ± 6.5	>50	>25
chrysophaentin E **1.5**		11 ± 3.8	8.9 ± 2.8	>25	>25
chrysophaentin F **1.8**		5.3 ± 2.0	4.2 ± 1.3	>25	9.5 ± 3.0
chrysophaentin G **1.9**		17 ± 5.4	12 ± 3.1	>50	25 ± 7.3
chrysophaentin H **1.10**		4.5 ± 1.4	4.7 ± 1.4	>25	9.4 ± 2.8

In contrast, chrysophaentins D and G which exhibit extensive bromination on rings *A* and *C* showed approximately an 8-13-fold decrease in potency relative to their chlorinated counterparts across all 4 bacterial strains. This may be due to the increased size of the bromine atoms causing steric clashes or they may perturb the overall macrocyclic structure of these chrysophaentins leading to less efficient binding. Examination of the potency of acyclic chrysophaentin E showed reduced activity against *S. aureus* and MRSA in comparison to macrocyclic chrysophaentins A and F. It was also completely inactive towards *E. faecium* and VREF, thus highlighting the importance of a macrocyclic structure.

The origin of the chrysophaentins biological activity has been found to arise from the inhibition of the cell division protein filamentous temperature sensitive mutant Z (FtsZ) *via* competition with the nucleotide substrate at the GTP binding site.[1,14] Saturation Transfer Difference (STD) NMR and molecular docking studies were used to establish that the aromatic protons on the *A*, *B* and *C* rings of chrysophaentin A and the olefinic protons show the strongest contribution to binding. The lack of evidence for interactions involving ring *D* may explain the similar potencies of chrysophaentins F and H and provides credence to the argument that this ring's role may only be to provide a suitable three dimensional structure to facilitate binding.

1.2.1 FtsZ

FtsZ is an essential GTPase that is a critical part of the bacterial cytoskeleton responsible for cell division. It is highly conserved amongst bacteria and archaea, with analysis of the protein sequence showing 40-50% identity across the two domains. Its structure and function is a homologue to the eukaryotic cell division protein tubulin, however the two proteins only share 20% protein sequence homology, thus introducing a possible avenue for selective inhibition.[15,16] With few exceptions, FtsZ is responsible for all aspects of the complex process of bacteria cell division from identification of the division site to cytokinesis. At the time of cell division, FtsZ migrates to the centre of the cell and undergoes GTPdependent head-to-tail polymerisation in order to form single-stranded protofilaments. These then combine to form a contractile structure known as the Z-ring. Simultaneously, FtsZ also recruits additional proteins (FtsZ A, FtsI, FtsK, ZipA, MinC, Ezr A, ClpX and Sep F) which together form the divisome and play a variety of roles including stabilisation of the Z-ring and cell wall synthesis.[17] The Z-ring induces the separation of the nucleus and the chromosome and upon its contraction; the 2 newly formed cells separate (Figure 1.5).



A. Bacterial cell prior to the beginning of cell division with FtsZ distributed throughout the cell; B. DNA replication; C. Cell elongation and FtsZ protein migration to the mid-cell and formation of protofilaments; D. Separation of chromosomes and formation of the Z-ring; E. Formation of the septum that divides the cell; F. Contraction of the Z-ring, leading to the formation of two daughter cells

Figure 1.5. Role of FtsZ during cell division.

Cells deficient in FtsZ cannot divide but continue to grow leading to a long, filamentous phenotype for rod-shaped bacteria (e.g. *E. coli*) and enlarged spheres for cocci-shaped bacteria (e.g. *S. aureus*).

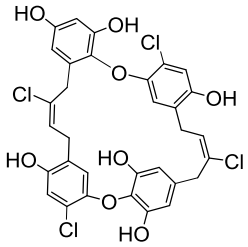
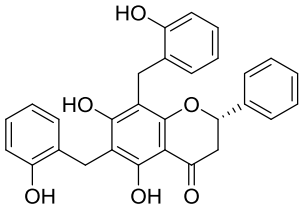
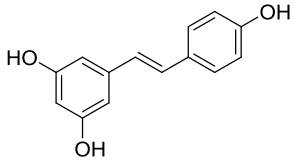
1.2.2 FtsZ as a Biological Target

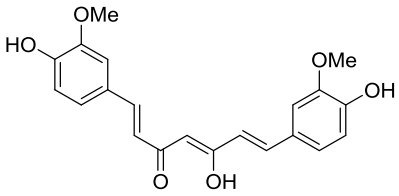
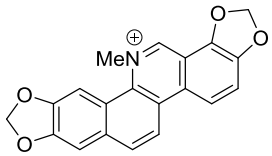
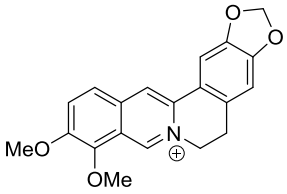
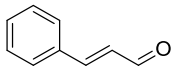
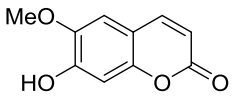
Currently, all known antibiotics either target a bacterial structure (e.g. cytoplasmic membrane) or a cellular process such as DNA transcription, translation, replication or peptidoglycan synthesis. In the crucial fight against antimicrobial resistance, new targets are continually being sought and the bacterial cytoskeleton may provide a new therapeutic avenue. Of these, FtsZ has arisen as a promising biological target due to its key role in all aspects of cell division. Inhibition or disruption of FtsZ activity could proceed *via* destabilisation of the protofilaments thus preventing Z-ring assembly or conversely by stabilisation of these protofilaments preventing their disassembly. Alternatively disruption of FtsZ activity could be achieved by preventing the synthesis of these protofilaments by inhibiting the initial polymerisation of FtsZ. However,

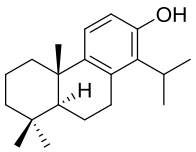
despite this attraction, no FtsZ inhibitors have made it to the clinic. Nonetheless, several classes of compound, of both natural and synthetic origin, have exhibited activity against FtsZ.

Of the natural products, activity is present across a variety structural scaffolds including phenols, polyphenols (of which the chrysophaentins are a member), alkaloids and terpenoids. Examples of inhibitors belonging to each of these classes, their mode of action and biological activity are summarised in Table 1.2. Initial reports and reviews into FtsZ inhibition listed viridotoxin, a polyphenol, as an inhibitor of FtsZ GTPase activity, however, this activity has been irreproducible and viridotoxin has been confirmed as a false positive.[18] The current therapeutic potential of some of the molecules detailed in Table 1.2 is mitigated by either their inhibition of tubulin (**1.65**) or their prolific and promiscuous binding of proteins and other aggregator-like properties (**1.62**, **1.66**, **1.69**).

Table 1.2. Natural Products that inhibit FtsZ and their mode of action.

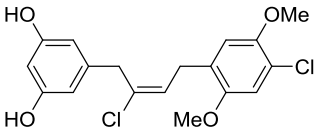
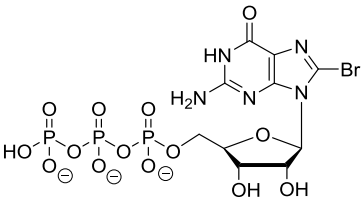
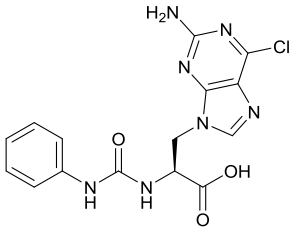
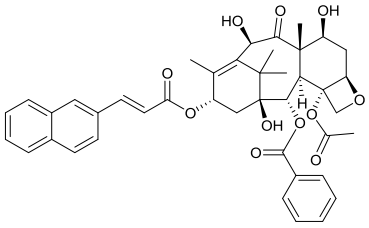
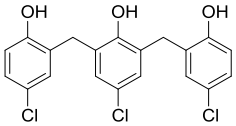
Compound Name and Structure	Compound class	Mode of action	Antibacterial activity
 **Chrysophaentin A, 1.1**	Polyphenols	• Inhibition of GTPase activity • Inhibition of FtsZ polymerisation[1,2,14]	**MIC_{50}** 1.8 µg/mL (*S. aureus*) 1.5 µg/mL (MRSA)
 **Dichamanetin, 1.62**	Polyphenols (flavanones)	• Inhibition of GTPase activity[19]	**MIC_{99}** 1.7 µM (*S. aureus*)
 **Resveratrol, 1.63**	Polyphenols	• Inhibition of Z-ring formation • Suppression of FtsZ mRNA expression[20]	**MIC_{99}** 142 µg/mL (*E. coli)*

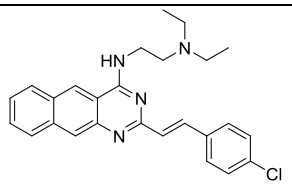
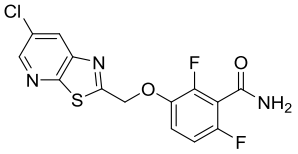
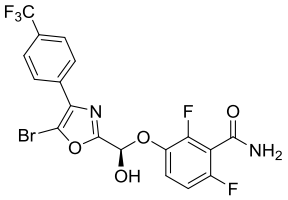
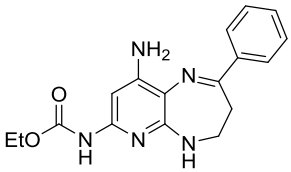
Compound Name and Structure	Compound class	Mode of action	Antibacterial activity
 **Curcumin, 1.64**	Polyphenols	• Increases GTPase activity • Destabilises FtsZ polymerisation[21]	**MIC_{99}** 100 µM (*B. subtilis* 168)
 **Sanguinarine, 1.65**	Alkaloids	• Inhibition of FtsZ polymerisation • Reduced bundling of protofilaments[22]	**MIC_{99}** 10 µM (*B. subtilis* 168)
 **Berberine, 1.66**	Alkaloids	• Inhibition of GTPase activity • Inhibition of FtsZ polymerisation • Mislocalisation of FtsZ[23]	**MIC_{99}** 100 µg/mL (*B. subtilis* 168) 32-128 µg/mL (MRSA)
 **Cinnamaldehyde, 1.67**	Phenylpropanoids	• Inhibition of GTPase activity • Inhibition of FtsZ polymerisation[24]	**MIC_{99}** 0.25 µg/mL (MRSA)
 **Scopoletin, 1.68**	Coumarin derivative	• Inhibition of GTPase activity • Inhibition of FtsZ polymerisation[25]	**MIC ND** **IC_{50} (GTPase activity)** 22 µg/mL (*B. subtilis* 168)

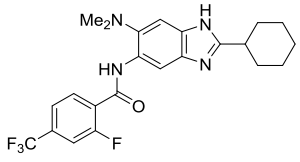
Compound Name and Structure	Compound class	Mode of action	Antibacterial activity
 **Totarol, 1.69**	Terpenoids	• Inhibition of GTPase activity • Inhibition of FtsZ polymerisation[26]	**MIC_{99}** 0.6 µg/mL (*B. subtilis* 168)

From a drug design perspective, molecules based on the endogenous substrate (GTP) and tubulin inhibitors provided the original templates. In addition to these, high throughput screening hits containing a variety of common drug motifs such as benzamides and the ubiquitous *N*-heterocyclic compounds have also yielded promising results. The most active FtsZ inhibitors so far, of either synthetic or natural origin, are PC190723 (**1.76**) and compound 1 (**1.77**).[27,28] PC190723 resensitises MRSA to β-lactam antibiotics thereby opening the door to possible combination therapies. Unfortunately, poor solubility and resultant poor bioavailability has hindered investigation of PC190723, however, to counteract this, 2 pro-drug derivatives possessing solubilising groups on the amide moiety have been developed and are currently in preclinical studies.[29] Structurally related compound 1, was found to not only have activity against SA and MRSA but also an *S. aureus* strain which had exhibited resistance to PC190723. Furthermore, from a therapeutic standpoint, it also showed no interaction with a variety of antibiotics, Vancomycin (glycopeptides), Linezolid (oxazolidinones), Oxacillin (penicillins) and Ceftazidine (cephalosporins). Hemichrysophaentin **1.70**, synthesised by Keffer *et al.* (See section 1.3.1) also showed strong antibiotic activity against both *S. aureus* and MRSA which, like its parent compound chrysophaentin A, arose from inhibition of GTPase activity by competition with GTP at the binding site.[2]

Table 1.3. Small molecule inhibitors of FtsZ and their mode of action.

Compound Name and Structure	Compound class	Mode of action	Antibacterial activity
 **Hemichrysophaentin, 1.70**	Polyphenols	• Inhibition of GTPase activity • Inhibition of FtsZ polymerisation[2]	**MIC_{50}** 12 ± 4.3 µM (*S. aureus*) 11 ± 5.4 µM (MRSA)
 **8-bromoguanosine 5'-triphosphate, 1.71**	GTP analogues	• Inhibition of GTPase activity[30]	**MIC ND** **K_i (GTPase activity)** 31.8 ±4.1 µM (*E. coli* BL21)
 **Gal Core 10, 1.72**	GTP analogues	• Inhibition of GTPase activity[31]	**MIC ND** IC_{50} (GTPase activity) 450 µM (*S. aureus*)
 **SB-RA-2001, 1.73**	Taxanes	• Increase in GTPase activity • Destabilisation of FtsZ polymerisation[32]	**MIC_{99}** 38 µM (*B. subtilis* 168)
 **Zantrin Z1, 1.74**	Zantrins	• Inhibition of GTPase activity • Decreasing protofilament length[33]	**MIC_{99}** 2.5 µM (*S. aureus* and MRSA)

Compound Name and Structure	Compound class	Mode of action	Antibacterial activity
 **Zantrin Z3, 1.75**	Zantrins	• Inhibition of GTPase activity • Stabilisation of FtsZ protofilaments[33]	**MIC_{99}** 5 μM (*S. aureus*) 10 μM (MRSA)
 **PC190723, 1.76**	Benzamides	• Activation of GTPase activity • Stabilisation of FtsZ protofilaments • Mislocalisation of FtsZ[18,27,29,34–37]	**MIC_{99}** 1.0 μg/mL (*S. aureus*, *B. subtilis 168* and MRSA)
 **Compound 1, 1.77**	Benzamides	• Activation of GTPase activity • Stabilisation of FtsZ protofilaments • Mislocalisation of FtsZ[28]	**MIC_{99}** 0.12 μg/mL (*S. aureus* and MRSA) 0.03 μg/mL (*B. subtilis 168)*
 **SRI-7614, 1.78**	Aminopyridines	• Inhibition of GTPase activity[38]	**MIC_{99}** 6.25 μM *(M. tuberculosis* H37Rv)

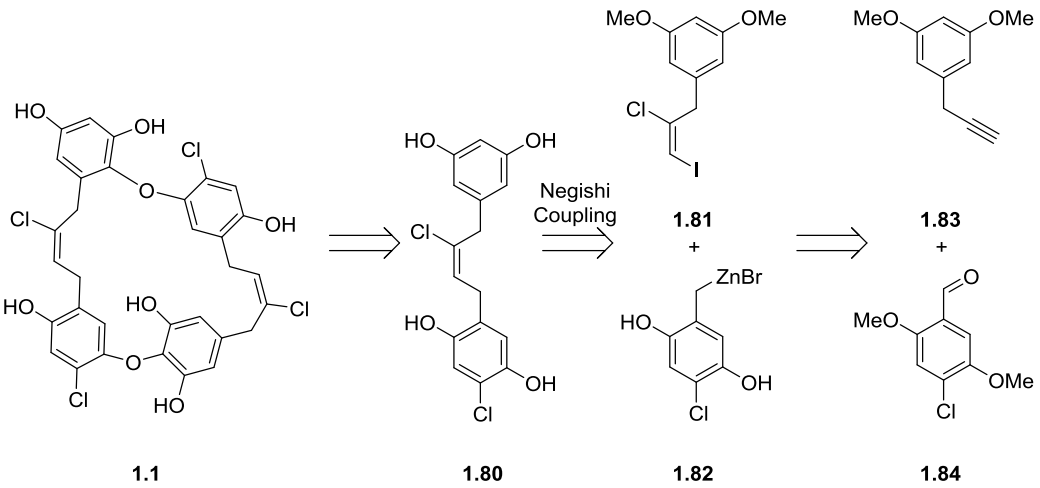
Compound Name and Structure	Compound class	Mode of action	Antibacterial activity
 **SB-P17G-A42, 1.79**	Benzimidazoles	• Activation of GTPase activity • Inhibition of FtsZ polymerisation • Depolymerisation of existing protofilaments[39]	**MIC_{99}** 0.8 µM *(M. tuberculosis* H37Rv)

1.3 Attempted Chrysophaentin Total Syntheses, Synthesis of Fragments and Analogues

To the best of our knowledge, no total synthesis of any of the chrysophaentins A-H has been published. However, the synthesis of key fragments and attempted syntheses have been reported previously and are summarised below.

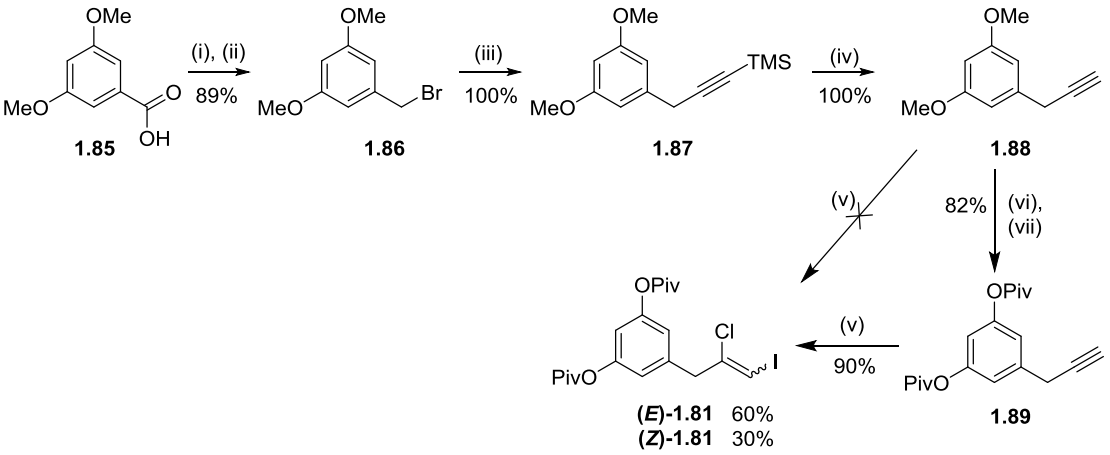
1.3.1 Keffer's Hemichrysophaentin Synthesis

Following the original isolation of the chrysophaentins, and faced with temporal and seasonal changes in the abundance of the source algae *Chrysophaeum taylori*, Keffer *et al.* embarked upon the development of a synthetic strategy toward the chrysophaentins.[2] Their approach followed the assumed biosynthetic pathway *via* a dimerisation of **1.80** (*c.f.* dimerisation of lunularin in the biosynthesis of the macrocyclic bisbibenzyls). Monomer **1.80** could be prepared by a Negishi coupling between vinyl iodide **1.81** and a benzylic zinc species **1.82**. The requisite vinyl iodide would be synthesised *via* the iodochlorination of **1.83** and the benzylic zinc species **1.82** could be provided by metalation of a benzylic halide originating from benzaldehyde derivative **1.84** (Scheme 1.1).



Scheme 1.1. Keffer *et al.* retrosynthetic analysis of chrysophaentin A **1.1**.

To prepare **1.81**, benzoic acid **1.85** was reduced to the alcohol, which was brominated to give **1.86** and then subjected to substitution with an organocuprate, formed *in-situ* by [(trimethylsilyl)ethynyl]magnesium bromide and CuBr, to give **1.87** in 87% yield over the three steps. Unfortunately, attempted iodochlorination of terminal alkyne **1.88** resulted mainly in overiodination products. However, upon conversion of the methyl ethers to deactivating pivaloyl esters, the iodochlorination reaction proceeded in excellent yield, although with low selectivity, to give a 2:1 mixture of alkenes (*E*)-**1.81** and (*Z*)-**1.81** which proved inseparable.

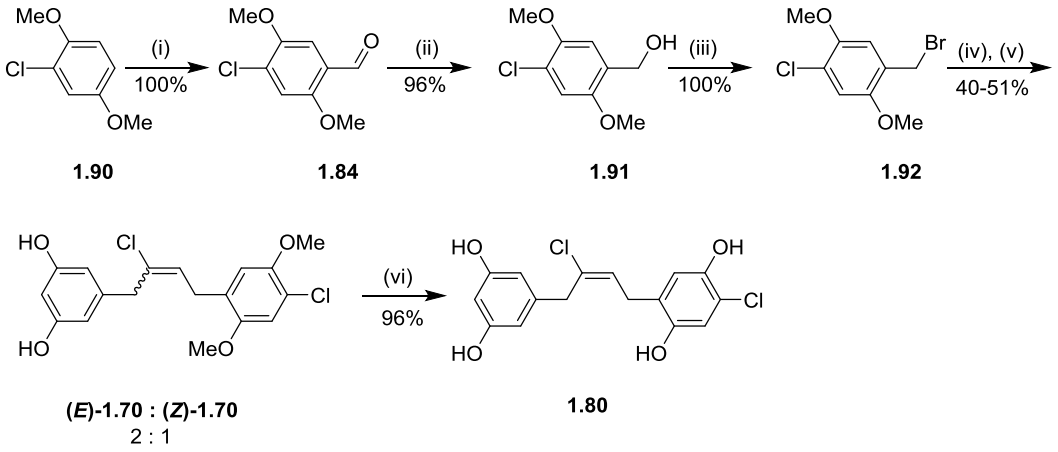


Reagents and conditions: (i) $LiAlH_4$ (2 equiv.), THF, 0 °C; (ii) PBr_3, DCM; (iii) EtMgBr (4 equiv.), TMS-acetylene (4 equiv.), CuBr (1 equiv.), THF, reflux; (iv) TBAF, AcOH, THF; (v) ICl, DCM; (vi) BBr_3, DCM; (vii) PivCl, DCM

Scheme 1.2. Synthesis of fragment **1.81**.

Synthesis of Negishi coupling partner **1.82** was accomplished through the *ortho*-formylation of protected hydroquinone **1.90**. The resultant aldehyde was subsequently reduced to alcohol **1.91**, converted into the benzyl bromide **1.92** and then treated with Zn^0. Through the use of

$Pd(OAc)_2$ and microwave heating, the organozinc was successfully coupled to the previously formed mixture of vinyl iodides (*E*)-**1.81** and (*Z*)-**1.81** providing vinyl chlorides (*E*)-**1.70** and (*Z*)-**1.70** in a 2:1 ratio after methanolysis of the pivaloate esters. Desired *(E)*-alkene **1.70** was isolated by supercritical fluid chromatography and then treated with BBr_3 to give hemichrysophaentin **1.80**.



Reagents and conditions: (i) hexamine, TFA, 95 ^{o}C; (ii) $NaBH_4$ (5 equiv.), EtOH; (iii) HBr, DCM; (iv) Zn^0 (5 equiv.), DMF, (*E*)-**1.81**/(*Z*)-**1.81**, $Pd(OAc)_2$ (0.05 equiv), P(*o*-Tol)$_3$ (0.1 equiv.), microwave, 120 ^{o}C, 4 min; (v) Cs_2CO_3, MeOH, DCM; (vi) BBr_3, DCM, 0 ^{o}C-RT

Scheme 1.3. Formation of hemichrysophaentin **1.80** by Keffer *et al.*

Although their approach was successful in providing chrysophaentin fragment **1.80**, the efficacy of the synthesis was diminished by the need to deprotect and reprotect intermediate **1.88** and by the low selectivity in the iodochlorination reaction (**1.89** to **1.81**). The authors are yet to report the completion of the synthesis of chrysophaentin A (**1.1**), however, interestingly, hemichrysophaentins **1.80** and (*E*)-**1.70** also showed biological activity against MRSA albeit with less potency than chrysophaentin A.

1.3.2 Brockway's Attempted Total Synthesis of Chrysophaentin A

In 2015, Brockway *et al.* published a synthesis of the diaryl ether cores common to chrysophaentins A, E and F (**1.93-1.94**) and their attempts to combine these to form chrysophaentin A (**1.1**).[40]

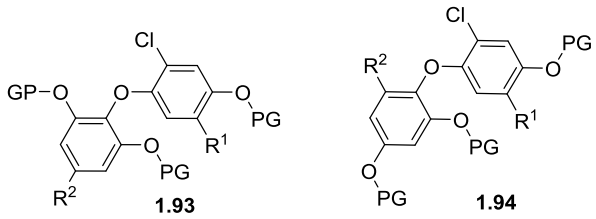
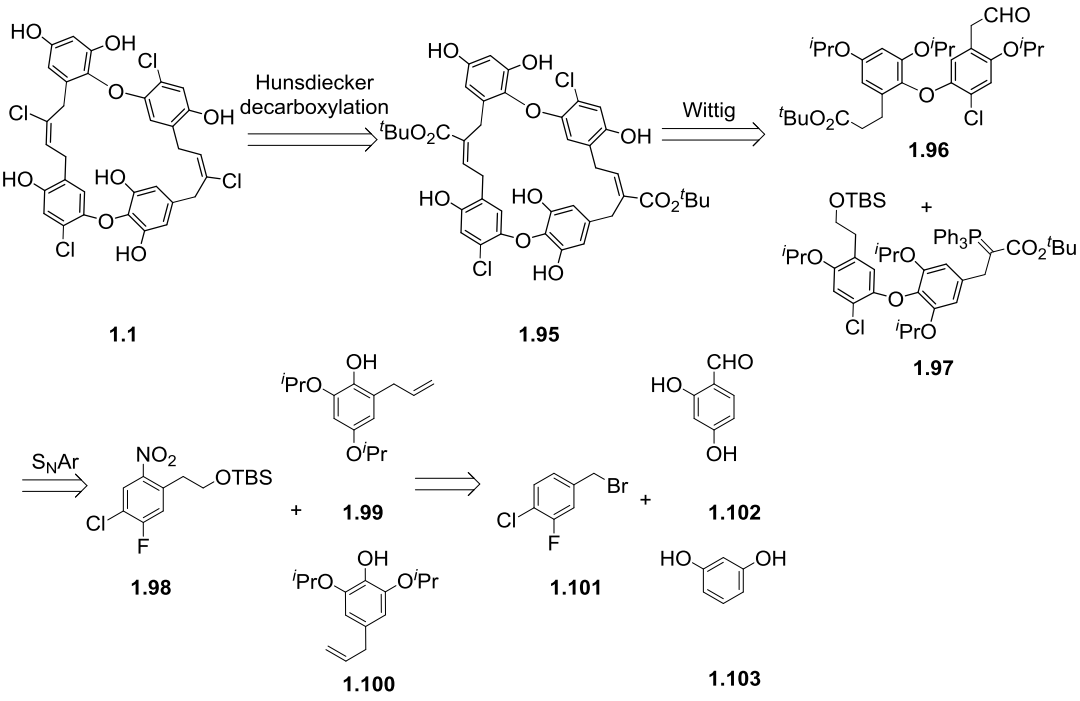


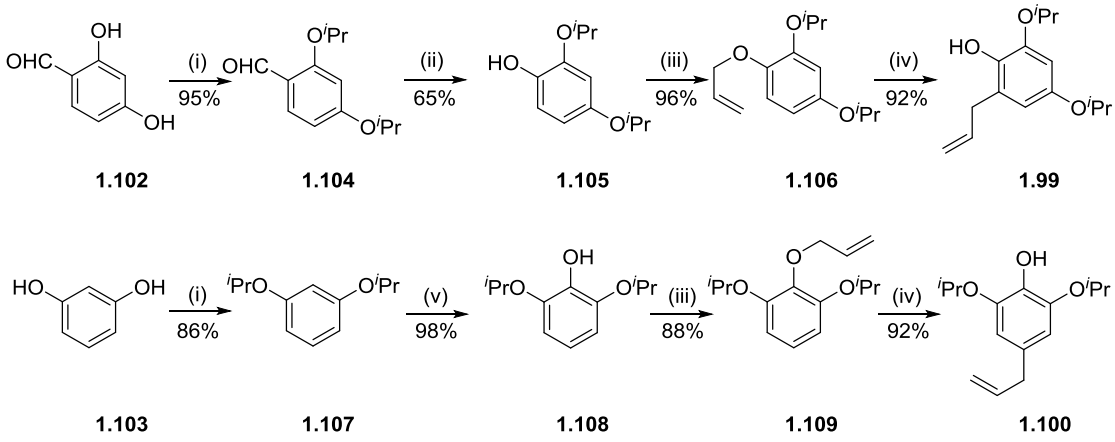
Figure 1.6. Diaryl cores common to chrysophaentins A (**1.93** and **1.94**), E (**1.93**) and F (**1.93**).

Their strategy involved formation of the macrocycle by two asynchronous Wittig reactions followed by a Hunsdiecker decarboxylation to install the (*E*)-vinyl chloride bridge (Scheme 1.4). The diaryl ethers could be formed by either a Chan-Evans-Lam coupling[41–43] or an S_NAr reaction. However, their initial attempts at the Chan-Evans-Lam coupling were unsuccessful leading to the sole pursuit of the S_NAr route. Thus, the two isomeric diaryl ethers could be formed from the nucleophilic substitution of **1.98** with either phenol **1.99** or **1.100**. The phenols themselves could in turn be prepared from either 2,4-dihydroxybenzaldeyde **1.102** or resorcinol **1.103**.



Scheme 1.4. Retrosynthetic analysis of chrysophaentin A **1.1** by Brockway *et al.*

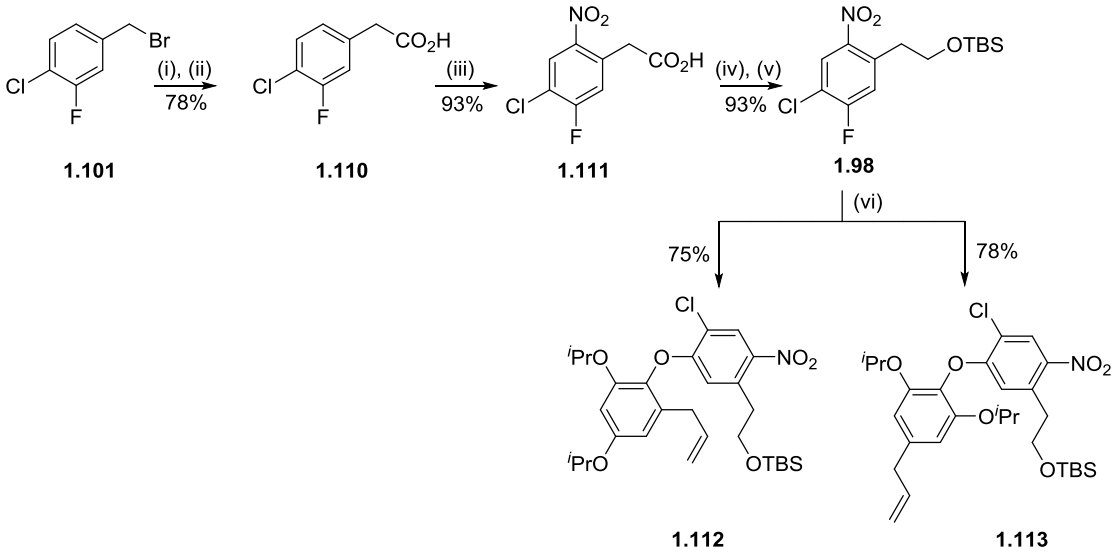
Synthesis of isomeric phenols **1.99** and **1.100** followed similar reaction pathways, with both utilising either Claisen or tandem Claisen-Cope rearrangements to install key allylic functionalities (Scheme 1.5). **1.99** was prepared *via* a Dakin oxidation of aldehyde **1.104** whereupon, the resultant phenol was then allylated. A Claisen rearrangement then furnished phenol **1.99** in 92% yield. The preparation of the isomeric phenol **1.100** required additional steps to install the central hydroxyl residue. An *ortho*-lithiation of **1.107**, followed by capture by a boron electrophile then provided **1.108** upon oxidation. Finally, allylation of the lone, unprotected phenol followed by tandem Claisen-Cope rearrangements installed the allyl group at the 4-position.



Reagents and conditions: (i) ^{i}PrBr, KI, K_2CO_3, DMF, 50 ^{o}C; (ii) MMPP, MeOH; (iii) allyl-Br, K_2CO_3, acetone, reflux; (iv) 185 ^{o}C, neat, 18 h; (v) a) ^{n}BuLi (1 equiv.), TMEDA (1 equiv.), THF –78 ^{o}C, b) $B(OMe)_3$ (2 equiv), c) aq. H_2O_2, NaOH

Scheme 1.5. Synthesis of phenols **1.99** and **1.100**.

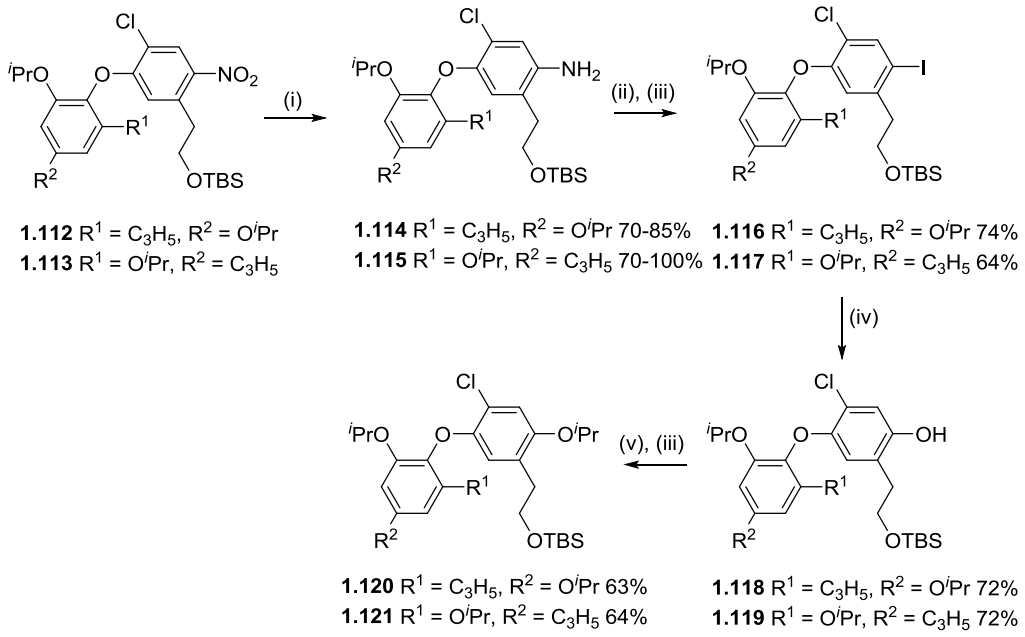
The required electrophile for the S_NAr reaction was prepared from benzyl bromide **1.101** in 5 steps and successfully coupled to phenols **1.99** and **1.100** in 75% and 78% yield respectively (Scheme 1.6).



Reagents and conditions: (i) KCN, H_2O, 1,4-dioxane, reflux; (ii) aq. NaOH, EtOH, reflux; (iii) HNO_3, H_2SO_4, 0 ^oC; (iv) BH_3.DMS (1.5 equiv.), THF, 0 ^oC-RT; (v) TBSCl, imidazole, DCM, RT; (vi) **1.99/1.100**, K_2CO_3, MeCN, 50 ^oC

Scheme 1.6. Synthesis of S_NAr substrate **1.98** and reaction with **1.99** and **1.100**.

However, conversion of the nitro group of **1.112** and **1.113** to the essential hydroxyl proved problematic; direct hydrolysis was unsuccessful, as was a Sandmeyer-type reaction from the corresponding aniline. The hydroxyl group was eventually installed using a long series of manipulations (Scheme 1.7). Firstly, the nitro group was reduced to the amine and then a Sandmeyer reaction provided aryl iodides **1.115** and **1.116**. Following this, a modified version of the previously used metalation-borylation-oxidation reaction sequence used in the synthesis of phenol **1.99** was employed. In this case, iodides **1.115** and **1.116** were metalated with the so-called "turbo Grignard" isopropylmagnesium chloride lithium chloride, trapped with tri-isopropylborate and oxidised to give **1.118** and **1.119**. Finally, this newly installed phenol was protected as the isopropyl ether. During this extensive series of transformations, the TBS ether needed to be reinstalled twice, thus reducing the efficacy of the synthesis even further.



1.112 $R^1 = C_3H_5$, $R^2 = O^iPr$
1.113 $R^1 = O^iPr$, $R^2 = C_3H_5$

1.114 $R^1 = C_3H_5$, $R^2 = O^iPr$ 70-85%
1.115 $R^1 = O^iPr$, $R^2 = C_3H_5$ 70-100%

1.116 $R^1 = C_3H_5$, $R^2 = O^iPr$ 74%
1.117 $R^1 = O^iPr$, $R^2 = C_3H_5$ 64%

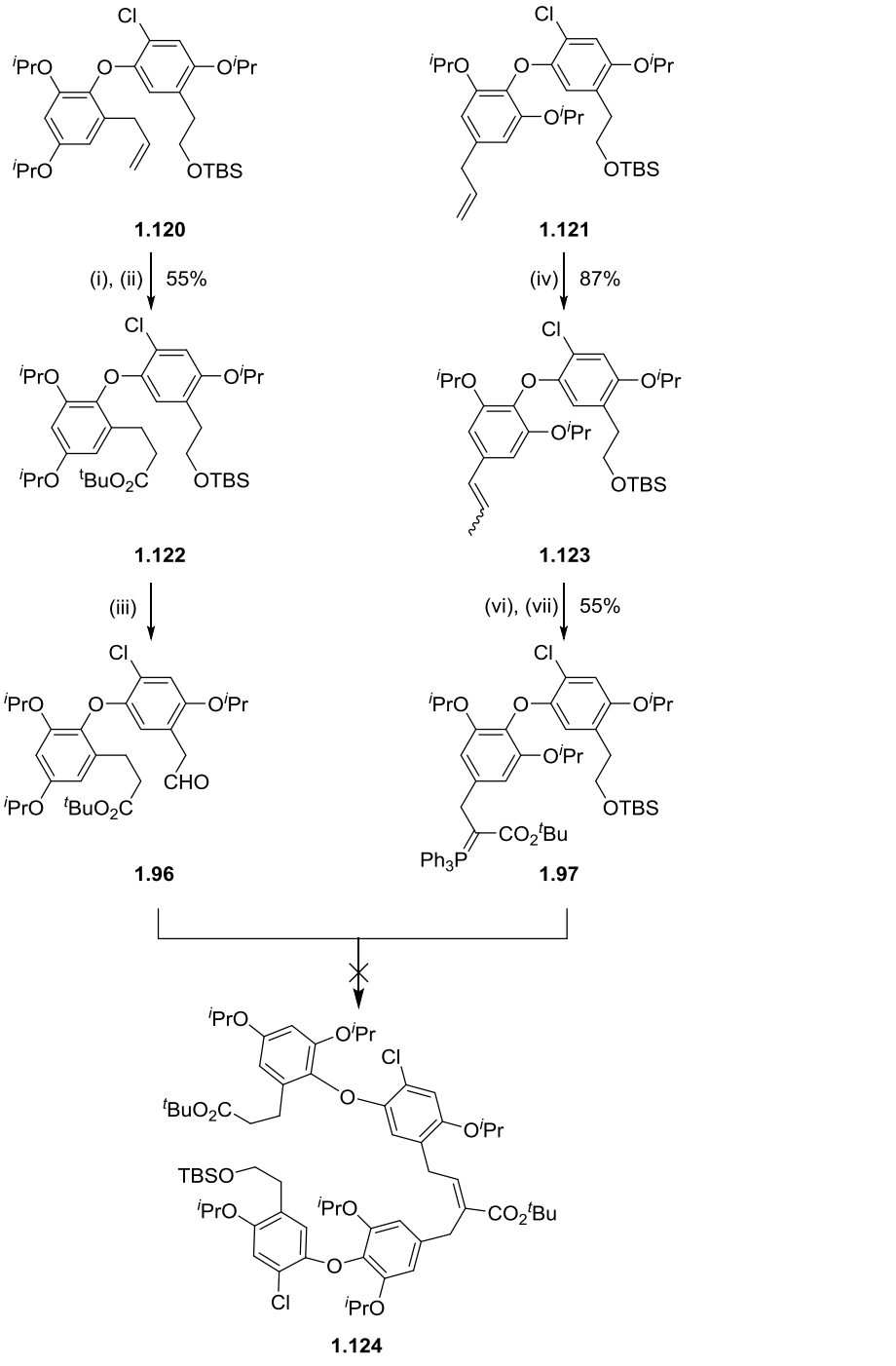
1.120 $R^1 = C_3H_5$, $R^2 = O^iPr$ 63%
1.121 $R^1 = O^iPr$, $R^2 = C_3H_5$ 64%

1.118 $R^1 = C_3H_5$, $R^2 = O^iPr$ 72%
1.119 $R^1 = O^iPr$, $R^2 = C_3H_5$ 72%

Reagents and conditions: (i) $SnCl_2.2H_2O$, EtOH; (ii) $NaNO_2$, *p*-TsOH, KI, MeCN; (iii) TBSCl, imidazole, DCM; (iv) a) ^{i}PrMgCl.LiCl (1.2 equiv.), THF b) $B(O^iPr)_3$ (3.3 equiv.), c) H_2O_2, aq. NaOH; (v) ^{i}PrBr, K_2CO_3, acetone

Scheme 1.7. Nitro-to-hydroxyl conversion to form **1.121** and **1.122**.

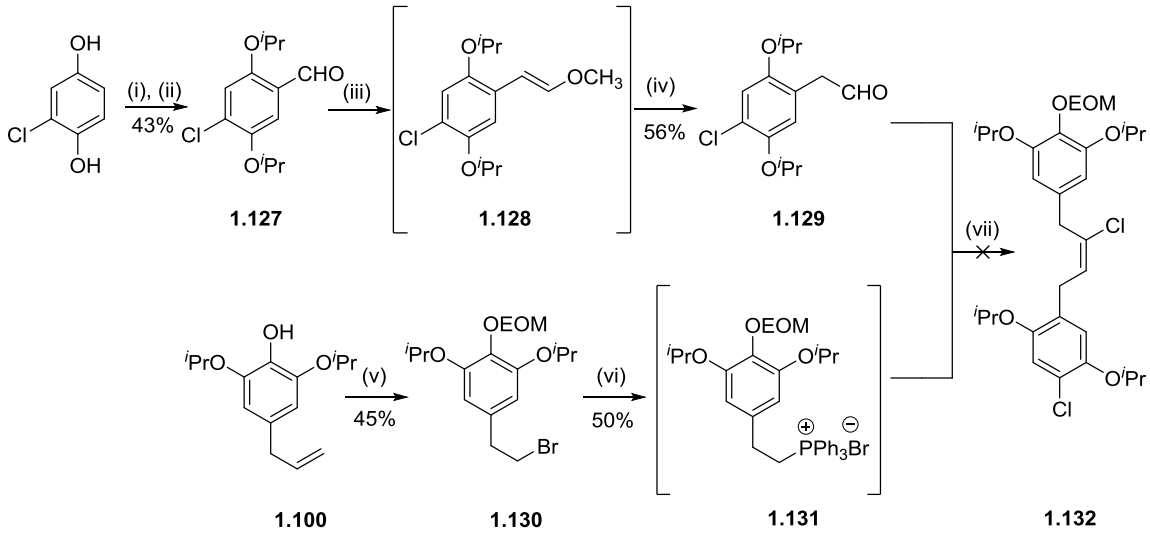
With the two diaryl ether fragments in hand, attention turned to the construction of the (*E*)-vinyl chloride subunit *via* a Wittig reaction followed by Hunsdiecker decarboxylation-halogenation. The required aldehyde (**1.96**) and phosphorus ylide components (**1.97**) were prepared from **1.120** and **1.121**; however, upon their combination none of the desired alkene product was detected (Scheme 1.8). Instead, it was assumed that aldehyde **1.96** had been completely consumed by self-aldol processes, which are common for phenylacetaldeydes.



Scheme 1.8. Attempted formation of **1.124** from aldehyde **1.96** and ylide **1.97**.

A second attempt to introduce the (*E*)-vinyl chloride subunit used Schlosser's SCOOPY (α-Substitution plus Carbonyl Olefination *via* β-Oxido Phosphorous Ylides) methodology[44] and was tested using a model system (Scheme 1.9). Model aldehyde **1.129** was synthesised from

chlorohydroquinone **1.125** in 4 steps, however **1.129** was very unstable and difficult to handle so **1.128** was converted to the corresponding alcohol which was oxidised to **1.129** with DMP as required. Ylide coupling partner **1.131** was prepared from previously synthesised **1.101** by protection of the phenol as its ethoxymethyl ether, followed by oxidative cleavage, reduction and bromination to yield **1.130**. The bromine atom was displaced with triphenylphosphine to give triphenylphosphonium salt **1.131,** which was deprotonated with PhLi, treated with aldehyde **1.129**, deprotonated again and then treated with an electrophilic chlorine reagent such as NCS. However, **1.131** was not detected and it was assumed that, again, the aldehyde partner, **1.129**, had decomposed.



Reagents and conditions: (i) Na, ^{i}PrBr, EtOH; (ii) hexamine, TFA; (iii) $^{\ominus}Cl\ ^{\oplus}Ph_3P$⌒O⁄, KO^{t}Bu, THF; (iv) a) $Hg(OAc)_2$ (1.2 equiv.), $NaBH_4$ (4 equiv.), b) DMP (1.5 equiv.), DCM; (v) a) EOMCl, $^{i}Pr_2NEt$, b) OsO_4, $NaIO_4$, THF, c) $NaBH_4$ (2 equiv.), EtOH, d) Ph_3P, Br_2, imidazole, Et_2O/MeCN (3:1); (vi) Ph_3P, MeCN; (vii) a) PhLi, LiBr, b) **1.129**, −78 °C-RT, (c) PhLi, NCS, −78 °C-RT

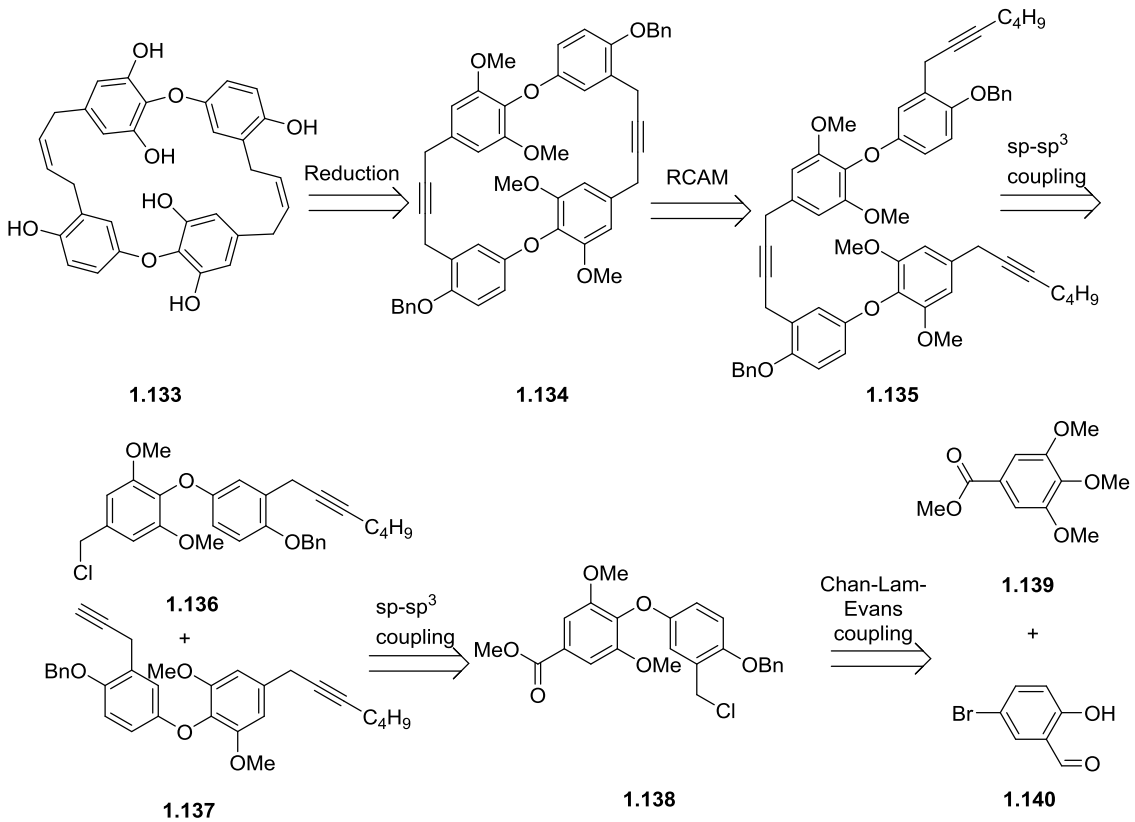
Scheme 1.9. Attempted synthesis of (*E*)-vinyl chloride **1.132** using Schlosser's SCOOPY system.

The failure of both these synthetic routes, which is thought to be due to the enolisability of aldehydes **1.96** and **1.129** preventing formation of the alkene, represents a significant obstacle in this methodology. The authors are currently exploring alternative routes to the (*E*)-vinyl chloride and chrysophaentin A, although nothing further has been published.

1.3.3 Synthesis of the Chrysophaentin F, G and H Core Framework

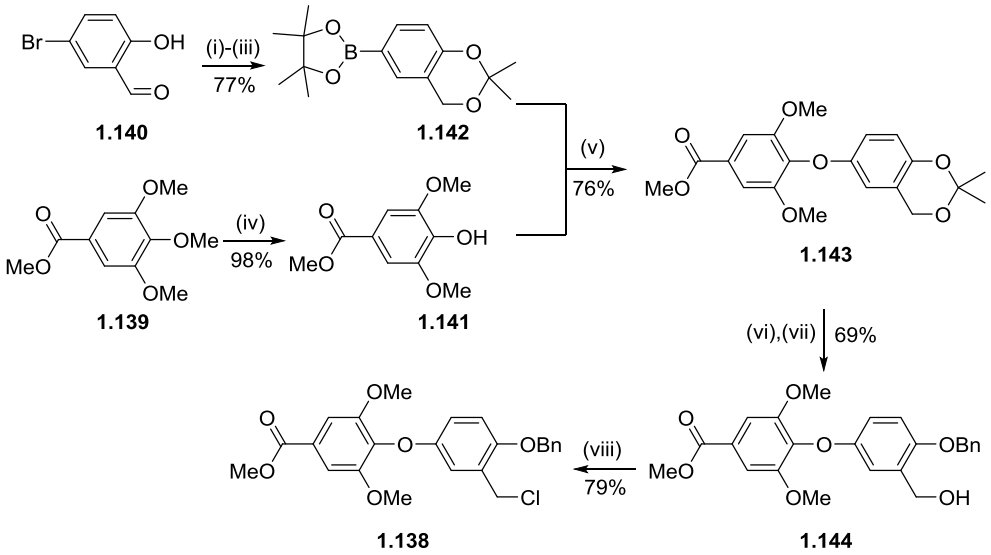
Within the Harrowven group, work on the total synthesis of the chrysophaentins began with the synthesis of the unhalogenated core of chrysophaentins F, G and H (**1.133**).[45] This analogue was chosen in order to establish the best strategy toward the natural product. This core was chosen over that of chrysophaentins A-D as it is a symmetrically linked macrocycle, thus introducing the possibility of using a common intermediate in its synthesis.

The synthetic plan envisaged that the macrocyclic structure could be formed *via* a ring closing alkyne metathesis which upon hydrogenation and global deprotection would provide chrysophaentin analogue **1.133** (Scheme 1.10). The precursor to the macrocylisation could be prepared from benzyl chloride **1.138** through a series of sp-sp^3 coupling reactions. The key diaryl ether moiety could be prepared by a variety of methods, for example, an Ullmann or Buchwald coupling or a S_NAr reaction. However, a Chan-Evans-Lam coupling[41–43] was chosen due to its mild reaction conditions and its efficacy in the synthesis of hindered 2,6-disubstituted substrates, as illustrated by the synthesis of thyroxine.[43] Therefore, benzyl chloride **1.138** would be prepared from phenol derived from **1.139** and a boronate species derived from **1.140**.



Scheme 1.10. Retrosynthetic analysis of the core structure of chrysophaentins F, G and H, **1.133**.

To access key benzyl chloride **1.138**, firstly commercially available salicylaldehyde **1.140** was subjected to a three-step reduction, protection and Miyaura borylation reaction sequence. Alongside this, **1.139** was selectively demethylated with MgI_2 to give phenol **1.141**. The phenol **1.141** and boronic ester **1.142** then underwent a Chan-Evans-Lam coupling catalysed by $Cu(OTf)_2$ to give diaryl ether **1.143**. This was then deprotected, the phenolic residue selectively re-protected as its benzyl ether and then the remaining benzylic alcohol was converted to the chloride to provide **1.138**. One drawback of this strategy was the use of the acetal protecting group which had to be removed and the phenolic OH reprotected, however when a benzyl protecting group was used for the initial stages, the yield of the borylation decreased dramatically.

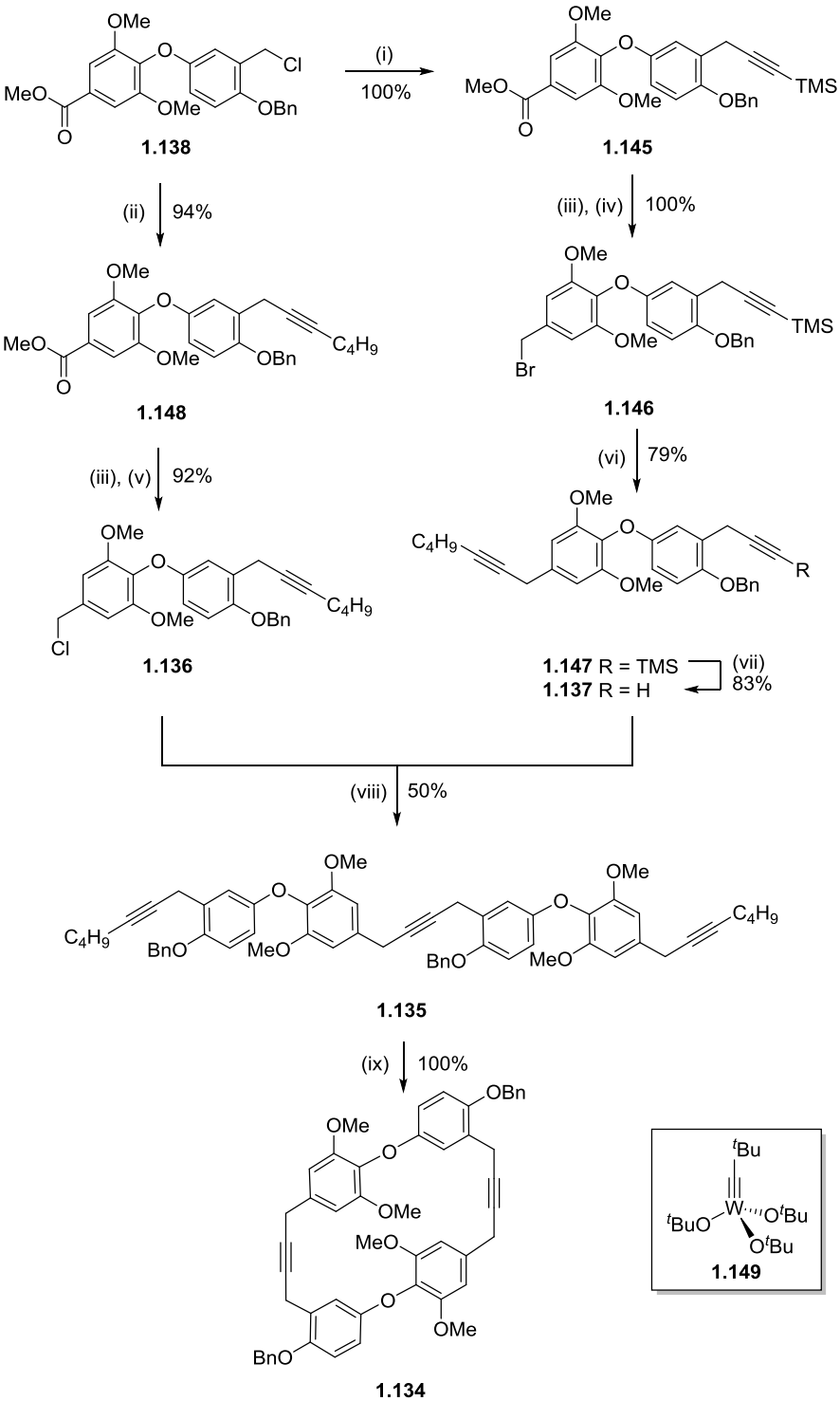


Reagents and conditions: (i) $NaBH_4$ (2.1 equiv.), MeOH, 0 °C; (ii) 2,2-dimethoxypropane, Na_2SO_4, acetone, 40 °C; (iii) B_2Pin_2 (1.2 equiv.), KOAc (2.2 equiv.), $Pd(dppf)Cl_2$ (0.1 equiv.), THF, 60 °C; (iv) MgI_2, 80 °C; (v) $Cu(OTf)_2$ (0.2 equiv.), 4 Å sieves, O_2, Py (7 equiv.), EtOH, 65 °C; (vi) AcOH, H_2O, 70 °C; (vii) BnBr, K_2CO_3, acetone 40 °C; (viii) NCS, PPh_3, THF, 0 °C-RT

Scheme 1.11. Preparation of key benzyl chloride **1.138**.

At this point the synthesis diverged. A Heck alkynylation or copper free Sonogashira coupling as described by Larsen *et al.*,[46] between **1.138** and either TMS acetylene or hex-1-yne gave alkynes **1.145** and **1.146** in excellent yields**.** The ester group of both these molecules was then reduced with $LiAlH_4$ and the resulting alcohol converted to a chloride (**1.136**) or a bromide (**1.146**). Attempts to use the previously utilised Heck alkynylation procedure to install an alkynyl residue in this position, however, only resulted in formation of the isomeric allene. Pleasingly, a switch to a Ni-catalysed coupling between an alkynylalane species and benzyl bromides developed by Biradar *et al.*,[47] led to the successful coupling of **1.146** and hex-1-yne to yield **1.147**. This was then subjected to a variety of deprotection conditions with TBAF and K_2CO_3 in MeOH resulting in only the allenic form. A switch to catalytic AgOTf, a milder method developed by Orsini *et*

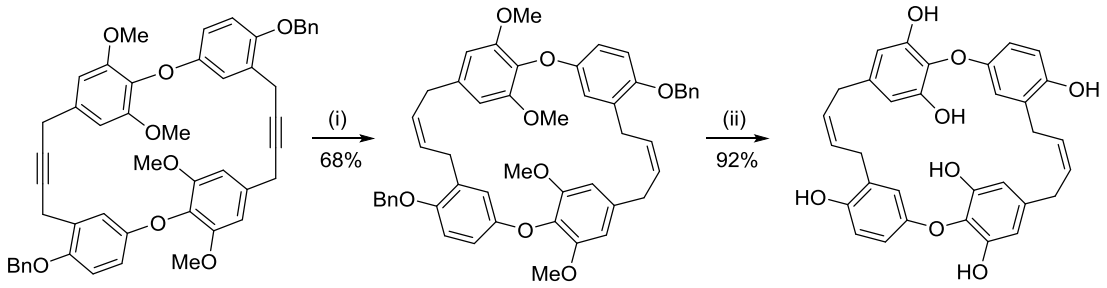
al.,[48] prevented this isomerisation and furnished terminal alkyne **1.137.** Benzyl chloride **1.136** and terminal alkyne **1.137** and were then subjected to the previously used Heck alkynylation protocol leading to the formation of triyne **1.135** and also showed no trace of allene formation despite the low 50% yield. This was then subjected to a ring closing alkyne metathesis reaction using Schrock's alkylidyne catalyst[49,50] **1.149** to give **1.134** in a quantitative yield.



Reagents and conditions: (i) TMS-acetylene (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C; (ii) hex-1-yne (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C; (iii) $LiAlH_4$ (1.1 equiv.), THF, 0 °C-RT; (iv) NBS, PPh_3, THF, 0 °C-RT; (v) NCS, PPh_3, THF, 0 °C-RT; (vi) a) hex-1-yne (2 equiv.) ^{n}BuLi (2 equiv.), then Et_2AlCl (2 equiv.) Et_2O, 0 °C-RT, b) **1.146**, $Ni(PPh_3)_2Cl_2$ (0.07 equiv.), Et_2O, RT; (vii) AgOTf, MeOH/H_2O/DCM, RT; (viii) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C; (ix) **1.149** (0.2 equiv.), PhMe, 80 °C

Scheme 1.12. Divergent and macrocyclisation steps of the synthesis.

The two alkyne bridges of macrocycle **1.134** were then reduced with Lindlar's catalyst and finally, global deprotection was achieved with BCl_3 and TBAI to furnish the chrysophaentin core **1.133**.



1.134 **1.150** **1.133**

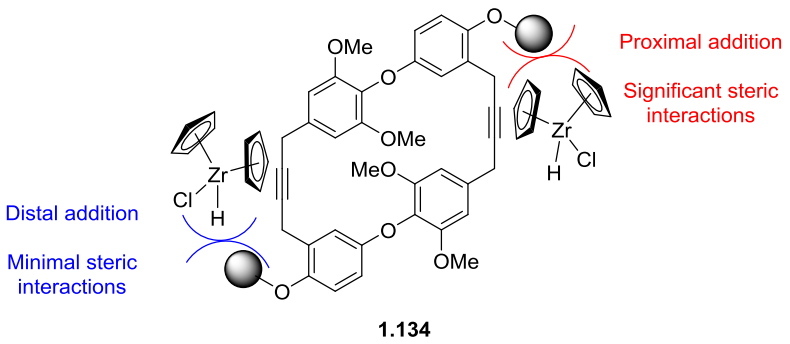
Reagents and conditions : (i) H_2, 5% Pd-$CaCO_3$, $Pd(OCOCH_3)_2$, quinoline, EtOAc/MeOH (1:1); (ii) BCl_3, TBAI, DCM, 0 ^oC-RT

Scheme 1.13. Completion of the synthesis of chrysophaentin analogue **1.133**.

1.3.4 Towards the Total Synthesis of Chrysophaentin F

Having established a synthesis of unchlorinated chrysophaentin analogue **1.133**, attention turned to applying this methodology to the natural chrysophaentins. Chrysophaentin F was chosen as the initial target as it is completely symmetrical and would thus be the most amenable to our convergent synthetic strategy.

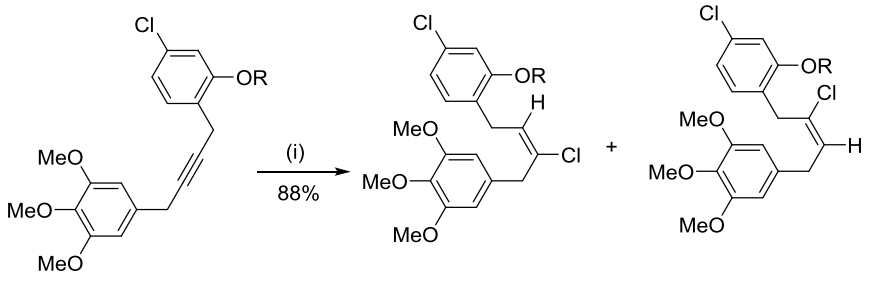
One architectural feature of the chrysophaentins not addressed in the work described above was the installation of the vinyl chloride bridge with the correct (*E*) geometry. It was theorised that this could be performed by a hydrozirconation reaction based on the established *cis*-addition of the Schwartz reagent across a C-C triple bond.[51–53] The organozirconium species formed can then react with an electrophilic quenching agent to provide a tri-substituted alkene. The use of iodine, NBS and NCS in this manner has been reported.[54–56] The regioselectivity of the *cis*-addition is highly dependent upon sterics thus it was hoped that by placing a large protecting group on the *ortho*-phenolic residue it would provide sufficient steric hinderance and direct the addition of zirconium to the distal carbon (Figure 1.7).



1.134

Figure 1.7. Proximal vs distal addition of Schwartz's reagent to macrocycle **1.134**.

As macrocycle **1.133** was a high value substrate, this rationale was tested on two alternatively protected substrates **1.151** and **1.154**.



1.151 R = MOM
1.154 R = Bn

1.152 R = MOM 1:1
1.155 R = Bn 2:1

1.153 R = MOM
1.156 R = Bn

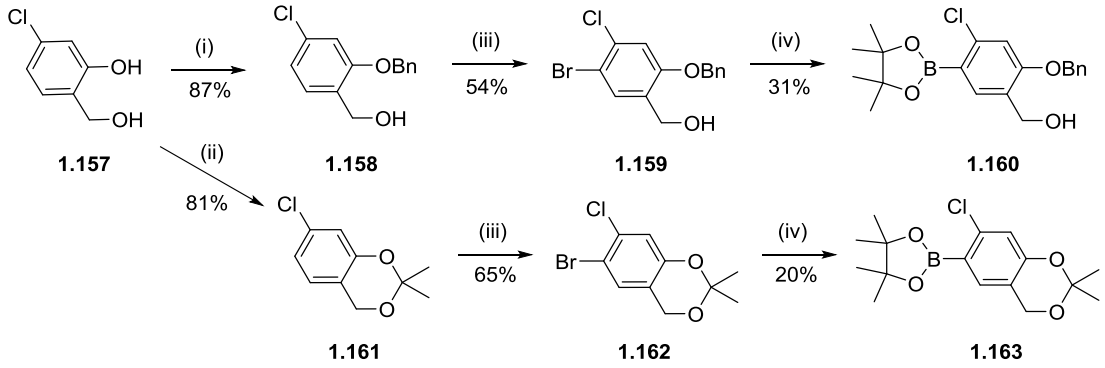
Reagents and conditions: (i) a) $ZrCp_2Cl_2$ (2 equiv.), DIBAL (2 equiv.), THF, 0-40 °C, b) NCS (1 equiv.), DCM, RT

Scheme 1.14. Hydrozirconation and chlorination to form hemichrysophaentins **1.152** and **1.155** and regioisomers **1.153** and **1.156**.

When a small MOM group was used, no selectivity was observed and regioisomers **1.152** and **1.153** were formed in a 1:1 ratio. However, the use of a larger benzyl protecting group resulted in a 2:1 ratio in favour of the desired regiochemistry, thus providing credence to our hypothesis regarding the ability of the steric bulk on the proximal *ortho*-phenolic residue to control the initial hydrozirconation. Although on this substrate the regioselectivity was only 2:1, it is possible that this will be higher on a macrocyclic substrate such as **1.134**, as there are fewer degrees of rotational freedom. It is also possible that the regioselectivity could be increased by using an excess of Schwartz reagent which would favour the thermodynamic product *via* isomerisation of a dimetalated alkane intermediate.[51]

With a route to the macrocyclic core and a chlorination strategy established, work started in earnest towards chrysophaentin F. Salicylic alcohol **1.157** was either benzyl (**1.158**) or acetal

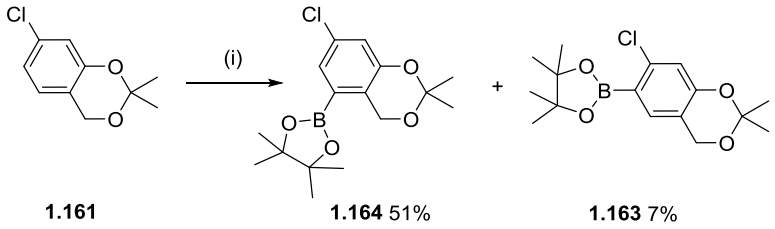
(**1.161**) protected and then subjected to variety of bromination conditions with heating at 60 °C in MeCN providing the best results. However, attempts to form boronic esters **1.160** and **1.163** using the Miyaura borylation conditions established previously returned a disappointing 20% and 31% yield respectively.



Reagents and conditions : (i) BnBr, K_2CO_3, acetone, 45 ^oC; (ii) 2,2-dimethoxypropane, *p*-TSA, Na_2SO_4, acetone, 40 ^oC; (iii) NBS, MeCN, 60 ^oC; (iv) B_2Pin_2 (1.2 equiv.), KOAc (2.8 equiv.), $Pd(dppf)Cl_2$ (0.1 equiv.), THF, 65 ^oC

Scheme 1.15. Preparation of boronic esters **1.160** and **1.163**.

Changing the solvent to either 1,4-dioxane or DMSO, raising the reaction temperature to 95 °C, increasing the catalyst loading to 20 mol% and switching to microwave irradiation each led to no improvement in isolated yield. An alternative C-H activation using $[Ir(COD)(OMe)]_2$ was attempted,[57,58] however, this led to isomeric boronic ester **1.163** as the major product (7:1) as determined by NMR.

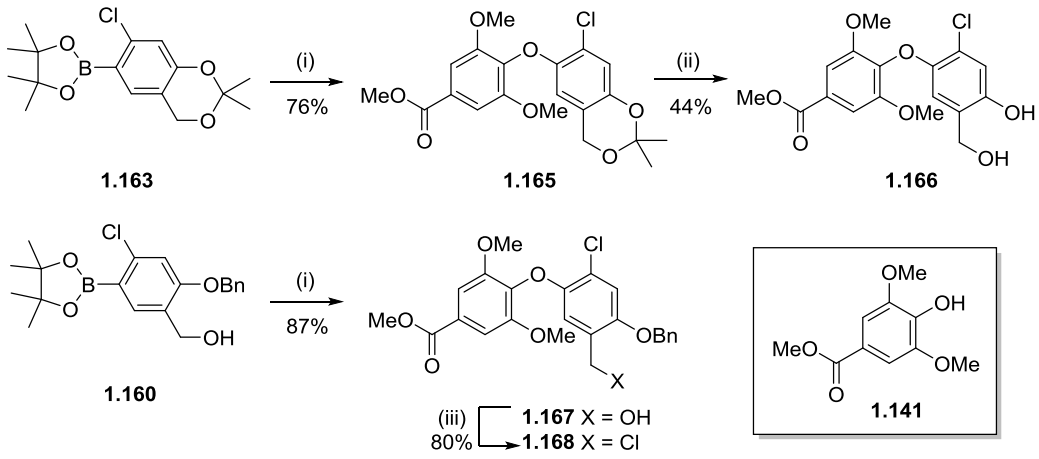


Reagents and conditions: (i) $[Ir(COD)(OMe)]_2$ (0.008 equiv.), dtbpy (0.015 equiv.), B_2Pin_2 (0.5 equiv.), 1,4-dioxane, 100 ^oC

Scheme 1.16. Alternative boron ester synthesis *via* C-H activation.

Through recovery of unreacted starting material and repeated reactions sufficient quantities of boronic esters **1.160** and **1.163** were prepared to test the Chan-Evans-Lam coupling reaction. Pleasingly, the coupling proceeded in high yield for both substrates, however, a low yield for the acetal deprotection of **1.165** led to sole use of the benzyl protected substrate in future reactions.

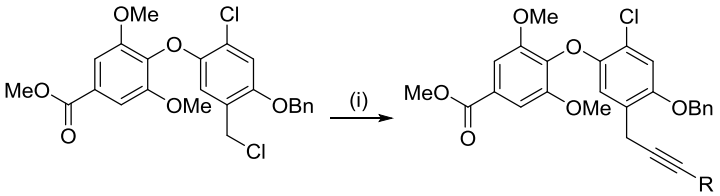
The subsequent conversion to key benzyl chloride intermediate **1.168** proceeded without incident.



Reagents and conditions: (i) **1.141** (1 equiv.), $Cu(OTf)_2$ (0.2 equiv.) Py (8 equiv.), 4 Å sieves, O_2, EtOH, 65 ^oC; (ii) AcOH, H_2O, 70 ^oC, (iii) NCS, PPh_3, THF, 0 ^oC-RT

Scheme 1.17. Chan-Evans-Lam coupling of boronic esters **1.160** and **1.163** with phenol **1.141**.

Transformation of benzyl chloride **1.168** into either ^{n}butyl or TMS capped alkynes **1.169** and **1.170** gave puzzling results. Whereas coupling with hex-1-yne proceeded without issue, the analogous reaction with TMS-acetylene gave a poor 23% yield. The reaction was repeated with examination of several reaction parameters including fresh batches of catalyst and other reagents as well as the equivalents of these reagents but to no avail. Other approaches to alkyne **1.170** were also examined, including the Nickel-alkynylalane coupling which had previously proved effective in problematic couplings, but these were also unsuccessful. A switch to using a TIPS protected alkyne for the Heck alkynylation afforded some improvement with alkyne **1.171** isolated in 34% yield. Sadly, these low yields put paid to further progress at this time.



1.168

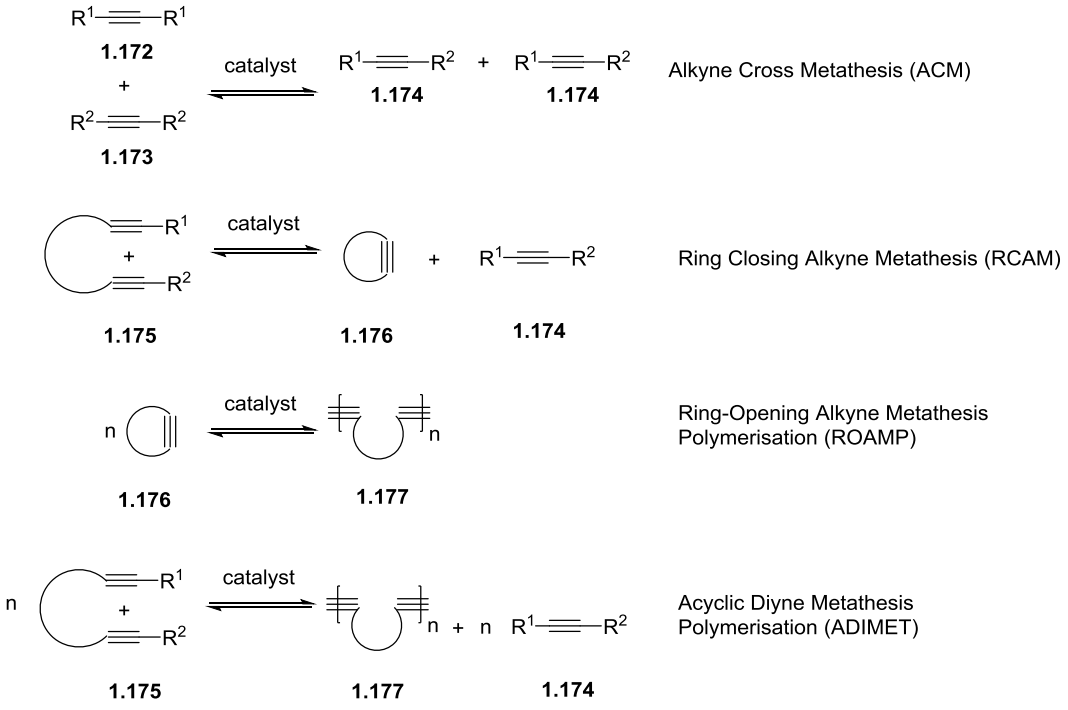
1.169 R = C_4H_9 75%
1.170 R = TMS 23%
1.171 R = TIPS 34%

Reagents and conditions: (i) ≡—R (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C

Scheme 1.18. Alkynylation of benzyl chloride **1.168** with hex-1-yne, TMS-acetylene and TIPS-acetylene.

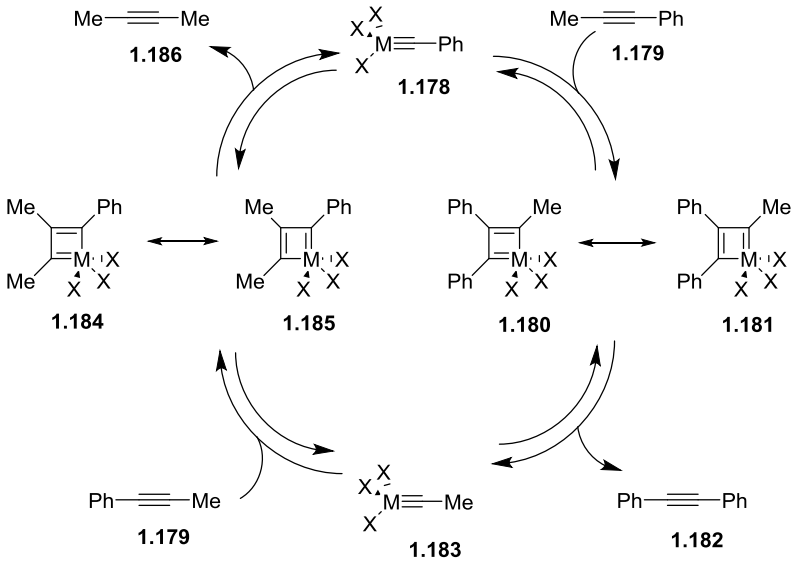
1.4 Alkyne Metathesis and its Application in Total Synthesis

The synthetic strategy developed in the Harrowven group utilises several key transition metal catalysed C-C bond forming reactions, none more important than the W-catalysed alkyne metathesis to form the macrocyclic structure of the chrysophaentins. Alkyne metathesis is a process that involves the scrambling of two alkyne units which can either be intermolecular (alkyne cross metathesis) or intramolecular (ring closing alkyne metathesis). This methodology is also prevalent in the polymer industry where ring opening alkyne metathesis and acyclic diyne metathesis polymerisation variants are commonly used (Scheme 1.19).



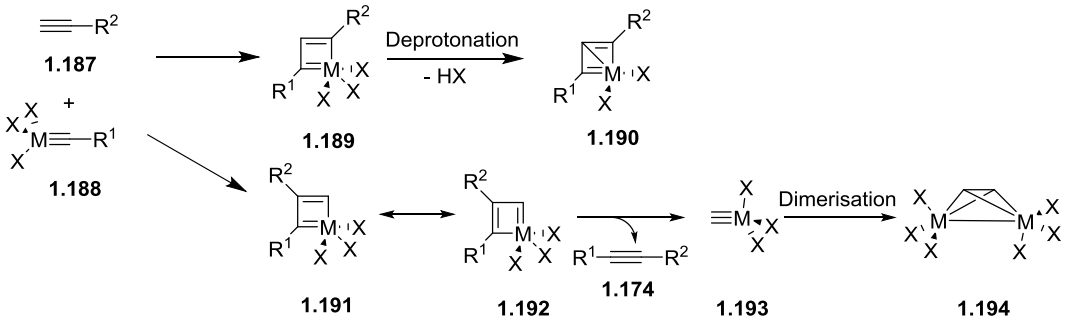
Scheme 1.19. Types of alkyne metathesis process.

The mechanism for alkyne metathesis established by Katz and McGinnis in 1975 is analogous to that of alkene metathesis.[59] The metal carbyne catalyst **1.178** and 1-phenyl-1-propyne **1.179** undergo a formal [2+2] cycloaddition to form metallocyclobutadiene intermediate **1.180** (Scheme 1.20). This can rearrange to give a new metallocyclobutadiene **1.181** which then undergoes cycloreversion to provide alkyne **1.182** and the alkylidyne complex **1.183**. This new complex remains catalytically competent and re-enters the catalytic cycle. It should be noted that each step of the catalytic cycle is reversible, thus it is critical that one of the reaction mixture components be removed to drive the reaction to completion. Typically, methyl-capped alkynes are used as the product, 2-butyne **1.186**, is sufficiently volatile to be easily removed either by heating, vacuum or through the use of 5 Å molecular sieves that are perfectly sized to sequester this alkyne.



Scheme 1.20. Mechanism of alkyne metathesis exemplified by the conversion of 1-phenyl-1-propyne **1.179** to tolane **1.182** and butyne **1.186**.

Originally, it was thought that alkyne metathesis was only possible for non-terminal alkynes as the use of a terminal alkyne led to significant catalyst degradation. This was believed to be due to deprotonation of metallocyclobutadiene **1.189** leading to a catalytically inactive metallacycle **1.190** or, alternatively, by the dimerization of methylidyne complexes **1.193** to form a dimetallatetrahedrane species **1.194** (Scheme 1.21).



Scheme 1.21. Catalyst decomposition pathways for the metathesis of terminal alkynes.

However, in 2012, Tamm and co-workers developed a Mo-alkylidyne catalyst (**1.200**) capable of both internal and terminal alkyne metathesis.[60] They speculated that the catalyst is able to overcome the above stated issues by disfavouring metallacycle formation through the use of non-coordinating solvents and the low basicity of the chosen alkoxide ligand, and also through the use of high dilution to hinder bimolecular decomposition pathways. Subsequently, Fürstner *et al.* were also able to affect metathesis of terminal alkynes utilising a similar Mo-alkylidyne catalyst **1.202.**[61,62]

Despite the mechanistic similarities to alkene metathesis, all known alkene metathesis catalysts were found to be inactive towards alkynes and surprisingly, so were a range of Fischer carbyne complexes. Instead, all known alkyne metathesis catalysts are classified as Schrock carbyne complexes. According to organometallic chemistry conventions, Fischer carbyne complexes such as **1.195** are classified as "low valent" as the transition metal exists in its lowest oxidation state and the carbyne ligand is considered as monoanionic. The unpaired electrons on the carbon atom are used to form covalent σ and π bonds with the metal, and the carbon atom also possesses an empty orbital with which to accept electrons from the metal. Schrock carbyne complexes (e.g. **1.149**) are defined as having the metal centre in its highest possible oxidation state and the alkylidyne unit is considered to be trianionic. In this case, the 3 unpaired electrons on the carbon atom form 3 covalent bonds with the metal centre (Figure 1.8).

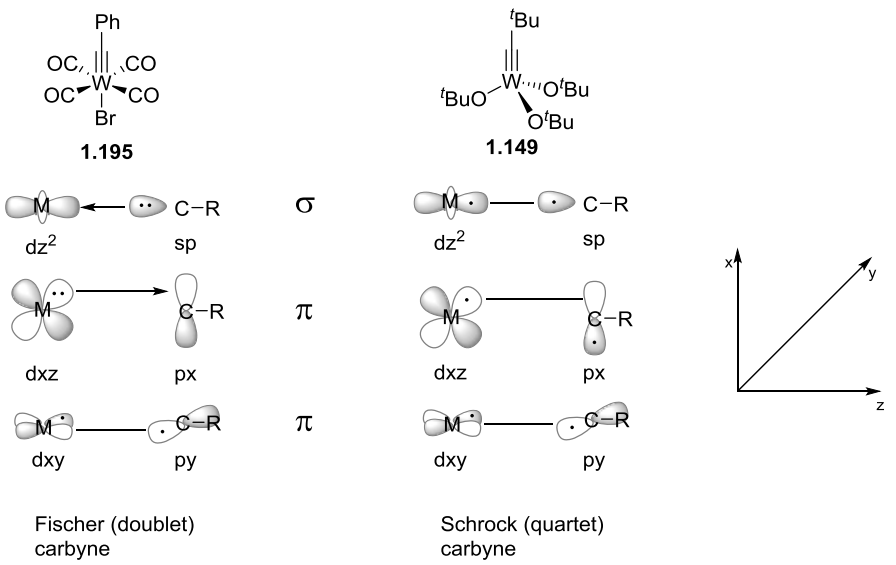


Figure 1.8. Fischer vs Schrock carbyne complex bonding.

Alkyne metathesis catalysts also generally contain large alkoxide or phenolate ligands, whose added steric bulk help to protect the metal centre and prevent dimerization and decomposition of the catalyst. The electronics of these ancillary ligands are also important for catalytic activity and tuning the Lewis acidity of the metal centre.[63] The R group on the alkylidyne ligand, however, has little impact on catalytic activity as it is lost in the first catalytic cycle.

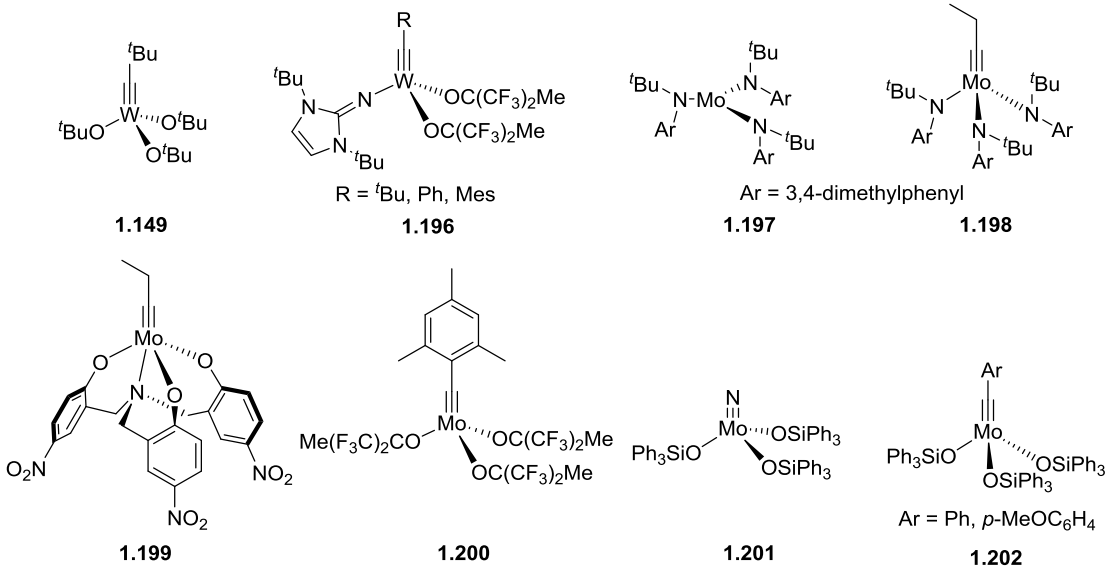


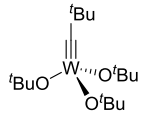
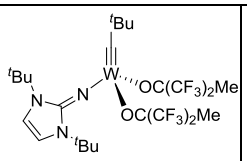
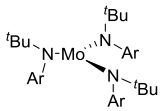
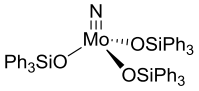
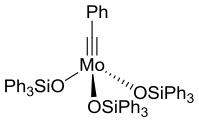
Figure 1.9. Examples of alkyne metathesis catalysts.[49,50,60,64–67]

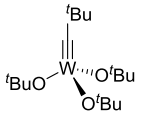
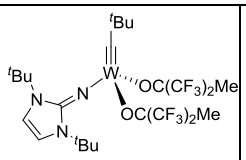
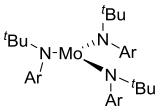
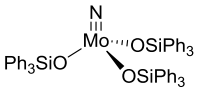
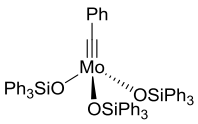
The first well defined alkyne metathesis catalyst was tungsten alkylidyne complex **1.149** developed by Schrock *et al.* in 1980, of which many derivatives have been prepared to attempt to improve the functional group tolerances of catalysts of this type.[49,50] However, even with these improvements, many substrates remained unviable and that, combined with the high air

and moisture sensitivity of these catalysts, limited their practical application. To that end, over the last 10-15 years, Fürstner *et al.* have developed a series of highly active Mo based catalysts. The first of these built upon work by Cummins *et al.* who had published triamido molybdenum(III) complexes, [Mo{NR(Ar)}$_3$], which could cleave the N–N triple bond in the dinitrogen molecule in a stoichiometric fashion.[68–70] Although these complexes (e.g. **1.197**) were inactive towards metathesis, *in-situ* activation with DCM and other *gem*-dihalides, was able to effect metathesis at a catalyst loading of 10 mol%.[64] This system increased the substrate scope to those containing moderately basic amines, nitro and nitrile groups as well as aldehydes and ketones. However, this catalyst was significantly more sensitive to acidic protons in comparison to **1.149** and also still required the use of stringently dry and inert conditions.

For that reason, the most significant catalysts developed by Fürstner are undoubtedly Mo-nitride[65] and Mo-alkylidyne[66,67] complexes (**1.201** and **1.202**) that possess triphenylsilanolate ligands. These ligands not only provide sufficient steric hindrance to prevent bimolecular decomposition of the Mo-alkylidyne unit but also temper the Lewis acidity of the Mo centre leading to increased functional group compatibility. Crucially, these catalysts also have air stable derivatives. Complexation of the active catalyst with pyridine conferred short term air stability, whereas the use of a phenanthroline or 2,2-bipyridine ligand was found to imbue the catalyst indefinite air stability. These N-donor ligands can be removed either *via* heating or through the use of metal salts, such as $MnCl_2$, which bind more strongly to the phenanthroline ligand and release the active catalyst *in-situ*. Mo-alkylidyne complex **1.202**, is the most active alkyne metathesis complex known to date with activity at even 0.1 mol% loading and also at temperatures as low as −10 °C. Catalysts of type **1.202** have, however, been found to be less effective when the substrate contains multiple protic sites. Conversely, catalysts containing chelating ligands such as **1.199**, that were originally utilised in material science, have been found to be more accepting of both phenol and alcohol groups.[67,71,72] A summary of the functional group compatibilities of catalysts **1.149, 1.196-1.197** and **1.201-1.202** are detailed in Table 1.4.

Table 1.4. Functional group tolerances of catalysts **1.149, 1.196**, **1.197, 1.201** and **1.202**.[63–67]

	 **1.149**	 **1.196**	 **1.197**	 **1.201**	 **1.202**
Acetal	X	X	✓	✓	✓
Acid chloride	X	X	-	X	✓
Aldehyde	X	X	Aliphatic ✓ Aromatic ✓	X	Aliphatic ✓ Aromatic X
Alkene	✓	✓	✓	✓	✓
Alkenyl iodide	-	-	-	-	✓
Alkyl chloride	-	-	✓	✓	✓
Amide	-	-	X	-	✓
Amine	X	X	✓	✓	✓
Aryl halide (F, Cl, Br)	X	✓	✓	✓	✓
Carba-mate	✓	✓	✓	✓	✓
Carbazole	X	X	-	-	✓
Ester	✓	✓	✓	✓	✓
Ether	✓	✓	✓	✓	✓
Epoxide	X	X	X	X	✓
Furan	✓	✓	✓	✓	✓
Indole	X	X	✓	✓	✓
Ketone	✓	✓	✓	✓	✓
Nitrile	-	-	✓	X	✓

	 **1.149**	 **1.196**	 **1.197**	 **1.201**	 **1.202**
Nitro	X	✓	✓	✓	✓
Pyridine	X	X	✓	✓	✓
Silyl ether	✓	✓	✓	✓	✓
Sulfon-amide	✓	✓	✓	✓	✓
Sulfonate	-	-	-	✓	✓
Sulfone	✓	✓	✓	✓	✓
Thiazole	X	X	✓	✓	✓
Thiocarba-mate	-	-	-	-	✓
Thioether	X	✓	✓	✓	✓
Thio-phene	-	-	✓	✓	✓
Trifluoro-methyl	-	-	✓	✓	✓

1.4.1 Alkyne v Alkene Metathesis in Total Synthesis

In comparison to alkene metathesis, which has been rapidly applied to total synthesis since its inception, the application of alkyne metathesis to this field has been sporadic. This is, in part, down to the disparate numbers and commercial availability of the required catalysts compared to alkene metathesis. Currently, there are over 15 commercially available catalysts for alkene metathesis in comparison to just two for alkyne metathesis. Schrock and Grubbs have been highly active in the field of alkene metathesis, resulting in a wide variety of catalysts with enhanced functional group tolerances, activities and stabilities and were awarded the Nobel Prize for Chemistry in 2005 along with Chauvin. However, during this time, the corresponding field of alkyne metathesis remained largely abandoned as illustrated in Figure 1.10. It is only in the last 15 years or so that alkyne metathesis catalyst development has resumed in earnest, with the publication of highly active and air stable catalysts with increased functional group

tolerances. Consequently, it is only recently that alkyne metathesis has been able to realise its full potential in the field of total synthesis.

The main application of alkyne metathesis in total synthesis has been in cases where alkene metathesis has proved ineffective. By its very nature, alkene metathesis can form either an *E* or *Z*-alkene product but generally results in a mixture of these 2 isomers. Bias towards the (*E*)-product is either innate by virtue of its increased thermodynamic stability over the (*Z*)-product or it requires removal of the *Z*-isomer by a selective ethenolysis.[73] On the other hand, (*Z*)-selective catalysts have only been developed recently.[73–78] Alternatively, an alkyne metathesis followed by a selective reduction has been found to be a reliable method to single isomer formation.

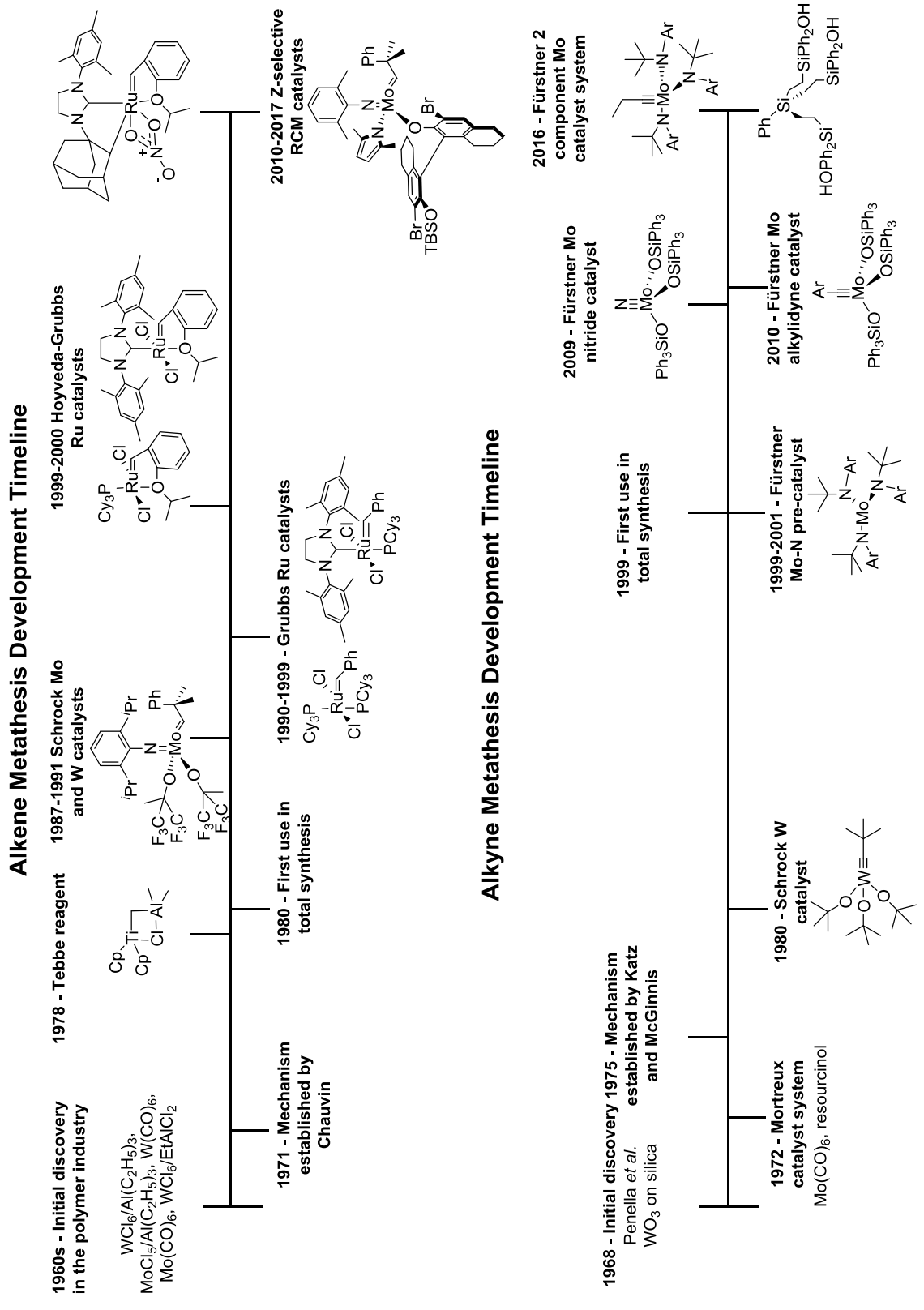


Figure 1.10. Comparative development timelines for the fields of alkene[74–79] and alkyne[49,64–67,80,81] metathesis.

1.4.2 RCAM in the Synthesis of (*Z*)-alkenes

In the absence of (*Z*)-selective RCM catalysts, RCAM followed by a selective *syn*-reduction was first used in the late 1990s and early 2000s in the synthesis of ambrettolide (**1.204**) and civetone (**1.205**), prostaglandin E2 (**1.206**) and the turrianes (**1.207**) which are efficient DNA-cleaving agents (Figure 1.11).[82–85] These syntheses utilised either the Mortreux *in-situ* system, Schrock's tungsten alkylidyne catalyst **1.149** or the Cummins-Fürstner-Moore system of **1.197**/DCM.

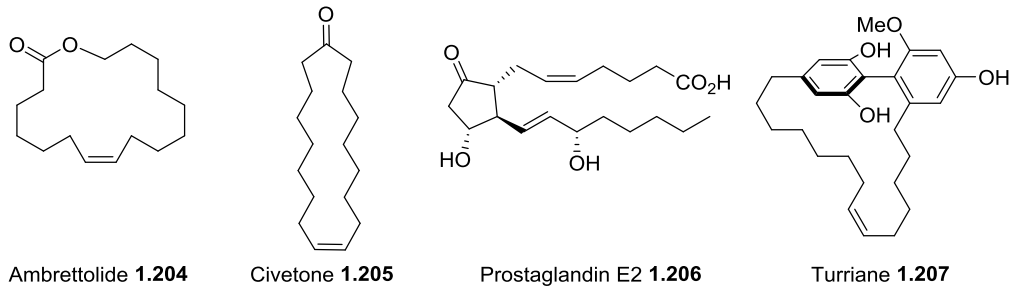
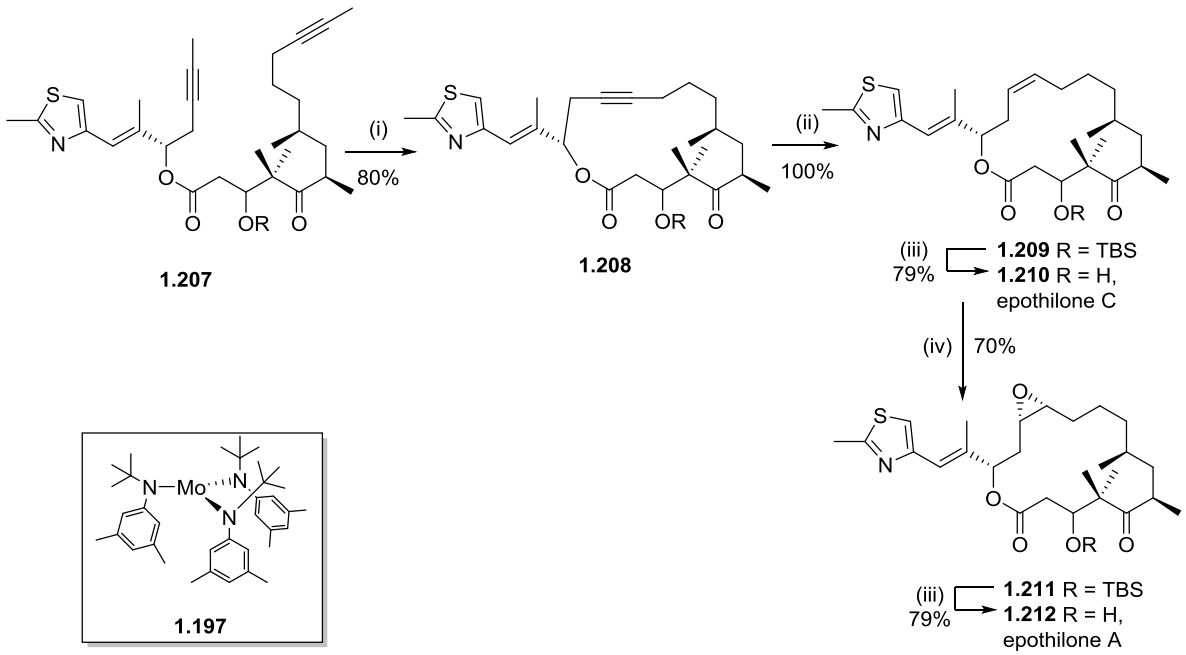


Figure 1.11. Initial use of RCAM in total synthesis.

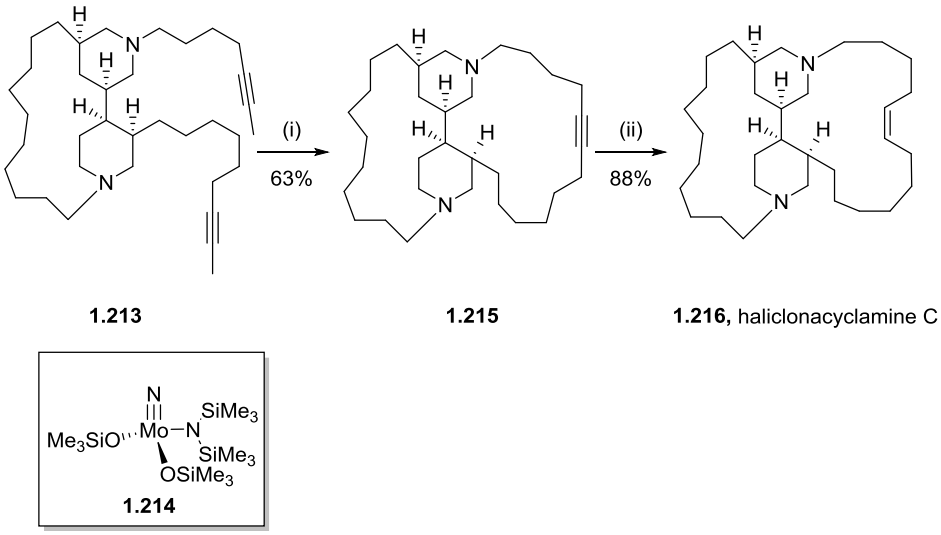
Soon after this, the RCAM-*syn*-reduction methodology was applied to more complex molecules. The synthesis of epothilones A and C, which possess potent anticancer activity, *via* RCM had been hindered by lack of stereocontrol over the newly formed alkene with an *Z*:*E* ratio of 1:2 to 1.7:1.[86] To counteract this, Fürstner *et al.* employed a RCAM utilising their recently developed pre-catalyst **1.197** to provide alkyne macrocycle **1.208** which was reduced using Lindlar conditions to give (Z)-alkene **1.209**.[86] This was then deprotected to provide epothilone C (**1.210**) or epoxidised and deprotected to furnish epothiolone A (**1.211**) (Scheme 1.22). This synthesis demonstrated the increased functional group tolerance of this trisamido precatalyst over the more traditional Schrock catalyst, as the thiazole ring of **1.207** was well tolerated.



Reagents and conditions: (i) **1.197** (0.1 equiv.), PhMe/DCM, 80 ^{o}C; (ii) Lindlar catalyst, quinoline, H_2 (1 atm), DCM; (iii) aq. HF, Et_2O/MeCN; (iv) dimethyldioxirane

Scheme 1.22. Total synthesis of epothilones A and C *via* RCAM by Fürstner *et al.*

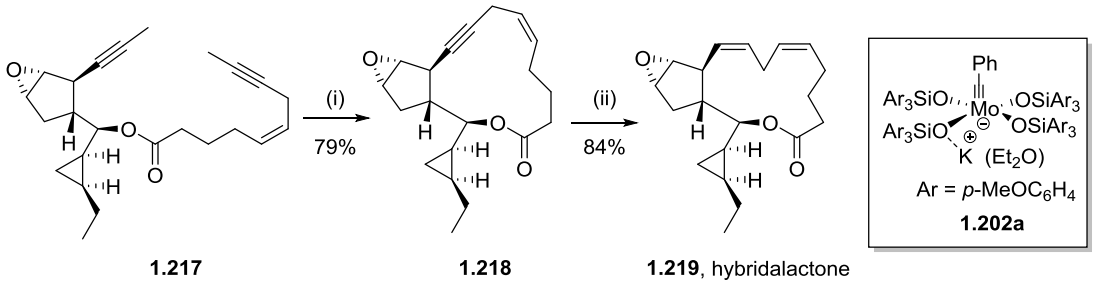
Further advances in catalyst development, moving toward Mo-nitride and Mo-alkylidyne based systems, has enabled the synthesis of molecules possessing highly sensitive functional groups. Haliclonacyclamine C (**1.216**), a tetracyclic alkaloid with cytotoxic, antibiotic and antifungal properties, posed a complex synthetic challenge due to its four stereocentres and (*Z*)-alkene moiety in the alkyl side chain. An attempt to install this group *via* RCM using Grubbs I, by Smith *et al.*[87] showed significant bias towards the (*E*)-isomer (6:1). However, a switch to a RCAM based strategy utilising a Mo-nitride catalyst, formed *in-situ* from **1.214** and Ph_3SiOH, furnished haliclonacyclamine C after Lindlar reduction (Scheme 1.23).[87] Although a variety of catalyst systems and conditions were trialled, this *in-situ* method was the sole success.



Reagents and conditions: (i) **1.214** (0.5 equiv.), Ph_3SiOH (1.5 equiv.), PhMe, 130 °C; (ii) Lindlar catalyst, H_2 (1 atm), EtOAc, RT

Scheme 1.23. Total synthesis of haliclonacyclamine C by Smith *et al.*

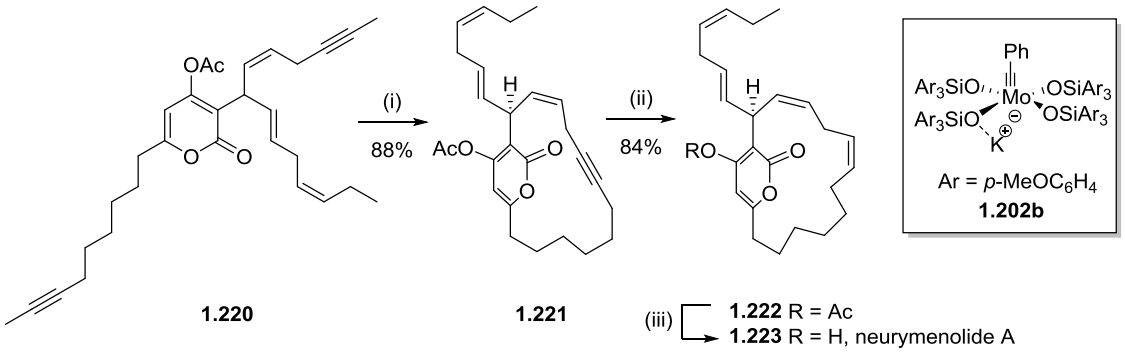
Even after the introduction of a (*Z*)-selective RCM catalysts,[73–78] alkyne metathesis could still provide access to molecules that remain inaccessible by RCM. Hybridalactone (**1.219**), a marine oxylipin, contains 2 alkene groups and any attempt to form the ring *via* RCM would simply result in a ring contraction due to the presence of the additional alkene moiety. However, this opened the door for alkyne metathesis as this methodology leaves alkene groups untouched. Hybridalactone also contains both a highly acid sensitive ester moiety as well as an epoxide that had been found to be particularly susceptible to ring opening, even from weak nucleophiles. These challenges were overcome by the use of a derivative of Fürstner's newly developed Mo-alkylidyne catalyst, **1.202a**.[88] In this case, the ligands themselves proved not sufficiently nucleophilic enough to open the delicate epoxide ring, removing this as an issue. The metathesis was accomplished using 15 mol% of the catalyst, yielding alkyne macrocycle **1.218** in 79% yield which was subsequently reduced to provide hybridalactone (Scheme 1.211).



Reagents and conditons: (i) **1.202a** (0.15 equiv.), 5 Å MS, PhMe, 70 °C; (ii) $Ni(OAc)_2 \cdot 4H_2O$, $NaBH_4$, ethylenediamine, H_2 (1 atm), EtOH

Scheme 1.24. Total synthesis of hybridalactone using Mo-alkylidyne catalyst **1.202a**.

Another related adduct of the primary Mo-alkylidyne based system was also used in the total synthesis of neurymenolide A (**1.223**), a marine natural product with activity against MRSA and VREF. It possesses three (*Z*)-configured olefins and one (*E*)-alkene rendering it, again, unsuitable for synthesis by RCM. The arrangement of these double bonds also presents an additional challenge; the 1,4-diene array can rapidly isomerise and two of the alkenes can also migrate to be conjugated with the pyrone ring. Therefore, mild reaction conditions were required to keep this delicate motif intact and the highly active catalyst **1.202b** was able to accomplish the RCAM at ambient temperature (Scheme 1.25). Neurymenolide A was found to be very unstable and rapidly degraded on contact with both silica and alumina so characterisation and comparison to natural material was conducted using known acetate derivative **1.222**.[89]



Reagents and conditions: (i) **1.202b** (0.05 equiv.), 5 Å MS, PhMe, RT; (ii) Lindlar catalyst, quinoline, H_2 (1 atm), EtOAc/hex-1-ene; (iii) K_2CO_3, MeOH, 0 ^oC

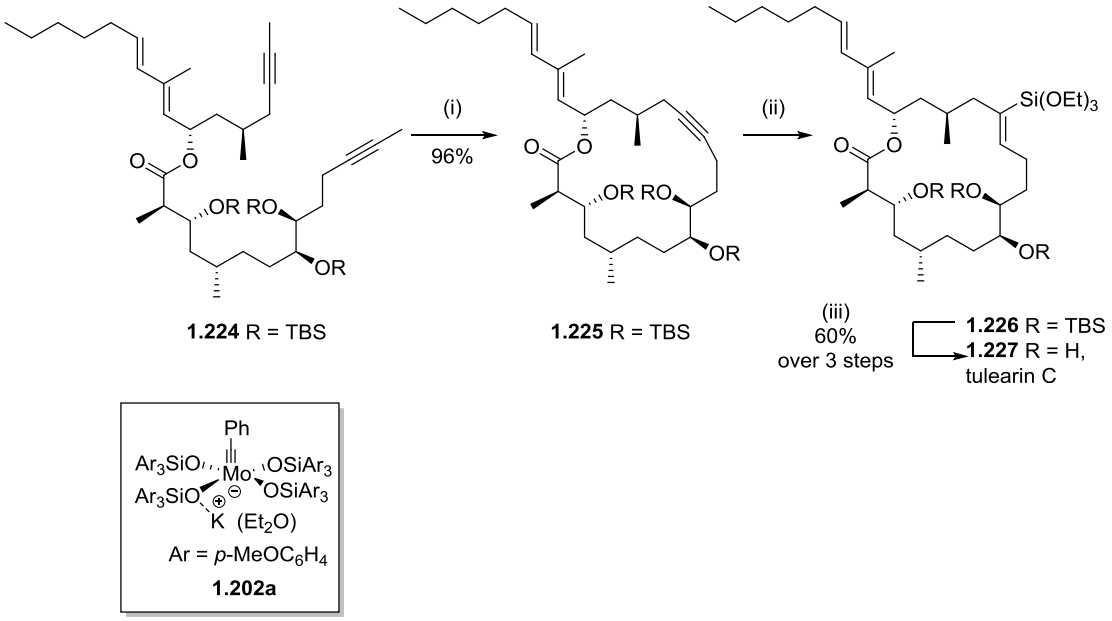
Scheme 1.25. Total synthesis of neurymenolide A by Fürstner *et al*.

1.4.3 RCAM in the Synthesis of (*E*)-alkenes

In contrast to Lindlar reduction, traditional methods for *trans*-reduction of alkynes, such as the Birch reduction, are harsh and thus have a narrow application in total synthesis due to the variety of functionalities usually present in these molecules. However, two-step procedures such as trans-hydrosilylation,[90,91] hydroboration[92] or hydrostannation[93] followed by protodemetalation would provide the (*E*)-alkene under much milder conditions. Therefore, in combination with RCAM these methods provide can an alternative to RCM in the formation of macrocyclic (*E*)-alkenes.

This strategy was exemplified by the Fürstner group in their synthesis of tulearin C (**1.227**), a member of a small macrolide family that have shown strong anti-cancer activity. A previous synthesis of the related tulearin A by RCM by Mandel *et al.* led to a disappointing *E*:*Z* ratio of 1.9:1 thus, opening the door to an alternative strategy.[94] Macrocyclisation was achieved using 4

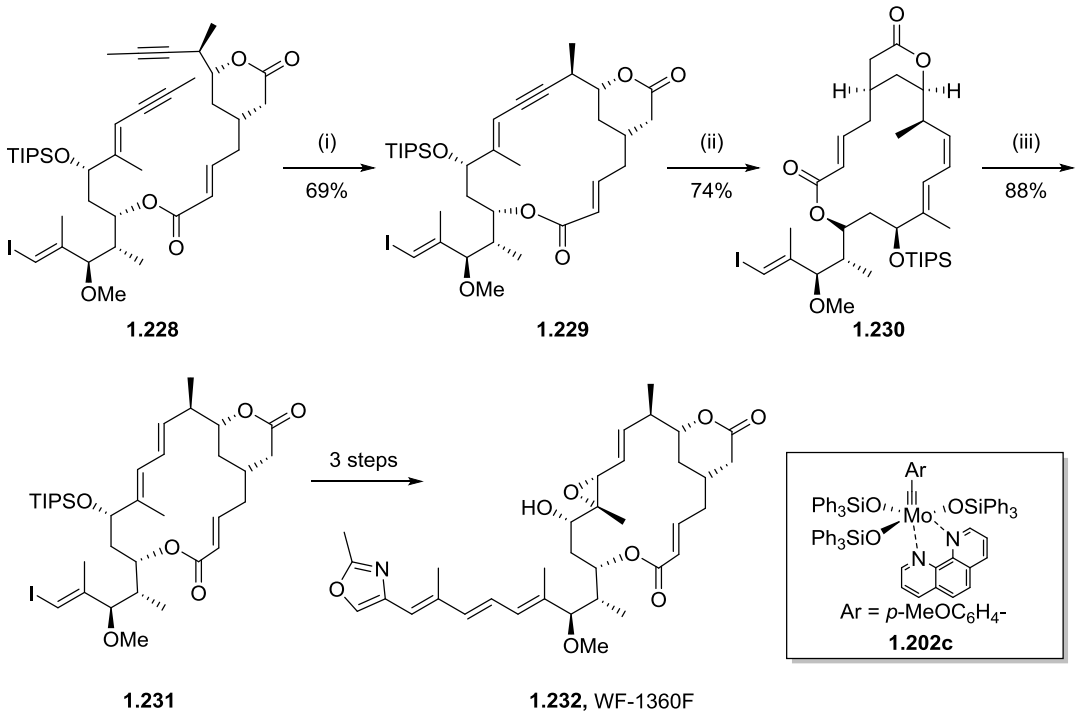
mol% of Mo-alkylidyne catalyst **1.202a** in an excellent 96% yield.[95] Subsequent trans-hydrosilylation followed by immediate proto-desilylation and deprotection furnished tulearin C **1.227** (Scheme 1.26).



Reagents and conditions: (i) **1.202a** (0.04 equiv.), 5 Å MS, PhMe, 50 °C; (ii) $(EtO)_3SiH$ (8 equiv.), $[Cp^*Ru(MeCN)_3]PF_6$ (0.1 equiv.) 0 °C; (iii) a) AgF, THF/MeOH/H_2O, RT b) TBAF, THF, RT

Scheme 1.26. Total synthesis of tulearin C by Fürstner *et al*.

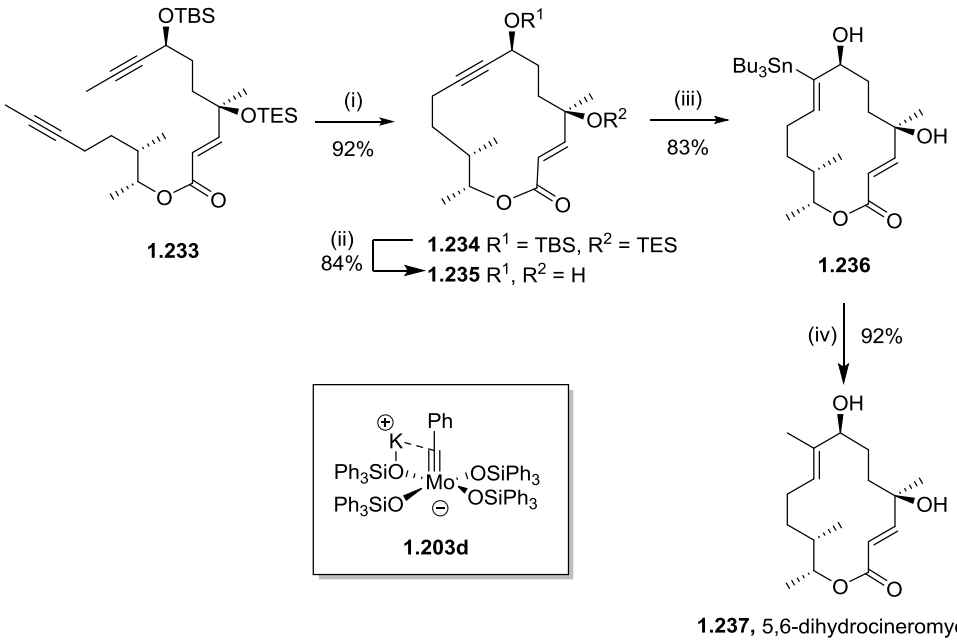
In their synthesis of WF-1360F (**1.232**), a member of the rhizoxin family, Neuhaus *et al.* utilised an alternative method for the conversion of an alkyne into an (*E*)-alkene (Scheme 1.27). The initial RCAM was performed using the air stable phenanthroline derivative of Mo-alkylidyne catalyst **1.203c** and, although it required high temperatures, the macrocycle was formed in 69% yield.[96] Attempts to convert the alkyne to the (*E*)-alkene through the use of conventional hydrometalation methods either resulted in failure or in the case of hydrosilylation, a very low yield for the ensuing protodesilylation step. Ultimately, alkyne **1.229** had to be first converted into (*Z*)-alkene **1.230** and then a radical isomerisation achieved by AIBN/PhSH provided the (*E*)-alkene in a ratio of 20:1 with the Z-isomer.



Reagents and conditions: (i) **1.203c** (0.1 equiv.), $MnCl_2$ (0.1 equiv.), 5 Å MS, PhMe, 125 ^{o}C; (ii) a) $[Co_2(CO)_8]$ (2 equiv.), DCM, RT, b) 1-ethylpiperidine hypophosphite (10 equiv.), reflux, C_6H_6; (iii) AIBN, PhSH, C_6H_6, reflux

Scheme 1.27. Synthesis of WF-1360F by Neuhaus *et al.*

RCAM has also been used to prepare trisubstituted (*E*)-alkenes *via* modification of the resultant alkyne moiety. In their synthesis of 5,6-dihydrocinemycin B (**1.237**), a polyketide natural product related to antibiotic albocycline, the Fürstner group utilised a proximal hydroxyl group to direct a *trans*-hydrostannation and a subsequent methyl-Stille coupling to accomplish this transformation (Scheme 1.28).[97] The resultant 2-methyl-but-2-en-1-ol moiety is common throughout the polyketide natural product family thus promoting further use of this methodology in total synthesis.



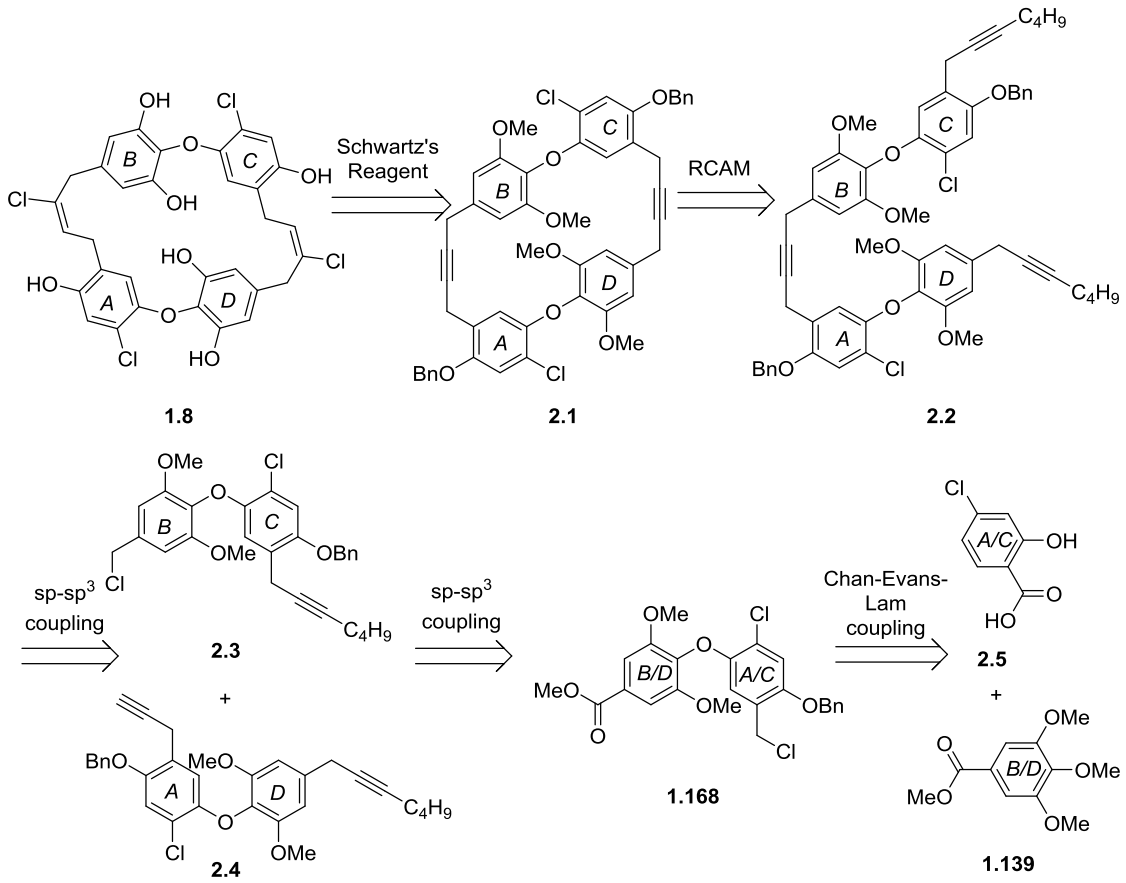
Reagents and conditions: (i) **1.203d** (0.1 equiv.), 5 Å MS, PhMe, RT; (ii) HF.Py, THF, Py; (iii) Bu_3SnH (1.15 equiv.), $[Cp^*RuCl_2]_n$ (0.05 equiv.), DCM; (iv) $[Pd(PPh_3)_4]$ (0.05 equiv.), $[Ph_2PO_2][NBu_4]$ (1.1 equiv.), CuTC (1.1 equiv.), MeI (1.5 equiv.), DMF

Scheme 1.28. Synthesis of 5,6-dihydrocineromycin B.

Chapter 2 Results and Discussion: Chrysophaentin F

2.1 Retrosynthesis

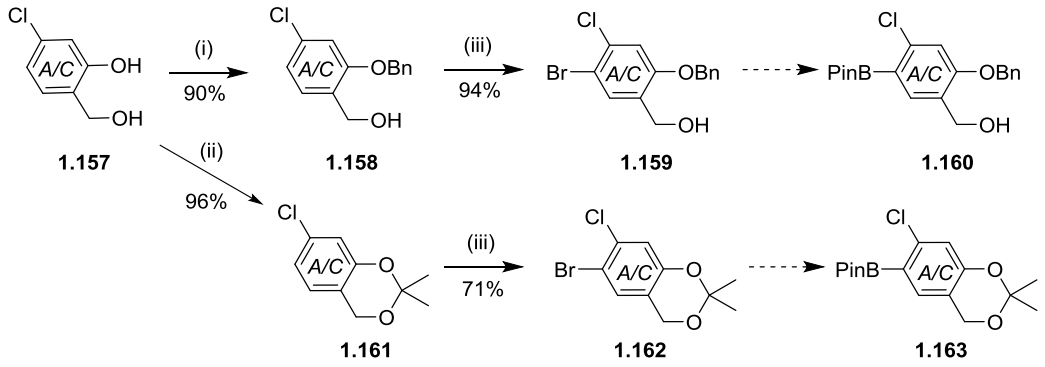
Our plan was to achieve the total synthesis of chrysophaentin F by combining the previously developed strategy towards an unchlorinated analogue (**1.133**) and initial studies into the installation of the (*E*)-vinyl chlorides of the natural product (Section 1.3.4). Thus, the retrosynthetic analysis of chrysophaentin F, as detailed in Scheme 2.1, envisages installation of the (*E*)-vinyl chlorides *via* the hydrochlorination of diyne **2.1** mediated by Schwartz's reagent. The parent diyne itself would be prepared by ring closing alkyne metathesis from complex triyne precursor **2.2**. The formation of this intermediate would be achieved through a series of metal catalysed sp-sp^3 couplings which would install crucial alkyne functionalities. Both fragments for the synthesis of **2.2** could be prepared from benzyl chloride **1.168** due to the symmetry present in the natural product. This key intermediate would be prepared by a Chan-Evans-Lam coupling between a boronic ester derived from salicylic acid **2.5** and a phenol derived from **1.139**.



Scheme 2.1. Retrosynthetic analysis of chrysophaentin F.

2.2 Optimisation of *A/C* Ring Synthesis

The starting point for our investigation was to optimise the formation of the required boronic ester **1.160** for the Chan-Evans-Lam coupling. Initial efforts to prepare both this compound and the precursor had proved disappointing relative to that of its unchlorinated analogue, with a poor 54% yield for the bromination step (**1.158** to **1.159**) and 31% for the borylation (**1.159** to **1.160**) respectively. As we were unsure whether the free benzylic alcohol played a role in our difficulties, acetal protected substrates **1.161** and **1.162** were also synthesised and examined. Firstly, alternative bromination conditions were sought and pleasingly, by switching the solvent and reaction temperature from MeCN at 60 °C to DMF at RT, **1.159** and **1.162** were isolated in 71% and 94% yields respectively (Scheme 2.2). For substrate **1.158**, it proved crucial that only 1 equivalent of NBS was used as amounts greater than this resulted in a small amount of oxidation of the benzyl alcohol to the corresponding aldehyde.



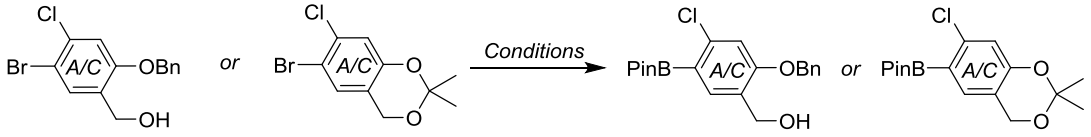
Reagents and conditions : (i) BnBr, K_2CO_3, acetone, 45 °C; (ii) 2,2-dimethoxypropane, *p*-TSA, Na_2SO_4, acetone, 40 °C; (iii) NBS, DMF, RT

Scheme 2.2. Preparation of aryl bromides **1.159** and **1.162**.

Next, attention turned to the subsequent borylation reaction; **1.159/1.162** to **1.160/1.163**. Firstly, the original Miyuara borylation methodology was pursued with the reaction parameters being examined. Initially the catalyst loading was studied and an increase from 10 to 20 mol% led to an increase in yield of 31% to 55% (Table 2.1, entries 2 and 3). However, the reaction appeared to stall with reaction times > 48 h showing no further improvement. Next, the base was switched from KOAc to KOPh, however this led to no enhancement in yield (Table 2.1, entry 4). As an increase in reaction temperature would not be possible using the original solvent of THF without using a sealed system, alternative solvents were tested, both at the initial reaction temperature of 65 °C and at 80 °C. Although, the use of both 1,4-dioxane and DMSO led to negligible improvement in yield at 65 °C, increasing the temperature to 80 °C led to a significant increase in yield with boronic ester **1.160** being isolated in 78% yield in 1,4-dioxane and 67%

yield when performed in DMSO (Table 2.1, entries 5-8). The reaction was repeated using the original 10 mol% catalyst loading and provided **1.160** in comparable yield (Table 2.1, entry 9). The reaction was also performed on the acetal protected substrate **1.162** with similar success (Table 2.1, entry 10).

Table 2.1. Optimisation of synthesis of boronic esters **1.160** and **1.163**.



1.159 **1.162** **1.160** **1.163**

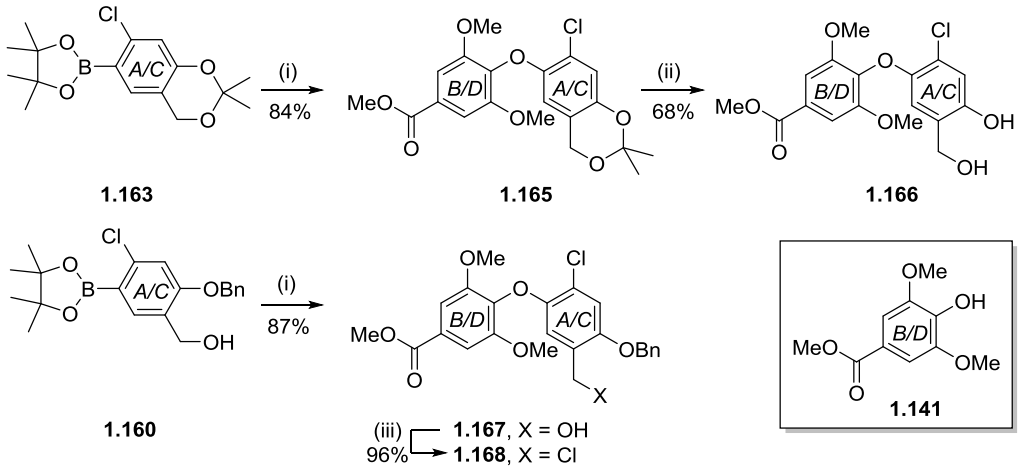
Entry	Substrate	Reaction Conditions	Yield
1	**1.162**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (10 mol%), KOAc (2.8 equiv.), THF, 65 °C	23%
2	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (10 mol%), KOAc (2.8 equiv.), THF, 65 °C	31%
3	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (20 mol%), KOAc (2.8 equiv.), THF, 65 °C	55%
4	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (20 mol%), KOPh (2.8 equiv.), THF, 65 °C	52%
5	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (20 mol%), KOAc (2.8 equiv.), 1,4-dioxane, 65 °C	57%
6	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (20 mol%), KOAc (2.8 equiv.), DMSO, 65 °C	54%
7	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (20 mol%), KOAc (2.8 equiv.), 1,4-dioxane, 80 °C	78%
8	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (20 mol%), KOAc (2.8 equiv.), DMSO, 80 °C	67%
9	**1.159**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (10 mol%), KOAc (2.8 equiv.), 1,4-dioxane, 80 °C	84%
10	**1.162**	B_2Pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (10 mol%), KOAc (2.8 equiv.), 1,4-dioxane, 80 °C	71%

11	**1.162**	(i) ^{n}BuLi (2 equiv.), Et_2O/THF, -78 °C, (ii) B_2Pin_2 (1.5 equiv.), RT	70%
12	**1.159**	(i) ^{n}BuLi (2 equiv.), Et_2O/THF, -78 °C, (ii) B_2Pin_2 (1.5 equiv.), RT	79%

Concurrently, an alternative halogen-lithium exchange based strategy was investigated where the aryllithium intermediate was quenched by bis(pinacolato)diboron to provide the desired boronic esters. As halogen-lithium exchange of aryl bromides is generally faster than deprotonation of alcohols, it was thought that the free benzylic alcohol of substrate **1.159** would not pose too much of a problem. Also, as halogen lithium exchange proceeds in the order I>Br>>Cl, it was thought that the Ar-Cl bond would also prove non-problematic provided a large excess of ^{n}BuLi was not used. Pleasingly, boronic esters **1.160** and **1.161** were isolated in 70% and 79% yields respectively using this methodology (Table 2.1, entries 11 and 12). However, this proved difficult to replicate upon scale-up, leading to significant amounts of protonated material which could not be separated from the desired boronic ester. Thus, the Suzuki-Miyaura methodology was subsequently used exclusively.

2.3 Preparation of *AD* and *BC* Fragments

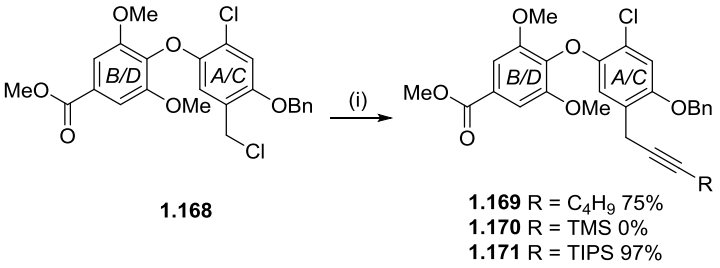
Having established improved syntheses of boronic esters **1.160** and **1.161** attention turned to their coupling with phenol **1.141**. Pleasingly, when exposed to the Chan-Evans-Lam conditions previously developed, diaryl ethers **1.165** and **1.167** were isolated in 84% and 87% yield respectively (Scheme 2.3). These conditions employed 7.5 equivalents of pyridine and while Chan-Evans-Lam couplings do generally require increased equivalents of base, it was thought that this could be reduced somewhat. Happily, reducing the amount of pyridine to the more typical 5 equivalents led to the desired products in comparable yield. As the deprotection of **1.165** proved problematic, with the initial conditions trialled giving diol **1.166** in 68% yield, it was decided to put this approach on hold in favour of the analogous strategy employing the benzyl protecting group (*i.e.* **1.160**).



Reagents and conditions: (i) **1.141** (1 equiv.), $Cu(OTf)_2$ (20 mol%), Py (5 equiv.), O_2, 4 Å MS, EtOH, 65 °C; (ii) AcOH, H_2O, 70 °C, (iii) NCS, PPh_3, THF, 0 °C-RT

Scheme 2.3. Chan-Evans-Lam coupling to provide diaryl ethers **1.165** and **1.167**.

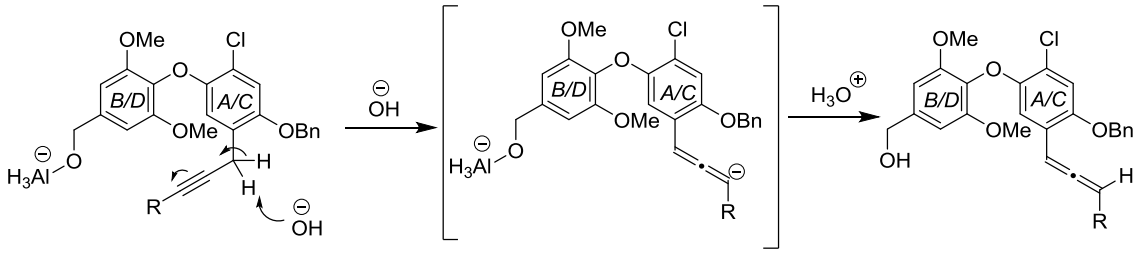
With benzyl chloride **1.168** in hand, this common intermediate could then be transformed into the two required *BC* and *AD* fragments **2.3** and **2.4** respectively. Firstly, **1.168** was coupled with hex-1-yne and TMS-acetylene (Scheme 2.4). Unfortunately, while the reaction with hex-1-yne proceeded without incident, with the silylalkyne it either gave no reaction or negligible amounts of product. The reaction was repeated with increased catalyst loading, increased number of equivalents of the TMS-alkyne and also in a sealed tube to prevent its potential loss by evaporation but to no avail. The solvent was also changed to either THF or 1,4-dioxane but these proved equally unrewarding. However, switching the silyl protecting group from TMS to the more stable TIPS group proved fruitful with alkyne **1.171** isolated in 97% yield. This striking difference in reactivity remains unclear, but it cannot be due to volatility as both TMS- and TIPS-acetylene have a boiling point of ca. 50 °C at atmospheric pressure. Also, as a coupling between TMS-acetylene and a benzyl chloride had been accomplished both in the original paper[46] and when using an unchlorinated analogue of **1.168**, it is not due to the instability of TMS-protected alkynes under the reaction conditions.



Reagents and conditions: (i) ≡—R (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C

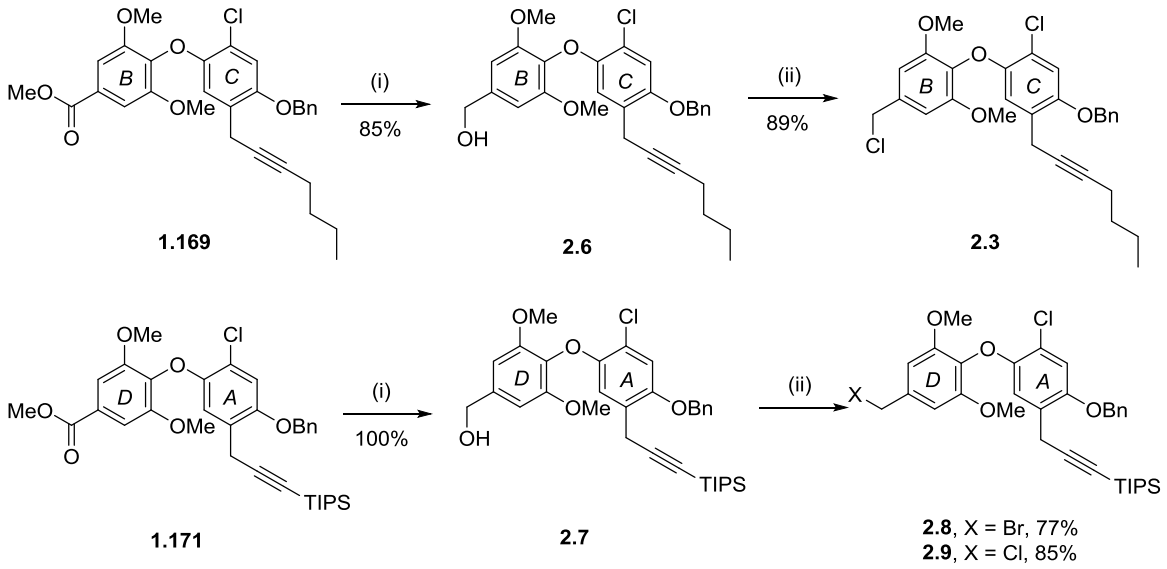
Scheme 2.4. Heck alkynylation of benzyl chloride **1.168** with TMS-acetylene, TIPS-acetylene and hex-1-yne.

The ester groups of **1.169** and **1.171** were then reduced with either $LiAlH_4$ or DIBAL to provide alcohols **2.6** and **2.7** in quantitative and 85% yield respectively. While the use of $LiAlH_4$ generally resulted in higher yields, it also occasionally led to isomerisation of the alkyne moieties to their allenic forms. This transformation was more prevalent for the ^{n}Bu capped alkyne **1.169** than for the silyl protected substrate. While it can be rationalised that the allene isomer is more stable than the alkyne due to the increased conjugation with the highly electron rich aromatic ring, it is not thought that $LiAlH_4$ itself is a strong enough base to remove the benzylic proton. Instead, we imagine that LiOH, formed from the reaction between $LiAlH_4$ and any trace amounts of water present in the reaction mixture, is the likely culprit as both NaOH and KOH been found to induce this isomerisation previously (Scheme 2.5).[98,99]



Scheme 2.5. Proposed mechanism for the observed isomerisation of alkynes **1.169** and **1.171** with $LiAlH_4$.

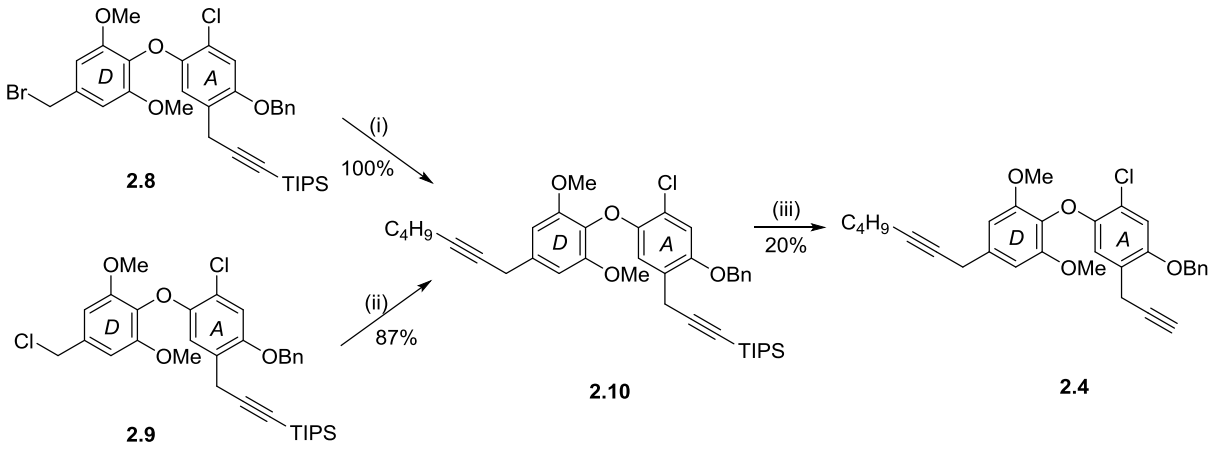
Alcohols **2.6** and **2.7** were then converted into either a benzyl chloride or bromide though the use of PPh_3 and NCS or NBS (Scheme 2.6).



Reagents and conditions (i) $LiAlH_4$ (1.1 equiv.), THF, 0 ^oC then RT; (ii) NBS or NCS, PPh_3, THF, 0 ^oC then RT

Scheme 2.6. Preparation of benzyl bromide **2.8** and chlorides **2.9** and **2.3**.

We then sought to introduce the second alkyne group though a metal catalysed sp-sp^3 coupling. In work on the unchlorinated analogue, Heck alkynylation of a benzyl chloride analogous to **2.9** and hex-1-yne had resulted in only the allenic product being isolated when conducted in MeCN. This led to the use of an alternative Ni-catalysed process.[47] However, as noted in Larsen's original Heck alkynylation paper,[46] the allene product can be favoured by increases in temperature, or the amount of base and also by solvent effects. It was found that the use of either THF, 1,4-dioxane or toluene was crucial to eliminating allene formation. Armed with this information, we decided to see if it was possible to obtain the alkyne product using this methodology as well as testing the Ni-catalysed organoaluminium coupling. To our surprise, Heck alkynylation of **2.9** and hex-1-yne in MeCN, 1,4-dioxane and THF all led to the alkyne isomer with MeCN providing the highest yield (87%). This result is perplexing as the additional chlorine substituent on the *A*/*C* ring should be too remote to induce a change in reactivity. The alternative Ni-catalysed process also proved successful with diyne **2.10** formed in quantitative yield (Scheme 2.7).



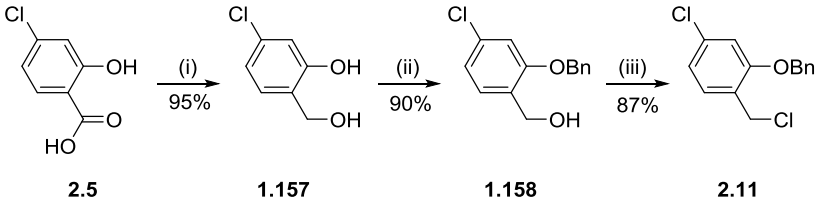
Reagents and conditions: (i) a) hex-1-yne (2 equiv.), ^{n}BuLi (2 equiv.), then Et_2AlCl (2 equiv.), Et_2O, 0 ^{o}C-RT, b) **2.8**, $Ni(PPh_3)_2Cl_2$ (0.06 equiv.), RT; (ii) hex-1-yne (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 ^{o}C; (iii) AgF, MeCN, RT

Scheme 2.7. Preparation of *BC* fragment **2.3.**

Subsequent deprotection of the TIPS group of **2.10** proved challenging; the use of TBAF, TBAF in AcOH and AgOTf all only returned starting material. A procedure developed by Kim *et al.*[100] and later expanded upon by Escamilla and co-workers,[101] using AgF in MeOH or MeCN at RT was then attempted and, although partially successful, only gave terminal alkyne **2.4** in 20% yield (when conducted in MeCN). The remaining mass balance was unaccounted for with no evidence of alkyne-allene isomerisation detected nor any recognisable fragments of either the product or starting material isolated. While the authors state that the reaction is more efficient when conducted in MeOH rather than MeCN or mixtures of the two solvents, poor solubility of **2.10** in MeOH prevented this from being investigated.

2.3.1 Alternative Protection Strategy

With the TIPS protecting group proving stubborn to remove, our attention turned to alternatively protected alkynes. Since trimethylsilyl protected alkynes had proven untenable in the coupling step, *vide supra*, we decided to examine both triethylsilyl and *tert*-butyldimethylsilyl protected alkynes. Due to the number of synthetic steps involved in the preparation of TES and TBS analogues of **2.10**, we decided to initially investigate the viability of these protecting groups on model substrates **2.12** and **2.13** which could be prepared from model benzyl chloride **2.11**. This was readily synthesised from salicylic acid **2.5** in good yield over three steps (Scheme 2.8).

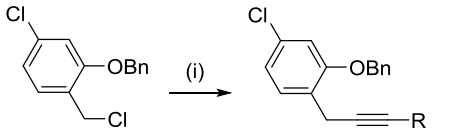


2.5 **1.157** **1.158** **2.11**

Reagents and conditions: (i) $LiAlH_4$ (1.5 equiv.), THF, 0-40 ^oC; (ii) BnBr, K_2CO_3, acetone, 40 ^oC; (iii) NCS, PPh_3, THF, 0 ^oC-RT

Scheme 2.8. Synthesis of model benzyl chloride **2.11.**

Next we attempted to couple either TES- or TBS-acetylene to benzyl chloride **2.11**. Surprisingly, the Heck alkynylation procedure which had failed to yield the TMS-protected analogue was successful in providing TES and TBS alkynes **2.12** and **2.13**, both in 95% yield (Scheme 2.9).



2.11

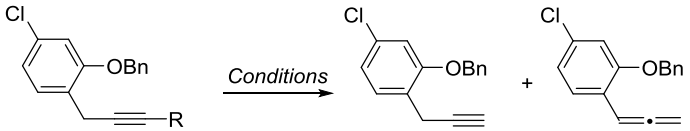
2.12 R = TES 95%
2.13 R = TBS 95%

Reagents and conditions: (i) ≡—R (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 ^oC

Scheme 2.9. Heck alkynylation of **2.12** and TES or TBS-acetylene.

In order to confirm if this success was down to the change of substrate, the coupling of benzyl chloride **2.11** and TMS-acetylene was attempted and returned only recovered starting material. The reasons for this dramatic difference in reactivity between the three differently protected silyl acetylenes is remains unclear. However, with alkynes **2.12** and **2.13** in hand, a range of deprotection conditions were screened as detailed in Table 2.2.

Table 2.2. Conditions screened for the deprotection of TES and TBS-alkynes **2.12** and **2.13.**



2.12 R = TES
2.13 R = TBS

2.14 **2.15**

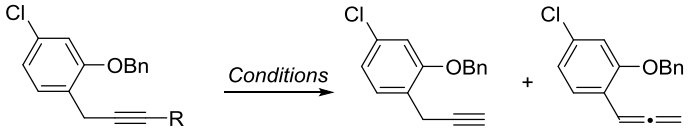
Entry	Substrate	Reaction Conditions	Result
1	**2.12**	TBAF (1.1 equiv.), THF, 0 °C	**2.15**
2	**2.13**	TBAF (1.1 equiv.), THF, 0 °C	**2.14:2.15** (1:1)
3	**2.13**	TBAF (1.1 equiv.), DCM, 0 °C	**2.15**
4	**2.12**	CsF (4 equiv.), DMF, MeOH, RT	**2.14:2.15** (1:1)
5	**2.13**	CsF (4 equiv.), DMF, MeOH, RT	**2.13**
6	**2.13**	CsF (8 equiv.), AcOH, MeOH, RT	**2.13**
7	**2.13**	AgF (1.5 equiv.), MeCN	**2.13**
8	**2.12**	$AgNO_3$ (0.5 equiv.), DCM, MeOH, H_2O, RT	**2.12**
9	**2.12**	AgOTf (0.5 equiv.), DCM, MeOH, H_2O, RT	**2.12**
10	**2.13**	$AgNO_3$ (0.5 equiv.), DCM, MeOH, H_2O, RT	**2.13**
11	**2.13**	AgOTf (0.5 equiv.), DCM, MeOH, H_2O, RT	**2.13**

Unfortunately, all of the conditions screened failed in cleanly providing terminal alkyne **2.14**. The majority of the basic conditions employed (Table 2.2, entries 1-7) instead led to the formation of allene **2.15** as a result of isomerisation of terminal alkyne **2.14**. The propensity for the isomerisation of benzylic alkynes had been observed in prior work on this project as well as by others.[99,102–104] Indeed, it has been observed under various other conditions such as with NaOH,[98] KOH,[99] and K_2CO_3 in MeOH.[105] It is, again, assumed that the allene is the most stable

product due to conjugation with the electron rich aromatic ring. Attempts to use milder reaction conditions, such as catalytic silver salts with less basic counterions, sadly returned only starting material (Table 2.2, entries 8-11).[48,100,101]

For compounds which have been found to display this tendency to isomerise, the use of acetic acid to temper the basicity of the fluoride anion of TBAF has proved effective. Unfortunately, a 1:1 ratio of AcOH and TBAF resulted only in return of the starting material for both substrates (Table 2.3). This reaction was further investigated in order to determine the optimal ratio of AcOH and TBAF required to keep the fluoride ion sufficiently nucleophilic to attack the silicon atom, but not sufficiently basic to induce isomerisation. However, this proved to be more exacting than initially anticipated, with TBAF:AcOH ratios of 1:0.1 to 1:0.6 leading to exclusive allene formation and 1:0.7 to 1:0.9 simply returning starting material. It was concluded that a reaction would at best be capricious and was therefore unsuitable for this transformation, especially as it would be used at a late stage in the synthesis.

Table 2.3. Screening of ratios of AcOH and TBAF in the deprotection of **2.12** and **2.13.**



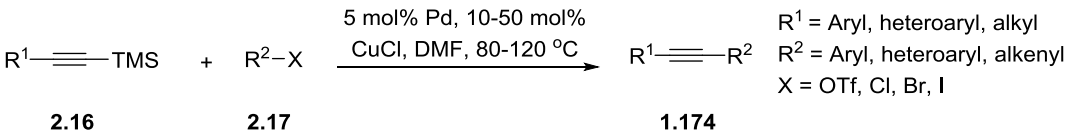
2.12 R = TES
2.13 R = TBS

2.14 **2.15**

Entry	Substrate	Reaction Conditions	Result
1	**2.12**	1:1 TBAF (4 equiv.), AcOH (4 equiv.), THF, RT	**2.12**
2	**2.13**	1:1 TBAF (4 equiv.), AcOH (4 equiv.), THF, RT	**2.13**
3	**2.12**	1:0.9 TBAF (4 equiv.), AcOH (3.6 equiv.), THF, RT	**2.12**
4	**2.12**	1:0.8 TBAF (4 equiv.), AcOH (3.2 equiv.), THF, RT	**2.12**
5	**2.12**	1:0.7 TBAF (4 equiv.), AcOH (2.8 equiv.), THF, RT	**2.12**

Entry	Substrate	Reaction Conditions	Result
6	**2.12**	1:0.6 TBAF (4 equiv.), AcOH (2.4 equiv.), THF, RT	**2.15**
7	**2.13**	1:0.5 TBAF (4 equiv.), AcOH (2 equiv.), THF, RT	**2.15**
8	**2.13**	1:0.4 TBAF (4 equiv.), AcOH (1.6 equiv.), THF, RT	**2.15**
9	**2.13**	1:0.3 TBAF (4 equiv.), AcOH (1.2 equiv.), THF, RT	**2.15**
10	**2.13**	1:0.2 TBAF (4 equiv.), AcOH (0.8 equiv.), THF, RT	**2.15**
11	**2.13**	1:0.1 TBAF (4 equiv.), AcOH (0.4 equiv.), THF, RT	**2.15**

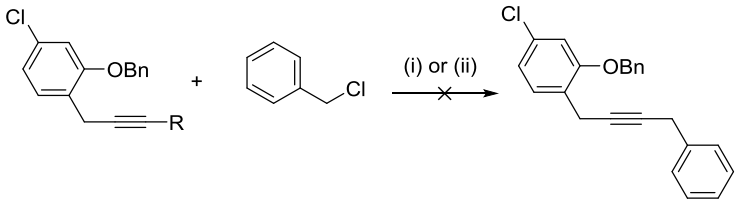
As the deprotection of both **2.12** and **2.13** failed to provide terminal alkyne **2.14**, we wondered if we could take advantage of the characteristics of the silyl group to act as a "super proton" and couple the protected alkyne directly. A so-called "sila-Sonogashira" coupling, first published by Nishihara *et al.* in 1997,[106] detailed the successful coupling of alkynylsilanes with aryl or alkenyl triflates (Scheme 2.10). Further work has since expanded the range of substrates to include aryl chlorides,[107,108] bromides[109] and iodides.[110]



Scheme 2.10. "sila-Sonogashira" reaction as described and developed by Nishihara *et al.*

Although there was no literature precedent for a "sila-Sonogashira" coupling with a silyl group larger than TMS or with a benzyl chloride substrate, the coupling of **2.12** or **2.13** with benzyl chloride was attempted using the mildest published conditions (Scheme 2.11). These were

chosen as Larsen *et al.* had described increased alkyne-allene isomerisation in Heck alkynylation reactions conducted above 80 °C.[46] However, there was only starting material remaining after 24 h. The reaction temperature was then raised to 100 °C but this also failed to generate the coupled product. This failure is likely due to the increased steric bulk around the silicon atom in comparison to trimethylsilyl thus, hindering the approach of the Cu species and preventing Si-Cu transmetallation. Larsen's Heck alkynylation procedure that had been utilised previously was also attempted but to no avail.



2.12 R = TES
2.13 R = TBS

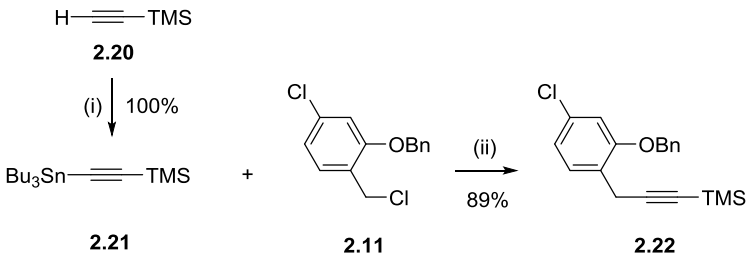
2.18

2.19

Reagents and conditions: (i) $Pd(PPh_3)_4$ (0.05 equiv.), CuCl (1 equiv.), DMF, 80 ^oC; (ii) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 ^oC

Scheme 2.11. Attempted "sila-Sonogashira" coupling of TES and TBS alkynes **2.13** and **2.14** with benzyl chloride.

As both the deprotection and "sila-Sonogashira" coupling of **2.12** and **2.13** were unsuccessful, we were forced to revisit the trimethylsilyl group as an option. This prompted us to question if it could it be coupled to benzyl chloride **2.11** and eventually to benzyl chloride **1.168**, using alternative methods. Firstly, a copper promoted coupling developed by Davies *et al.*[111] was trialled but this only returned starting material. Next, it was envisaged that a Stille coupling between an alkynylstannane and our benzyl chlorides might provide the desired TMS protected alkyne. Thus, the organostannane **2.21** was synthesised from TMS-acetylene and Bu_3SnCl and then coupled with benzyl chloride **2.11** (Scheme 2.12).[40]



2.21

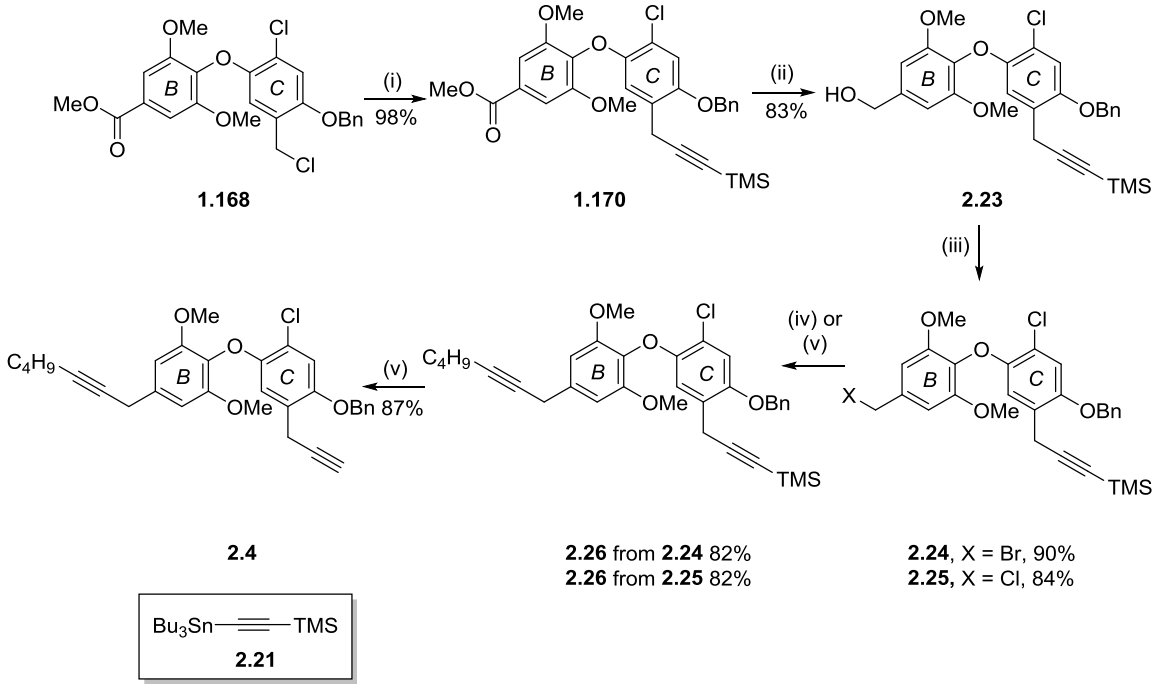
2.11

2.22

Reagents and conditons: (i) a) ^nBuLi (1 equiv.), THF, –78-0 ^oC, b) Bu_3SnCl (1 equiv.), THF, –78 ^oC-RT; (ii) **2.21** (1.5 equiv.), $Pd(dppf)Cl_2$.DCM (0.04 equiv.) KF (4 equiv.) 1,4-dioxane, 80 ^oC

Scheme 2.12. Preparation of **2.21** and subsequent Stille coupling with **2.11.**

Pleasingly, **2.22** was isolated in 89% yield, following purification using 9:1 silica:K_2CO_3 to remove the tin impurities.[112] Thus, the procedure was then applied to benzyl chloride **1.168** yielding **1.170** in an excellent 98% yield (Scheme 2.13). **1.170** was then reduced to benzyl alcohol **2.23** with either $LiAlH_4$ then halogenated to provide benzyl bromide **2.24** and benzyl chloride **2.25**. To introduce the second alkyne functionality, two procedures were trialled: a Heck alkynylation between benzyl chloride **2.25** and hex-1-yne and a Ni-catalysed coupling between benzyl bromide **2.24** and an organoaluminium species derived from hex-1-yne. Again, in stark contrast to the unchlorinated analogue (Section 1.3.3), Heck alkynylation of **2.25** with hex-1-yne in either MeCN or 1,4-dioxane gave alkyne isomer **2.26** in high yield with MeCN providing the better yield (82%). The alternative Ni-catalysed process also proved successful with **2.24** formed in identical 82% yield. Finally, removal of the TMS group was accomplished using either catalytic AgOTf as described by Orsini *et al.*[48] or with TBAF in acetic acid, successfully providing terminal alkyne **2.4** in 87% yield. Overall, this switch from a TIPS protecting group back to a TMS protecting group led to an increase in the overall yield of **2.4** from 15% to 52% for the five synthetic steps from benzyl chloride **1.168**.

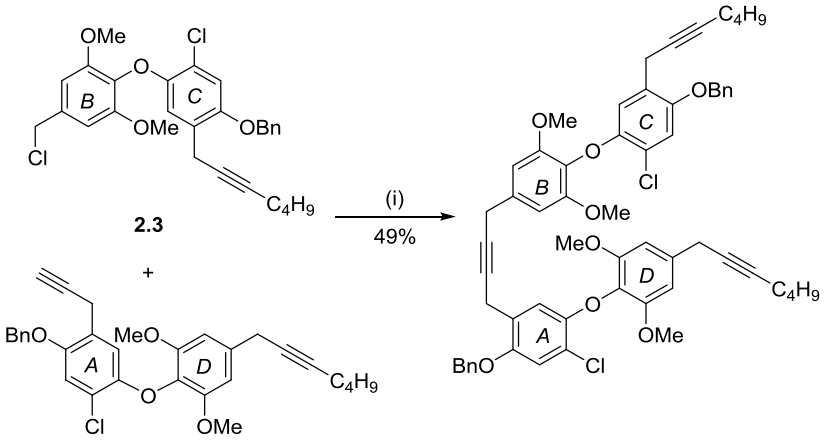


Reagents and conditions: (i) **2.21** (1.5 equiv.), $Pd(dppf)Cl_2$ (0.04 equiv.), KF (4 equiv.) 1,4-dioxane, 80 °C; (ii) $LiAlH_4$ (1.1 equiv.), THF, 0 °C-RT; (iii) NBS or NCS,PPh_3, THF, 0 °C-RT; (iv) a) hex-1-yne (2 equiv.), ^{n}BuLi (2 equiv.), then Et_2AlCl (2 equiv.), Et_2O, 0 °C-RT, b) **2.24**, $Ni(PPh_3)_2Cl_2$ (0.06 equiv.), RT; (v) **2.25**, hex-1-yne (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C; (vi) AgOTf, $MeOH/H_2O$/DCM, RT

Scheme 2.13. Improved synthesis of terminal alkyne **2.4** *via* TMS-protected alkynes **1.170, 2.23-2.26.**

2.4 Completion of Synthesis

With both the *AD* and *BC* fragments in hand, the synthetic endgame could be enacted. Using the Heck alkynylation conditions developed previously, alkyne **2.3** and benzyl chloride **2.4** were coupled to provide triyne **2.2** in a 33% yield (Scheme 2.14). It was initially thought that this low yield may be due to the propensity of the terminal alkyne moiety of **2.3** to isomerise to its allenic form. However, although the mass recovery of the terminal alkyne coupling partner was lower than expected, the material recovered showed no evidence of isomerisation, thus eliminating this as a possible decomposition pathway. However, the fact remained that a significant amount of alkyne **2.3** was consumed by other, unidentified decomposition pathways during the reaction. Therefore, the reaction time was reduced from 18 to 12 h which led to an increase in the isolated yield from 33 to 49% as well as the recovery of unconsumed benzyl chloride **2.3** and alkyne **2.4**.



Reagents and conditions: (i) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.) MeCN, 65 °C

Scheme 2.14. Synthesis of triyne **2.2** from benzyl chloride **2.3** and alkyne **2.4**.

Having successfully assembled our macrocyclisation precursor **2.2**, the ring closure step could be investigated, starting with the selection of a suitable alkyne metathesis catalyst. At the time, W based Schrock catalyst **1.149** as well as more recent Mo based catalysts **1.201a** and **1.202c** were all commercially available.

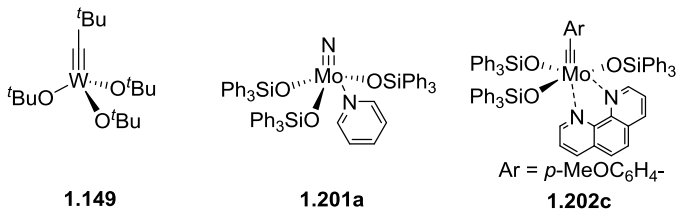
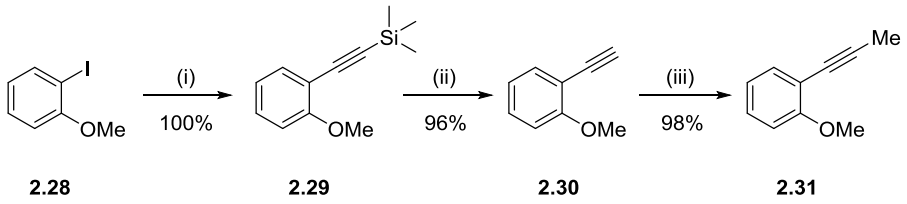


Figure 2.1. Commercially available alkyne metathesis catalysts

To determine their suitability, test alkyne metathesis reactions were conducted using both 1-phenyl-1-propyne **2.27** and (2-Methoxyphenyl)propyne **2.31** which are common test substrates for these reactions. (2-Methoxyphenyl)propyne **2.31** was prepared from iodoanisole **2.28** in 3 steps as illustrated in Scheme 2.15.

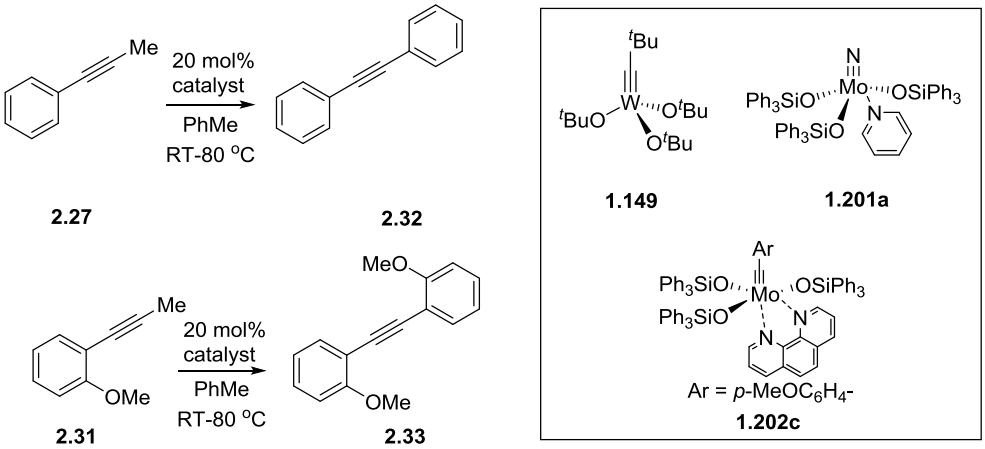


2.28 **2.29** **2.30** **2.31**

Reagents and conditions: (i) TMS-acetylene (1.2 equiv.), Et_3N, $Pd(PPh_3)_2Cl_2$ (0.02 equiv.), CuI (0.1 equiv.), 55 ^oC; (ii) KOH, MeOH, RT; (iii) a) ^nBuLi (1.2 equiv.) THF, -78 ^oC, b) MeI (2 equiv.), –78 ^oC-RT

Scheme 2.15. Synthesis of (2-Methoxyphenyl)propyne **2.31**.

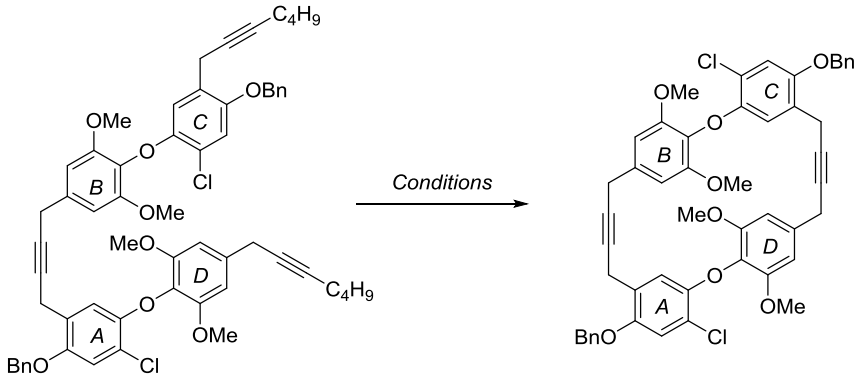
Pleasingly, all three catalysts proved competent with product alkynes **2.32** and **2.33** detected by LC-MS or GC-MS and confirmed by ^1H NMR.



Scheme 2.16. Metathesis of 1-phenyl-1-propyne **2.27** and (2-Methoxyphenyl)propyne **2.28** by catalysts **1.149, 1.201a** and **1.202c**.

Thus, our attention turned to the RCAM of triyne **2.2** with each of the three alkyne metathesis catalysts. The results are summarised in Table 2.4.

Table 2.4. Reaction conditions examined for the formation of **2.1**.



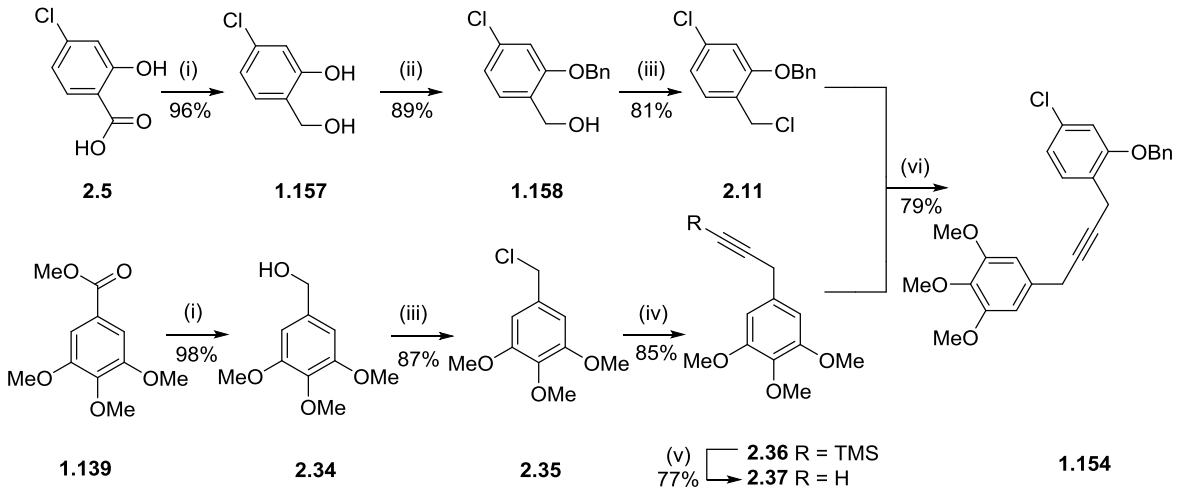
2.2 **2.1**

Entry	Catalyst	Loading	Temperature	Result
1	**1.149**	20 mol%	80 °C	SM
2	**1.149**	100 mol%	80 °C	SM
3	**1.201a**	5 mol%	80 °C	SM
4	**1.201a**	15 mol%	80 °C	SM
5	**1.201a**	100 mol%	RT	SM
6	**1.201a**	100 mol%	80 °C	SM
7	**1.202c**	5 mol%	RT	SM
8	**1.202c**	15 mol%	RT	SM
9	**1.202c**	15 mol%	80 °C	38%
10	**1.202c**	25 mol%	80 °C	52% (71% brsm)
11	**1.202c**	25 mol%	40 °C	66% (84% brsm)

Firstly, **2.2** was exposed to 20 mol% of Schrock catalyst **1.149** at 80 °C, but the reaction returned only recovered starting material (Table 2.4, entries 1-3). The catalyst loading was then raised to 100% but to no avail. As this catalyst had proven successful in the earlier work towards the unchlorinated core of chrysophaentin F, it is imagined that the presence of the additional aryl chloride moieties is likely to be responsible for this failure. Next, Mo-nitrido catalyst **1.201a** and Mo-alkylidyne catalyst **1.202c** were trialled. Both were used as their air-stable pre-catalyst derivatives with the active catalyst released *in-situ* by heating, in case of the former, and through

the use of $MnCl_2$ in the case of the latter. Unfortunately, Mo-nitrido catalyst **1.201a** proved ineffectual at a range of catalyst loadings and reaction temperatures (Table 2.4, entries 4-6). However, while Mo-alkylidyne proved equally ineffective at room temperature (Table 2.4, entries 7-8), raising the temperature to 80 °C in the presence of 15 mol% of **1.202c** provided macrocycle **2.1** in 38% yield (Table 2.4, entry 9). This was increased to 52% yield by increasing the catalyst loading to 25 mol% and was further increased to 66% by lowering the reaction temperature to 40 °C (Table 2.4, entry 10-11).

Having successfully performed the RCAM step of the synthesis one challenge remained; the installation of the (*E*)-vinyl chlorides. Due to the high value of the macrocyclic substrate **2.1**, the investigations were conducted using acyclic model substrate **1.154** which was prepared as detailed in Scheme 2.17.

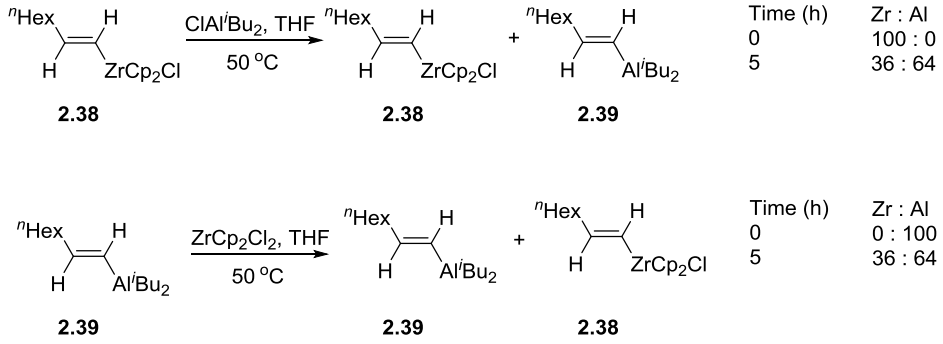


Reagents and conditions: (i) $LiAlH_4$ (1.5 equiv.), THF, 0-40 °C; (ii) BnBr, K_2CO_3, acetone, 45 °C; (iii) NCS, PPh_3, THF, 0 °C-RT; (iv) TMS-acetylene (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C; (v) TBAF, AcOH, THF, RT; (vi) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.),Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C

Scheme 2.17. Synthesis of hydrozirconation-chlorination test substrate **1.154**.

Following the initial work conducted in Section 1.3.4, it was established that the use of 2 equivalents of Schwartz's reagent (formed *in-situ* from Cp_2ZrCl_2 and DIBAL)[56] led to a 2:1 ratio of regioisomers in favour of the desired regiochemistry. However, according to Schwartz's original paper, selectivity can be improved through the use of additional equivalents of the reagent, either present throughout the reaction or added following the initial hydrozirconation.[51] Therefore, we decided to investigate the influence of both the number and addition order of further equivalents of Schwartz's reagent. Also, we explored if there were any differences in selectivity arising from the use of Schwartz's reagent itself and that generated *in-situ* by

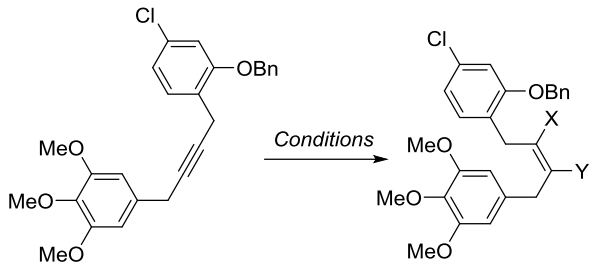
Negishi's method.[56] The Negishi paper suggested that the reagent formed by Cp_2ZrCl_2 and DIBAL was not a genuine equivalent to $HZrCp_2Cl$ and that the presence of $^{i}Bu_2AlCl$ can be detrimental for some reactions. They also observed a slow reverse transmetallation process in which the intermediate alkenyl group was transferred from Zr (**2.38**) to Al (**2.39**) to give the two species in equilibrium (Scheme 2.18).



Scheme 2.18. Transmetallation observed during the use of Cp_2ZrCl_2 and DIBAL as reported by Negishi and co-worker.

The results of these investigations are summarised in Table 2.5. Firstly, the original conditions using the *in-situ* method with 2 equivalents were applied and successfully replicated to provide regioisomers **1.154** and **1.155** in a 2:1 ratio. This was then compared to the use of Schwartz's reagent itself and surprisingly the use of 2 equivalents in THF led to only a 1:1 mixture of regioisomers (Table 2.5, entry 2). Increasing the number of equivalents to 3 increased this to 4:3, but the 2:1 ratio obtained with the *in-situ* generated method could not be replicated (Table 2.5, entry 3). Switching the solvent to either toluene or DCM also led to no improvement in selectivity and slowed the reaction. Thus for our substrate, **1.155**, the use of the *in-situ* generated method was advantageous. This may be due to the presence of $^{i}Bu_2AlCl$ as it may help dissociate the Schwartz's reagent oligomers that are present in solution making it more freely available to perform the hydrozirconation. It is also possible that the observed equilibrium between the organozirconium and organoaluminium species is a contributing factor. Next, we attempted to improve the selectivity through the use of a further equivalent of Schwartz's reagent which was either added at the start of the reaction (Table 2.5, entry 6) or added after the initial hydrozirconation with 2 equivalents (Table 2.5, entry 7). However, neither led to an improvement in the ratio of regioisomers.

Table 2.5. Conditions screened for the hydrozirconation/chlorination to form hemichrysophaentin **1.155** and regioisomer **1.156**.



1.154

1.155 X = H, Y = Cl
1.156 X = Cl, Y = H

Entry	Method	Equiv.	Regioselectivity **1.155:1.156**
1	(i) $ZrCp_2Cl_2$, DIBAL, THF, 0-40 °C; (ii) NCS, DCM, RT	2	2:1
2	(i) $Cp_2Zr(H)Cl$, THF, 0-40 °C; (ii) NCS, DCM, RT	2	1:1
3	(i) $Cp_2Zr(H)Cl$, THF, 0-40 °C; (ii) NCS, DCM, RT	3	4:3
4	(i) $Cp_2Zr(H)Cl$, PhMe, 0-40 °C; (ii) NCS, DCM, RT	2	1:1
5	(i) $Cp_2Zr(H)Cl$, DCM, 0 °C-RT; (ii) NCS, DCM, RT	2	1:1
6	(i) $ZrCp_2Cl_2$, DIBAL, THF, 0-40 °C; (ii) NCS, DCM, RT	3	2:1
7	(i) $ZrCp_2Cl_2$, DIBAL, THF, 0-40 °C; (ii) $ZrCp_2(H)Cl$, THF, 0-40 °C; (iii) NCS, DCM, RT	3 (2 *in-situ* + 1 commercial)	2:1

With the best hydrozirconation conditions now established, they were then applied to macrocyclic substrate **2.1**. The crude ^{1}H NMR revealed two major alkene signals; one at 5.94 ppm and two overlapping signals at 5.82 ppm in an approximate ratio of 2:1 (Figure 2.2). This ratio was confirmed by LC-MS which showed 2 peaks at similar retention times, both containing m/z 935, 937, 939, 941 $[M+Na]^+$ and 951, 953, 955, 957 $[M+K]^+$ in a ratio of approximately 8:10:5:1 which is characteristic of 4 chlorine atoms.

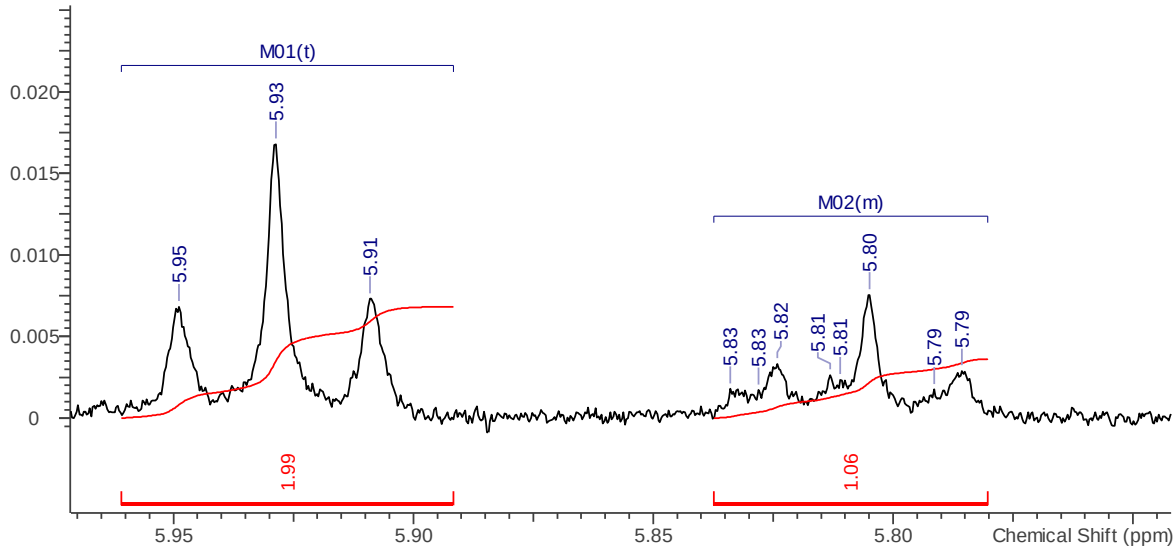
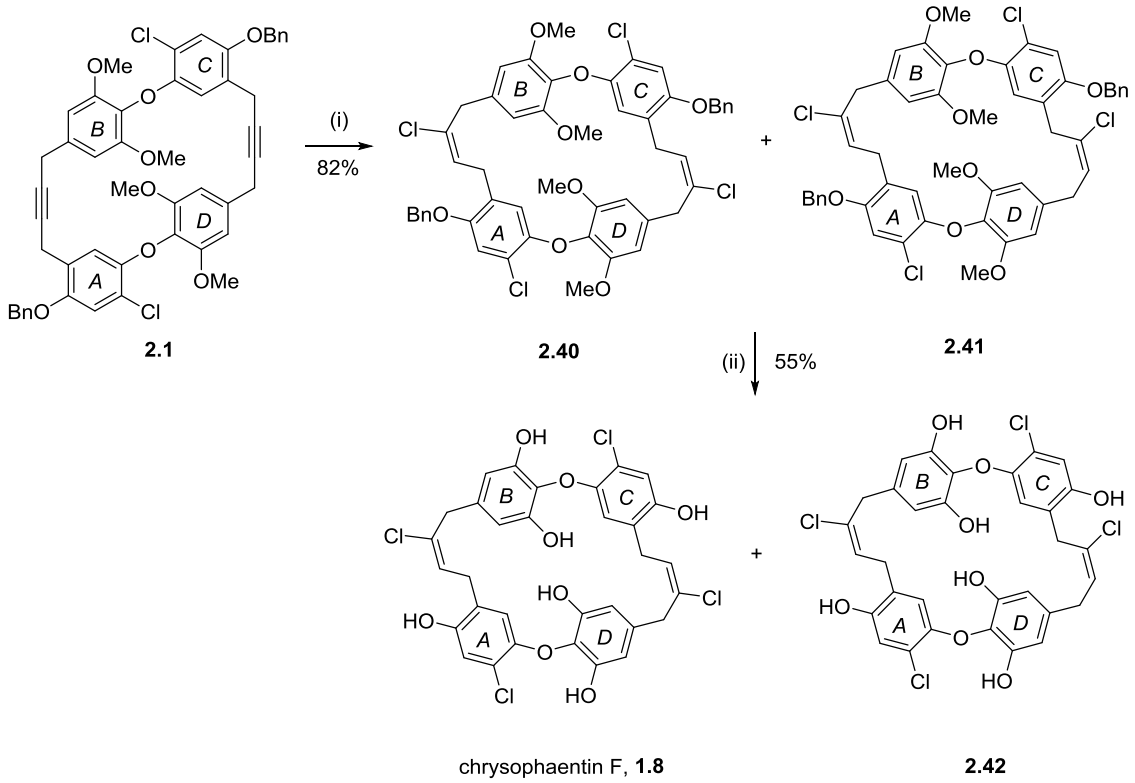


Figure 2.2. Crude ^{1}H NMR of the hydrochlorination of **2.1**.

In order to confirm whether the desired regiochemistry had been achieved the mixture was deprotected using BCl_3 and TBAI in DCM (Scheme 2.20) and the ^{1}H and ^{13}C NMR compared to the literature data.[1]



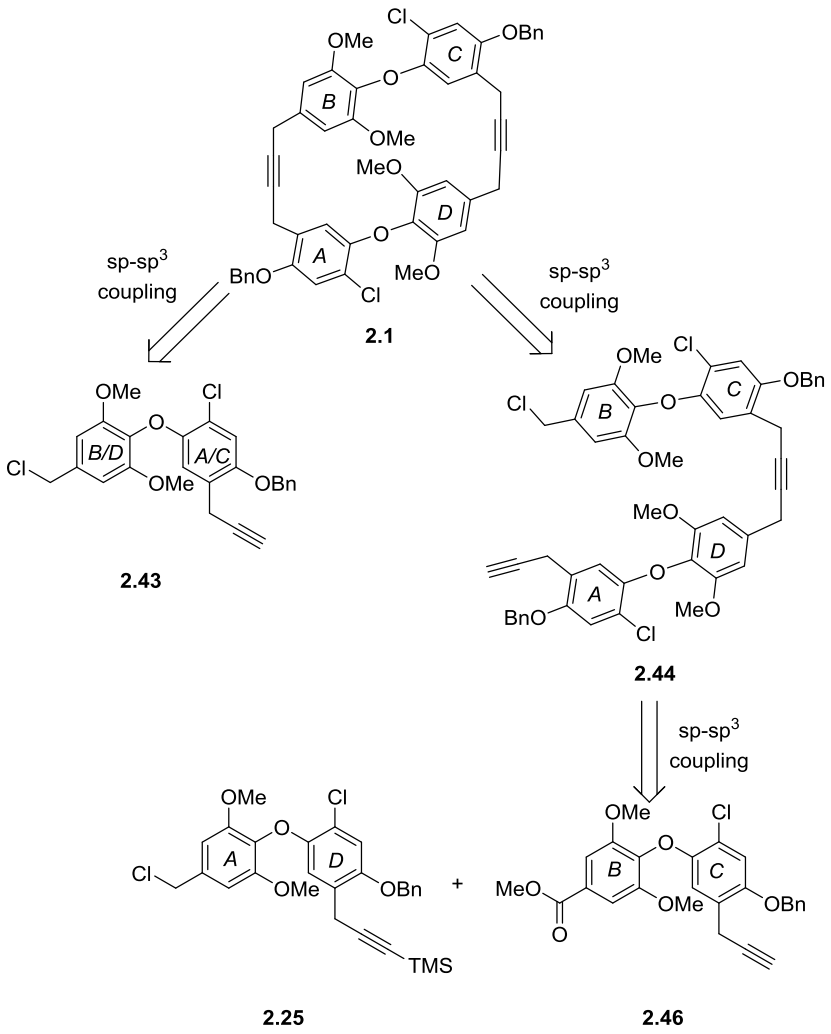
Reagents and conditions: (i) a) Cp_2ZrCl_2 (4 equiv.), DIBAL (4 equiv.), THF, 0-40 ^oC, b) NCS (2 equiv.), DCM, RT; (ii) BCl_3, TBAI, DCM, –78-0 ^oC

Scheme 2.20. Synthesis of chrysophaentin F as the major component of a 2:1 mixture of regioisomers.

Pleasingly, when the two spectra were compared, chrysophaentin F was confirmed as the major component of the mixture (See Section 2.5). Thus, we attempted to separate the two regioisomers to isolate chrysophaentin F in pure form. Alas, column chromatography, prep TLC and HPLC were all ineffective and the latter led to degradation of the material. Unfortunately, attempts to prepare more of this mixture of regioisomers to facilitate separation by alternative methods were prevented by the withdrawal from sale of the alkyne metathesis catalyst **1.202c**.

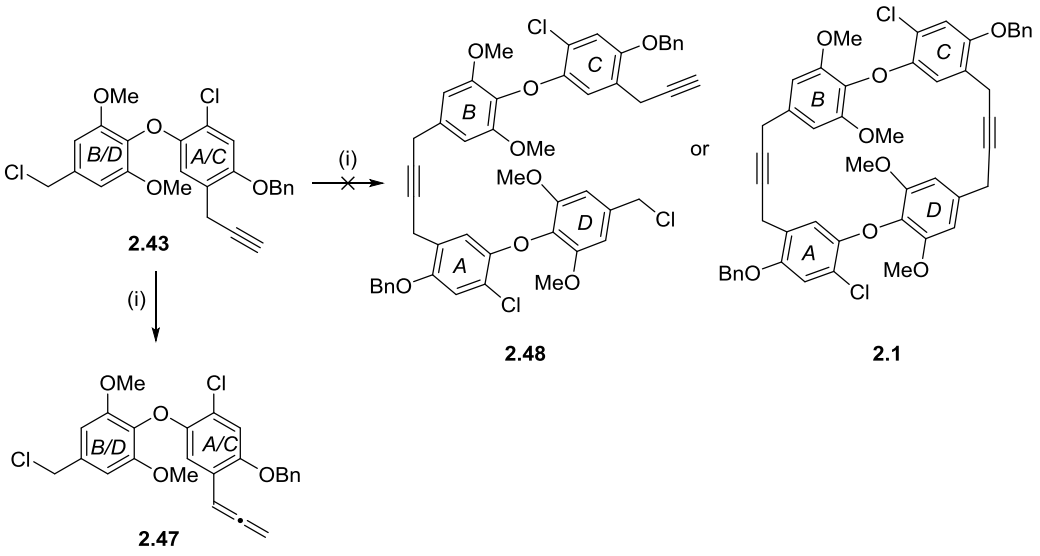
2.5 Alternative Routes

The unavailability of Mo-catalyst **1.202c** prompted us to seek an alternative synthesis of macrocyclic diyne **2.1**. We envisaged that it could be prepared *via* two simultaneous sp-sp^3 couplings between **2.40** (Scheme 2.21). Alternatively, the target could be prepared in a step-wise fashion from **2.41** and **2.42**.



Scheme 2.21. Alternative sp-sp^3 coupling based strategies for the preparation of diyne **2.1**.

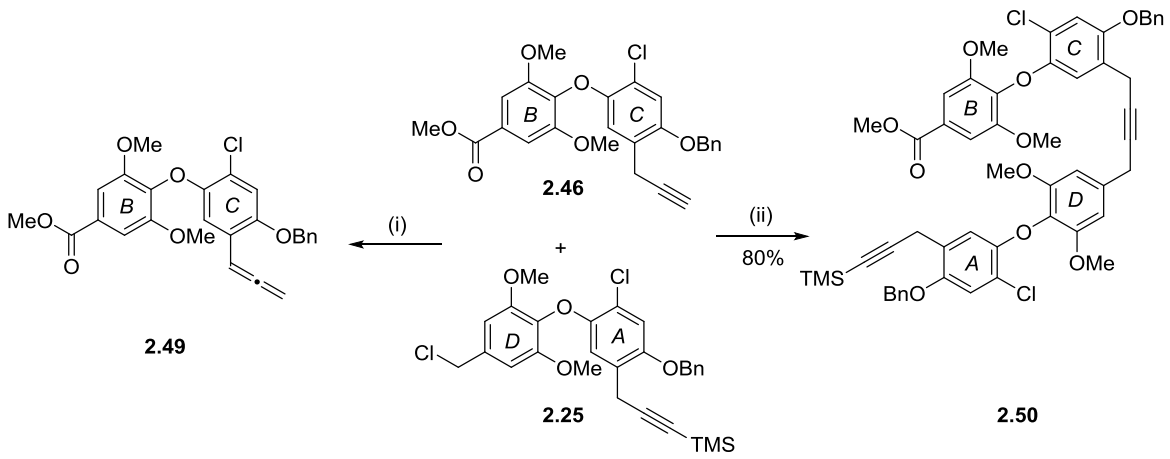
Unfortunately, the attempted Heck alkynylation of **2.43** to **2.1** led solely to the isomerisation of the terminal alkyne to allene **2.47** when performed in both MeCN and 1,4-dioxane and using 1 equivalent of Cs_2CO_3 (Scheme 2.22). This particularly facile isomerisation had been an ever present frustration throughout our work on the total synthesis of chrysophaentin F, yet also highly unpredictable.



Reagents and conditions: (i) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN or 1,4-dioxane, 65 ^oC

Scheme 2.22. Isomerisation of alkyne **2.39** to allene **2.42**.

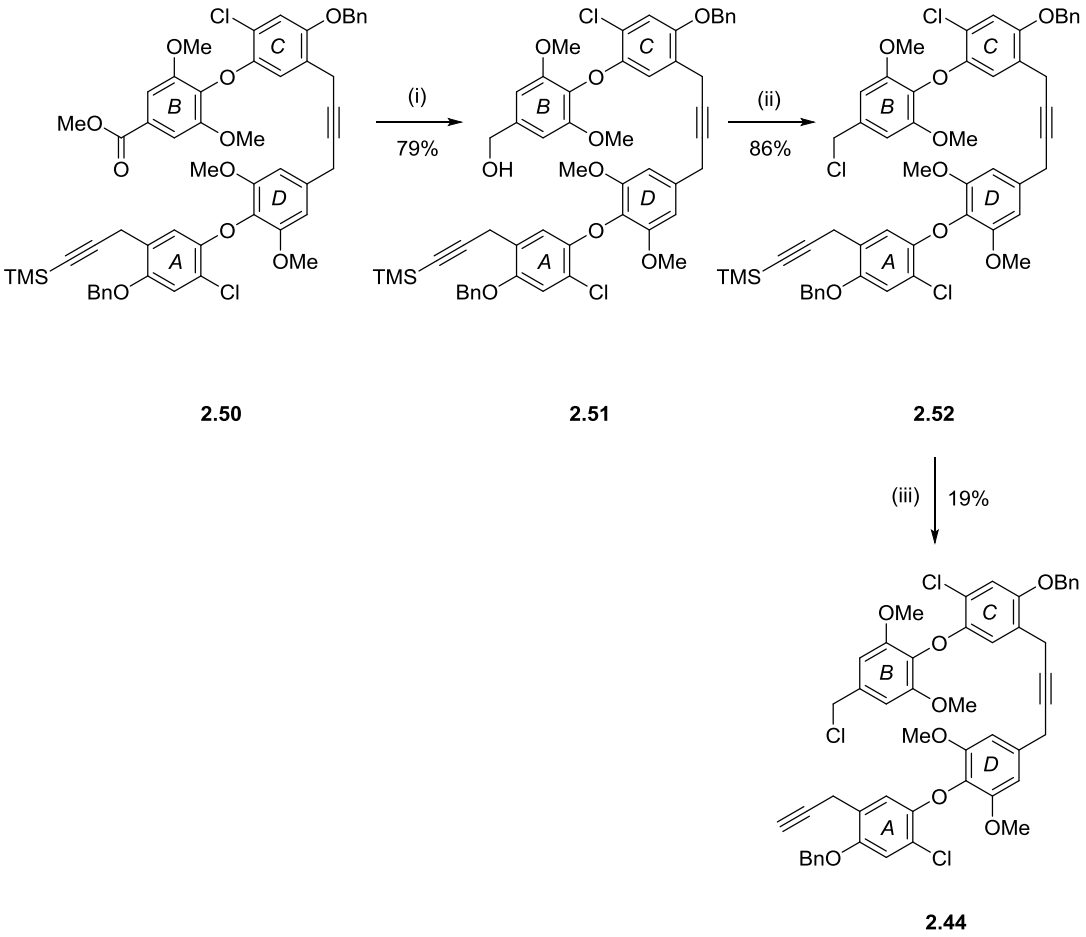
This was again highlighted when we sought to prepare **2.1** *via* a stepwise sp-sp^3 coupling method starting with the coupling of benzyl chloride **2.25** and terminal alkyne **2.46**. When MeCN was used as the solvent, again only isomerisation to allene **2.49** was observed with benzyl chloride **2.23** remaining unconsumed. However, when conducted in either 1,4-dioxane or THF, the coupled product **2.50** was isolated in good yield and no isomerisation was detected under these conditions (Scheme 2.23). It should be noted, however, that alkyne **2.46** must decompose by other methods as when 2 equivalents of **2.46** were used, with 1 equivalent of benzyl chloride **2.23**, a significant portion of the latter remained unreacted.



Reagents and conditions: (i) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 ^oC; (ii) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.),Cs_2CO_3 (1.1 equiv.), 1,4-dioxane, 65 ^oC

Scheme 2.23. Solvent effects observed in the isomerisation of alkyne **2.46**.

The ester group of **2.50** was then reduced using DIBAL to provide alcohol **2.51**, which was subsequently transformed into benzyl chloride **2.52** in 86% yield (Scheme 2.24). However, attempts to remove the TMS protecting group proved difficult. The use of either AgOTf or $AgNO_3$ as described by Orsini and co-workers[48] returned only starting material. The use of TBAF in AcOH (1:1) proved more fruitful, though it was found necessary to use 10 equivalents of TBAF to enact significant removal of the TMS group and increasing the equivalents further did nothing to improve the yield.

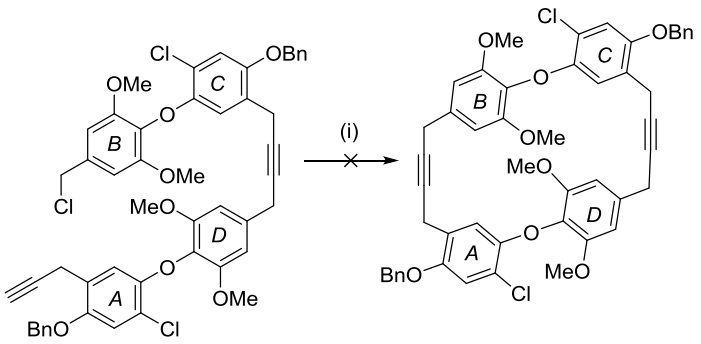


2.50 **2.51** **2.52** **2.44**

Reagents and conditions: (i) DiBAL (2.1 equiv.), THF, 0 ^{o}C-RT; (ii) NCS, PPh_3, THF, 0 ^{o}C-RT; (iii) TBAF, AcOH, THF, RT

Scheme 2.24. Preparation of ring closure precursor **2.44**.

Nevertheless, with the small amount of material isolated from the deprotection the ring closure was attempted. Alas, when the sp-sp^3 coupling was performed on diyne **2.44**, it only resulted in decomposition of the starting material (Scheme 2.25). Based on this observation as well as the similar decomposition of alkyne **2.46** in the initial sp-sp^3 coupling, it is thought that a terminal alkyne group on ring *A*/*C* is inherently unstable.



2.44 **2.1**

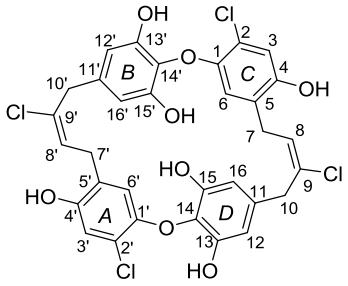
Reagents and conditions: (i) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), 1,4-dioxane, 65 ^oC

Scheme 2.25. Attempted ring closure by sp-sp^3 coupling.

2.6 NMR Analysis

Having been unable to isolate chrysophaentin F in pure form, the confirmation that the synthesis of the natural product had been achieved became a pressing concern. As evidenced by the data summarised in Table 2.6, both the ^1H and ^{13}C NMR spectra from our synthetic sample exhibited primary signals that matched those reported in the literature.

Table 2.6. Comparison of literature and synthetic NMR signals for chrysophaentin F, **1.8**.



chrysophaentin F, 1.8

Position	Literature δ_C	Literature δ_H	Synthetic δ_C	Synthetic δ_H	HMBC interactions
1, 1′	148.2		148.5		
2, 2′	120.4		120.6		
3, 3′	117.3	6.90 (2H, s, 2 x ArH)	117.6	6.89 (2H, s, 2 x ArH)	1, 2, 4, 5
4, 4′	150.7		151.0		
5, 5′	126.5		126.9		
6, 6′	115.1	6.42 (2H, s, 2 x ArH)	115.4	6.42 (2H, s, 2 x ArH)	1, 2, 4, 7
7, 7′	31.0	3.35 (4H, d, *J* = 8.3 Hz, 2 x CH_2)	30.9	3.35 (4H, d, *J* = 8.7 Hz, 2 x CH_2)	4, 5, 6, 8, 9
8, 8′	127.2	5.89 (2H, t, *J* = 8.3 Hz, 2 x =CH)	127.2	5.89 (2H, t, *J* = 8.3 Hz, 2 x =CH)	7, 9
9, 9′	134.3		134.5		
10, 10′	39.8	3.54 (4H, br s, 2 x CH_2)	40.0	3.53 (4H, br s, 2 x CH_2)	9, 11, 12, 16
11, 11′	137.0		137.3		
12, 16, 12′, 16′	110.0	6.23 (4H, s, 4 x ArH)	110.3	6.22 (4H, s, 4 x ArH)	10, 12, 16, 13, 15
13, 15, 13′, 15′	151.3		151.5		
14, 14′	130.0		130.2		

COSY and HMBC analyses were also undertaken and these confirmed that the vinyl chloride groups possessed the correct regiochemistry. In particular, the alkene proton at 5.89 ppm showed a large coupling to a CH_2 group at 3.35 ppm which, in turn, showed long order interactions to carbons present on the *A/C* rings (4, 5, 6, 8). Conversely, the other CH_2 group at 3.54 ppm showed no interaction with the alkene proton and exhibited long order interactions to carbons present on the *B/D* (11, 12, 16) rings (Figure 2.3).

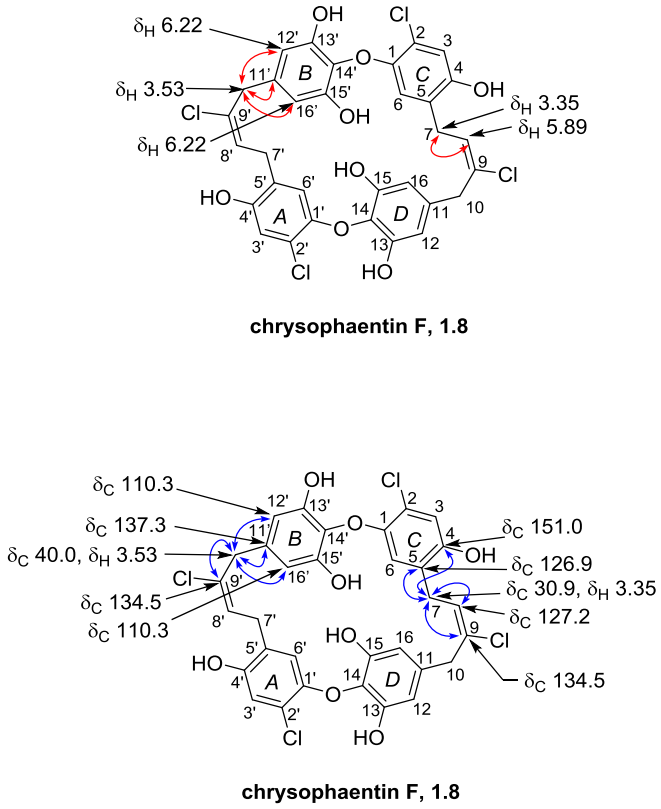


Figure 2.3. COSY (red) and HMBC (blue) interactions of the vinyl chlorides of chrysophaentin F **1.8**.

As the hydrozirconation of alkynes by Schwartz's reagent is known to proceed in a stereospecific fashion *via* a concerted 4-centered process, we were confident that the vinyl chlorides also possessed the correct stereochemistry. However, if desired, this could be confirmed by further NMR analysis. The presence or absence of cross peaks between the two CH_2 resonances in an NOESY NMR experiment would confirm if the two groups are *cis* or *trans* to each other. Alternatively, it has been established that alkyl protons *cis* to a chlorine atom appear further downfield than those *trans* to a chlorine atom.[113–115] This was also borne out by the chemical shifts observed by Keffer *et al.* for hemichrysophaentins **(*E*)-** and **(*Z*)-1.70** as well as for **(*E*)-** and **(*Z*)-1.80** (Figure 2.4).[2] Therefore, the stereochemistry of the vinyl chlorides present in the

synthetic chrysophaentin F sample could also be established by the observed chemical shifts for the CH_2 group proximal to the chlorine containing *A/C* rings.

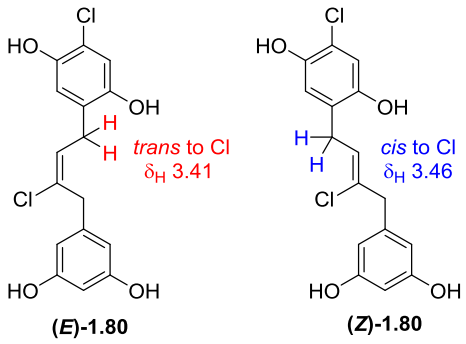
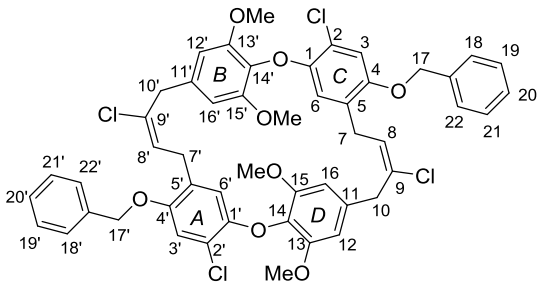


Figure 2.4. Differing chemical shifts observed for hemichrysophaentins **(*E*)-** and **(*Z*)-1.80**.

Having established the presence of chrysophaentin F, our attention turned to the identity of the other isomer. Unfortunately, due to the small amount of material isolated this was not possible for the deprotected analogue so we returned to the fully protected mixture in order to identify the second component. Using the established 2:1 ratio of chrysophaentin F to the unknown isomer, the peaks responsible for the protected analogue of chrysophaentin F were identified as summarised in Table 2.7. Again, the COSY and HMBC interactions of the alkene proton (5.94 ppm) and the neighbouring CH_2 group (3.47 ppm) were used to establish the regiochemistry of the hydrochlorination.

Table 2.7. ^{1}H and ^{13}C NMR data for protected chrysophaentin F analogue **2.40**.



2.40

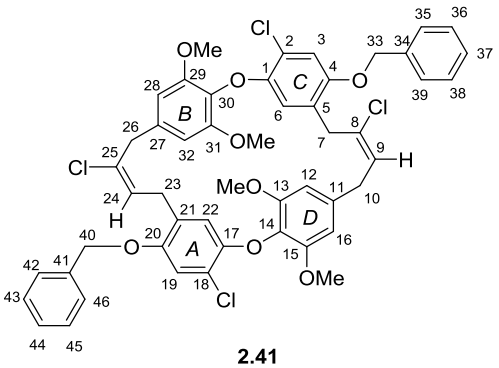
Position	δ_c	δ_H	HMBC interactions
1, 1’	148.0		
2, 2’	119.7		
3, 3’	115.0	7.02 (2H, s, 2 x ArH)	1, 2, 5, 7

Position	δ_c	δ_H	HMBC interactions
4, 4’	150.8		
5, 5’	127.5		
6, 6’	113.8	6.34 (2H, s, 2 x ArH)	1, 2, 5, 4, 7
7, 7’	30.0	3.47 (4H, d, *J* = 8.1 Hz, 2 x CH_2)	4, 6, 8, 9
8, 8’	126.1	5.94 (2H, t, *J* = 8.1 Hz, 2 x =CH)	5, 7, 9
9, 9’	133.4		
10, 10’	40.0	3.59 (4H, br s, 2 x CH_2)	9, 12, 14, 16
11, 11’	135.0		
12, 16, 12’, 16’	105.6	6.23 (4H, s, 4 x ArH)	9, 10, 12, 16, 13, 15
13, 15, 13’, 15’	152.8		
OMe-13, OMe-15, OMe-13’, OMe 15’	56.0	3.54 (12H, s, 4 x CH_3)	13, 15
14, 14’	130.1		
17, 17’	70.8	5.10 (4H, s, 2 x CH_2)	4, 18, 19, 20, 21, 22, 23
18, 18’	136.6		
19, 20, 21, 22, 23, 19’, 20’, 21’, 22’, 23’	128.9, 127.9, 127.4	7.53 - 7.30 (10 H, m, 10 x ArH)	4, 18, 19, 20, 21, 22, 23

Thus, the remaining peaks must correspond to the regioisomer. In this, the remaining alkene region showed 2 overlapping triplets which in the COSY spectrum showed coupling to two different CH_2 groups. One of these, 3.22 ppm, showed coupling to the carbons present on the dimethoxy aryl ring in the HMBC experiment, thus implying a vinyl chloride group orientated with its proton proximal to the *B*/*D* ring. Conversely, the other CH_2 signal, 3.50 ppm, was more difficult to identify as the signal overlapped with that for the 4 x OMe groups belonging to the major isomer. However, this region also contained two further CH_2 peaks, implying that the

minor isomer was not symmetrical. Thus, we conclude that the peak at 3.50 ppm must be proximal to a Cl containing ring, *A* or *C* ring and therefore, that the minor regioisomer is **2.41**. Although many of the signals could not be conclusively identified as several signals are coincident, tentative assignments based on couplings observed in COSY and HMBC experiments are summarised in Table 2.8.

Table 2.8. ^{1}H and ^{13}C NMR data for protected chrysophaentin F analogue **2.41**.



2.41

Position	δ_c	δ_H
1, 17	148.2	
2, 18	119.7	
3, 19	114.1	7.06 (2H, s, 2 x ArH)
4, 20	151.0	
5, 21	127.5	
6, 22	113.9	6.41 (2H, s, 2 x ArH)
7	33.2	3.79 /3.66 (2H, br s, CH_2)
8	130.1	5.82 (1H, t, *J* = 8.1 Hz, =CH)
9	127.0/130.0	
10	36.0	3.22 (2H, d, *J* = 8.1 Hz, CH_2)
11	135.4/135.2	
12, 16, 28, 32	105.6	6.17 (4H, s, 4 x ArH)
13, 15, 29, 31	153.0	
OMe-13, OMe-15,	56.3	3.62 (12H, s, 4 x CH_3)

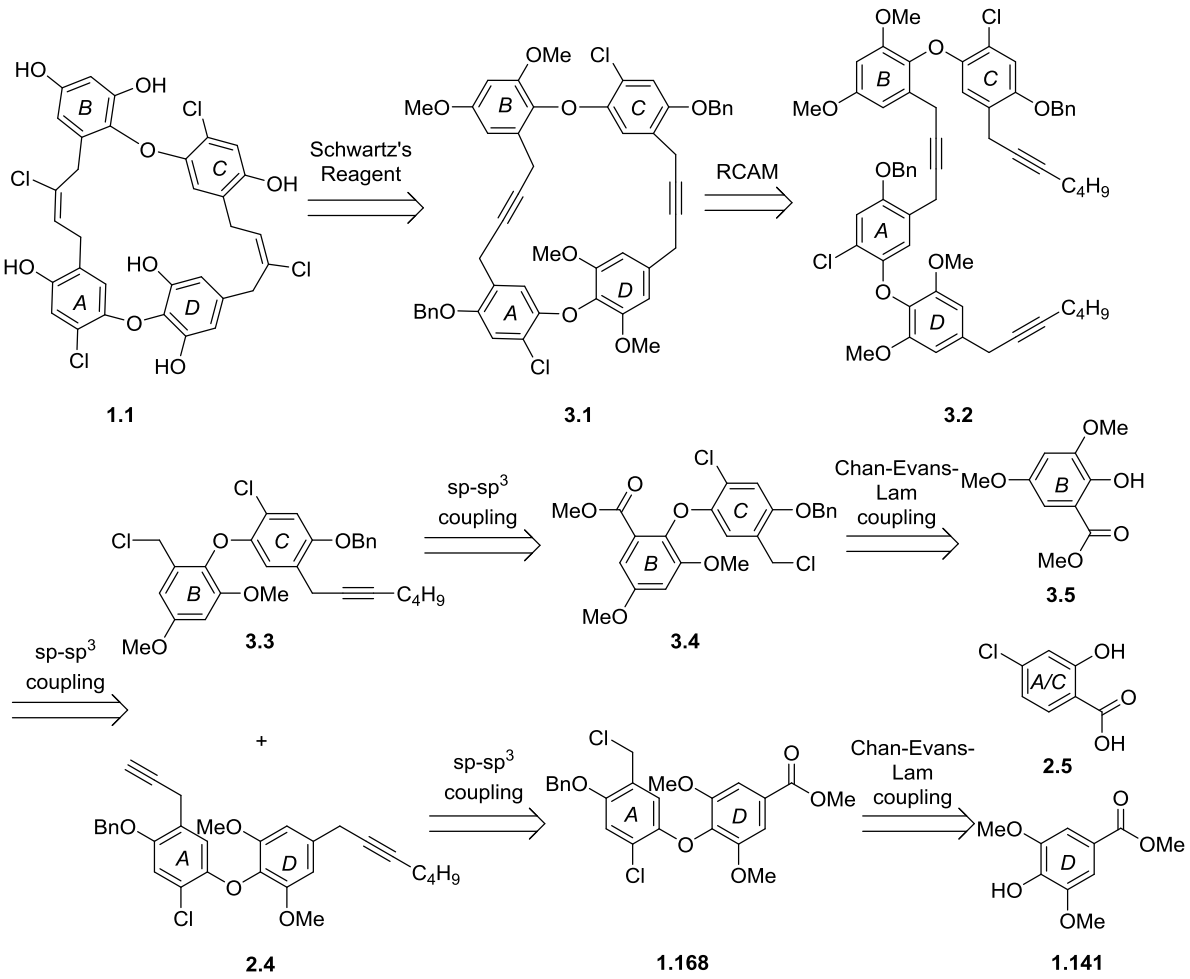
Position	δ_c	δ_H
OMe-29, OMe-31		
14, 30	130.1	
23	30.0	3.50 (2H, br s, CH_2)
24	127.0/130.0	5.82 (1H, t, *J* = 8.1 Hz, =CH)
25	130.0	
26	39.9	3.79/3.66 (2H, x, CH_2)
27	135.4/135.2	
33, 40	70.9	5.09 (4H, s, 2 x CH_2)
34	136.6/135.2	
35, 36, 37, 38, 39, 42, 43, 44, 45, 46	128.6, 127.9, 127.2	7.53 - 7.30 (10H, m, 10 x ArH)
41	136.6/135.2	

Notably, due to the C_2-symmetry present in isomer **2.41**, it is possible for 2 molecules possessing this configuration to be synthesised per molecule of chrysophaentin F. Thus, the regioselectivity for each of the hydrochlorination reaction is 4:1 in favour of the correct isomer rather than the observed 2:1 ratio.

Chapter 3 Results and Discussion: Chrysophaentin A

3.1 Retrosynthesis

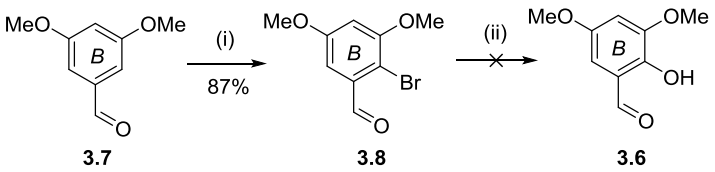
While chrysophaentin A provides more of a challenge than chrysophaentin F, as it is asymmetrically linked, we envisaged that a similar approach could be applied to this molecule (Scheme 3.1). The end game of the synthesis would remain the same with **1.1** being formed by a RCAM followed by hydrochlorination and global deprotection. Triyne **3.2**, the precursor to the macrocyclisation, could be prepared analogously from previously prepared terminal alkyne **2.4** and benzyl chloride **3.3** *via* a sp-sp^3 coupling such as the Heck alkynylation or the nickel catalysed alkynylalane coupling used previously. The new diaryl ether fragment **3.4** could be prepared using a Chan-Evans-Lam coupling between the previously synthesised boronic ester derived from **2.5** and phenol **3.5**.



Scheme 3.1. Retrosynthetic analysis of chrysophaentin A (**1.1**).

3.2 Synthesis of *B* Ring Fragment

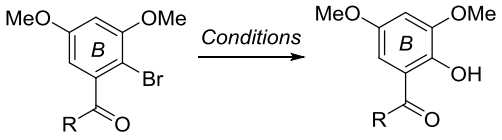
With the synthesis of benzyl chloride **1.168** and boronic ester **1.160** already accomplished during the work conducted on the total synthesis of chrysophaentin F, the first challenge was the synthesis of the phenol required for the Chan-Evans-Lam coupling. As we required a modifiable group on the *B* ring to facilitate the later introduction of alkyne functionalities, we targeted both **3.5** and its aldehyde derivative **3.6**. Phenol **3.6** had been previously prepared by Liao *et al.*[116] in their synthesis of benzocamphorin H from 3,5-dimethoxybenzaldhyde by bromination of the aromatic ring to facilitate a Cu-catalysed hydroxylation to the desired compound. However, although the bromination proceeded without incident, the attempted hydroxylation returned only starting material. The reaction was repeated several times with increased equivalents of both Cu and NaOH but without success. Prior activation of the Cu powder by both mechanical and chemical methods, including activation by iodine,[117] was also attempted but to no avail.



Scheme 3.2. Attempted synthesis of phenol **3.6** following a procedure by Liao *et al*.[116]

Thus, alternative conditions for the hydroxylation step were examined. A search of the literature revealed that a variety of copper catalysts, ligands, additives, solvent mixtures, and bases have been utilised in this transformation.[118–125] A selection of these procedures were tested on both aldehyde and ester substrates, **3.8** and **3.9** and the results are summarised in Table 3.1.

Table 3.1. Screening of conditions for the hydroxylation **3.8** and **3.9**.

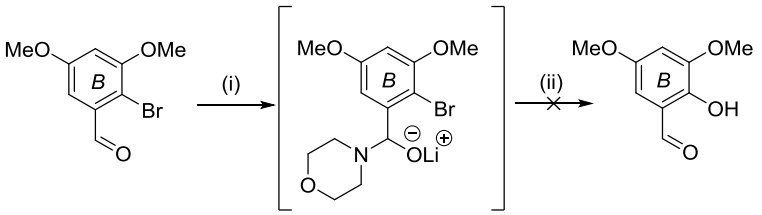


3.8, R = H
3.9, R = OMe

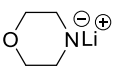
3.6, R = H
3.5, R = OMe

Substrate	Catalyst	Ligand	Additive	Base	Solvent	Temp (°C)	Result
3.8	CuI	1,10-phen	-	KOH	H_2O/DMSO	100	**3.8**
3.9	CuI	1,10-phen	-	KOH	H_2O/DMSO	100	**3.12**
3.8	CuI	Triethanol amine	TBAB	CsOH	H_2O	100	**3.8**
3.8	$Cu(OH)_2$	Glycolic acid	-	NaOH	H_2O/DMSO	120	**3.8**
3.8	$Cu(OAc)_2$	D-Glucose	-	KOH	H_2O/DMSO	120	**3.8**

Unfortunately, all the procedures trialled led to recovery of starting material or saponification of the ester group. Next, a halogen-lithium exchange based method, developed by Borchardt and co-worker,[126] was attempted. The methodology involved the *in-situ* protection of the aldehyde moiety by lithium morpholide and oxygenation of the aryllithium intermediate by nitrobenzene (Scheme 3.3). However, this also proved unsuccessful.

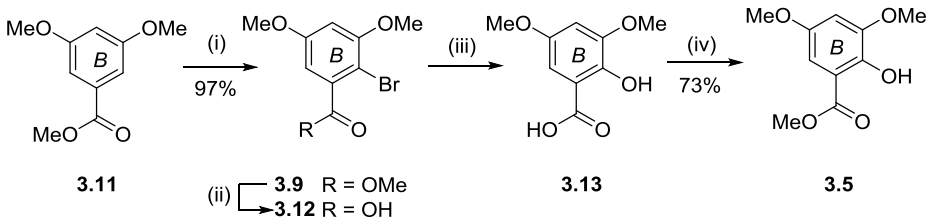


3.8 **3.10** **3.6**

Reagents and conditions: (i)  , THF, –78 to –50 °C; (ii) a) ^{n}BuLi, –78 °C, b) $PhNO_2$

Scheme 3.3. Attempted synthesis of **3.6** following a procedure by Borchardt and co-worker.[126]

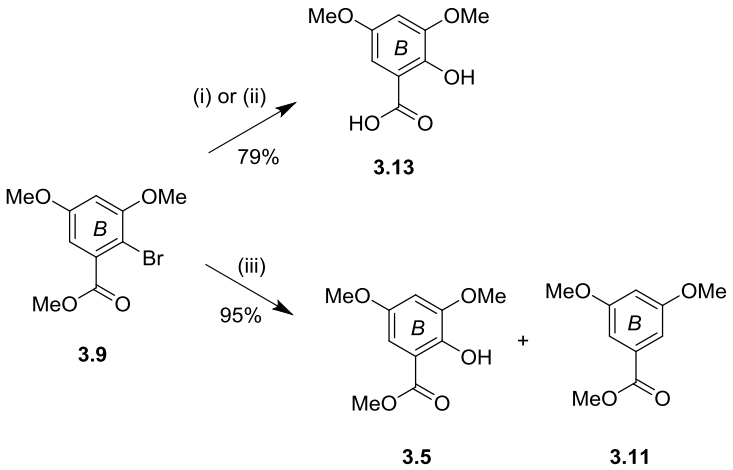
Wang *et al.*[127] had prepared phenol **3.5** in a three step esterification-bromination-hydroxylation reaction sequence from 3,5-dimethoxybenzoic acid, in which the ester intermediate required saponification for the hydroxylation reaction to proceed. This was successfully replicated starting from ester **3.11**, to give phenol **3.13** and then the ester functionality was re-introduced providing **3.5** in a 73% yield over three steps (Scheme 3.4).



Reagents and conditions: (i) NBS, MeCN, RT; (ii) K_2CO_3 (3 equiv.), TBAB (0.02 equiv.), H_2O, reflux; (iii) Cu (0.2 equiv.), Py (2 equiv.), H_2O, reflux; (iv) MeOH, H_2SO_4, reflux

Scheme 3.4. Synthesis of phenol **3.5**.

Although the three step method was successful in providing phenol **3.5**, the saponification and reformation of the ester limited the efficacy of this procedure. Therefore, we attempted to use the Cu/pyridine/H_2O mixture to accomplish the direct hydroxylation of both aldehyde **3.8** and ester **3.9**. However, both experiments returned starting material. Next, we examined the saponification and hydroxylation steps more closely. As the two reactions are conducted subsequently without isolation of **3.12** or removal of K_2CO_3 and TBAB, the reagents used for the saponification also played a role in the hydroxylation step. Firstly, we wondered if the reagents for the two steps were compatible which proved correct as a mixture of K_2CO_3, TBAB, pyridine and 20 mol% Cu powder in H_2O was able to accomplish both the saponification and hydroxylation upon reflux for 18 h (Scheme 3.4). We then investigated whether it was possible to modify these conditions to prevent the undesired saponification. Firstly, the phase transfer catalyst was omitted, but this still resulted in saponification. Next, the equivalents of K_2CO_3 and pyridine were examined. The original procedure used 3 equivalents of K_2CO_3 and 2 equivalents of pyridine, however, lowering both of these to 1 equivalent resulted in no saponification and the formation of phenol **3.5** in 95% yield together with a small amount of dehalogenated starting material (Scheme 3.5). With these conditions established, we next applied them to aldehyde **3.8** but found them to be ineffective.

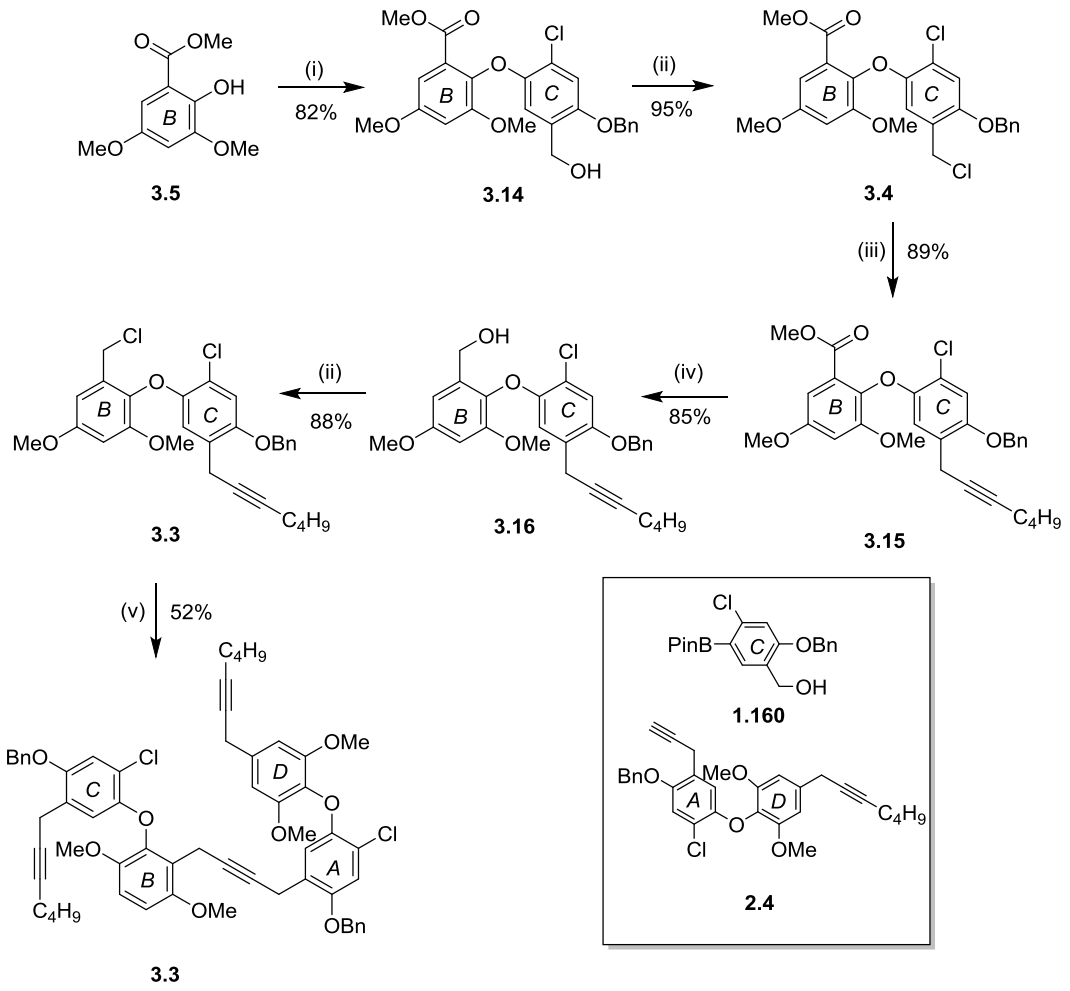


Reagents and conditions: (i) K_2CO_3 (3 equiv.), TBAB (0.02 equiv.), Cu (0.2 equiv.), Py (2 equiv.),H_2O, reflux; (ii) 3 equiv. K_2CO_3, Cu (20 mol%), 2 equiv. Py, H_2O, reflux; (iii) K_2CO_3 (1 equiv.), Cu (0.2 equiv.), Py (1 equiv.), H_2O, reflux

Scheme 3.5. Optimisation of the synthesis of **3.5**.

3.3 Progress Towards Chrysophaentin A

Having established a convenient gram-scale synthesis of phenol **3.5**, the next task was its coupling to boronic ester **1.160**. Pleasingly, when subjected to the previously established Chan-Evans-Lam coupling conditions (20 mol% $Cu(OTf)_2$ and 5 equiv. pyridine in EtOH at 65 °C), diaryl ether **3.14** was isolated in a 93% yield. Conversion of the benzyl alcohol to the benzyl chloride was then achieved with PPh_3 and NCS. Benzyl chloride **3.4** was then successfully coupled with hex-1-yne to provide **3.15** in 89% yield. Subsequent ester reduction to benzyl alcohol **3.16** and its transformation into benzyl chloride provided us with the desired coupling partner for the final sp-sp^3 coupling step. This new *BC* fragment, **3.3**, was then successfully coupled with the previously synthesised *AD* fragment, **2.4**, to provide triyne **3.2** in 52% yield (Scheme 3.6).



Reagents and conditions: (i) **1.160**, $Cu(OTf)_2$ (0.2 equiv.), Py (5 equiv.), EtOH, 65 ^oC; (ii) PPh_3, NCS, THF, 0 ^oC-RT; (iii) hex-1-yne (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 ^oC; (iv) $LiAlH_4$ (1.1 equiv.), THF, 0 ^oC-RT; (v) **2.4** (1.2 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.) XPhos (0.18 equiv.) Cs_2CO_3 (1.1 equiv.), MeCN, 65 ^oC

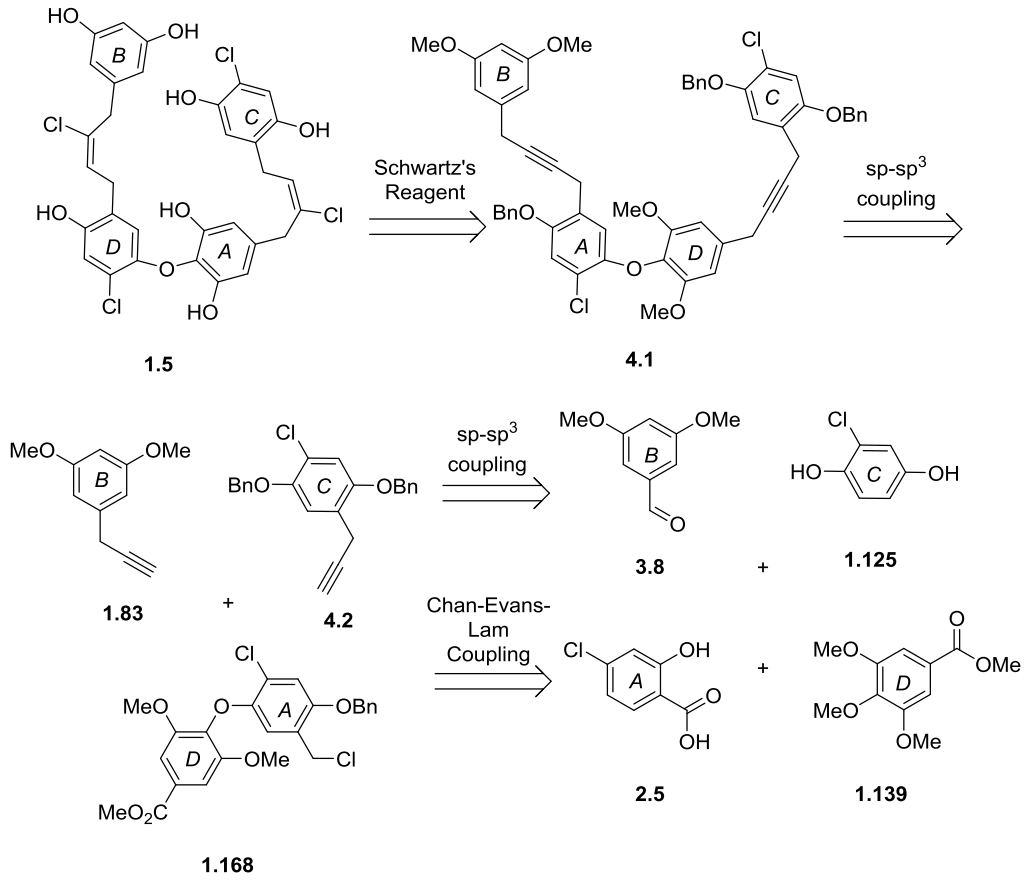
Scheme 3.6. Preparation of RCAM precursor **3.3**.

Unfortunately, at this time we found that commercial suppliers had withdrawn Mo catalyst **1.202c** from sale so we were unable to attempt the RCAM step.

Chapter 4 Results and Discussion: Chrysophaentin E

4.1 Retrosynthesis

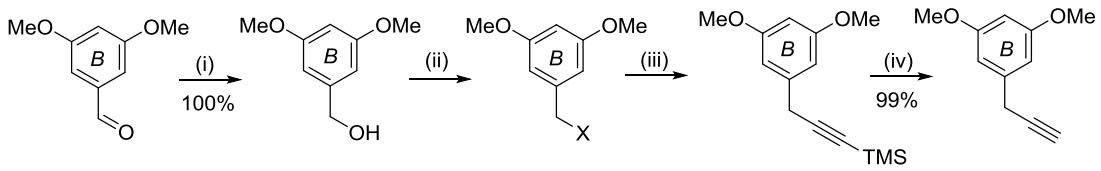
With issues surrounding catalyst availability for the ring closing alkyne metathesis step in our approach to the chrysophaentins, we recognised that the acyclic chrysophaentin E was still a potential target for us. Chrysophaentin E is a linear derivative of the symmetrical, tetrachloromacrocycle chrysophaentin F only lacking the diaryl ether bond between arenes *B* and *C*. Therefore, we believe that chrysophaentin E (**1.5**) might be accessed from our established synthetic route with little modification. Thus, the common *AD* ring motif **1.168** could be subjected to two sp-sp^3 couplings with benzylic alkynes **1.88** and **4.2** to give acyclic diyne **4.1**. In turn, this could be subjected to the previously developed hydrozirconation-chlorination sequence, leading after deprotection to chrysophaentin E **1.5**. The selectivity of hydrochlorination in the synthesis was recognised as a potential problem as the precursor diyne **4.1** would possess more rotational degrees of freedom than the cyclic system used previously. Nonetheless, as a 2:1 selectivity had been obtained for related reactions in model studies we remain confident that the desired regiochemical outcome would still be favoured (See Section 1.3.4). A synthesis of benzylic alkyne fragment **1.88** had been previously reported by Keffer *et al.* in their attempted synthesis of chrysophaentin A. We imagine that the final fragment, **4.2**, could be prepared from hydroquinone **1.125** through the use of an *ortho*-formylation reaction to install the key transformable aldehyde group.



Scheme 4.1. Retrosynthetic analysis of chrysophaentin E, **1.5**.

4.2 Synthesis of *B* Ring Fragment

The synthesis of *B* ring fragment **1.88** was achieved using similar methodology to that used by Keffer *et al.* in their attempted synthesis of chrysophaentin A.[2] Thus, 3,5-dimethoxybenzaldehyde was reduced to alcohol **4.3** which was then converted into either benzyl bromide **1.86** or chloride **4.4** *via* an Appel reaction. Three different metal catalysed coupling procedures were then attempted to introduce the key alkyne functionality: a Pd-catalysed Heck alkynylation,[46] a Ni-catalysed organoaluminium coupling[47] and an organocuprate coupling.[2] The results of these coupling reactions are summarised in Table 4.1. The Ni-catalysed organoaluminium coupling proved most effective with **1.87** isolated in quantitative yield. Finally, deprotection of TMS-acetylene **1.87** was achieved using a 1:1 mixture of TBAF and AcOH to provide the *B* ring fragment **1.83** in 98% overall yield over the 4 steps (Scheme 4.2).

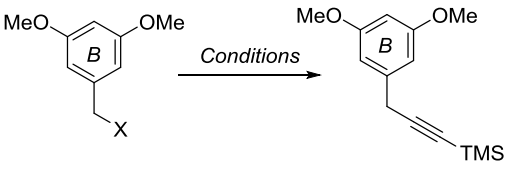


3.7 **4.3** **1.86**, X = Br 99% **4.4**, X = Cl 87% **1.87** **1.83**

Reagents and conditions : (i) $NaBH_4$ (2 equiv.), MeOH, 0 °C-RT; (ii) PPh_3, NBS/NCS, THF, 0 °C-RT; (iii) See Table **4.1**; (iv) TBAF, AcOH, THF

Scheme 4.2. Preparation of *B* ring fragment **1.83**.

Table 4.1. Metal catalysed couplings of benzyl halides **1.86** and **4.4**



1.86, X = Br 99% **4.4**, X = Cl 87% **1.87**

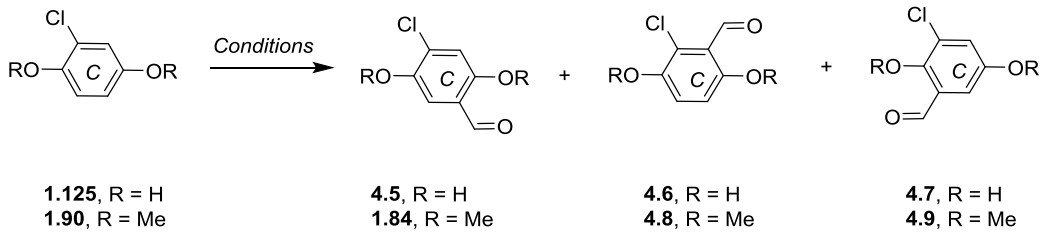
Substrate	Reaction Conditions	Result
1.86	MeMgBr (4 equiv.), CuBr (1 equiv.), TMS acetylene (4 equiv.), THF, reflux	**1.87** (72%)
1.86	(i) ^{n}BuLi (2 equiv.), TMS acetylene (2 equiv.), Et_2AlCl (4 equiv.), Et_2O, 0 °C - RT (ii) $Ni(PPh_3)_2Cl_2$ (0.06 equiv.), Et_2O, RT	**1.87** (100%)
4.4	$PdCl_2(MeCN)_2$ (0.06 equiv.), XPhos (0.18 equiv.), TMS acetylene (1.5 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C	**1.87** (77%)

4.3 Synthesis of *C* Ring Fragment

The formylation of aromatic rings is a well-known transformation and we envisaged that the tetra-substituted *C* arene **4.2** could prepared from chlorohydroquinone **1.125** *via* an ortho-formylation reaction. A range of formylating agents have proved effective for these transformations including carbon monoxide in the Gattermann-Koch reaction, hexamine in the Duff reaction, chloroform in the Reimer-Tiemann reaction, DMF and $POCl_3$ in the Vilsmeier-Haack reaction, dichloromethyl methyl ether in the Rieche reaction and formaldehyde itself.[128–134] Directed ortho-metalation (DOM) followed by the addition of DMF is also a common method.

While, phenols have proven common substrates for these reactions, they can prove problematic giving low yields and/or low regioselectivity. In fact, greater success has been usually found when the phenol group is protected as an ether. Therefore, the above mentioned conditions were tested on both hydroquinone **1.125** and its methylated derivative **1.90** and the results are detailed in Table 4.2.

Table 4.2. Ortho-formylation of hydroquinone **1.125** and protected hydroquinone **1.90**.



1.125, R = H
1.90, R = Me

4.5, R = H
1.84, R = Me

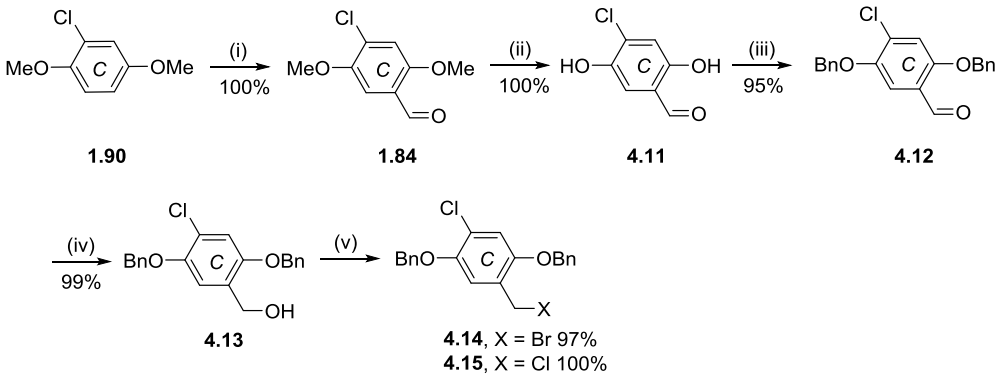
4.6, R = H
4.8, R = Me

4.7, R = H
4.9, R = Me

Entry	Substrate	Reaction Conditions	Result
1	**1.125**	$MgCl_2$, paraformaldehyde, NEt_3, 75 °C	**X**
2	**1.125**	$CHCl_3$, NaOH, EtOH, reflux	**X**
3	**1.125**	hexamine, TFA, 95 °C	1:1 **4.5**:**4.6** (92%)
4	**1.125**	DMF, $POCl_3$, NaOH, H_2O, 0-35 °C	**X**
5	**1.90**	$MgCl_2$, paraformaldehyde, NEt_3, 75 °C	**X**
6	**1.90**	hexamine, TFA, 95 °C	**1.84** (100%)
7	**1.90**	$CHCl_3$, NaOH, EtOH, reflux	**X**
8	**4.10**	hexamine, TFA, 95 °C	**X**

When hydroquinone **1.125** was used as the substrate, the vast majority of the reaction conditions trialled resulted in a low mass recovery of starting material as the only identified component in the reaction mixture. However, the Duff reaction (Table 4.2, entry 3) proved more effective with the desired aldehyde **4.5** and regioisomer **4.6** formed in a 1:1 ratio. Unfortunately, this mixture of regioisomers was only partially separable. Nonetheless, encouraged by this result and we repeated using methyl protected hydroquinone **1.90** as the substrate and found that it gave the desired aldehyde **1.84** in quantitative yield with no other regioisomers observed by ^{1}H NMR (Table 4.1, entry 6). However, we were aware that the subsequent hydrochlorination step

would benefit from having a large protecting group on these phenolic residues so we next tested the reaction on benzyl protected substrate **4.10**. Alas, this led to only recovered starting material, presumably due to the steric bulk of the benzyl groups preventing the approach of the bulky hexamine. Consequently, we found that it was necessary to remove the methyl ethers using boron tribromide (87% yield) then reprotect the resulting hydroquinone **4.11** using benzyl bromide and K_2CO_3 then proceeded in near quantitative yield to furnish **4.12** (Scheme 4.3). Reduction of the aldehyde delivered alcohol **4.13** which was converted into either benzyl bromide **4.14** or benzyl chloride **4.15** through the action of NCS/NBS and PPh_3.

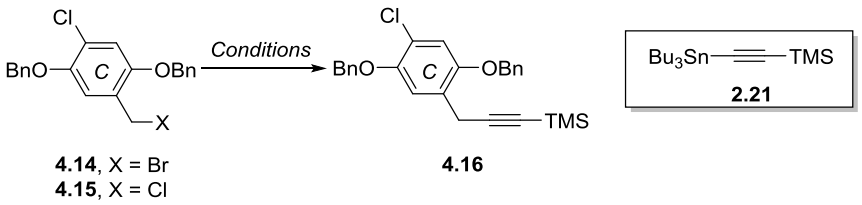


Reagents and conditions: (i) hexamine, TFA, 95 ^oC; (ii) BBr_3, DCM, RT; (iii) BnBr, K_2CO_3, acetone, 40 ^oC; (iv) $NaBH_4$ (2 equiv.), MeOH, 0 ^oC-RT; (v) NBS or NCS, PPh_3, THF, 0 ^oC-RT

Scheme 4.3. Preparation of benzyl halides **4.14** and **4.15**.

With benzyl halides **4.14** and **4.15** in hand, we then sought to introduce the key alkyne functionality to complete the synthesis of the *C* ring fragment. The conditions trialled for the coupling between these molecules and TMS-acetylene are summarised in Table 4.3.

Table 4.3. Metal catalysed couplings of benzyl halides **4.14** and **4.15**.

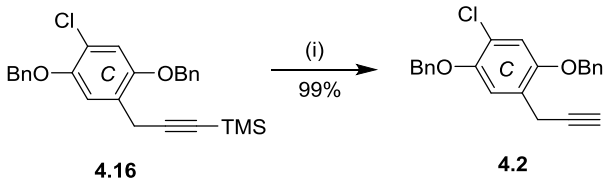


4.14, X = Br
4.15, X = Cl

4.16

Substrate	Reaction Conditions	Result
4.14	(i) ^{n}BuLi (2 equiv.), TMS acetylene (2 equiv.), Et_2AlCl (2 equiv.), Et_2O, 0 °C - RT (ii) $Ni(PPh_3)_2Cl_2$ (0.06 equiv.), Et_2O, RT	**4.14**
4.14	MeMgBr (4 equiv.), CuBr (1 equiv.), TMS acetylene (4 equiv.), THF, reflux	**4.14**
4.15	$PdCl_2(MeCN)_2$ (0.06 equiv.), XPhos (0.18 equiv.), TMS acetylene (1.5 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C	**4.15**
4.15	$Pd(dppf)Cl_2$ (0.04 equiv.), **2.21** (1.5 equiv.) KF (4 equiv.) 1,4-dioxane, 80 °C	**4.16** (98%)

Attempts to couple benzyl bromide **4.14** with an organoaluminium derivative of TMS-acetylene resulted in negligible product formation which was, unfortunately, unaffected by both increases in catalyst loading and equivalents of organoaluminium reagent.[135] The analogous coupling of the organomagnesium derivative suffered from a similar fate. Both reactions also gave a low mass balance, which we attribute to the instability of benzyl bromide **4.14**, which degraded upon storage even when protected from light. Thus, it was hoped that a switch to the more stable benzyl chloride **4.15** would lead to greater success. However, the Pd-catalysed coupling with TMS-acetylene only returned starting material, which was not entirely unexpected considering the difficulties encountered in our attempted coupling of TMS-acetylene and benzyl chlorides **2.11** and **1.168** during studies conducted on the synthesis of chrysophaentin F (See Section 2.3). As a Stille coupling had proven successful previously, these conditions were also applied to benzyl chloride **4.15**. Pleasingly, they led to alkyne **4.16** isolated in 95% yield. TMS deprotection was then accomplished using TBAF in AcOH giving alkyne **4.2** in near quantitative yield with no evidence of alkyne-allene isomerisation.



4.16 **4.2**

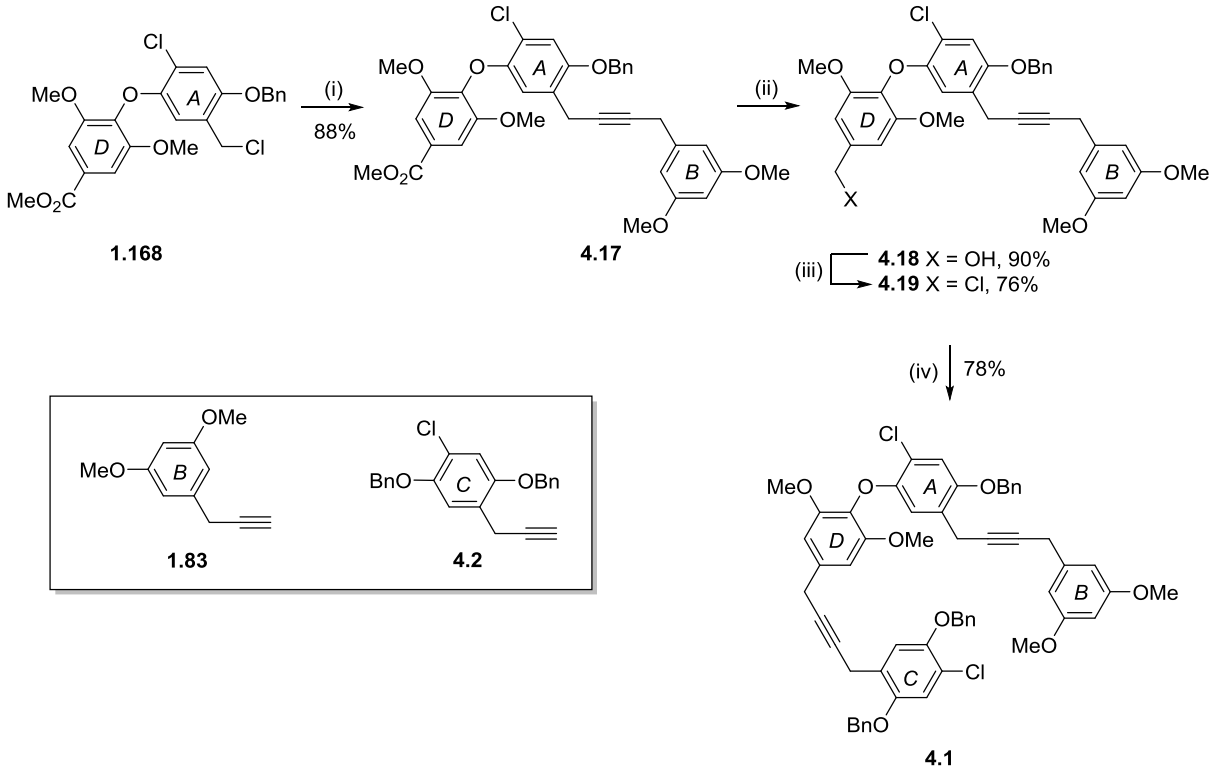
Reagents and conditions: (i) TBAF, AcOH (1:1), THF, RT

Scheme 4.4. Deprotection of **4.17** to provide the *C* Ring fragment **4.2**.

Irngartinger *et al.* had noted that a methyl protected derivative of **4.2** was found to oligimerise in solution and upon storage at −20 °C.[136] Even though this was not observed for **4.2**, as a precaution the *C* ring fragment was stored as the protected alkyne **4.16** and deprotected to **4.2** as required.

4.4 Progress Towards Chrysophaentin E

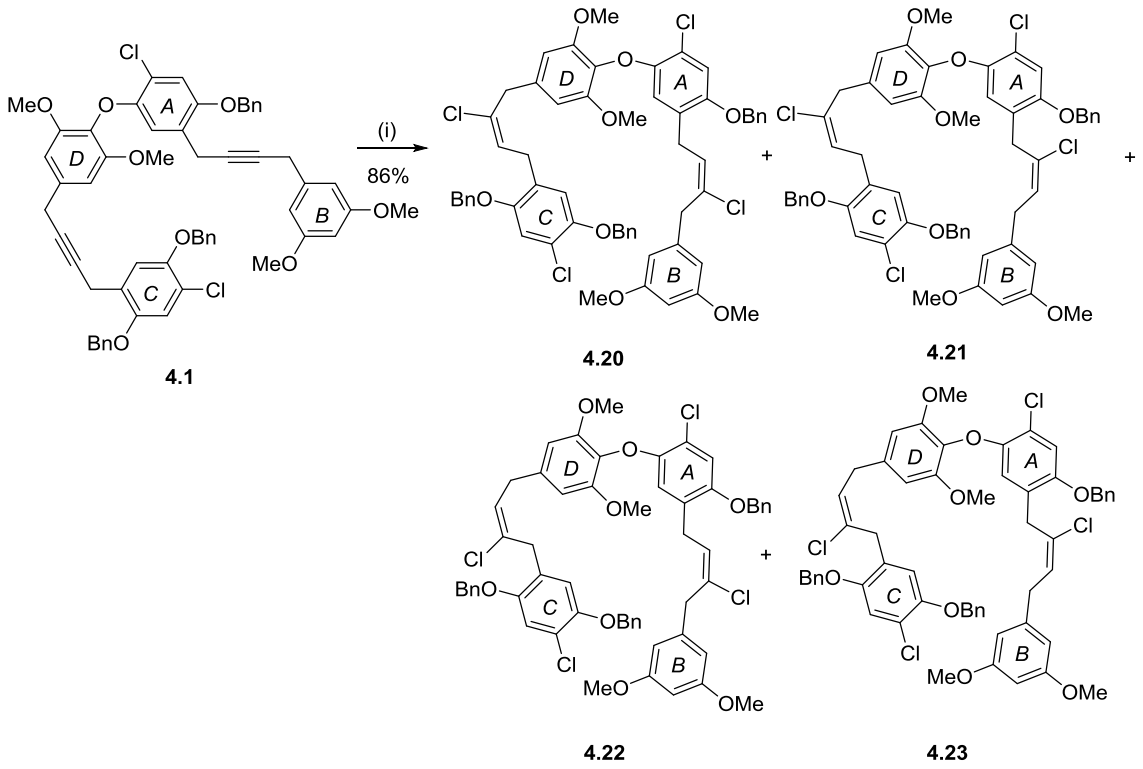
With both the *B* and *C* ring fragments in hand, we next sought to combine them with the previously prepared *AD* fragment (**1.168**) to deliver the core structure of chrysophaentin E. Firstly, benzyl chloride **1.168** was coupled with the *B* ring alkyne fragment **1.88** in 80% yield (Scheme 4.5). An analogous reaction in which the alkyne and benzyl chloride functionalities were swapped was also successfully realised albeit in lower yield. The ester group of **4.17** was then reduced with DIBAL to furnish alcohol **4.18** which was subsequently converted into chloride **4.19** through the use of PPh_3 and NCS. Next, **4.19** and the *C* ring fragment **4.2** were subjected to the Heck alkynylation conditions employed previously, and pleasingly these led to diyne **4.1** in 78% yield with no evidence of alkyne-allene isomerisation.



Reagents and conditions: (i) **1.83** (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C; (ii) DIBAL, THF, 0 °C-RT; (iii) NCS, PPh_3, THF, 0 °C-RT; (iv) **4.2** (1.5 equiv.), $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN, 65 °C

Scheme 4.5. Synthesis of diyne **4.1**.

Following this successful coupling, one final task remained, the installation of the (*E*)-vinyl chloride groups. Thus, diyne **4.1** was exposed to the hydrozirconation-chlorination methodology utilised in the aforementioned total synthesis of chrysophaentin F.



Reagents and conditions: (i) a) Cp_2ZrCl_2 (4 equiv.), DIBAL (4 equiv.), THF, 0-40 °C, b) NCS (2 equiv.), DCM, RT

Scheme 4.6. Hydrochlorination of **4.1** leading to possible regioisomers **4.20**-**4.23**.

This led to a complex product mixture with three main signals present in a ratio of 2:1:1, as well as a small undefined signal in the alkene region of the crude ^{1}H NMR (Figure 4.1).

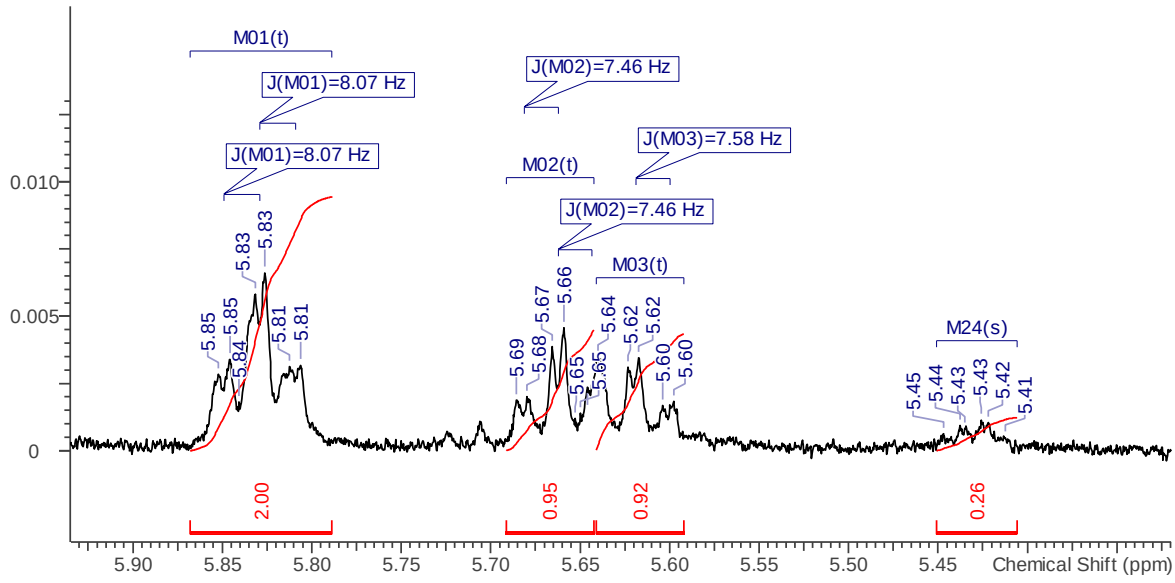
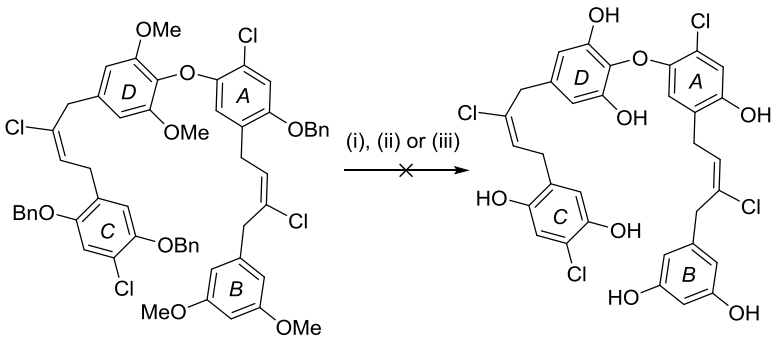


Figure 4.1. Signals present in the alkene region of the crude ^{1}H NMR of regioisomers **4.20**-**4.23**.

Therefore, in order to confirm the presence of chrysophaentin E we attempted to deprotect the mixture to enable comparison with literature data.[1] Unfortunately, the global deprotection conditions employed successfully for chrysophaentin F, BCl_3 and TBAI,[137] led to decomposition of the material. Other deprotection conditions were also attempted, including $AlBr_3$/EtSH[138] and BBr_3, but these too led to decomposition of the starting material.



4.20 + isomers **4.21-4.23** **1.5** + isomers **4.24-4.26**

Reagents and Conditions: (i) BCl_3, TBAI, DCM, –78-0 ^oC; (ii) BBr_3, DCM, –78-0 ^oC; (iii) a) Al, Br_2, DCM, 40 ^oC; b) EtSH, DCM, RT

Scheme 4.7. Attempted deprotection of mixture of regioisomers **4.20-4.23**.

4.5 NMR Analysis

These failures led us to return to the protected substrate, **4.20-4.23,** to establish the regioselectivity of the hydrochlorination reaction. Alas, attempts to separate the mixture of protected isomers **4.20-4.23** by column chromatography and HPLC proved ineffective. Thus, we were forced to identify the regioisomers formed using the NMR data obtained on the mixture. As noted previously, the alkene region of the ^1H NMR appeared to contain three main signals in a ratio of 2:1:1 at 5.83, 5.66 and 5.60 ppm as well as a small, additional and poorly resolved signal at 5.43 ppm. As this minor component was removed following purification of the mixture by column chromatography, it is possible that it belonged to a minor regioisomer.

Analysis of the COSY spectrum attained on the mixture showed that the signal at 5.83 ppm showed coupling to 2 different CH_2 groups, indicating that this signal was due to two different alkene protons. Further examination of the CH_2 region revealed the likely presence of 8 different CH_2 groups consistent with the isolated material being a 1:1 of two regioisomers. This ratio and number of products was also suggested by the presence of two doublets and two triplets in the aromatic region of the ^1H NMR which we attributed to the resonances of the protons on ring *B*. Due to extensive overlapping of the signals corresponding to the benzyl and methoxy protecting

groups, as well as a significant proportion of the protons belonging to rings *A*-*D*, our analysis of the NMR spectra was largely confined to the alkene region and attached CH_2 groups. The chemical shift as well as the observed H-H and H-C interactions for the protons in these regions is summarised in Table 4.4.

Table 4.4. Chemical shift, ^{1}H-^{1}H and ^{1}H-^{13}C interactions for key signals in the identification of regioisomers of chrysophaentin E.

δ_H ppm	**δ_C ppm**	**^{1}H-^{1}H Interactions**	**^{1}H-^{13}C Interactions**
5.83 (2H, t, *J* = 8.1 Hz, 2 x =CH)	127.3	3.18 (2H, d, *J* = 8.2 Hz, CH_2) 3.37 (2H, d, *J* = 8.1 Hz, CH_2)	
5.66 (1H, t, *J* = 7.5 Hz, =CH)	126.6	3.21 (2H, d, *J* = 8.1 Hz, CH_2)	
5.60 (1H, t, *J* = 7.5 Hz, =CH)	127.3	3.00 (2H, m, CH_2)	
3.66 (2H, m, CH_2)	34.0	6.88 (1H, s, 1 x ArH)	132.0, 124.7, 117.9
3.52 (2H, br s, CH_2)	39.8	6.32 (1H, d, *J* = 2.5 Hz, ArH)	133.1, 127.3, 106.1
3.48 (2H, br s, CH_2)	34.6	6.44 (2H, s, ArH)	
3.37 (2H, d, *J* = 8.1 Hz, CH_2)	29.9	5.83 (2H, t, *J* = 8.1 Hz, 2 x =CH)	150.3, 132.5, 127.2, 117.3
3.32 (2H, br s, CH_2)	39.8	6.13 (2H, d, *J* = 2.3 Hz, 2 x ArH)	139.4, 133.1, 127.2, 106.1
3.21 (2H, d, *J* = 8.1 Hz, CH_2)	29.2	5.66 (1H, t, *J* = 7.5 Hz, =CH)	132.8, 127.4, 115.5
3.18 (2H, d, *J* = 8.2 Hz, CH_2)	34.6	5.83 (2H, t, *J* = 8.1 Hz, 2 x =CH) 6.20 (2H, s, 2 x ArH)	137.0, 131.9, 127.2, 106.1
3.00 (2H, m, CH_2)	34.1	5.60 (1H, t, *J* = 7.5 Hz, =CH)	141.8

From the 2D spectra it can be determined that the CH_2 signals at 3.32 ppm and 3.32 ppm show a coupling to a 2H doublet present at 6.13 and 6.03 ppm respectively. Therefore, it follows that these CH_2 groups are attached to the *B* ring. Also, as neither of these signals exhibit coupling to any of the alkene protons, both of these CH_2 groups must be proximal to the Cl atom rather than the H atom of the vinyl chloride moieties (Figure 4.2). This was further evidenced by a HMBC interaction between the two CH_2 signals with the carbon at 133.1 ppm which is in the expected range for the C-Cl carbon of the vinyl chloride group.

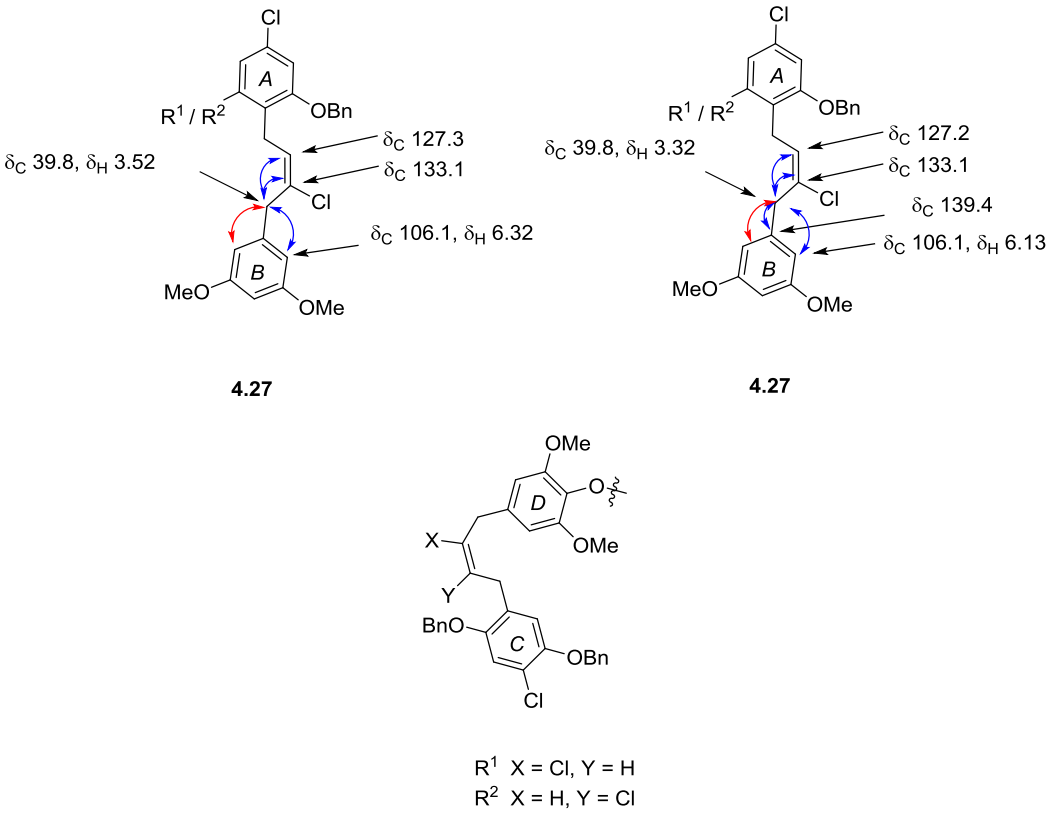
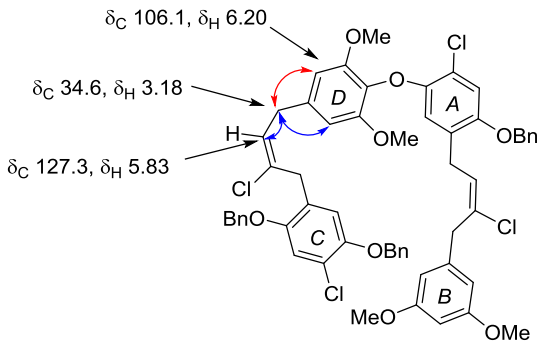


Figure 4.2. ^{1}H-^{1}H COSY (red) and HMBC (blue) interactions showing the regiochemistry of the vinyl chloride of the A-B fragment for both isomers.

The regiochemical assignment was also confirmed by the COSY and HMBC interactions of the CH_2 signals at 3.37 and 3.21 ppm. These signals each showed HMBC interactions with carbons that, based on their chemical shifts (115.5 and 127.4 ppm), are highly likely to belong to either arene *A* or *C*. As these signals exhibit a ^{1}H-^{1}H coupling to the alkene protons at 5.83 ppm and 5.66 ppm respectively, it follows that there are at least two vinyl chloride groups in where the alkene proton is proximal to ring *A*/*C*.

Of the remaining CH_2 groups, the signal at 3.18 ppm showed a COSY interaction with the 2H singlet at 6.20 ppm and an equivalent HMBC interaction to the carbon at 106.1 ppm. Based on their chemical shifts, these signals are highly likely to belong to the other dimethoxyarene, ring *D.* This CH_2 signal also couples to one of the alkene protons present at 5.83 ppm, which implies that for one isomer, the vinyl chloride is orientated with the its chlorine atom carbon proximal to ring *C* (Figure 4.3). Therefore, as both regioisomers contain fragment **4.27**, one of the regioisomers must be **4.22**.



4.22

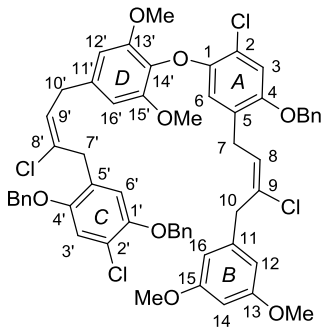
Figure 4.3. ^{1}H-^{1}H COSY (red) and HMBC (blue) interactions confirming the presence of regioisomer **4.22**.

The CH_2 signal at 3.00 ppm displayed a coupling to the remaining alkene proton at 5.60 ppm and showed a HMBC interaction with the carbon at 141.8 ppm. This carbon signal is more difficult to assign conclusively but is typical for an aromatic carbon bonded to an alkoxide and therefore, is likely to belong to either ring *A* or *C*. However, a precise assignment is rendered reduntant by the fact that the remaining isomer must possess A-B fragment **4.27** and that regioisomer **4.22** has already been identified. Thus, the second regioisomer must be chrysophaentin E precursor **4.20**.

Analysis of the penultimate CH_2 signal at 3.66 ppm showed that it displayed HMBC interactions with aromatic carbons at 117.9 and 124.7 ppm, which are credible for a chlorine containing arene (ring *A*/*C*). The HMBC spectra also revealed an interaction with a carbon at 132.0 ppm which is likely to be a vinyl chloride carbon. It follows, as this signal shows no coupling to any of the alkene protons, that this CH_2 is proximal to ring *C* in regioisomer **4.22**.

The remaining CH_2 signal at 3.48 ppm, showed a ^{1}H-^{1}H interaction with a 2H singlet at 6.44 ppm, which would be expected for the sole outstanding CH_2 group that is proximal to ring *D* in regioisomer **4.20**. Unfortunately, the data attained did not allow us to distinguish between the *A* and *C* rings so we are unable to conclusively assign which alkene protons and which CH_2 signals belonged to each isomer. Those assignments known are described in Tables 4.5 and 4.6.

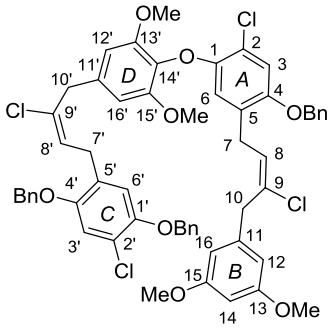
Table 4.5. Assigned chemical shifts of regioisomer **4.22**



4.22

Position	δ_c	δ_H
7’	34.0	3.66 (2H, m, CH_2)
8’	132.0	
9	133.2	
9’	127.3	5.83 (2H, t, *J* = 8.1 Hz, 2 x =CH)
10	39.8	3.52/3.32 (2H, br s, CH_2)
10’	34.6	3.18 (2H, br s, CH_2)
12, 16	106.1	6.32/6.13 (2H, d, *J* = 2.3 Hz, CH_2)
12’, 16’	106.1	6.20 (2H, s, CH_2)

Table 4.6. Assigned chemical shifts of protected chrysophaentin E, **4.20**

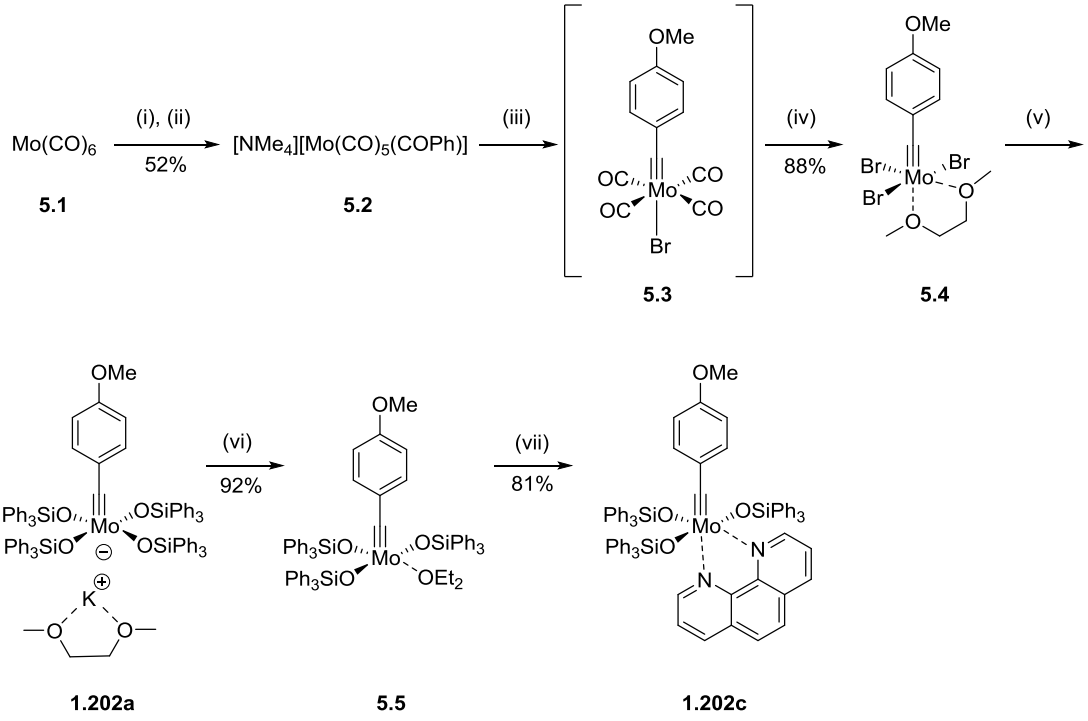


4.20

Position	δ_c	δ_H
9	133.2	
10	39.8	3.52/3.32 (2H, br s, CH_2)
10’	34.6	3.48 (2H, br s, CH_2)
12, 16	106.1	6.32/6.13 (2H, d, *J* = 2.3 Hz, CH_2)
12’, 16’	106.1	6.44 (2H, s, CH_2)

Chapter 5 Conclusions and Future Work

During the course of this PhD, the main aim has been the total synthesis of chrysophaentin F. This has been achieved with chrysophaentin F isolated as the major component of a 2:1 mixture of regioisomers. Thus, the immediate aim of any future work would be to attempt a variety of purification methods to facilitate the isolation of chrysophaentin F in a pure form. To do this, an alternative commercial supplier for crucial RCAM catalyst **1.202c** would need to be procured or the catalyst would need to be prepared in-house[66] (Scheme 5.1).



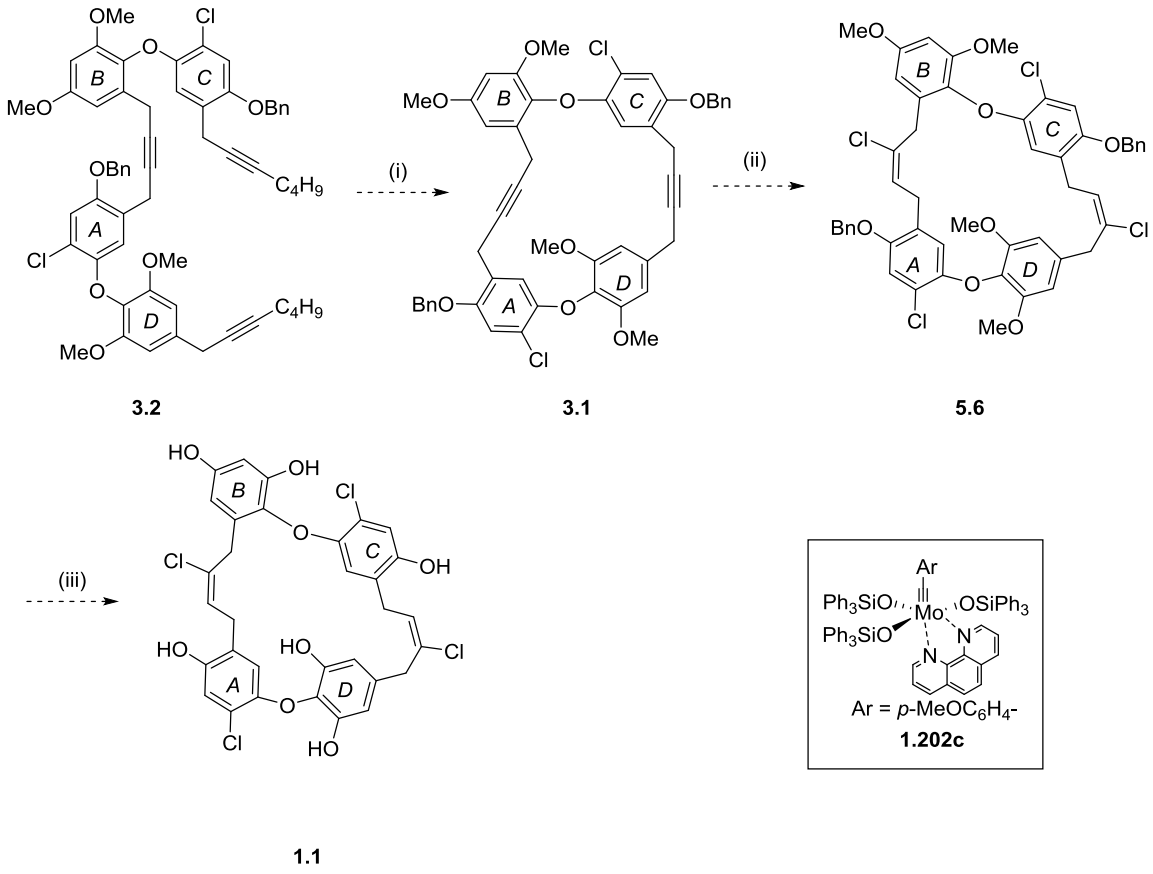
Reagents and conditions: (i) PhLi (1 equiv.), Et_2O, reflux; (ii) NMe_4Br, H_2O; (iii) oxalyl bromide, DCM, −78 °C to −15 °C; (iv) Br_2, 1,2-dimethoxyethane, DCM, −78 °C to RT; (v) Ph_3SiOK (4 equiv), PhMe; (vi) Et_2O; (viii) 1,10-phenanthroline, PhMe/Et_2O

Scheme 5.1. Synthesis of catalyst **1.202c** by Fürstner *et al.*

Hopefully, once the catalyst had been prepared, it would be able to facilitate the RCAM of **2.2** to **2.1** and thus, provide the quantities of chrysophaentin F and its regioisomer, **2.39** needed to screen a variety of purification methods. It may be possible to separate the two regioisomers by reverse-phase chromatography as slight separation was observed when the mixture was analysed by LC-MS. Alternatively, Keffer *et al.* were able to separate the (*E*)- and (*Z*)- isomers of hemichrysophaentin **1.70** by supercritical fluid chromatography so this may be another option.

Preparation of **1.202c** would also allow our RCAM strategy to be conducted on chrysophaentin A precursor **3.2** to see if it is equally effective for the preparation of macrocycle **3.1**. Once

prepared, it would need to be subjected to our hydrozirconation-chlorination methodology then deprotected to hopefully provide chrysophaentin A and any related regioisomers.



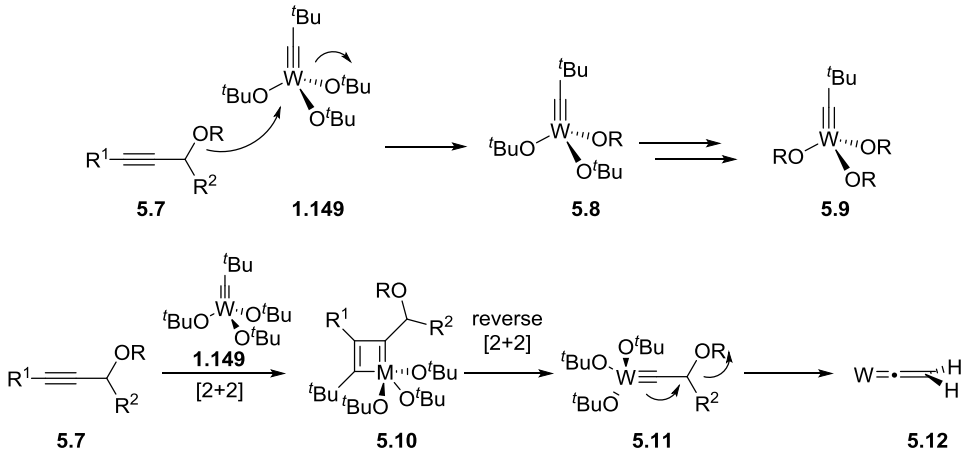
Reagents and conditions: (i) **1.202c** (0.25 equiv.), $MnCl_2$ (0.25 equiv.), PhMe, 40 °C; (ii) a) Cp_2ZrCl_2 (4 equiv.), DIBAL (4 equiv.), THF 0-40 °C, b) NCS, RT; (iii) BCl_3, TBAI, DCM −78-0 °C

Scheme 5.2. Completion of the total synthesis of chrysophaentin A, **1.1**.

For completion of the total synthesis of chrysophaentin E, the initial challenge would be the establishment of deprotection conditions to remove the three benzyl and four methyl ethers present in advanced precursor **4.20**. As previous attempts had resulted in decomposition of the material, it is clear that chrysophaentin E is more sensitive than its macrocyclic relative, chrysophaentin F, which was cleanly deprotected using BCl_3/TBAI. The cleavage of aryl methyl ethers is typically achieved with strong protic[139] or Lewis acids,[140,141] bases,[142] nucleophiles,[143] and alkali metals.[144] As these appear harsh, it may be necessary to use a different protecting group strategy to realise the total synthesis of chrysophaentin E. Due to the position of the hydroxyl groups in question, it is important that the new protecting group is not too large to impact the formation of the hindered diaryl ether bond. With this in mind, the use of a methoxymethyl (MOM) protected ether could prove effective as it can be cleaved under milder acidic conditions.[145–147]

Once syntheses of chrysophaentins A, E and F have been achieved, attention could focus on our synthetic route. In particular, it would be helpful to improve the selectivity of the hydrozirconation reaction. It is clear that the benzyl group provides some beneficial directing influence on the hydrozirconation reaction, however, as it is remote from the alkyne it may be difficult to increase the steric impact of the benzyl group significantly. Tactically, the adoption of a larger protecting group with steric bulk closer to the oxygen atom may prove more effective. Initial studies into the use of both TIPS and TBS groups ran into difficulties in the protection stages, as the neighbouring benzylic alcohol caused some migration of the silyl group. Thus, a silicon based protecting group is unlikely to provide a satisfactory solution. Instead, a bulky carbon based group such as trityl or perhaps even an ^{i}propyl or ^{t}butyl could prove to be more stable and would certainly increase steric bulk close to the alkyne. This in turn could improve selectivity in the hydrozirconation reaction.

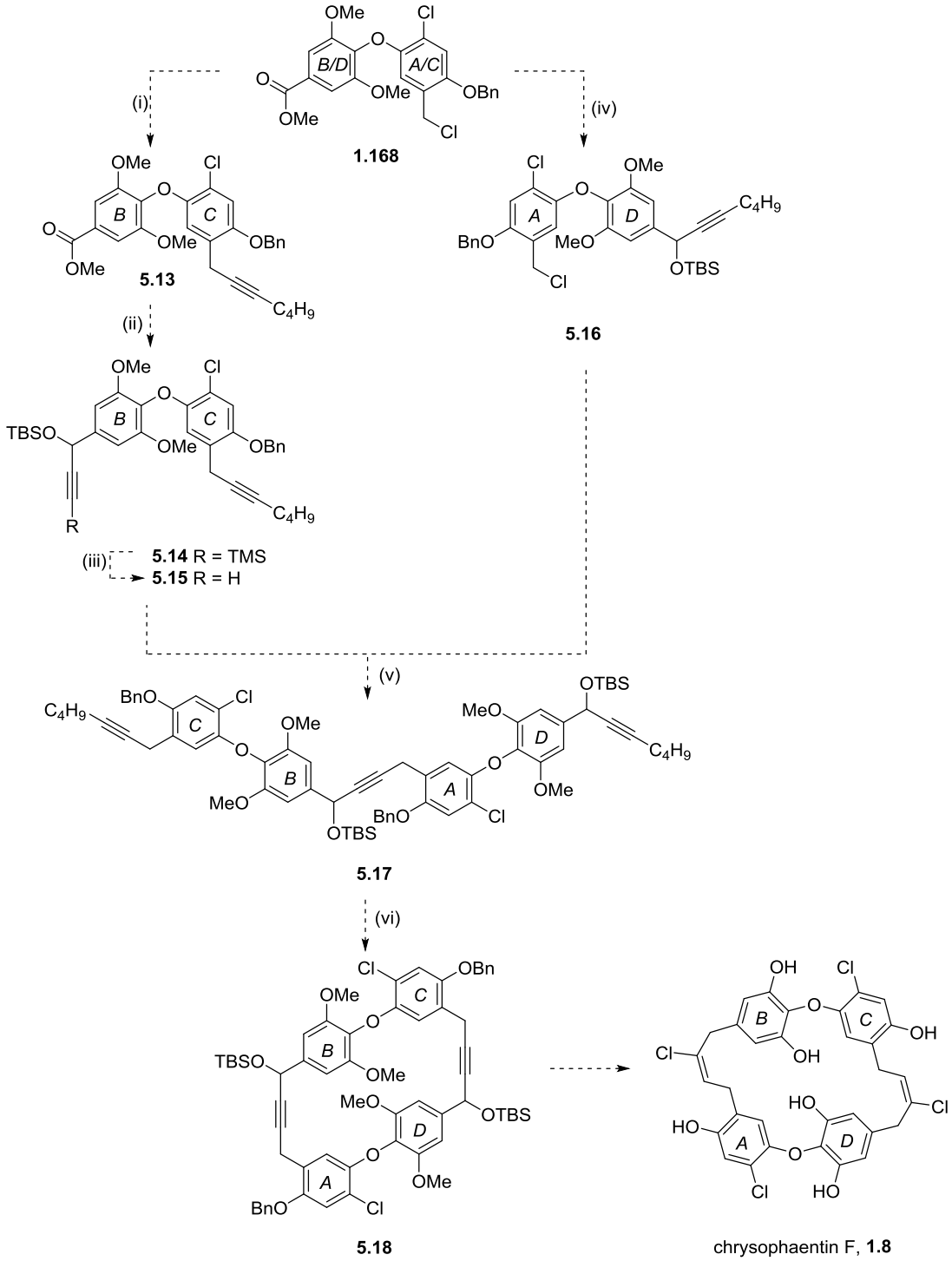
As an alternative, it may be possible to use the proximal phenolic residue as a directing group for hydrometallation of the alkyne. While the phenolic residue is quite remote from the alkyne, the strained nature of the macrocycle may mean that reactions proceed *via* a low energy confirmation that directs the addition of the M-H complex to the triple bond. On the other hand, the use of propargylic alcohol groups to direct the regiochemistry of a hydrometallation is well known, with Red-Al proving particularly effective.[148] However, within the realm of alkyne metathesis, alcohols have been found to be tricky substrates due to the inherent Lewis acidity of the metal centre and their ability to substitute the critical alkoxide or silanoate ligands of the catalyst (Scheme 5.3). Propargylic alcohols in particular, both in their protected and unprotected form, have proved to be particularly problematic due to their properties as a good leaving group and thus are easily lost from a metal carbyne complex such as **5.11**.



Scheme 5.3. Side reactions observed during the metathesis of propargylic alcohols.

However, catalysts including and based upon **1.202** have proved successful in some cases, including in the field of total synthesis.[67,97,149–152] Larsen *et al.* also showed that protected alcohols were tolerated by their Heck alkynylation methodology.[46] Thus, our original synthetic strategy would be amenable to this modification.

The use of propargylic alcohol groups to direct the hydrometallation of alkynes has been found to result in different regio- and stereochemistries based upon the metal chosen. For example, both hydroalumination and hydrosilylation can result in either *cis*- or *trans*- addition yet, hydroalumination generally results in the metal distal to the hydroxyl group whereas, hydrosilylation results in the silyl group proximal to the directing group.[90,153–156] With Schwartz's reagent, the stereoselective *cis*-addition is maintained but the regiochemistry can be switched by the addition of MeLi and $ZnCl_2$.[157] Therefore, two possible alternative routes to chrysophaentin F could be designed, with the directing groups proximal to either rings *B* and *D* or *A* and C rings. As the most common preparation of propargylic alcohols is *via* the addition of an alkynyl organometallic such as a Grignard reagent to a carbonyl compound, the former strategy is the easiest option. Thus, our common diaryl ether intermediate **1.168** could be first coupled with hex-1-yne to provide **5.13**, then addition of [(trimethylsilyl)ethynyl]magnesium bromide would furnish *BC* fragment **5.15** following deprotection of the silyl group. The *AD* fragment **5.16** could be prepared by the addition of hex-1-yn-1-ylmagnesium bromide and then coupled with **5.15** to provide RCAM precursor **5.16** (Scheme 5.4). Upon successful ring closure and hydrometallation-halogenation, the propargylic alcohols could be cleaved in a two step process by firstly converting the alcohol to a better leaving group (e.g. OTs) and then elimination with $LiAlH_4$ or through the action of chlorodiphenylsilane and $InCl_3$.[158]

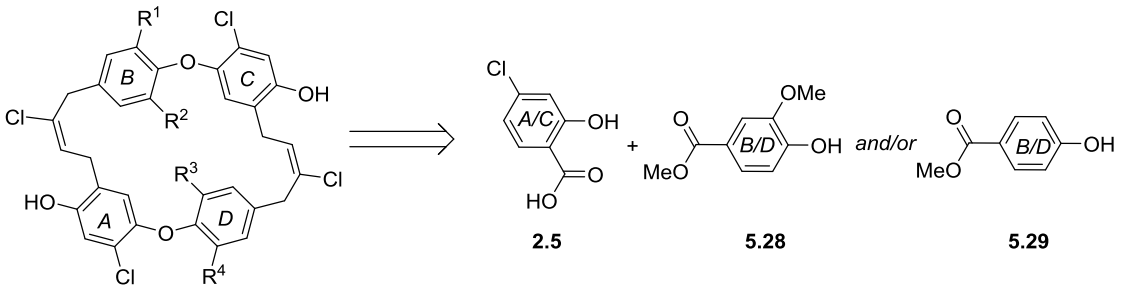


Reagents and conditions: (i) hex-1-yne (1.5 equiv.) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN; (ii) a) [(trimethylsilyl)ethynyl]magnesium bromide (2 equiv.), THF, b) TBSCl, imidazole, DCM; (iii) AgOTf, MeOH/H_2O/DCM; (iv) hex-1-yn-1-ylmagnesium bromide (2 equiv.), THF; (v) $Pd(MeCN)_2Cl_2$ (0.06 equiv.), XPhos (0.18 equiv.), Cs_2CO_3 (1.1 equiv.), MeCN; (vi) **1.202c** (0.25 equiv.), $MnCl_2$ (0.25 equiv.), PhMe

Scheme 5.4. Alternative synthesis of chrysophaentin F *via* propargylic alcohol directed hydrometallation-chlorination.

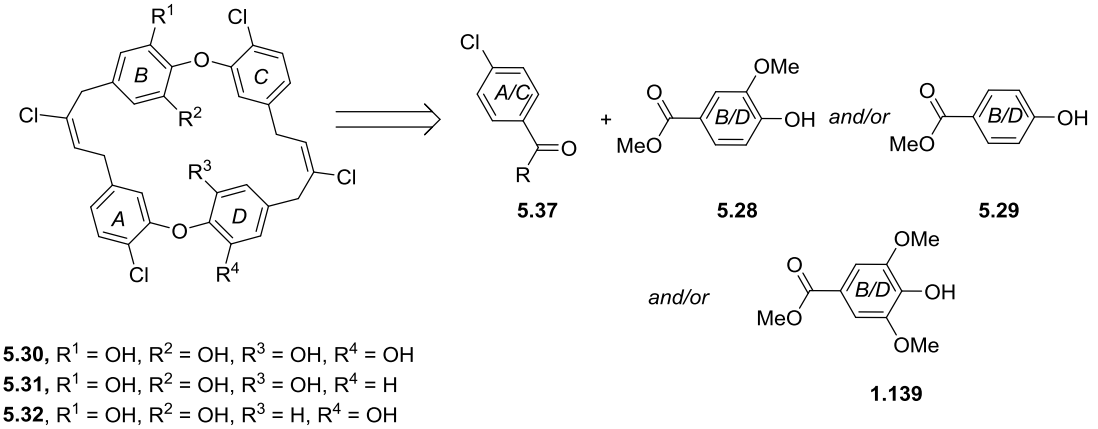
From a therapeutic perspective, the synthetic methodology developed herein should be amenable to the synthesis of a variety of chrysophaentin analogues. The hydrozirconation-

chlorination approach group could also be used to vary the nature of the tri-substituted alkene groups through the use of different electrophiles. Also, while frustrating from the perspective of total synthesis, the unnatural regioisomers provided by the hydrozirconation-chlorination can be termed new "chrysophaentins". These are intriguing biological prospects and may help to determine if the regiochemistry of the vinyl chloride is crucial for biological activity. Initial structure activity relationships have revealed that the hydroxyl groups of the chrysophaentins are needed for activity.[2] However, as this was deduced from a hexaacetate derivative of chrysophaentin A, it is unknown if all six hydroxyl groups are necessary. Thus, our methodology provides a means to synthesise derivatives of the chrysophaentins which possess or delete hydroxyl groups at various positions (Scheme 5.5).



2.5 **5.28** **5.29**

5.19, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH
5.20, R^1 = OH, R^2 = H, R^3 = OH, R^4 = H
5.21, R^1 = H, R^2 = OH, R^3 = OH, R^4 = H
5.22, R^1 = OH, R^2 = OH, R^3 = H, R^4 = H
5.23, R^1 = OH, R^2 = H, R^3 = H, R^4 = H
5.24, R^1 = H, R^2 = OH, R^3 = H, R^4 = H
5.25, R^1 = H, R^2 = H, R^3 = H, R^4 = H
5.26, R^1 = OH, R^2 = OH, R^3 = OH, R^4 = H
5.27, R^1 = OH, R^2 = OH, R^3 = H, R^4 = OH



5.37 **5.28** **5.29**

1.139

5.30, R^1 = OH, R^2 = OH, R^3 = OH, R^4 = OH
5.31, R^1 = OH, R^2 = OH, R^3 = OH, R^4 = H
5.32, R^1 = OH, R^2 = OH, R^3 = H, R^4 = OH
5.33, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH
5.34, R^1 = OH, R^2 = H, R^3 = OH, R^4 = H
5.34, R^1 = OH, R^2 = H, R^3 = H, R^4 = H
5.36, R^1 = H, R^2 = OH, R^3 = H, R^4 = H

Scheme 5.5. Retrosynthesis of chrysophaentin F analogues **5.19**-**5.27** and **5.30**-**5.36**.

Chapter 6 Experimental

6.1 General Method

All commercial compounds were used as received, unless otherwise stated.

DCM and NEt_3 were distilled from CaH_2, EtOH from $Mg(OEt)_2$, THF and Et_2O from Na/benzophenone and PhMe from sodium, all under argon.

All air and water sensitive reactions were carried out in flame-dried glassware under an argon atmosphere.

All reactions were monitored by TLC on precoated plates (Merck silica gel 60 F254) and the products were visualised with 254 nm/326 nm UV followed by most commonly, Phosphomolybdic acid (PMA), *p*-anisaldehyde, DNPH or $KMnO_4$ as appropriate.

Purification by column chromatography was accomplished with silica Merck, Geduran® Si 60 Å pore size, 40-63 µm particle size or Sigma-Aldrich, technical grade 60 Å pore size, 230-400 mesh particle size and 40-63 µm particle size. Petroleum ether was used as fraction 40-60 °C. Purification by preparative layer chromatography, was carried out on Analtech Inc silica gel GF UV254 plates 20 x 20 cm.

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AVII, AVIIIHD 400 FT-NMR Spectrometer (400/100 MHz) at 298 K unless otherwise stated. Variable temperature analysis was conducted on Bruker AVIIIHD500 FT-NMR Spectrometer (500/125 MHz). Analyses were carried out in deuterated chloroform ($CDCl_3$) unless otherwise stated, which Goss Scientific or Sigma-Aldrich supplied. Assignments were made on the basis of chemical shifts, coupling constants (*J*), DEPT-135, COSY, HSQC, HMBC and comparison with literature values where available. Residual solvent peaks were used as reference. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, spt = septet, m = multiplet or a combination of the above), coupling constant *J* (Hz), integration and attribution. Coupling constants (*J*) are rounded to the nearest 0.1 Hz.

Infrared spectra (IR) were recorded on a Nicolet 380/iS5 Laboratory FT-IR spectrometer. Spectra were acquired from pure samples or evaporated solution in $CDCl_3$. Absorptions are described as s (strong), m (medium), w (weak) or br (broad) and reported in cm^{-1}.

Melting points were measured on a microscopic Electrothermal IA9100 Digital Melt Point Apparatus and are uncorrected.

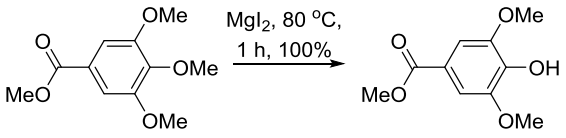
ESI mass spectra were recorded using a Waters (Manchester, UK) TQD mass spectrometer equipped with a triple quadrupole analyser. Samples were introduced to the mass spectrometer *via* an Acquity H-Class quaternary solvent manager (with TUV detector at 254 nm, sample and column manager). Ultra-performance liquid chromatography was undertaken *via* a Waters BEH C18 column (50 mm x 2.1 mm 1.7 µm). Gradient 20% MeCN (0.2% formic acid) to 100% MeCN (0.2% formic acid) in five minutes at a flow rate of 0.6 mL/min. MeOH or MeCN were used as the sample preparation solvents.

EI spectra were measured on a Thermo (Hemel Hempstead, UK) Trace GC-MS equipped with a single quadrupole analyser. Gas chromatography was undertaken *via* a Phenomenex ZB5-MS 30 m x 0.25 mm 0.25 µm thickness non-polar column using helium as a carrier gas at 1.2 mL/ min. The injector temperature was set at 240 ºC and 1 µL of sample was injected in splitless mode. Low resolution mass spectra were recorded over a mass range of *m/z* 40-500 using positive ion electron ionisation (or chemical ionisation using ammonia as a reagent gas) at 70 eV. DCM was used as the sample preparation solvent. Samples indicated as (EI-Direct) were analysed by electron ionisation *via* direct insertion probe on the Thermo Mat 900 XP double focusing high resolution mass spectrometer system.

APPI (atomospheric pressure photoionisation) spectra were measured using a solariX mass spectrometer equipped with Fourier Transform Ion Cyclotron Resonance (FT-ICR).

6.2 Chrysophaentin F

Methyl 4-hydroxy-3,5-dimethoxybenzoate (1.141)



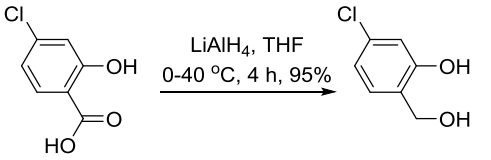
1.139 **1.141**

$C_{11}H_{14}O_5$ MW: 226.23 $C_{10}H_{12}O_5$ MW: 212.20

Adapted from a procedure by Bao *et al.*[141] To a suspension of magnesium turnings (3.65 g, 0.15 g per atom) in Et_2O (100 mL) at 0 °C was added iodine (19.2 g, 75.6 mmol). After 2 h at reflux, was added a solution of methyl-3,4,5-trimethoxybenzoate **1.139** (7.92 g, 35.0 mmol) in DCM (50 mL). The solvent was then removed by distillation and the temperature raised to 80 °C. After 1 h, H_2O (100 mL), $Na_2S_2O_3$ (10% aqueous solution, 20 mL) and EtOAc (40 mL) were added to the reaction mixture. The aqueous phase separated and extracted with EtOAc (3 x 40 mL). The organic phases were combined, washed with H_2O (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound **1.141** as a pale yellow solid (7.42 g, 35.0 mmol, 100%) with physical and spectroscopic data were consistent with reported values.[159]

MP:	105.3 - 107.1 °C (EtOAc) (lit. 105 - 107 °C).[159]
IR ν_{max} (neat, cm^{-1}):	3303 br s, 2944 w, 2840 w, 1694 s, 1611 m, 1594 m, 1518 m, 1459 m, 1371 w, 1333 s, 1232 s, 1180 s, 1103 s, 845 w, 755 s.
^{1}H NMR (400 MHz; $CDCl_3$):	δ ppm 7.33 (2H, s, 2 x Ar**H**), 5.91 (1H, br s, O**H**), 3.95 (6H, s, 2 x C**H$_3$**), 3.91 (3H, s, C**H$_3$**).
^{13}C NMR (100 MHz; $CDCl_3$):	δ ppm 166.8 (**C**), 146.6 (2 x **C**), 139.2 (**C**), 121.1 (**C**), 106.6 (2 x **C**H), 56.4 (2 x **C**H_3), 52.1 (**C**H_3).
LRMS (HPLC-MS; ESI^-):	211 $[M-H]^-$ (58%).

5-Chloro-2-(hydroxymethyl)phenol (1.157)



2.5

$C_7H_5ClO_3$
MW: 172.56

1.157

$C_7H_7ClO_2$
MW: 172.56

To a solution of 4-chloro-2-hydroxybenzoic acid (**2.5**) (5.18 g, 0.30 mmol) in THF (100 mL) at 0 °C was added a solution of $LiAlH_4$ (1M in THF, 45 mL, 45.0 mmol) dropwise over 10 minutes. After 4 h at 40 °C, MeOH (20 mL) and saturated Rochelle's salt (30 mL) were then added and the solution was stirred for 2 h. The aqueous phase was separated and extracted with EtOAc (3 x 50 mL). The organic phases were combined then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (100% EtOAc) to afford the title compound **1.157** as an off-white solid (4.50 g, 28.3 mmol, 95%) with physical and spectroscopic data consistent with reported values.[160]

MP: 118.0 - 119.5 °C (EtOAc) (lit. 119 - 120 °C).[161]

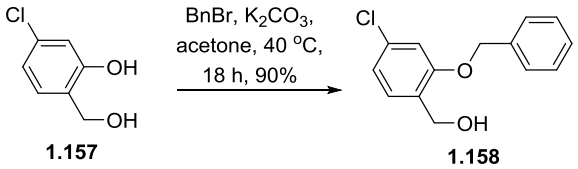
IR ν_{max} (neat, cm^{-1}): 3714 br, 2921 w, 2154 w, 2055 m, 1981 m, 1953 m, 1608 w, 1570 w, 1471 w, 1209 w, 1076 w, 1007 w, 810 w.

^{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**), 6.84 (1H, dd, *J* = 8.1, 2.0 Hz, Ar**H**), 4.87 (2H, s, C**H$_2$**), 2.12 (1H, br s, O**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 157.0 (**C**), 134.8 (**C**), 128.5 (**C**H), 122.9 (**C**), 120.2 (**C**H), 117.1 (**C**H), 64.4 (**C**H_2).

LRMS (HPLC-MS; ESI^-): 159 $[M^{37}Cl\text{-}H]^-$ (36%), 157 $[M^{35}Cl\text{-}H]^-$ (100%).

(2-(Benzyloxy)-4-chlorophenyl)methanol (1.158)



1.157

$C_7H_7ClO_2$
MW:158.58

1.158

$C_{14}H_{13}ClO_2$
MW: 248.71

To a solution of phenol **1.157** (5.00 g, 31.5 mmol) in acetone (210 mL) was added K_2CO_3 (12.6 g, 91.4 mmol) and benzyl bromide (5.93 g, 4.12 mL, 34.7 mmol). After 18 h at 40 °C, the reaction mixture was cooled and concentrated *in vacuo*. The resulting residue was partitioned between EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was separated and extracted with EtOAc (3 x 50 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (30-40% EtOAc in petroleum ether) afforded the title compound **1.158** as a white solid (7.06 g, 28.4 mmol, 90%) with physical and spectroscopic data consistent with reported values.[162]

MP: 58.0 - 59.1 °C (EtOAc) (lit. 57.5 - 59 °C EtOAc).[45]

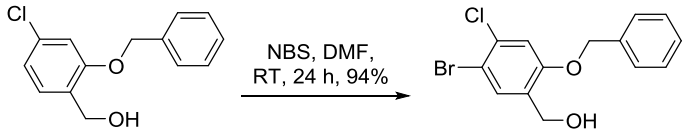
IR ν_{max} (neat, cm^{-1}): 3289 br s, 2919 w, 2862 w, 1597 m, 1585 m, 1489 m, 1450 m, 1404 m, 1365 m, 1241 s, 1225 s, 1053 s, 1043 s, 1026 s, 903 s, 835 m, 725 s, 690 s.

^{1}H NMR (400 MHz; MeCN-d_3): δ ppm 7.48-7.30 (6H, m, 6 x Ar**H**), 7.02 (1H, d, *J* = 2.0 Hz, Ar**H**), 6.98 (1H, dd, *J* = 8.1, 2.0 Hz, Ar**H**), 5.12 (2H, s, C**H$_2$**), 4.59 (2H, d, *J* = 6.0 Hz, C**H$_2$**), 3.11 (1H, t, *J* = 6.0 Hz, O**H**).

^{13}C NMR (101 MHz; MeCN-d_3): δ ppm 158.1 (**C**), 138.4 (**C**), 134.7 (**C**), 130.25 (**C**), 130.1 (2 x **C**H), 129.7 (**C**H), 129.2 (2 x **C**H), 128.6 (**C**H), 121.7 (**C**H), 113.5 (**C**H), 71.5 (**C**H$_2$), 60.0 (**C**H$_2$).

LRMS (GC-MS; EI): 250 $[M^{37}Cl]^{+\cdot}$ (0.1%), 248 $[M^{35}Cl]^{+\cdot}$ (1%).

(2-(Benzyloxy)-5-bromo-4-chlorophenyl)methanol (1.159)



1.158

$C_{14}H_{13}ClO_2$
MW: 248.71

1.159

$C_{14}H_{12}BrClO_2$
MW: 327.60

To a solution of **1.158** (6.50 mg, 26.1 mmol) in DMF (52 mL) was added *N*-bromosuccinimide (4.88 g, 27.4 mmol). After 24 h at RT, EtOAc (200 mL) and H_2O (700 mL) were added. The organic phase was separated, washed with H_2O (3 x 150 mL) and brine (150 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in petroleum ether) afforded the title compound **1.159** (8.01 g, 24.4 mmol, 94%) as an off-white solid with data consistent with reported values.[45]

MP: 89.0 - 91.5 °C (EtOAc).

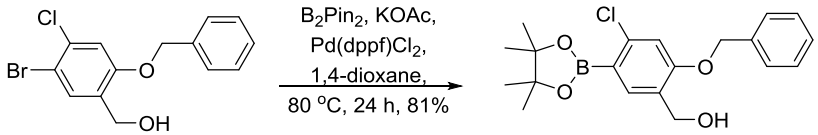
IR ν_{max} (neat, cm^{-1}): 3260 br s, 2917 w, 2864 w, 1596 m, 1585 m, 1488 m, 1450 m, 1242 s, 1041 m, 1001 m, 900 m, 835 m, 725 m, 690 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.58 (1H, s, Ar**H**), 7.44-7.37 (5H, m, 5 x Ar**H**), 7.05 (1H, s, Ar**H**), 5.09 (2H, s, C**H₂**), 4.69 (2H, d, *J* = 6.4 Hz, C**H₂**), 2.07 (1H, t, *J* = 6.5 Hz, O**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 155.8 (**C**), 135.7 (**C**), 133.8 (**C**), 132.7 (**C**H), 130.2 (**C**), 128.8 (2 x **C**H), 128.5 (**C**H), 127.4 (2 x **C**H), 113.8 (**C**), 113.2 (**C**H), 70.7 (**C**H_2), 60.6 (**C**H_2).

HRMS (ESI^+): Calculated for $C_{14}H_{12}BrClNaO_2^+$ $[M^{79}Br^{35}Cl+Na]^+$ 348.9601, found 348.9603.

(2-(Benzyloxy)-4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl)-methanol (1.160)



1.159

$C_{14}H_{12}BrClO_2$
MW: 327.60

1.160

$C_{20}H_{24}BClO_4$
MW: 374.67

A flask charged with bromoarene **1.159** (5.00 g, 15.3 mmol), bis(pinacolato)diboron (4.65 g, 18.3 mmol) and KOAc (4.20 g, 42.8 mmol) was evacuated and filled with argon in 3 cycles. 1,4-dioxane (80 mL) was then added, followed by Pd(dppf)Cl_2 (1.87 g, 2.30 mmol) and the reaction mixture was degassed with argon for 5 minutes. After 24 h at 80 °C, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in petroleum ether) afforded the title compound **1.160** as an off-white solid (4.65 g, 12.4 mmol, 81%) with physical and spectroscopic data consistent with reported values.[45]

MP: 100.8 - 102.0 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}): 3408 br s, 2974 w, 2925 w, 1600 m, 1371 m, 1324 s, 1232 w, 1140 s, 1120 m, 1052 w, 968 w, 851 m, 731 m, 697 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.68 (1H, s, Ar**H**), 7.44-7.37 (5H, m, 5 x Ar**H**), 6.97 (1H, s, Ar**H**), 5.12 (2H, s, C**H_2**), 4.69 (2H, d, *J* = 4.4 Hz, C**H_2**), 2.06 (1H, t, *J* = 6.7 Hz, O**H**), 1.37 (12H, s, 4 x C**H_3**),

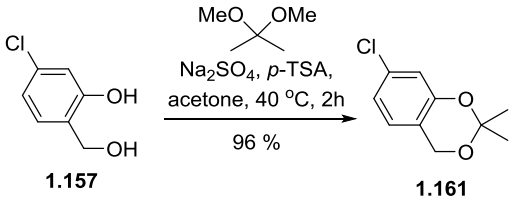
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 158.9 (**C**), 140.5 (**C**), 136.9 (**C**), 135.9 (**C**), 128.8 (2 x **C**H), 128.3 (**C**H), 127.4 (**C**), 127.3 (2 x **C**H), 113.2 (**C**H), 83.9 (**C**), 70.3 (**C**H_2), 61.3 (**C**H_2), 24.8 (4 x **C**H_3) with one C resonance not observed.

LRMS (HPLC-MS; ESI^+): 399 $[M^{37}Cl+Na]^+$ (1%), 397 $[M^{35}Cl+Na]^+$ (5%).

357 $[M^{37}Cl\text{-}H_2O+H]^+$ (23%), 397 $[M^{35}Cl\text{-}H_2O+H]^+$ (68%).

HRMS (ESI^+): Calculated for $C_{20}H_{24}BClNaO_4^+$ $[M^{79}Br^{35}Cl+Na]^+$ 397.1352, found 397.1352.

7-Chloro-2,2-dimethyl-4*H*-benzo[d][1,3]dioxine (1.161)



1.157

$C_7H_7ClO_2$
MW:158.58

1.161

$C_{10}H_{11}ClO_2$
MW: 198.65

To a solution of salicylic alcohol **1.157** (500 mg, 3.15 mmol) in acetone (10 mL) was added 2,2-dimethoxypropane (1.93 mL, 15.8 mmol), Na_2SO_4 (1.79 g, 12.6 mmol) and *p*-TSA (108 mg, 0.63 mmol). After 2 h at 40 °C, the reaction mixture was concentrated *in vacuo*. The resulting residue was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was separated and extracted with EtOAc (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% Et_2O in petroleum ether) afforded the title compound **1.161** as a white solid (598 mg, 3.01 mmol, 96%) with physical and spectroscopic data consistent with reported values.[45]

MP: 64.6 - 65.1 °C ($CDCl_3$/petroleum ether) (lit. 64.5 - 65.2 °C $CHCl_3$).[45]

IR ν_{max} ($CDCl_3$, cm^{-1}): 3288 br s, 2928 w, 2880 w, 1595 m, 1585 m, 1455 m, 1427 m, 1340 m, 1293 s, 1202 s, 1064 s, 1055 s, 1006 s, 862 s, 827 s, 700 s, 654 s.

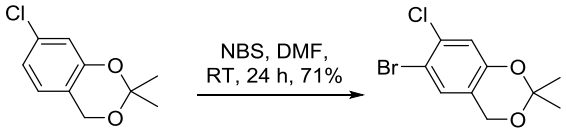
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.89 (2H, m, 2 x Ar**H**), 6.85 (1H, d, *J* = 1.1 Hz, Ar**H**), 4.82 (2H, s, C**H_2**), 1.54 (6H, s, 2 x C**H_3**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 151.9 (**C**), 133.2 (**C**), 125.6 (**CH**), 120.5 (**C**H), 117.9 (**C**), 117.3 (**C**H), 99.9 (**C**), 60.6 (**C**H_2), 24.7 (2 x **C**H_3).

LRMS (GC-MS; EI): 199 $[M^{37}Cl]^{+\cdot}$ (10%), 197 $[M^{35}Cl]^{+\cdot}$ (51%).

142 $[M^{37}Cl\text{-}C_3H_6O]^{+\cdot}$(28%), 140 $[M^{35}Cl\text{-}C_3H_6O]^{+\cdot}$ (100%).

6-Bromo-7-chloro-2,2-dimethyl-4*H*-benzo[d][1,3]dioxine (1.162)



1.161

$C_{10}H_{11}ClO_2$
MW:198.65

1.162

$C_{10}H_{10}BrClO_2$
MW:277.54

To a solution of **1.161** (300 mg, 1.51 mmol) in DMF (3 mL) was added *N*-bromosuccinimide (296 mg, 1.66 mmol). After 24 h at RT, EtOAc (20 mL) and H_2O (50 mL) were added. The organic phase was separated, washed with H_2O (3 x 15 mL) and brine (15 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5% Et_2O in petroleum ether) afforded the title compound **1.162** as an off-white solid (299 mg, 1.08 mmol, 71%) with physical and spectroscopic data consistent with reported values.[45]

MP: 45.0 - 46.8 °C ($CDCl_3$/petroleum ether) (lit. 44.5 - 46 °C $CHCl_3$)[45]

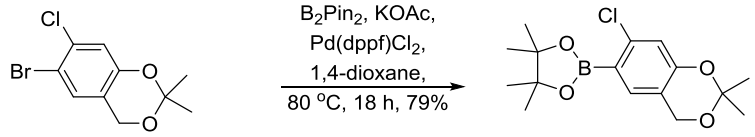
IR ν_{max} (neat, cm^{-1}): 3285 br s, 2992 w, 2858 w, 1599 m, 1565 m, 1473 m, 1453 s, 1337 s, 1229 s, 1100 m, 1064 m, 962 m, 845 m, 728 m, 649 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.22 (1H, t, *J* = 1.0 Hz, 1 x Ar**H**), 6.96 (1H, s, Ar**H**), 4.79 (2H, d, *J* = 0.6 Hz, C**H$_2$**), 1.53 (6H, s, 2 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 151.1 (**C**), 133.3 (**C**), 129.2 (**C**H), 119.8 (**C**), 119.0 (**C**H), 112.5 (**C**), 100.2 (**C**), 60.0 (**C**H_2), 24.6 (2 x **C**H_3).

LRMS (GC-MS; EI): 280 $[M^{81}Br\ ^{37}Cl]^{+\cdot}$ (3%), 278 $[M^{79}Br\ ^{37}Cl]^{+\cdot}$ $[M^{81}Br\ ^{35}Cl]^{+\cdot}$ (12%), 276 $[M^{79}Br\ ^{35}Cl]^{+\cdot}$ (10%).

2-(7-Chloro-2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.163)



1.162

$C_{10}H_{10}BrClO_2$
MW: 277.54

1.163

$C_{16}H_{22}CClO_4$
MW: 324.61

A flask charged with bromoarene **1.162** (100 mg, 0.36 mmol), bis(pinacolato)diboron (110 mg, 0.43 mmol) and KOAc (78 mg, 0.79 mmol) was evacuated and filled with argon in 3 cycles. 1,4-dioxane (3 mL) was then added, followed by $Pd(dppf)Cl_2$ (26 mg, 0.04 mmol) and the reaction mixture was degassed with argon for 5 minutes. After 18 h at 80 °C, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (0-5% Et_2O in petroleum ether) afforded the title compound **1.163** (92 mg, 0.28 mmol, 79%) as a pale yellow oil with physical and spectroscopic data consistent with reported values.[45]

IR ν_{max} ($CDCl_3$, cm^{-1}): 3402 br s, 2982 w, 2940 w, 1606 m, 1570 m, 1373 w, 1353 m, 1329 s, 1285 w, 1132 m, 1106 m, 961 m, 871 w.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (1H, s, Ar**H**), 6.85 (1H, s, Ar**H**), 4.81 (2H, s, C**H$_2$**), 1.53 (6H, s, 2 x C**H$_3$**), 1.36 (12H, s, 4 x C**H$_3$**)

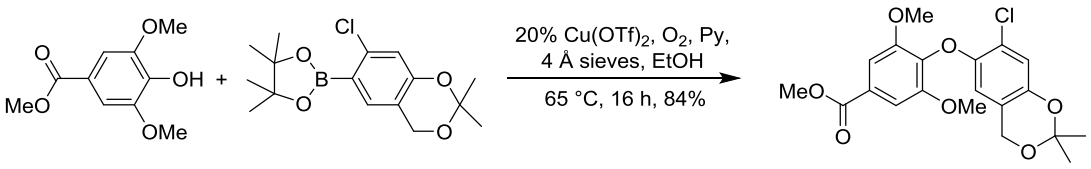
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 154.1 (**C**), 139.1 (**C**), 133.2 (**C**H), 118.1 (**C**H), 117.4 (**C**), 100.2 (**C**), 83.4 (**C**), 60.5 (**C**H_2), 24.8 (4 x **C**H_3), 24.7 (2 x **C**H_3) with one C resonance not observed.

LRMS (HPLC-MS): 327 $[M^{37}Cl+H]^+$ (1.5%), 325 $[M^{35}Cl+H]^+$ (4%).

347 $[M^{37}Cl+Na]^+$ (0.6%), 349 $[M^{35}Cl+Na]^+$ (1.5%).

HRMS (ESI^+): Calculated for $C_{16}H_{22}BClNaO_4^+$ $[M^{79}Br^{35}Cl+Na]^+$ 347.1195, found 347.1186.

Methyl 4-((7-chloro-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)oxy)-3,5-dimethoxybenzoate (1.165)



1.141 **1.163** **1.165**

$C_{10}H_{12}O_5$ 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 **1.141** (50 mg, 0.23 mmol), boronic ester **1.163** (76 mg, 0.23 mmol) and copper triflate (21 mg, 0.06 mmol) in EtOH (2.5 mL) containing powdered 4 Å molecular sieves was placed under a slight positive pressure of oxygen. Pyridine (0.09 mL, 1.15 mmol) was then added and the reaction mixture was heated at 65 °C for 16 h. The reaction mixture was then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10-20% EtOAc in petroleum ether) afforded the title compound **1.165** as a white solid (79 mg, 0.20 mmol, 84%).

MP: 161.5 - 162.9 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2983 w, 2938 w, 2839 w, 1715 s, 1596 s, 1491 s, 1464 s, 1413 s, 1338 m, 1282 w, 1125 s, 1044 m, 881 m, 862 m, 754 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (2H, s, 2 × Ar**H**), 6.92 (1H, s, Ar**H**), 6.13 (1H, s, Ar**H**), 4.64 (2H, s, C**H$_2$**), 3.95 (3H, s, C**H$_3$**), 3.84 (6H, s, 2 × C**H$_3$**), 1.50 (6H, s, 2 × C**H$_3$**).

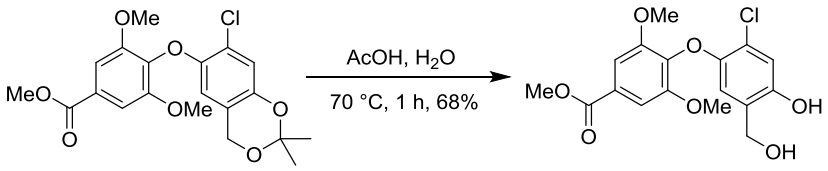
^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 166.5 (**C**O), 153.0 (2 x **C**), 147.6 (**C**), 146.0 (**C**), 136.6 (**C**), 127.2 (**C**), 121.8 (**C**), 118.7 (**C**H), 118.1 (**C**), 110.2 (**C**H), 106.9 (2 x **C**H), 99.5 (**C**), 60.5 (**C**H_2), 56.5 (2 x **C**H_3), 52.4 (**C**H_3), 24.6 (2 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 411 $[M^{37}Cl+H]^+$ (4%), 409 $[M^{35}Cl+H]^+$ (11%).

433 $[M^{37}Cl+Na]^+$ (0.6%), 431 $[M^{35}Cl+Na]^+$ (2%).

HRMS (ESI^+): Calculated for $C_{20}H_{21}ClNaO_7^+$ $[M^{35}Cl+Na]^+$ 431.0868, found 431.0870.

Methyl 4-(2-chloro-4-hydroxy-5-(hydroxymethyl)phenoxy)-3,5-dimethoxybenzoate (1.166)



1.165

$C_{20}H_{21}ClO_7$
MW: 408.83

1.166

$C_{17}H_{17}ClO_7$
MW: 368.77

A suspension of acetal **1.165** (50.0 mg, 0.12 mmol) in water (0.4 mL) and AcOH (0.9 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 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 and concentrated *in vacuo*. Purification by column chromatography (30-40% EtOAc in petroleum ether) afforded the title compound **1.166** as a white solid (30 mg, 0.08 mmol, 68%).

MP: 148.8 - 149.5 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 3458 br s, 2953 w, 1713 s, 1597 m, 1497 m, 1464 s, 1412 s, 1342 s, 1212 m, 1185 s, 1126 s, 996 m, 760 s.

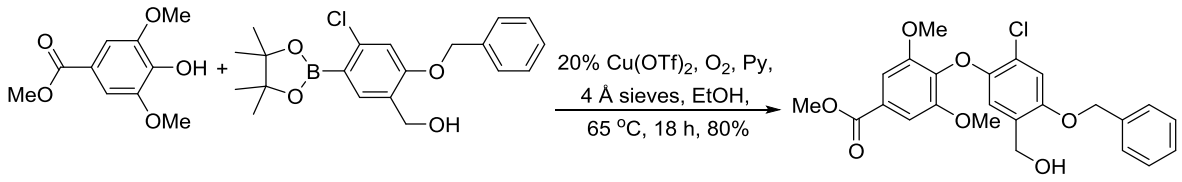
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.38 (2H, s, 2 × Ar**H**), 7.05 (1H, s, Ar**H**), 6.41 (1H, s, Ar**H**), 4.90 (s, 2H, C**H$_2$**), 3.96 (3H, s, C**H$_3$**), 3.85 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 166.2 (**C**O), 153.0 (2 x **C**), 150.6 (**C**), 147.5 (**C**), 136.7 (**C**), 127.3 (**C**), 125.0 (**C**), 120.5 (**C**), 119.8 (**C**H), 117.4 (**C**H), 107.1 (2 x **C**H), 62.7 (**C**H_2), 56.5 (2 x **C**H_3), 52.4 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 353 $[M^{37}Cl\text{-}OH]^+$ (30%), 351 $[M^{35}Cl\text{-}OH]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{17}H_{17}ClNaO_7^-$ $[M^{35}Cl+Na]^+$: 391.0555, found 391.0547.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(hydroxymethyl)phenoxy)-3,5-dimethoxybenzoate (1.167)



1.141 **1.160** **1.167**

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

$C_{20}H_{24}BClO_4$ MW: 374.67

$C_{24}H_{23}ClO_7$ MW: 458.89

To a solution of phenol **1.141** (991 mg, 4.67 mmol), boronic ester **1.160** (1.75 g, 4.67 mmol) and copper triflate (338 mg, 0.93 mmol) in EtOH (70 mL) was added powdered molecular sieves (1:1 phenol; 991 mg). The reaction mixture was then put under a slight positive pressure of oxygen and pyridine (2.83 mL, 35.0 mmol) was added. After 18 h at 65 °C the reaction mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc in petroleum ether) afforded **1.167** as a pale orange solid (1.86 g, 4.06 mmol, 87%) with physical and spectroscopic data consistent with reported values.[45]

MP: 145.0 - 146.5 °C (EtOAc) (lit. 146 - 147 °C EtOAc).[45]

IR ν_{max} (neat, cm^{-1}): 3497 br, 2929 w, 2839 w, 1699 m, 1597 m, 1491 m, 1462 w, 1337 s, 1215 s, 1184 s, 1126 s, 1113 s, 993 m, 864 m, 760 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44-7.35 (5H, m, 5 x Ar**H**), 7.04 (1H, s, Ar**H**), 6.52 (1H, s, Ar**H**), 5.07 (2H, s, Ar**H**), 4.54 (2H, d, *J* = 6.2 Hz, C**H$_2$**), 3.95 (3H, s, C**H$_3$**), 3.84 (6H, s, 2 x C**H$_3$**), 2.05 (1H, t, *J* = 6.5 Hz, O**H**).

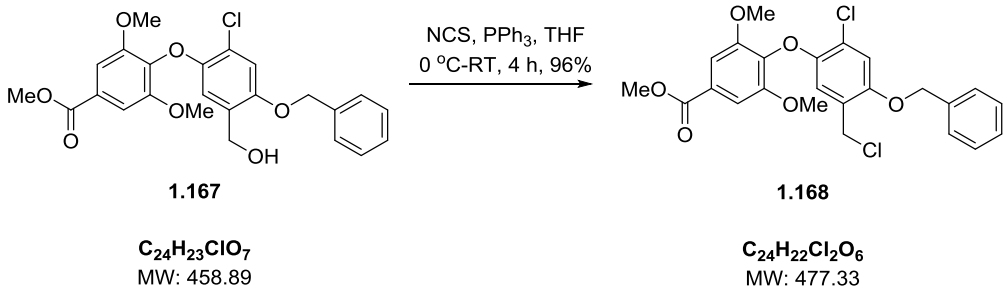
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 166.5 (**C**O), 153.1 (2 x **C**), 151.3 (**C**), 147.9 (**C**), 136.7 (**C**), 136.3 (**C**), 129.0 (**C**), 128.7 (2 x **C**H), 128.3 (**C**H), 127.4 (2 x **C**H), 127.3 (**C**), 121.5 (**C**), 114.9 (**C**H), 114.1 (**C**H), 107.1 (2 x **C**H), 71.0 (**C**H_2), 61.3 (**C**H_2), 56.5 (2 x **C**H_3), 52.3 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 483 $[M^{37}Cl+Na]^+$ (1%), 481 $[M^{35}Cl+Na]^+$ (8%).

443 [M^{37}Cl-OH]$^+$ (100%), 441 [M^{35}Cl-OH]$^+$ (43%).

HRMS (ESI$^+$): Calculated for $C_{24}H_{23}ClNaO_7^+$ [M^{35}Cl+Na]$^+$ 481.1025, found 481.1019.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(chloromethyl)phenoxy)-3,5-dimethoxybenzoate (1.168)



1.167 **1.168**

$C_{24}H_{23}ClO_7$ MW: 458.89 **$C_{24}H_{22}Cl_2O_6$** MW: 477.33

To a solution of benzyl alcohol **1.167** (8.53 g, 18.6 mmol) in THF (100 mL) at 0 °C was added PPh_3 (5.85 g, 22.3 mmol) and *N*-chlorosuccinimide (2.97 g, 22.3 mmol). After 4 h at RT, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (60-70% $CHCl_3$ in petroleum ether) afforded the title compound **1.168** as an off-white solid (8.50 g, 17.8 mmol, 96%) with physical and spectroscopic data consistent with reported values.[45]

MP: 175.0 - 176.2 °C (EtOAc) (lit. 174 - 176 °C EtOAc).[45]

IR ν_{max} (neat, cm^{-1}): 2942 w, 2838 w, 1728 m, 1599 m, 1500 s, 1340 m, 1257 m, 1221 s, 1132 s, 997 m, 866 m, 760 m.

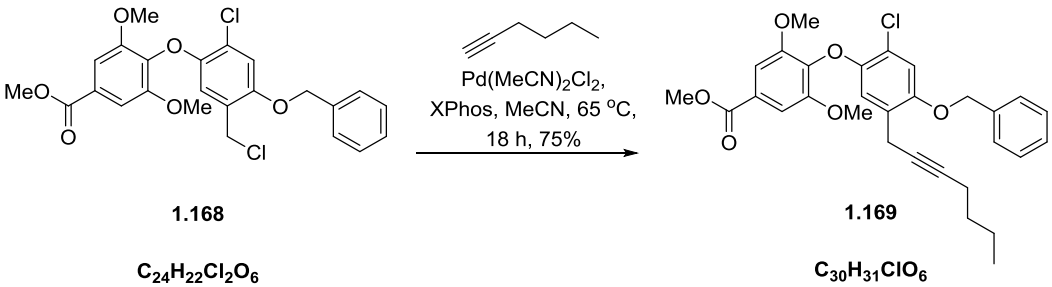
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46-7.36 (7H, m, 7 x Ar**H**), 7.04 (1H, s, Ar**H**), 6.56 (1H, s, Ar**H**), 5.10 (2H, s, C**H$_2$**), 4.50 (2H, s, C**H$_2$**), 3.96 (3H, s, C**H$_3$**), 3.84 (6H, s, 2 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 166.5 (**C**O), 152.9 (2 x **C**), 151.4 (**C**), 147.8 (**C**), 136.5 (**C**), 136.4 (**C**), 128.6 (2 x **C**H), 128.1 (**C**H), 127.4 (**C**), 127.3 (2 x **C**H), 125.5 (**C**), 123.0 (**C**), 116.6 (**C**H), 114.7 (**C**H), 107.1 (2 x **C**H), 71.1 (**C**H$_2$), 56.5 (2 x **C**H$_3$), 52.4 (**C**H$_3$), 40.9 (**C**H$_2$).

LRMS (HPLC-MS; ESI$^+$): 499 [M^{35}Cl+Na]$^+$.

HRMS (ESI$^+$): Calculated for $C_{24}H_{22}Cl_2NaO_6$ [$M^{35}Cl^{35}$Cl+Na]$^+$ 499.0686, found 499.0693.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (1.169)



1.168

$C_{24}H_{22}Cl_2O_6$
MW: 477.33

1.169

$C_{30}H_{31}ClO_6$
MW: 523.02

A flask charged with benzyl chloride **1.168** (200 mg, 0.42 mmol), $Pd(MeCN)_2Cl_2$ (7 mg, 0.03 mmol), XPhos (36 mg, 0.08 mmol) and Cs_2CO_3 (151 mg, 0.46 mmol) was evacuated and filled with argon in 3 cycles. Hex-1-yne (0.75 mL, 0.67 mmol) and MeCN (2 mL) were then added sequentially and the reaction mixture was degassed with argon for 5 minutes. After 18 h at 65 °C, the reaction mixture was filtered through a pad of silica, concentrated *in vacuo* and purification by column chromatography (10% EtOAc in petroleum ether) to afford the title compound **1.169** as a pale brown solid (164 mg, 0.31 mmol, 75%).

MP: 138.5 - 140.0 °C (EtOAc) (lit. 138 - 139 °C).[45]

IR ν_{max} (neat, cm^{-1}): 2954 w, 1712 m, 1458 m, 1422 m, 1336 s, 1213 m, 1128 m, 997 m, 866 m, 760 m.

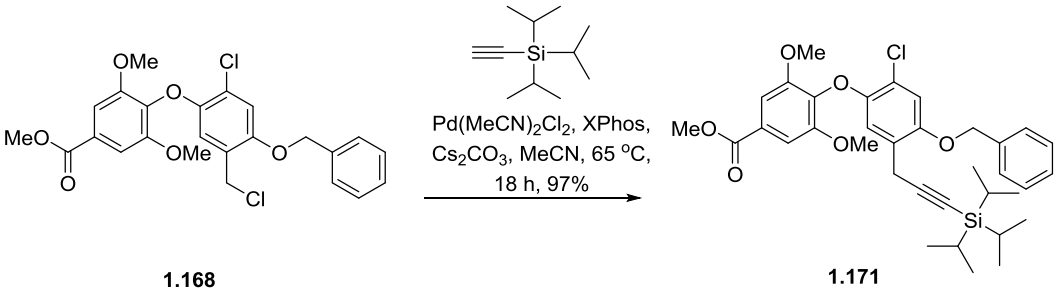
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.42 - 7.34 (7H, m, 7 x Ar**H**), 6.96 (1H, s, Ar**H**), 6.79 (1H, s, Ar**H**), 5.04 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.85 (6H, s, 2 x C**H$_3$**), 3.44 (2H, s, C**H$_2$**), 2.07 - 1.97 (2H, m, C**H$_2$**), 1.29 - 1.25 (4H, m, 2 x C**H$_2$**), 0.84 (3H, t, *J* = 7.3 Hz, C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 165.6 (**C**O), 153.2 (2 x **C**), 150.8 (**C**), 147.7 (**C**), 137.0 (**C**), 136.8 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (**C**), 127.1 (2 x **C**H), 126.0 (**C**), 120.0 (**C**), 115.5 (**C**H), 113.6 (**C**H), 107.1 (2 x **C**H), 83.2 (**C**), 76.4 (**C**), 70.8 (**C**H_2), 56.5 (2 x **C**H_3), 52.3 (**C**H_3), 31.0 (**C**H_2), 21.9 (**C**H_2), 19.6 (**C**H_2), 18.3 (**C**H_2), 13.4 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 589 $[M^{37}Cl+Na+MeCN]^+$ (1%), 587 $[M^{35}Cl+Na+MeCN]^+$(7%).

HRMS (ESI^+) Calculated for $C_{30}H_{31}ClNaO_6^+$ $[M^{35}Cl+Na]^+$ 545.1701, found 545.1704.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (1.171)



1.168

$C_{24}H_{22}Cl_2O_6$
MW: 477.33

1.171

$C_{35}H_{43}ClO_6Si$
MW: 623.26

A flask charged with benzyl chloride **1.168** (180 mg, 0.38 mmol), $Pd(MeCN)_2Cl_2$ (6 mg, 0.02 mmol), XPhos (32 mg, 0.068 mmol) and Cs_2CO_3 (136 mg, 0.418 mmol) was evacuated and filled with argon in 3 cycles. TIPS-acetylene (0.136 mL, 0.608 mmol) and MeCN (3 mL) were then added sequentially and the reaction degassed with argon for 5 minutes. After 18 h at 65 °C, the reaction mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in petroleum ether) afforded the title compound **1.171** as a pale orange solid (230 mg, 0.37 mmol, 97%).

MP: 87.0 - 89.0 °C (EtOAc) (lit. 83 - 84 °C EtOAc).[45]

IR ν_{max} (neat, cm^{-1}): 2941 m, 2864 m, 1718 w, 1491 m, 1462 s, 1414 m, 1340 s, 1211 s, 1188 s, 1130 s, 1017 m, 996 m, 760 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46-7.30 (7H, m, 7 x Ar**H**), 6.98 (1H, s, Ar**H**), 6.86 (1H, s, Ar**H**), 5.03 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.81 (6H, s, 2 x C**H$_3$**), 3.61 (2H, s, C**H$_2$**), 0.96-0.90 (21H, m, 6 x C**H$_3$** and 3 x C**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 166.4 (**C**O), 152.9 (2 x **C**), 150.6 (**C**), 147.8 (**C**), 136.6 (**C**), 136.5 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.22 (**C**), 127.0 (2 x **C**H), 124.9 (**C**), 120.0 (**C**), 114.6 (**C**H), 113.2 (**C**H), 107.0 (2 x **C**H), 104.3 (**C**), 83.7 (**C**), 70.6

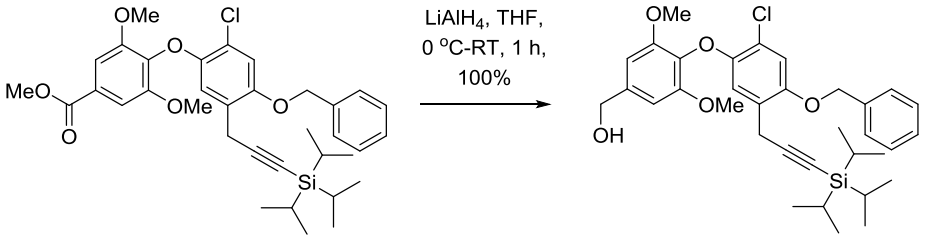
(**C**H_2), 56.4 (2 x **C**H_3), 52.3 (**C**H_3), 20.7 (**C**H_2), 18.5 (6 x **C**H_3), 11.1 (3 x **C**H).

LRMS (HPLC-MS; ESI^+): 625 $[M^{37}Cl+H]^+$ (15%), 623 $[M^{35}Cl+H]^+$ (35%).

HRMS (ESI^+): Calculated for $C_{35}H_{44}ClO_6Si^+$ $[M^{35}Cl+H]^+$: 623.2590, found: 623.2599.

Calculated for $C_{35}H_{43}ClNaO_6Si^+$ $[M^{35}Cl+Na]^+$: 645.2410, found: 645.2423.

(4-(4-(Benzyloxy)-2-chloro-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (2.7)



1.171

$C_{35}H_{43}ClO_6Si$
MW: 623.26

2.7

$C_{34}H_{43}ClO_5Si$
MW: 595.25

To a solution of benzyl ester **1.171** (1.00 g, 1.60 mmol) in THF (25 mL) at 0 °C was added a solution of $LiAlH_4$ (1M in THF, 1.92 mL, 1.92 mmol) over 5 minutes. After 1 h at RT, MeOH (25 mL) and sat. Rochelle's salt (40 mL) were added and the solution stirred for 1 h. The aqueous phase was separated and extracted with EtOAc (3 x 30 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (40% EtOAc in petroleum ether) afforded the title compound **2.7** as a cream solid (948 mg, 1.59 mmol, 100%).

MP: 128.0 - 129.4 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}): 3579 br w, 2937 m, 2917 m, 2860 m, 2177 w, 1600 m, 1489 m, 1466 m, 1383 m, 1217 m, 1184 m, 1124 s, 1009 w, 752 m, 679 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46-7.32 (5H, m, 5 x Ar**H**), 6.98 (1H, s, Ar**H**), 6.86 (1H, s, Ar**H**), 6.65 (2H, s, 2 x Ar**H**), 5.02 (2H, s, C**H$_2$**), 4.69 (2H, d, *J* = 6.0 Hz, C**H$_2$**), 3.78 (6H, s, 2 x C**H$_3$**), 3.61

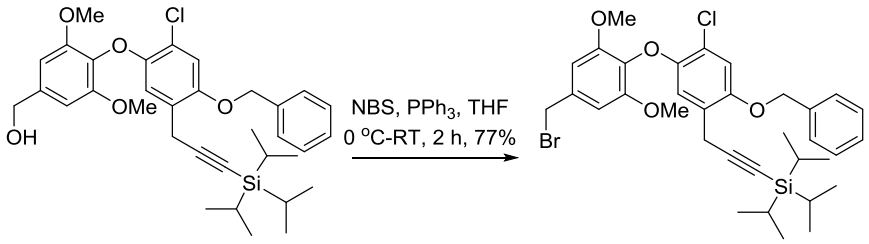
(2H, s, C**H₂**), 1.64 (1H, t, *J* = 6.1 Hz, O**H**), 1.02-0.88 (21H, m, 6 x C**H₃** and 3 x C**H**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.2 (2 x **C**), 150.3 (**C**), 148.3 (**C**), 138.3 (**C**), 136.8 (**C**), 131.8 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 124.9 (**C**), 120.0 (**C**), 114.8 (**C**H), 113.4 (**C**H), 104.8 (**C**), 103.9 (2 x **C**H), 83.0 (**C**), 70.7 (**C**H_2), 65.5 (**C**H_2), 56.3 (2 x **C**H_3), 20.7 (**C**H_2), 18.6 (6 x **C**H_3), 11.1 (3 x **C**H).

LRMS (HPLC-MS; ESI^+): 619 $[M^{37}Cl+Na]^+$ (43%), 617 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{34}H_{43}ClNaO_5Si$ $[M^{35}Cl+Na]^+$ 617.2460; found 617.2464.

(3-(2-(Benzyloxy)-5-(4-(bromomethyl)-2,6-dimethoxyphenoxy)-4-chlorophenyl)prop-1-yn-1-yl)triisopropylsilane (2.8)



2.7

$C_{34}H_{43}ClO_5Si$
MW: 595.25

2.8

$C_{34}H_{42}BrClO_4Si$
MW: 658.15

To a solution of benzyl alcohol **2.7** (750 mg, 1.26 mmol) in THF (18 mL) at 0 °C was added PPh_3 (365 mg, 1.39 mmol) and *N*-bromosuccinimide (247 mg, 1.39 mmol). After 2 h at RT, 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 x 15 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in petroleum ether) afforded the title compound **2.8** as a cream solid (638 mg, 0.97 mmol, 77%).

MP: 100.0 - 102.3 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2939 m, 2860 m, 1597 m, 1489 m, 1466 s, 1416 w, 1386 m, 1337 m, 1242 w, 1184 s, 1128 s, 1112 s, 1011 w, 750 m, 678 s.

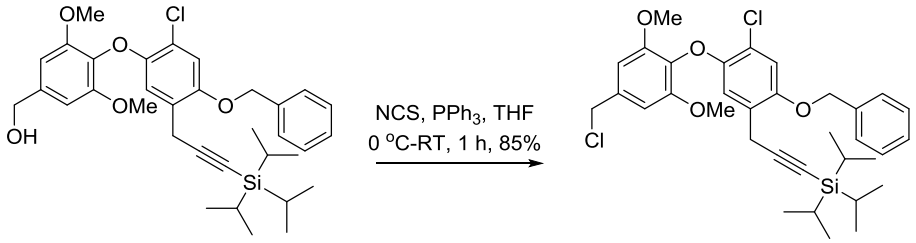
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.49-7.30 (5H, m, 5 x Ar**H**), 6.97 (1H, s, Ar**H**), 6.87 (1H, s, Ar**H**), 6.66 (2H, s, 2 x Ar**H**), 5.02 (2H, s, C**H$_2$**), 4.48 (2H, s, C**H$_2$**), 3.78 (6H, s, 2 x C**H$_3$**), 3.61 (2H, s, C**H$_2$**), 0.98-0.95 (21H, m, 3 x C**H** and 6 x C**H$_3$**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 153.1 (2 x **C**), 150.5 (**C**), 148.2 (**C**), 136.7 (**C**), 134.7 (**C**), 132.7 (**C**) 128.6 (2 x **C**H), 128.0 (**C**H), 127.3 (2 x **C**H), 125.0 (**C**), 120.2 (**C**), 115.0 (**C**H), 113.4 (**C**H), 106.5 (2 x **C**H), 104.8 (**C**), 83.1 (**C**), 70.7 (**C**H_2), 56.4 (2 x **C**H_3), 33.8 (**C**H_2), 20.7 (**C**H_2), 18.6 (6 x **C**H_3), 11.1 (3 x **C**H).

LRMS (HPLC-MS; ESI^+): 683 $[M^{37}Cl^{81}Br+Na]^+$ (33%), 681 $[M^{35}Cl^{81}Br+Na]^+$ and $[M^{37}Cl^{79}Br+Na]^+$ (100%), 679 $[M^{35}Cl^{79}Br+Na]^+$ (71%).

HRMS (ESI^+): Calculated for $C_{34}H_{42}BrClNaO_4Si$ $[M^{79}Br^{35}Cl+Na]^+$ 679.1616, found 679.1603.

(3-(2-(Benzyloxy)-4-chloro-5-(4-(chloromethyl)-2,6-dimethoxyphenoxy)phenyl)prop-1-yn-1-yl)triisopropylsilane (2.9)



2.7

$C_{34}H_{43}ClO_5Si$
MW: 595.25

2.9

$C_{34}H_{42}Cl_2O_4Si$
MW: 613.69

To a solution of benzyl alcohol **2.7** (100 mg, 0.17 mmol) in THF (2 mL) at 0 °C was added PPh_3 (53 mg, 0.20 mmol) and *N*-chlorosuccinimide (27 mg, 0.20 mmol). After 1 h at RT, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (0-10% EtOAc in petroleum ether) afforded the title compound **2.9** as a white solid (89 mg, 0.15 mmol, 85%).

MP: 134.4 - 136.6 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2939 m, 2861 m, 2181 w, 1599 m, 1488 m, 1466 m, 1415 w, 1384 m, 1337 m, 1242 w, 1184 s, 1120 s, 1010 w, 750 m, 678 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45-7.30 (5H, m, 5 x Ar**H**), 6.98 (1H, s, Ar**H**), 6.87 (1H, s, Ar**H**), 6.66 (2H, s, 2 x Ar**H**), 5.02 (2H, s, C**H$_2$**), 4.58 (2H, s, C**H$_2$**), 3.78 (6H, s, 2 x C**H$_3$**), 3.61 (2H, s, C**H$_2$**), 0.99-0.94 (21H, m, 3 x C**H** and 6 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.2 (2 x **C**), 150.4 (**C**), 148.2 (**C**), 136.7 (**C**), 134.5 (**C**), 133.6 (**C**) 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 125.0 (**C**), 120.1 (**C**), 114.8 (**C**H), 113.4 (**C**H), 105.9 (2 x **C**H), 104.7 (**C**), 83.2(**C**), 70.7 (**C**H_2), 56.4 (2 x **C**H_3), 46.5 (**C**H_2), 30.9 (**C**H_2), 18.6 (6 x **C**H_3), 11.1 (3 x **C**H).

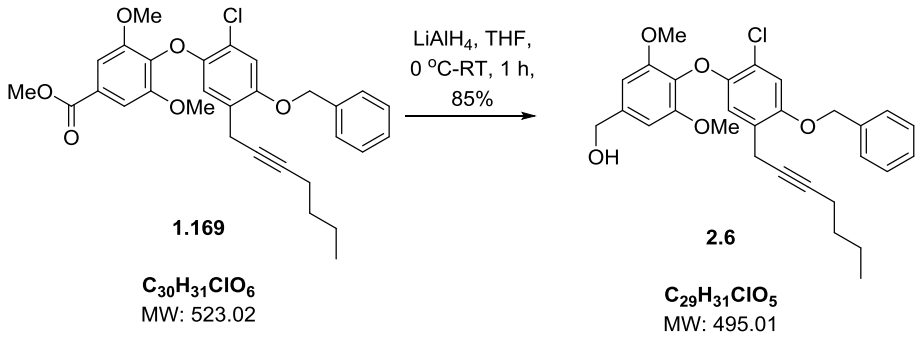
LRMS (HPLC-MS, ESI^+): 617 $[M^{37}Cl^{37}Cl+H]^+$ (9%), 615 $[M^{37}Cl^{35}Cl+H]^+$ and $[M^{35}Cl^{37}Cl+H]^+$ (52%), 613 $[M^{35}Cl^{35}Cl+H]^+$ (79%).

639 $[M^{37}Cl^{37}Cl+Na]^+$ (1%), 637 $[M^{37}Cl^{35}Cl+Na]^+$ and $[M^{35}Cl^{37}Cl+Na]^+$ (6%), 635 $[M^{35}Cl^{35}Cl+Na]^+$ (10%).

HRMS (ESI^+): Calculated for $C_{34}H_{43}Cl_2O_4Si$ 613.2302 $[M^{35}Cl^{35}Cl+H]^+$, found 613.2294.

Calculated for $C_{34}H_{42}Cl_2NaO_4Si$ 635.2122 $[M^{35}Cl^{35}Cl+Na]^+$, found 635.2116.

(4-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (2.6)



1.169

$C_{30}H_{31}ClO_6$
MW: 523.02

2.6

$C_{29}H_{31}ClO_5$
MW: 495.01

To a solution of benzyl ester **1.169** (292 mg, 0.56 mmol) in THF (4.5 mL) at 0 °C was added a solution of $LiAlH_4$ (1M in THF, 0.56 mL, 0.56 mmol) over 5 minutes. After 1 h at RT, MeOH (1 mL) and sat. Rochelle's salt (2 mL) were added and the solution stirred for 30 min. The aqueous phase was separated and extracted with Et_2O (3 x 5 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (40% EtOAc in petroleum ether) afforded the title compound **2.6** as a pale yellow oil (236 mg, 0.48 mmol, 85%).

IR ν_{max} (neat, cm^{-1}): 3384 w, 2956 w, 2926 m, 2858 m, 2361 w, 2332 w, 1597 m, 1491 m, 1459 m, 1215 m, 1187 m, 1126 s, 696 m.

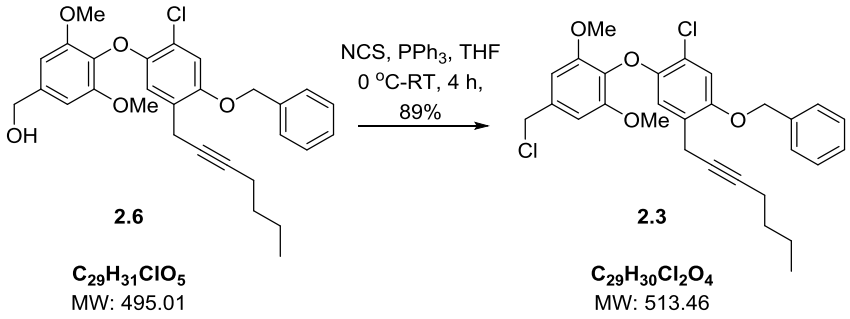
^{1}H NMR (400 MHz; DMSO-d_6): δ ppm 7.48-7.30 (5H, m, 5 x Ar**H**), 7.15 (1H, s, Ar**H**), 6.77 (2H, s, 2 x Ar**H**), 6.65 (1H, s, Ar**H**), 5.28 (1H, t, *J* = 5.7 Hz, O**H**), 5.12 (2H, s, C**H$_2$**), 4.52 (2H, d, *J* = 5.6 Hz, C**H$_2$**), 3.71 (6H, s, 2 x C**H$_3$**), 3.38 (2H, s, C**H$_2$**), 2.08 (2H, m, C**H$_2$**), 1.29-1.20 (4H, m, 2 x C**H$_2$**), 0.82 (3H, t, *J* = 7.1 Hz, C**H$_3$**).

^{13}C NMR (101 MHz; DMSO-d_6): δ ppm 152.4 (2 x **C**), 149.8 (**C**), 147.5 (**C**), 146.6 (**C**), 140.8 (**C**), 137.0 (**C**), 128.4 (2 x **C**H), 127.8 (**C**H), 127.3 (2 x **C**H), 125.5 (**C**), 118.1 (**C**), 114.1 (**C**H), 113.8 (**C**H), 103.2 (2 x **C**H), 83.2 (**C**), 76.6 (**C**), 70.0 (**C**H_2), 62.9 (**C**H_2), 55.9 (2 x **C**H_3), 30.3 (**C**H_2), 21.3 (**C**H_2), 19.0 (**C**H_2), 17.5 (**C**H_2), 13.3 (**C**H_3).

LRMS (HPLC-MS; ESI^-): 519 $[M^{37}Cl+Na]^+$ (37%), 517 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{29}H_{31}ClNaO_5$ $[M^{35}Cl+Na]^+$ 517.1752, found 517.1750.

2-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-5-(chloromethyl)-1,3-dimethoxybenzene (2.3)



2.6

$C_{29}H_{31}ClO_5$
MW: 495.01

2.3

$C_{29}H_{30}Cl_2O_4$
MW: 513.46

To a solution of benzyl alcohol **2.6** (200 mg, 0.40 mmol) in THF (4 mL) at 0 °C was added PPh_3 (115 mg, 0.44 mmol) and *N*-chlorosuccinimide (59 mg, 0.44 mmol). After 4 h at RT, sat. $NaHCO_3$ (2 mL) and sat. $Na_2S_2O_3$ (2 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 x 3 mL). The organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in petroleum ether) afforded the title compound **2.3** as a pale yellow solid (183 mg, 0.36 mmol, 89%).

MP: 104.5 - 105.5 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2964 w, 2933 w, 1601 m, 1491 m, 1460 m, 1423 m, 1389 m, 1338 m, 1247 m, 1219 m, 1190 m, 1124 s, 991 w, 864 w, 700 s, 640 m.

^{1}H NMR (400 MHz; MeCN-d_3): δ ppm 7.48-7.32 (5H, m, 5 x Ar**H**), 7.07 (1H, s, Ar**H**), 6.87 (2H, s, 2 x Ar**H**), 6.70 (1H, s, Ar**H**), 5.08 (2H, s, C**H$_2$**), 4.67 (2H, s, C**H$_2$**), 3.76 (6H, s, 2 x C**H$_3$**), 3.40 (2H, t, *J* = 2.0 Hz, C**H$_2$**), 2.04 (2H, m, C**H$_2$**), 1.31-1.27 (4H, m, 2 x C**H$_2$**), 0.86 (3H, t, *J* = 7.0 Hz, C**H$_3$**).

^{13}C NMR (101 MHz; MeCN-d_3): δ ppm 154.6 (2 x **C**), 151.9 (**C**), 149.1 (**C**), 142.1 (**C**), 138.5 (**C**), 137.5 (**C**), 129.9 (2 x **C**H), 129.4 (**C**H), 128.9 (2 x **C**H), 127.7 (**C**), 120.1 (**C**), 115.7 (**C**H), 115.5 (**C**H), 107.6 (2 x **C**H), 84.9 (**C**), 77.7 (**C**), 72.1 (**C**H_2), 57.4 (2 x

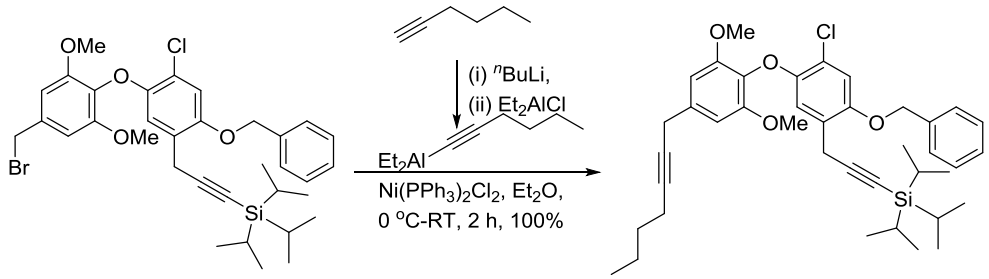
CH_3), 47.8 (**C**H_2), 32.2 (**C**H_2), 23.0 (**C**H_2), 20.4 (**C**H_2), 19.1 (**C**H_2), 14.3 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 515 $[M^{35}Cl+H]^+$ (5%), 513 $[M^{35}Cl+H]^+$ (11%).

535 $[M^{35}Cl+Na]^+$ (37%), 535 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{29}H_{30}Cl_2NaO_4$ $[M^{35}Cl^{35}Cl+Na]^+$ 535.1413; found 535.1412.

(3-(2-(Benzyloxy)-4-chloro-5-(4-(hept-2-yn-1-yl)-2,6-dimethoxyphenoxy)phenyl)prop-1-yn-1-yl)triisopropylsilane (2.10)



2.8

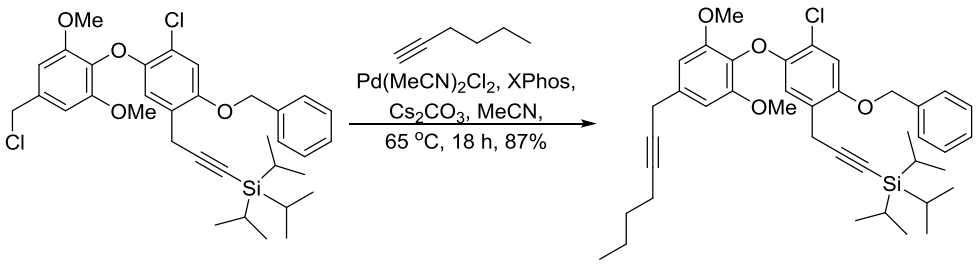
$C_{34}H_{42}BrClO_4Si$
MW: 658.15

2.10

$C_{40}H_{51}ClO_4Si$
MW: 659.38

To a solution of hex-1-yne (69 µL, 0.60 mmol) in Et_2O (8 mL) at 0 °C was added ^{n}BuLi (2.44M in hexane, 0.25 mL, 0.60 mmol) over 5 minutes. After 1 h at 0 °C, Et_2AlCl (1M in hexane, 0.60 mL, 0.60 mmol) was added over 5 minutes. After, 20 minutes at 0 °C and 2 h at RT, $Ni(PPh_3)_2Cl_2$ (14 mg, 0.021 mmol) was added and the resulting brown solution was stirred for 15 minutes then benzyl bromide **2.8** (200 mg, 0.30 mmol) was added. After a further 2 h at RT, NH_4Cl (8 mL) was carefully added. The aqueous layer was separated and extracted with Et_2O (3 x 8 mL). The organic phases were combined, washed with brine (8 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in petroleum ether) afforded the title compound **2.10** as a yellow solid (197 mg, 0.30 mmol, 100%).

Alternatively:



2.9

$C_{34}H_{42}Cl_2O_4Si$
MW: 613.69

2.10

$C_{40}H_{51}ClO_4Si$
MW: 659.38

A flask charged with benzyl chloride **2.9** (25 mg, 0.04 mmol), $Pd(MeCN)_2Cl_2$ (0.6 mg, 0.002 mmol), XPhos (3.4 mg, 0.007 mmol) and Cs_2CO_3 (14 mg, 0.044 mmol) was evacuated and filled with Ar in 3 cycles. Hex-1-yne (0.7 mL, 0.06 mmol) and MeCN (0.5 mL) were then added and the reaction mixture degassed with Ar for 5 minutes before heating to 65 °C for 18 h. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (0-10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (23 mg, 0.035 mmol, 87%).

MP: 98.5 - 100.2 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2960 m, 2927 w, 2860 w, 1599 w, 1491 w, 1426 w, 1372 w, 1259 s, 1086 s, 1012 s, 793 s.

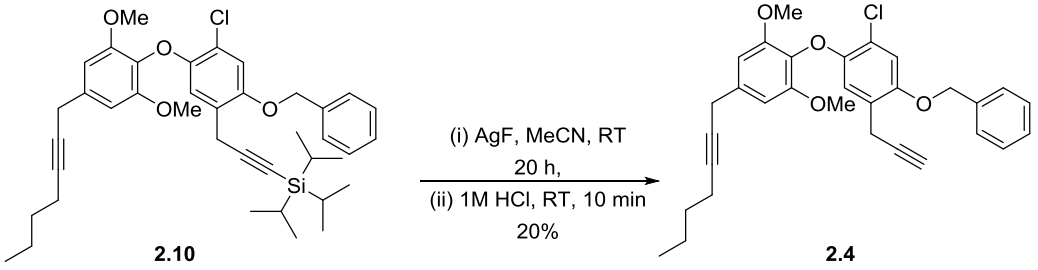
^{1}H NMR (400 MHz; MeCN-d_3): δ ppm 7.54-7.31 (5H, m, 5 x Ar**H**), 7.09 (1H, s, Ar**H**), 6.78 (1H, s, Ar**H**), 6.76 (2H, s, 2 x Ar**H**), 5.08 (2H, s, C**H$_2$**), 3.71 (6H, s, 2 x C**H$_3$**), 3.60 (2H, s, C**H$_2$**), 3.57 (2H, s, C**H$_2$**), 2.32-2.18 (2H, m, C**H$_2$**), 1.57-1.41 (4H, m, 2 x **CH$_2$**), 1.02-0.78 (24H, m, 7 x C**H$_3$**, 3 x C**H**).

^{13}C NMR (101 MHz; MeCN-d_3): δ ppm 154.2 (2 x **C**), 151.6 (**C**), 149.9 (**C**), 138.5 (**C**), 137.1 (**C**), 133.1 (**C**), 130.0 (2 x **C**H), 129.4 (**C**H), 128.9 (2 x **C**H), 126.7 (**C**), 120.3 (**C**), 115.6 (**C**H), 115.1 (**C**H), 106.4 (2 x **C**H), 106.2 (**C**), 84.8 (**C**), 84.7 (**C**), 78.4 (**C**), 72.1 (**C**H_2), 57.1 (**C**H_3), 32.3 (**C**H_2), 26.1 (**C**H_2), 23.1 (**C**H_2), 21.4 (**C**H_2), 19.4 (6 x **C**H_3), 19.4 (**C**H_2), 14.3 (**C**H_3), 12.3 (3 x **C**H).

LRMS (HPLC-MS; ESI^+): 683 $[M^{37}Cl+Na]^+$ (44%), 681 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{40}H_{51}ClNaO_4Si$ $[M^{35}Cl+Na]^+$ 681.3137, found 681.3130.

2-(4-(Benzyloxy)-2-chloro-5-(prop-2-yn-1-yl)phenoxy)-5-(hept-2-yn-1-yl)-1,3-dimethoxybenzene (2.4)



2.10

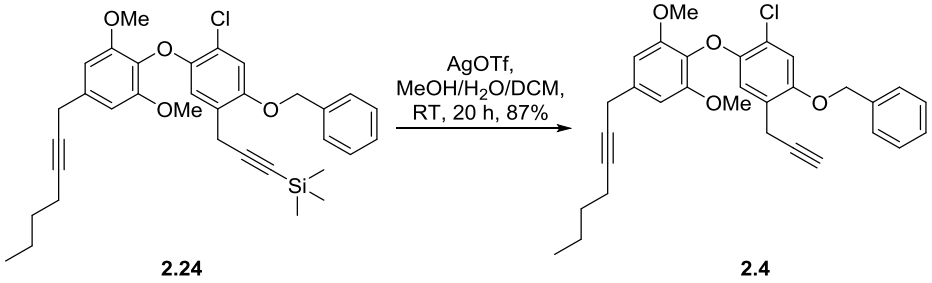
$C_{40}H_{51}ClO_4Si$
MW: 659.38

2.4

$C_{31}H_{31}ClO_4$
MW: 503.04

To a degassed solution of triisopropylsilylacetylene **2.10** (400 mg, 0.61 mmol) in MeCN (6.1 mL) in the dark was added AgF (116 mg, 0.91 mmol). After 20 h at RT, 1M HCl (1.83 mL, 1.83 mmol) was added. After a further 10 minutes, the reaction mixture was filtered and the filtrate was extracted with EtOAc (3 x 5 mL) and the organic phases were combined, washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5-15% Et_2O in petroleum ether) afforded the title compound **2.4** as an off white gelatinous solid (60 mg, 0.12 mmol, 20%).

Alternatively:



2.24

$C_{34}H_{39}ClO_4Si$
MW: 575.22

2.4

$C_{31}H_{31}ClO_4$
MW: 503.04

To a solution of TMS-alkyne **2.24** (100 mg, 0.17 mmol) in MeOH/H_2O/DCM (4:1:7; 1.2 mL: 0.3 mL: 2.0 mL) was added AgOTf (13 mg, 0.05 mmol). After 20 h in the dark, NH_4Cl (3 mL) was added. The aqueous phase was separated and extracted with DCM (3 x 5 mL). The organic phases were combined, washed with brine (5 mL), dried with $MgSO_4$, filtered and concentrated *in*

vacuo. Purification by column chromatography (5-15% Et_2O in petroleum ether) afforded the title compound **2.4** as a pale yellow gelatinous solid (74 mg, 0.15 mmol, 87%).

IR ν_{max} (neat, cm^{-1}): 3302 w, 2957 m, 2927 m, 2856 w, 1597 m, 1493 m, 1460 m, 1395 w, 1238 w, 1217 m, 1124 s.

^{1}H NMR (400 MHz; MeCN-d_3): δ ppm 7.48-7.32 (5H, m, 5 x Ar**H**), 7.10 (1H, s, Ar**H**), 6.78 (2H, s, 2 x Ar**H**), 6.65 (1H, s, Ar**H**), 5.09 (2H, s, C**H$_2$**), 3.75 (6H, s, 2 x C**H$_3$**), 3.60 (2H, t, *J* = 2.5 Hz, C**H$_2$**), 3.44 (2H, d, *J* = 2.6 Hz, C**H$_2$**), 2.28-2.24 (2H, m, C**H$_2$**), 2.23 (1H, t, *J* = 2.8 Hz, C**H**), 1.53-1.44 (4H, m, 2 x C**H$_2$**), 0.92 (3H, t, *J* = 7.0 Hz, C**H$_3$**).

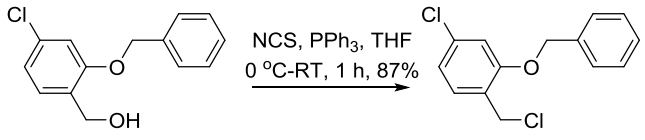
^{13}C NMR (101 MHz; MeCN-d_3): δ ppm 154.1 (2 x **C**), 151.5 (**C**), 149.0 (**C**), 138.1 (**C**), 137.3 (**C**), 131.1 (**C**), 129.6 (2 x **C**H), 129.1 (**C**H), 128.6 (2 x **C**H), 126.1 (**C**), 120.3 (**C**), 115.8 (**C**H), 115.4 (**C**H), 106.2 (2 x **C**H), 84.1 (**C**), 82.3 (**C**H), 78.4 (**C**), 71.9 (**C**H_2), 71.8 (**C**), 56.9 (2 x **C**H_3), 31.9 (**C**H_2), 25.8 (**C**H_2), 22.8 (**C**H_2), 19.8 (**C**H_2), 19.0 (**C**H_2), 14.0 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 505 $[M^{37}Cl+Na]^+$ (7%), 503 $[M^{35}Cl+Na]^+$ (15%).

527 $[M^{37}Cl+Na]^+$ (39%), 525 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{31}H_{31}ClNaO_4$ $[M^{35}Cl+Na]^+$ 525.1803, found 525.1791.

2-(Benzyloxy)-4-chloro-1-(chloromethyl)benzene (2.11)



1.158 — **$C_{14}H_{13}ClO_2$** MW: 248.71

2.11 — **$C_{14}H_{12}Cl_2O$** MW: 267.15

To a solution of benzyl alcohol **1.158** (500 mg, 2.01 mmol) in THF (12 mL) at 0 °C were added PPh_3 (633 mg, 2.41 mmol) and *N*-chlorosuccinimide (322 mg, 2.41 mmol). After 1 h at RT, 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). The organic phases were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5-10% Et_2O in petroleum ether) afforded the title compound **2.11** as a white solid (467 mg, 1.75 mmol, 87 %) with spectroscopic properties matching reported values.[45]

MP: 41.0 - 42.0 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 3032 w, 2931 w, 2872 w, 1595 m, 1581 m, 1489 s, 1455 m, 1407 m, 1381 m, 1246 s, 1115 w, 1094 m, 1024 m, 734 m, 694 m.

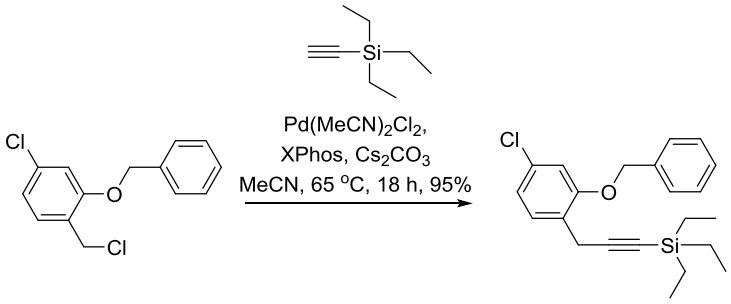
^{1}H NMR (400 MHz; acetone-d_6): δ ppm 7.56-7.55 (2H, d, *J* = 7.5 Hz, 2 x Ar**H**), 7.45-7.33 (4H, m, 4 x Ar**H**), 7.17 (1H, d, *J* = 1.8 Hz, Ar**H**), 7.01 (1H, dd, *J* = 8.1, 1.9 Hz, Ar**H**), 5.27 (2H, s, C**H$_2$**), 4.74 (2H, s, C**H$_2$**).

^{13}C NMR (101 MHz; acetone-d_6): δ ppm 157.3 (**C**), 136.8 (**C**), 134.9 (**C**), 131.7 (**C**H), 128.5 (2 x **C**H), 128.0 (**C**H), 127.3 (2 x **C**H), 125.4 (**C**), 120.7 (**C**H), 113.0 (**C**H), 70.2 (**C**H_2), 40.7 (**C**H_2).

LRMS (HPLC-MS; ESI^+): 267 $[M^{35}Cl^{35}Cl+H]^+$ (2%)

HRMS (EI): Calculated for $C_{14}H_{12}Cl_2O_2$ $[M^{35}Cl^{35}Cl]^{+\cdot}$ 266.0265, found 266.0263.

(3-(2-(Benzyloxy)-4-chlorophenyl)prop-1-yn-1-yl)triethylsilane (2.12)



2.11

$C_{14}H_{12}Cl_2O$
MW: 267.15

2.12

$C_{22}H_{27}ClOSi$
MW: 370.99

A flask charged with benzyl chloride **2.11** (100 mg, 0.37 mmol), $Pd(MeCN)_2Cl_2$ (6 mg, 0.02 mmol), XPhos (23 mg, 0.05 mmol) and Cs_2CO_3 (133 mg, 0.41 mmol) was evacuated and filled with argon

in 3 cycles. TES-acetylene (0.11 mL, 0.59 mmol) and MeCN (1 mL) were then added sequentially and the reaction mixture degassed with argon for 5 minutes. After 18 h at 65 °C, the reaction mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (100% petroleum ether) afforded the title compound **2.12** as a dark yellow oil. (130 mg, 0.35 mmol, 95%).

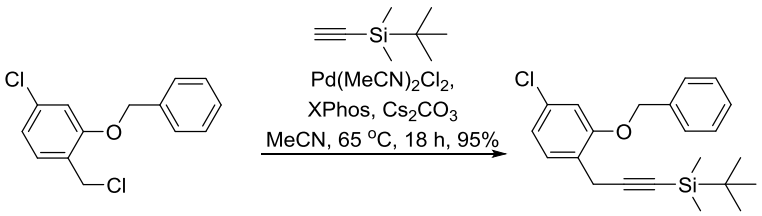
IR ν_{max} (neat, cm^{-1}): 2955 m, 2873 w, 2175 w, 2149 w, 1595 w, 1456 w, 1406 w, 1238 m, 1018 m, 723 s, 694 s.

^{1}H NMR (400 MHz; acetone-d_6): δ ppm 7.54 (3H, t, *J* = 8.2 Hz, 3 x Ar**H**), 7.45-7.32 (3H, m, 3 x Ar**H**), 7.13 (1H, s, Ar**H**), 7.13-7.10 (1H, m, Ar**H**), 5.20 (2H, s, C**H$_2$**), 3.70 (2H, s, C**H$_2$**), 1.05 (9H, t, *J* = 8.0 Hz, 3 x C**H$_3$**), 0.69 (6H, q, *J* = 7.9 Hz, 3 x C**H$_2$**).

^{13}C NMR (101 MHz; acetone-d_6): δ ppm 157.3 (**C**), 138.7 (**C**), 130.3 (**C**), 129.9 (**C**H), 129.3 (2 x **C**H), 128.8 (**C**H), 128.0 (2 x **C**H), 126.1 (**C**), 124.2 (**C**H), 116.1 (**C**H), 106.6 (**C**), 85.2 (**C**), 71.3 (**C**H_2), 21.9 (**C**H_2), 8.38 (3 x **C**H_3), 5.70 (3 x **C**H_2).

LRMS (HPLC-MS; ESI^+): 395 $[M^{37}Cl+Na]^+$ (8%), 393 $[M^{35}Cl+Na]^+$ (45%).

(3-(2-(Benzyloxy)-4-chlorophenyl)prop-1-yn-1-yl)(*tert*-butyl)dimethylsilane (2.13)



2.11

$C_{14}H_{12}Cl_2O$
MW: 267.15

2.13

$C_{22}H_{27}ClOSi$
MW: 370.99

A flask charged with benzyl chloride **2.11** (200 mg, 0.75 mmol), $Pd(MeCN)_2Cl_2$ (10 mg, 0.04 mmol), XPhos (48 mg, 0.10 mmol) and Cs_2CO_3 (270 mg, 0.83 mmol) was evacuated and filled with argon in 3 cycles. TBS-acetylene (0.22 mL, 1.20 mmol) and MeCN (2 mL) were then added sequentially and the reaction degassed with argon for 5 minutes. After 18 h at 65 °C, the reaction mixture was filtered through a pad of silica, concentrated *in vacuo* and purified by column

chromatography (100% petroleum ether) to give the title compound **2.13** as a yellow oil (264 mg, 0.71 mmol, 95%).

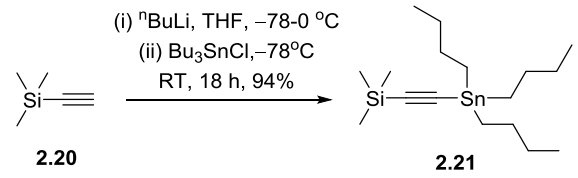
IR ν_{max} (neat, cm^{-1}): 2953 m, 2928 m, 2854 m, 2177 w, 1595 w, 1489 m, 1248 s, 1025 s, 824 s, 810 s, 773 s, 694 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.50-7.33 (6H, m, 6 x Ar**H**), 6.98 (1H, dd, *J* = 8.1, 1.9 Hz, Ar**H**), 6.90 (1H, d, *J* = 1.8 Hz, Ar**H**), 5.07 (2H, s, C**H$_2$**), 3.65 (2H, s, C**H$_2$**), 0.96 (9H, s, 3 x C**H$_3$**), 0.14 (6H, s, 2 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 156.3 (**C**), 136.4 (**C**), 133.0 (**C**), 129.7 (**C**H), 128.6 (2 x **C**H), 128.1 (**C**H), 127.2 (2 x **C**H), 124.0 (**C**), 120.8 (**C**H), 111.9 (**C**H), 104.1 (**C**), 85.6 (**C**), 70.2 (**C**H_2), 26.1 (3 x **C**H_3), 20.6 (**C**H_2), 16.6 (**C**), -4.5 (2 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 395 $[M^{37}Cl+Na]^+$ (13%), 393 $[M^{35}Cl+Na]^+$ (35%).

Trimethyl((tributylstannyl)ethynyl)silane (2.21)



2.20

$C_5H_{10}Si$
MW: 98.22

2.21

$C_{17}H_{36}SiSn$
MW: 387.27

To a solution of TMS-acetylene (0.29 mL, 2.04 mmol) in THF (2 mL) at –78 °C was added dropwise ^{n}BuLi (2.44 M in hexanes; 0.80 mL, 1.94 mmol) and the reaction mixture was gradually warmed to 0 °C over 30 minutes. The reaction mixture was again cooled to –78 °C and a solution of Bu_3SnCl (0.53 mL, 1.94 mmol) in THF (1.5 mL) was added dropwise. After 18 h at RT, H_2O (2 mL) and Et_2O (2 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **2.19** as a pale yellow oil (744 mg, 1.92 mmol, 94%) with physical and spectroscopic data consistent with reported values.[163]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 1.61-1.51 (6H, m, 3 x **C**H_2), 1.39-1.29 (6H, m, 3 x **C**H_2), 1.00 (6H, t, *J* = 8.1 Hz, 3 x **C**H_2), 0.91 (9H, t, *J* = 7.0 Hz, 3 x **C**H_3), 0.17 (9H, s, 3 x **C**H_3).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 118.8 (**C**), 113.2 (**C**), 28.8 (4 x **C**H_2), 26.9 (4 x **C**H_2), 13.7 (4 x **C**H_3), 11.1 (4 x **C**H_2), 0.26 (3 x **C**H_3).

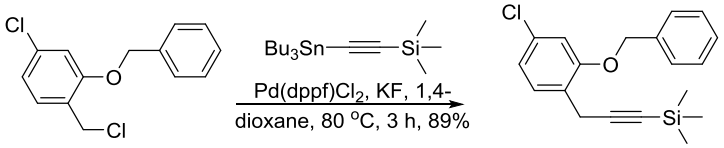
LRMS (GC-MS; EI): 388 $[M^{120}Sn]^{+\cdot}$ (50%), 386 $[M^{118}Sn]^{+\cdot}$ (26%), 384 $[M^{116}Sn]^{+\cdot}$ (10%).

331 $[M^{120}Sn\text{-}^{n}Bu]^{+\cdot}$ (100%), 329 $[M^{118}Sn\text{-}^{n}Bu]^{+\cdot}$ (82%), 327 $[M^{116}Sn\text{-}^{n}Bu]^{+\cdot}$ (49%).

274 $[M^{120}Sn\text{-}2^{n}Bu]^{+\cdot}$ (43%), 272 $[M^{118}Sn\text{-}2^{n}Bu]^{+\cdot}$ (34%), 270 $[M^{116}Sn\text{-}2^{n}Bu]^{+\cdot}$ (21%).

217 $[M^{120}Sn\text{-}3^{n}Bu]^{+\cdot}$ (50%), 215 $[M^{118}Sn\text{-}3^{n}Bu]^{+\cdot}$ (36%), 213 $[M^{116}Sn\text{-}3^{n}Bu]^{+\cdot}$ (17%).

(3-(2-(Benzyloxy)-4-chlorophenyl)prop-1-yn-1-yl)trimethylsilane (2.22)



2.11

$C_{14}H_{12}Cl_2O$
MW: 267.15

2.20

$C_{19}H_{21}ClOSi$
MW: 328.91

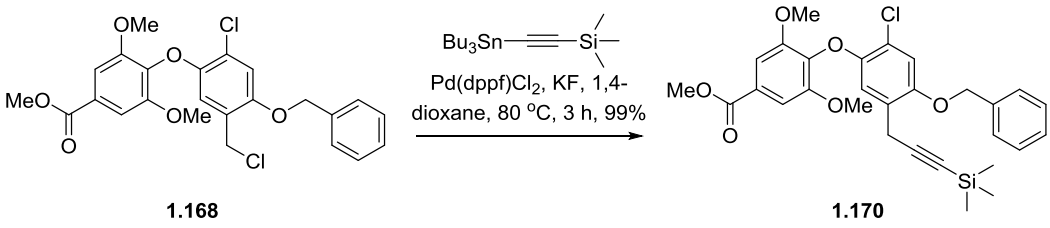
A flask charged with Pd(dppf)Cl_2.DCM (6 mg, 0.008 mmol) and KF (44 mg, 0.76 mmol) was evacuated and filled with argon in 3 cycles. Organostannane **2.21** (108 mg, 0.28 mmol), benzyl chloride **2.11** (50 mg, 0.19 mmol) and 1,4-dioxane (1.2 mL) were then added and the reaction mixture was degassed with argon for 5 minutes. After 3 h at 80 °C, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (9:1 silica:K_2CO_3, 100% petroleum ether) to afford the title compound **2.22** as a pale yellow oil (57 mg, 0.17 mmol, 89%).

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46-7.32 (7H, m, 7 x Ar**H**), 6.97 (1H, dd, *J* = 8.1 Hz, Ar**H**), 6.90 (1H, d, J = 2.0 Hz, Ar**H**), 5.07 (2H, s, C**H$_2$**), 3.71 (6H, s, 2 x C**H$_3$**), 3.63 (2H, s, C**H$_2$**), 0.15 (9H, s, 3 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 156.3 (**C**), 136.4 (**C**), 133.0 (**C**), 129.4 (2 x **C**H), 128.6 (**C**H), 128.1 (**C**), 127.1 (2 x **C**H), 123.9 (**C**), 120.8 (**C**), 112.0 (**C**H), 103.7 (**C**), 87.2 (**C**), 70.1 (**C**H_2), 20.6 (**C**H_2), 0.1 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 331 $[M^{35}Cl+H]^+$ (31%), 329 $[M^{37}Cl+H]^+$ (100%).

Methyl 4-(4-(benzyloxy)-2-chloro-5-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5 dimethoxybenzoate (1.170)



1.168

$C_{24}H_{22}Cl_2O_6$
MW: 477.33

1.170

$C_{29}H_{31}ClO_6Si$
MW: 539.10

A flask charged with $Pd(dppf)Cl_2$ (49 mg, 0.06 mmol) and KF (351 mg, 6.04 mmol) was evacuated and filled with argon in 3 cycles. Organostannane **2.21** (876 mg, 2.26 mmol), benzyl chloride **1.168** (720 mg, 1.51 mmol) and 1,4-dioxane (10 mL) were then added and the reaction mixture was degassed with argon for 5 minutes. After 3 h at 80 °C, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (9:1 silica:K_2CO_3,[112] 20% EtOAc in petroleum ether) to afford the title compound **1.170** as an off white solid (802 mg, 1.49 mmol, 99%).

MP: 133.1 - 135.3 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}): 2956 m, 2922 m, 2852 m, 1716 s, 1595 m, 1488 m, 1465 m, 1414 m, 1337 m, 1234 m, 1209 s, 1186 s, 1122 s, 841 s, 758 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.42-7.31 (7H, m, 7 x Ar**H**), 6.97 (1H, s, Ar**H**), 6.79 (1H, s, Ar**H**), 5.03 (2H, s, C**H$_2$**), 3.94 (3H, s, C**H$_3$**), 3.84 (6H, s, 2 x C**H$_3$**), 3.53 (2H, s, C**H$_2$**), 0.01 (9H, s, 3 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 166.6 (**C**O), 153.2 (2 x **C**), 150.8 (**C**), 147.9 (**C**), 136.8 (**C**), 136.8 (**C**), 128.7 (2 x **C**H), 128.2 (**C**H), 127.4 (**C**), 127.3 (2 x **C**H), 124.8 (**C**), 120.3 (**C**), 115.2 (**C**H),

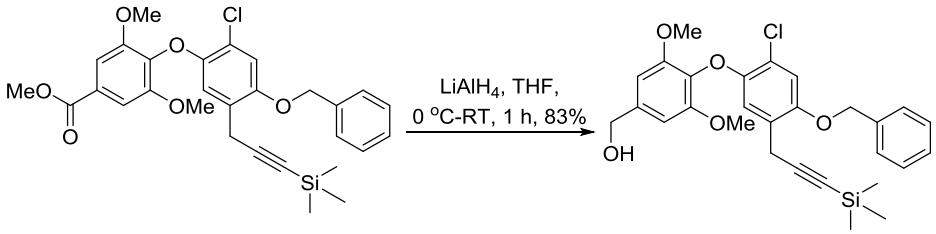
113.7 (**C**H), 107.2 (2 x **C**H), 103.4 (**C**), 87.7 (**C**), 70.9 (**C**H_2), 56.7 (2 x **C**H_3), 52.4 (**C**H_3), 20.8 (**C**H_2), 0.0 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 541 $[M^{37}Cl+H]^+$ (15%), 539 $[M^{35}Cl+H]^+$ (38%).

563 $[M^{37}Cl+Na]^+$ (40%), 561 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{29}H_{32}ClO_6Si$ 539.1651 $[M^{35}Cl+Na]^+$, found 539.1654

(4-(4-(Benzyloxy)-2-chloro-5-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (2.23)



1.170

$C_{29}H_{31}ClO_6Si$
MW: 539.10

2.23

$C_{28}H_{31}ClO_5Si$
MW: 511.09

To a solution of benzyl ester **1.170** (6.21 g, 11.5 mmol) in THF (175 mL) at 0 °C was added a solution of $LiAlH_4$ (1M in THF, 12.7 mL, 12.7 mmol) over 5 minutes. After 4 h at RT, MeOH (30 mL) and sat. Rochelle's salt (60 mL) were added and the solution stirred for 1 h. The aqueous phase was separated and extracted with EtOAc (3 x 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 (35-40% EtOAc in petroleum ether) afforded the title compound **2.23** as an off-white solid (5.22 g, 10.2 mmol, 89%).

MP: 108.5 - 110.0 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}): 3587 br, 2955 w, 2941 w, 2912 w, 2355 w, 2340 w, 2156 m, 2015 m, 1601 m, 1495 s, 1387 s, 1219 s, 1126 s, 1037 m, 841 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.42-7.31 (5H, m, 5 x Ar**H**), 6.97 (1H, s, Ar**H**), 6.80 (1H, s, Ar**H**), 6.69 (2H, s, 2 x Ar**H**), 5.03 (2H, s, C**H$_2$**), 4.70 (2H, d, *J* = 5.9 Hz, C**H$_2$**), 3.81 (6H, s, 2 x C**H$_3$**), 3.53

(2H, s, C**H₂**), 1.67 (1H, t, *J* = 6.1 Hz, O**H**), 0.05 (9H, s, 3 x C**H₃**).

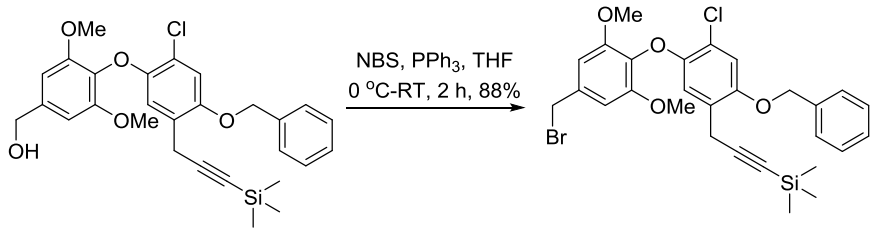
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.4 (2 x **C**), 150.4 (**C**), 148.2 (**C**), 138.6 (**C**), 136.8 (**C**), 131.8 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 124.5 (**C**), 120.0 (**C**), 114.9 (**C**H), 113.6 (**C**H), 104.0 (2 x **C**H), 103.6 (**C**), 87.2 (**C**), 70.7 (**C**H_2), 65.4 (**C**H_2), 56.4 (2 x **C**H_3), 20.7 (**C**H_2), 0.00 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 535 $[M^{37}Cl+H]^+$ (12%), 533 $[M^{35}Cl+H]^+$ (29%).

535 $[M^{37}Cl+Na]^+$ (32%), 533 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{28}H_{31}ClNaO_5Si$ $[M^{35}Cl+Na]^+$ 533.1521, found 533.1536.

(3-(2-(Benzyloxy)-5-(4-(bromomethyl)-2,6-dimethoxyphenoxy)-4-chlorophenyl)prop-1-yn-1-yl)trimethylsilane (2.24)



2.23

$C_{28}H_{31}ClO_5Si$
MW: 511.09

2.24

$C_{28}H_{30}BrClO_4Si$
MW: 573.98

To a solution of benzyl alcohol **2.23** (5.22 g, 10.2 mmol) in THF (150 mL) at 0 °C was added PPh_3 (3.21 g, 12.2 mmol) and *N*-bromosuccinimide (2.18 g, 12.2 mmol). After 3 h at RT, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (0-15% EtOAc in petroleum ether) to afford the title compound **2.24** as a cream solid (5.82 g, 10.1 mmol, 99%).

MP: 124.4 - 126.7 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2943 w, 2916 w, 2172 w, 1597 m, 1491 m, 1466 m, 1392 m, 1337 m, 1246 m, 1203 m, 1113 s, 1022 m, 841 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.47-7.31 (5H, m, 5 x Ar**H**), 6.96 (1H, s, Ar**H**), 6.80 (1H, s, Ar**H**), 6.70 (2H, s, 2 x Ar**H**), 5.03 (2H, s, C**H₂**),

4.48 (2H, s, C**H₂**), 3.81 (6H, s, 2 x C**H₃**), 3.54 (2H, s, C**H₂**), 0.06 (9H, s, 3 x C**H₃**).

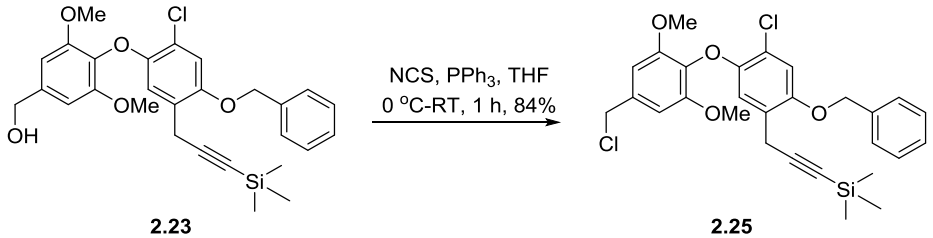
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.3 (2 x **C**), 150.5 (**C**), 148.0 (**C**), 136.7 (**C**), 135.0 (**C**), 131.7 (**C**), 128.5 (2 x **C**H), 127.9 (**C**H), 127.1 (2 x **C**H), 124.6 (**C**), 120.1 (**C**), 115.0 (**C**H), 113.5 (**C**H), 106.5 (2 x **C**H), 103.4 (**C**), 87.2 (**C**), 70.7 (**C**H_2), 56.4 (2 x **C**H_3), 33.7 (**C**H_2), 20.6 (**C**H_2), 0.00 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 577 $[M^{37}Cl^{81}Br+H]^+$ (5%), 575 $[M^{35}Cl^{81}Br+H]^+$, $[M^{37}Cl^{79}Br+H]^+$ (19%), 573 $[M^{35}Cl^{79}Br+H]^+$ (16%).

599 $[M^{37}Cl^{81}Br+Na]^+$ (32%), 597 $[M^{35}Cl^{81}Br+Na]^+$, $[M^{37}Cl^{79}Br+Na]^+$ (66%), 595 $[M^{35}Cl^{79}Br+Na]^+$ (56%).

HRMS (ESI^+): Calculated for $C_{28}H_{31}BrClO_4Si$ $[M^{35}Cl+H]^+$ 573.0858; found 573.0874.

(3-(2-(Benzyloxy)-4-chloro-5-(4-(chloromethyl)-2,6-dimethoxyphenoxy)phenyl)prop-1-yn-1-yl)trimethylsilane (2.25)



2.23

$C_{28}H_{31}ClO_5Si$
MW: 511.09

2.25

$C_{28}H_{30}Cl_2O_4Si$
MW: 529.53

To a solution of benzyl alcohol **2.23** (75 mg, 0.15 mmol) in THF (2 mL) at 0 °C was added PPh_3 (46 mg, 0.18 mmol) and *N*-chlorosuccinimide (24 mg, 0.18 mmol). After 1 h at RT, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (0-10% EtOAc in petroleum ether) to afford the title compound **2.25** as an off white solid (67 mg, 0.13 mmol, 84%).

MP: 118.9 - 120.7 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2959 w, 2941 w, 2172 w, 1716 w, 1598 m, 1491 s, 1465 s, 1391 m, 1337 m, 1246 w, 1214 m, 1120 s, 1023 m, 846 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.46-7.31 (5H, m, 5 x Ar**H**), 6.97 (1H, s, Ar**H**), 6.80 (1H, s, Ar**H**), 6.69 (2H, s, 2 x Ar**H**), 5.03 (2H, s, C**H$_2$**), 4.58 (2H, s, C**H$_2$**), 3.81 (6H, s, 2 x C**H$_3$**), 3.54 (2H, s, C**H$_2$**), 0.05 (9H, s, 3 x C**H$_3$**).

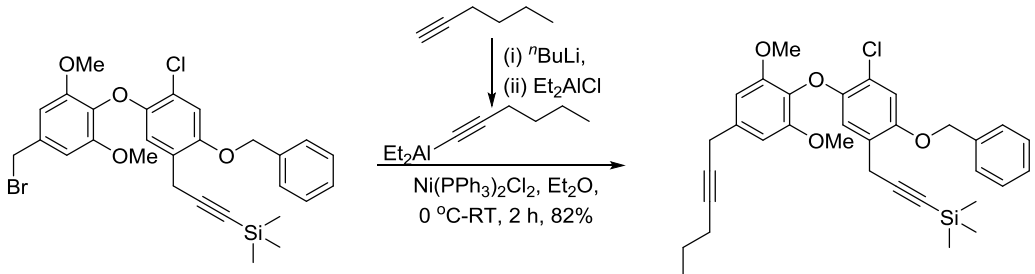
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.3 (2 x **C**), 150.5 (**C**), 148.1 (**C**), 136.7 (**C**), 134.8 (**C**), 132.6 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 124.6 (**C**), 120.1 (**C**), 115.0 (**C**H), 113.6 (**C**H), 106.0 (2 x **C**H), 103.4 (**C**), 87.3 (**C**), 70.7 (**C**H_2), 56.5 (2 x **C**H_3), 46.5 (**C**H_2), 20.6 (**C**H_2), 0.00 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 533 $[M^{37}Cl^{37}Cl+H]^+$ (4%), 531 $[M^{35}Cl^{37}Cl+H]^+$, $[M^{37}Cl^{35}Cl+H]^+$ (10%), 529 $[M^{35}Cl^{35}Cl+H]^+$ (28%).

555 $[M^{37}Cl^{37}Cl+Na]^+$ (5%), 553 $[M^{35}Cl^{37}Cl+Na]^+$, $[M^{37}Cl^{35}Cl+Na]^+$ (29%), 551 $[M^{35}Cl^{35}Cl+Na]^+$ (52%).

HRMS (ESI^+): Calculated for $C_{28}H_{30}Cl_2O_4Si$ $[M^{35}Cl^{35}Cl+Na]^+$ 551.1183; found 551.1188.

(3-(2-(Benzyloxy)-4-chloro-5-(4-(hept-2-yn-1-yl)-2,6-dimethoxyphenoxy)phenyl)prop-1-yn-1-yl)trimethylsilane (2.26)



2.24

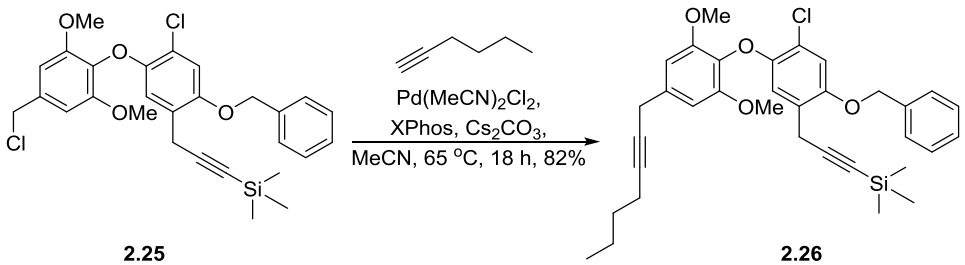
$C_{28}H_{30}BrClO_4Si$
MW: 573.98

2.26

$C_{34}H_{39}ClO_4Si$
MW: 575.22

To a solution of hex-1-yne (0.98 mL, 0.85 mmol) in Et_2O (15 mL) at 0 °C was added ^nBuLi (2.5M in hexane, 0.34 mL, 0.85 mmol) over 5 minutes. After 1 h at 0 °C, Et_2AlCl (1M in hexane, 0.85 mL, 0.85 mmol) was added over 5 minutes. After 20 minutes at 0 °C and 2 h at RT, $Ni(PPh_3)_2Cl_2$ (20 mg, 0.03 mmol) was added. The resulting brown solution was stirred for 15 minutes then benzyl bromide **2.24** (245 mg, 0.43 mmol) was added. After a further 2 h at RT, NH_4Cl (5 mL) was carefully added. The aqueous phase was separated and extracted with Et_2O (3 x 5 mL). The organic phases were combined, washed with brine (8 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5-10% EtOAc in petroleum ether) afforded the title compound **2.26** as a yellow oil (204 mg, 0.35 mmol, 82%).

Alternatively:



2.25

$C_{28}H_{30}Cl_2O_4Si$
MW: 529.53

2.26

$C_{34}H_{39}ClO_4Si$
MW: 575.22

A flask charged with benzyl chloride **2.25** (20 mg, 0.04 mmol), $Pd(MeCN)_2Cl_2$ (0.6 mg, 0.002 mmol), XPhos (3.4 mg, 0.007 mmol) and Cs_2CO_3 (14 mg, 0.042 mmol) was evacuated and filled with argon in 3 cycles before hex-1-yne (0.06 mL, 0.06 mmol) and MeCN (0.5 mL) were added. The reaction mixture was heated to 65 °C for 18 h and then concentrated *in vacuo*. Purification

by column chromatography (0-10% EtOAc in petroleum ether) to give the title compound **2.26** as a yellow oil (18 mg, 0.031 mmol, 82%).

IR ν_{max} (neat, cm^{-1}): 2958 w, 2935 w, 2871 w, 2177 w, 1699 w, 1597 m, 1491 m, 1462 m, 1215 s, 1126 s, 1025 m, 841 s.

^{1}H NMR (400 MHz; acetone-d_6): δ ppm 7.53 (2H, d, *J* = 7.0 Hz, 2 x Ar**H**), 7.41-7.33 (3H, m, 3 x Ar**H**), 7.13 (1H, s, Ar**H**), 6.84 (2H, s, 2 x Ar**H**), 6.83 (1H, s, Ar**H**), 5.17 (2H, s, C**H$_2$**), 3.77 (6H, s, 2 x C**H$_3$**), 3.63 (2H, t, *J* = 2.4 Hz, C**H$_2$**), 3.53 (2H, d, *J* = 0.7 Hz, C**H$_2$**), 2.34-2.19 (2H, m, C**H$_2$**), 1.60-1.39 (4H, m, 2 x C**H$_2$**), 0.92 (3H, t, *J* = 7.2 Hz, C**H$_3$**), 0.04 (9H, s, 3 x C**H$_3$**).

^{13}C NMR (101 MHz; acetone-d_6): δ ppm 154.1 (2 x **C**), 151.2 (**C**), 149.3 (**C**), 138.3 (**C**), 136.7 (**C**), 129.4 (2 x **C**H), 128.8 (**C**H), 128.4 (2 x **C**H), 125.5 (**C**), 123.7 (**C**), 120.1 (**C**), 115.2 (**C**H), 114.8 (**C**H), 106.1 (2 x **C**H), 104.2 (**C**), 88.1 (**C**), 83.7 (**C**), 78.1 (**C**), 71.5 (**C**H_2), 56.6 (2 x **C**H_3), 32.0 (**C**H_2), 25.7 (**C**H_2), 22.7 (**C**H_2), 21.00 (**C**H_2), 19.00 (**C**H_2), 14.00 (**C**H_3), 0.18 (3 x **C**H_3).

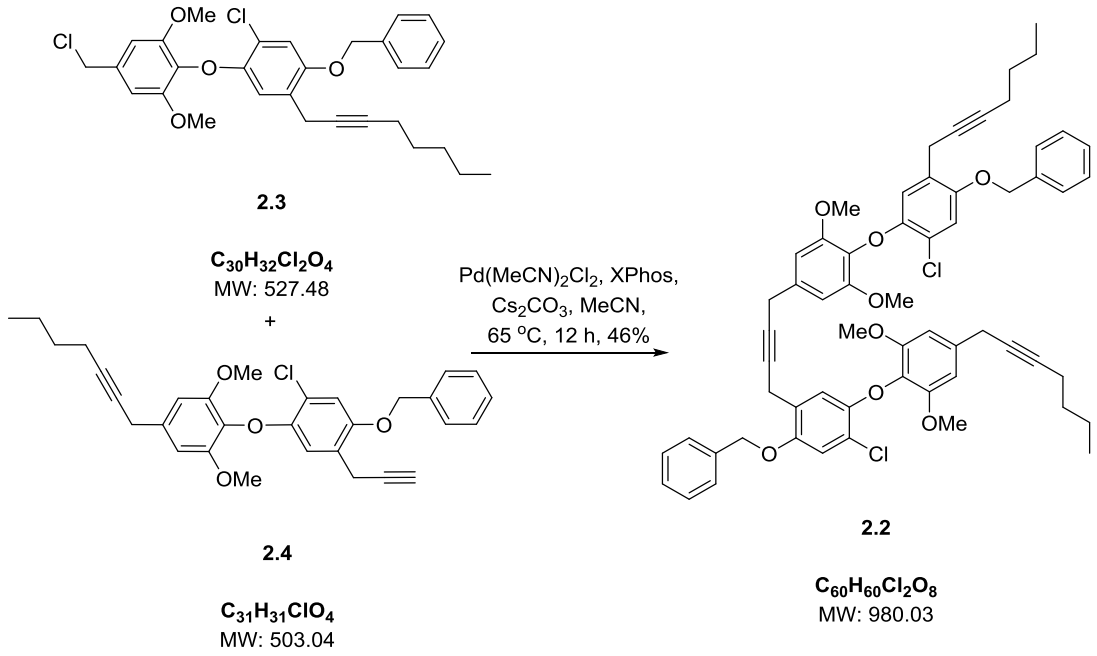
LRMS (HPLC-MS; ESI^+): 577 $[M^{37}Cl+H]^+$ (33%), 575 $[M^{35}Cl+H]^+$ (19%).

599 $[M^{37}Cl+Na]^+$ (44%), 597 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{34}H_{40}ClO_4Si$ $[M^{35}Cl+H]^+$ 575.2379; found 575.2360

Calculated for $C_{34}H_{39}ClNaO_4Si$ $[M^{35}Cl+Na]^+$ 597.2198, found 597.2184.

2-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-5-(4-(2-(benzyloxy)-4-chloro-5-(4-(hept-2-yn-1 yl)-2,6-dimethoxyphenoxy)phenyl)but-2-yn-1-yl)-1,3-dimethoxybenzene (2.2)



A flask containing terminal alkyne **2.4** (1.00 g, 1.99 mmol), benzyl chloride **2.3** (1.22 g, 2.39 mmol), $Pd(MeCN)_2Cl_2$ (31 mg, 0.12 mmol), XPhos (171 mg, 0.36 mmol) and Cs_2CO_3 (713 mg, 2.19 mmol) was evacuated and filled with argon in 3 cycles. MeCN (10 mL) was then added and the reaction mixture degassed with argon for a further 5 minutes. After 12 h at 65 °C, the reaction mixture was filtered through a pad of silica. Purification by column chromatography (10-25% Et_2O in petroleum ether) provided the title compound **2.2** as a pale yellow solid (900 mg, 0.92 mmol, 46%).

MP: 62.1 - 63.5 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2956 w, 2929 w, 2870 w, 2858 w, 1695 w, 1597 s, 1491 s, 1461 s, 1419 m, 1215 s, 1124 s, 997 m, 750 s, 696 s.

^{1}H NMR (400 MHz; acetone-d_6): δ ppm 7.55-7.30 (10H, m, 10 x Ar**H**), 7.14 (1H, s, Ar**H**), 7.11 (1H, s, Ar**H**), 6.83 (1H, s, Ar**H**), 6.80 (1H, s, Ar**H**), 6.78 (2H, s, 2 x Ar**H**), 6.73 (2H, s, 2 x Ar**H**), 5.18 (2H, s, C**H$_2$**), 5.15 (2H, s, C**H$_2$**), 3.73 (6H, s, 2 x C**H$_3$**), 3.68 (6H, s, 2 x C**H$_3$**), 3.60 (2H, t, *J* = 2.5 Hz, C**H$_2$**), 3.57 (2H, t, *J* = 2.3 Hz, C**H$_2$**), 3.53 (2H, t, *J* = 1.9 Hz, C**H$_2$**), 3.42 (2H, t, *J* = 2.6 Hz, C**H$_2$**), 2.29-2.22 (2H, m, C**H$_2$**), 2.03-2.00 (2H,

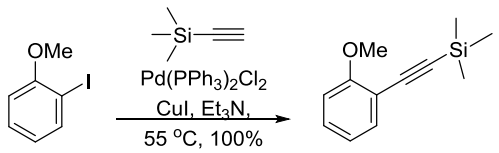
m, C**H₂**), 1.53-1.42 (4H, m, 2 x C**H₂**), 1.30-1.25 (4H, m, 2 x C**H₂**), 0.90 (3H, t, *J* = 7.2 Hz, C**H₃**), 0.81 (3H, t, *J* = 7.1 Hz, C**H₃**).

^{13}C NMR (101 MHz; acetone-d_6): δ ppm 154.14 (2 x **C**), 154.12 (2 x **C**), 150.4 (**C**), 150.3 (**C**), 148.23 (**C**), 148.20 (**C**), 137.33 (**C**), 137.33 (**C**), 137.30 (**C**), 135.89 (**C**), 135.87 (**C**), 130.52 (**C**), 130.50 (**C**), 129.45 (2 x **C**H), 129.43 (2 x **C**H), 127.81 (**C**H), 127.79 (**C**H), 127.38 (2 x **C**H), 127.35 (2 x **C**H), 125.8 (**C**), 125.7 (**C**), 119.2 (**C**), 118.9 (**C**), 115.2 (**C**H), 114.7 (**C**H), 113.9 (**C**H), 113.6 (**C**H), 105.02 (2 x **C**H), 104.97 (2 x **C**H), 84.1 (**C**), 83.1 (**C**), 82.7 (**C**), 80.0 (**C**), 79.8 (**C**), 77.4 (**C**), 70.6 (**C**H_2), 70.5 (**C**H_2), 55.57 (2 x **C**H_3), 55.55 (2 x **C**H_3), 31.0 (**C**H_2), 30.8 (**C**H_2), 24.8 (**C**H_2), 24.6 (**C**H_2), 21.7 (**C**H_2), 21.6 (**C**H_2), 19.2 (**C**H_2), 19.1 (**C**H_2) 18.0 (**C**H_2), 17.8 (**C**H_2), 13.00 (**C**H_3), 12.98 (**C**H_3).

LRMS (HPLC-MS; ESI$^+$): 1005 [M^{37}Cl^{37}Cl+Na]$^+$ (11%), 1003 [M^{35}Cl^{37}Cl+Na]$^+$, [M^{37}Cl^{35}Cl+Na]$^+$ (55%), 1001 [M^{35}Cl^{35}Cl+Na]$^+$ (100%).

HRMS (ESI$^+$): Calculated for $C_{60}H_{60}Cl_2NaO_8$ [M^{35}Cl^{35}Cl+Na]$^+$ 1001.3557, found 1001.3565.

((2-Methoxyphenyl)ethynyl)trimethylsilane (2.29)



2.27

C_7H_7IO
MW: 234.04

2.29

$C_{12}H_{16}OSi$
MW: 204.34

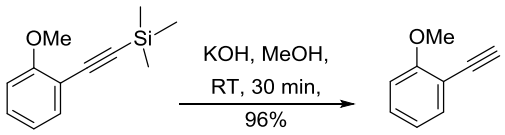
To a solution of 2-iodoanisole (0.65 mL, 5.00 mmol) and TMS-acetylene (0.85 mL, 6.0 mmol) in Et_3N (15 ml) was added $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol) and CuI (10 mg, 0.05 mmol). After 2 h at 55 °C, the reaction mixture was filtered and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc in petroleum ether) afforded the title compound **2.29** as a pale

yellow oil (1.02 g, 5.00 mmol, 100%) with physical and spectroscopic data consistent with reported values.[164]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44 (1H, dd, *J* = 7.6 1.6 Hz, Ar**H**), 7.31-7.26 (1H, m, Ar**H**), 6.91-6.84 (2H, m, 2 x Ar**H**), 3.89 (3H, s, C**H$_3$**), 0.27 (9H, s, 3 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 160.3 (**C**), 134.2 (**C**H), 130.0 (**C**H), 120.3 (**C**H), 112.3 (**C**H), 110.6 (**C**), 101.2 (**C**), 98.4 (**C**) 55.8 (**C**H_3), 0.1 (3 x **C**H_3).

1-Ethynyl-2-methoxybenzene (2.30)



2.29

$C_{12}H_{16}OSi$
MW: 204.34

2.30

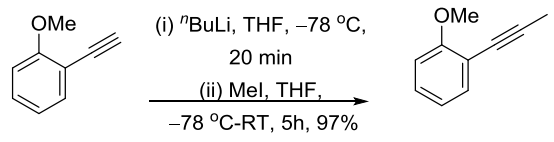
C_9H_8O
MW: 132.16

To a solution of TMS-alkyne **2.29** (1.02 g, 5.00 mmol) in MeOH (20 mL) was added dropwise a solution of KOH (2.53 g, 5.00 mmol) in H_2O (1 mL). After 30 minutes, the reaction mixture was concentrated *in vacuo* and the resulting residue diluted with brine (20 mL) and EtOAc (20 mL). The aqueous phase was separated and extracted with EtOAc (3 x 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (0-10% EtOAc in petroleum ether) afforded the title compound **2.30** as a yellow oil (634 mg, 4.80 mmol, 96%) with physical and spectroscopic properties consistent with reported values.[164]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.48 (1H, dd, *J* = 7.6, 1.7 Hz, Ar**H**), 7.37-7.30 (1H, m, Ar**H**), 6.97-6.86 (2H, m, 2 x Ar**H**), 3.92 (3H, s, C**H$_3$**), 3.32 (1H, C**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 160.5 (**C**), 134.2 (**C**H), 130.3 (**C**H), 120.4 (**C**H), 111.3 (**C**H), 110.6 (**C**), 81.1 (**C**H), 80.2 (**C**), 55.8 (**C**H_3).

1-Methoxy-2-(prop-1-yn-1-yl)benzene (2.28)



2.30

C_9H_8O
MW: 132.16

2.31

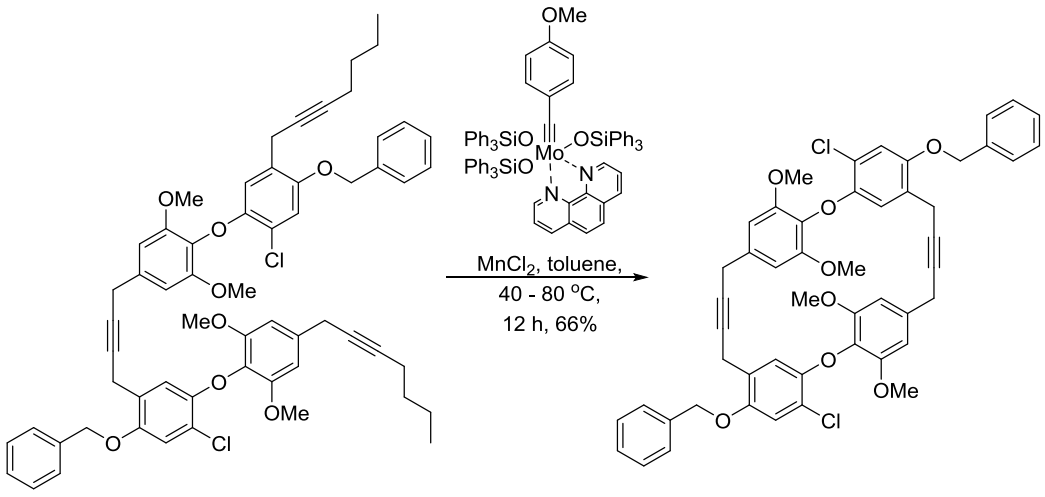
$C_{10}H_{10}O$
MW: 146.19

To a solution of alkyne **2.30** (484 mg, 3.66 mmol) in THF (5 mL) at -78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.76 mL, 4.39 mmol) and the reaction mixture stirred for 20 minutes. MeI (0.46 mL, 7.32 mmol) was then added dropwise and the reaction mixture stirred at RT for 5 h. NH_4Cl (5 mL) was then added, followed by DCM (10 mL) and the aqueous phase separated, extracted with DCM (3 x 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound **2.31** as an orange oil (519 mg, 3.55 mmol, 97%) with physical and spectroscopic data consistent with reported values.[164]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.38 (1H, dd, *J* = 7.6, 1.7 Hz, Ar**H**), 7.29-7.21 (1H, m, Ar**H**), 6.93-6.82 (2H, m, 2 x Ar**H**), 3.89 (3H, s, C**H$_3$**), 2.13 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 159.8 (**C**), 133.5 (**C**H), 130.0 (**C**H), 120.4 (**C**H), 113.0 (**C**H), 110.4 (**C**), 90.0 (**C**), 75.8 (**C**), 55.8 (**C**H_3), 4.8 (**C**H_3).

6,20-Bis(benzyloxy)-4,18-dichloro-14,28,29,32-tetramethoxy-2,16-dioxapentacyclo[24.2.2.2^{12,15}.1^{3,7}.1^{17,21}]tetratriaconta-1(28),3(34),4,6,12,14,17(31),18,20,26,29,32-dodecaen-9,23-diyne (2.1)



2.2

$C_{60}H_{60}Cl_2O_8$
MW: 980.03

2.1

$C_{50}H_{42}Cl_2O_8$
MW: 841.78

A solution of Mo catalyst **1.202c** (125 mg, 0.1 mmol) and $MnCl_2$ (13 mg, 0.1 mol) in toluene (4 mL) was heated to 80 °C for 1 h, then cooled to RT before added to a solution of triyne **2.2** (400 mg, 0.41 mmol) in toluene (2 mL) was added. The reaction mixture was heated to 40 °C for 12 h then cooled to RT and filtered through a short pad of silica. Purification by column chromatography (15-25% EtOAc in petroleum ether) to afford the title compound **2.1** as a pale yellow solid (227 mg, 0.27 mmol, 66%).

MP: 89.3 - 90.6 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2963 w, 2938 w, 1718 m, 1600 m, 1492 s, 1457 s, 1339 w, 1209 s, 1188 s, 1120 s, 994 m, 754 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45-7.33 (10H, m, 10 x Ar**H**), 7.01 (2H, s, 2 x Ar**H**), 6.98 (2H, s, 2 x Ar**H**), 6.52 (4H, s, 4 x Ar**H**), 5.05 (4H, s, 2 x C**H$_2$**), 3.72 (12H, s, 4 x C**H$_3$**), 3.59 (4H, br s, 2 x C**H$_2$**), 3.50 (4H, br s, 2 x C**H$_2$**).

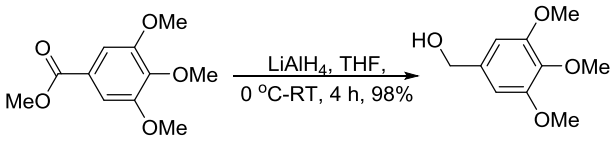
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.1 (4 x **C**), 150.2 (2 x **C**), 148.1 (2 x **C**), 136.7 (2 x **C**), 135.0 (2 x **C**), 134.3 (2 x **C**), 128.6 (4 x **C**H), 128.1 (2 x **C**H), 127.3 (4 x **C**H), 125.1 (2 x **C**), 119.0 (2 x **C**),

114.1 (2 x **C**H), 113.2 (2 x **C**H), 105.0 (4 x **C**H), 80.7 (2 x **C**), 80.2 (2 x **C**), 70.7 (2 x **C**H_2), 56.6 (4 x **C**H_3), 24.9 (2 x **C**H_2), 19.8 (2 x **C**H_2).

LRMS (HPLC-MS; ESI^+): 867 $[M^{37}Cl^{37}Cl+Na]^+$ (27%), 865 $[M^{35}Cl^{37}Cl+Na]^+$, $[M^{37}Cl^{35}Cl+Na]^+$ (79%), 863 $[M^{35}Cl^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{50}H_{42}Cl_2NaO_8$ $[M^{35}Cl^{35}Cl+Na]^+$ 863.2149, found 863.2146.

(3,4,5-Trimethoxyphenyl)methanol (2.34)



1.139

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

2.34

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

To a solution of ester **1.139** (5.00 g, 22.0 mmol) in THF (120 mL) at 0 °C was added $LiAlH_4$ (1M in THF; 24.0 mL, 24.0 mmol). After 4 h at RT, MeOH (20 mL), sat. Rochelle's salt (175 mL) and EtOAc (120 mL) were then added. The aqueous phase was separated and extracted with EtOAc (3 x 75 mL). The organic phases were combined, washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **2.34** as a pale yellow oil (4.29 g, 21.6 mmol, 98%) with physical and spectroscopic data consistent with reported values.[165]

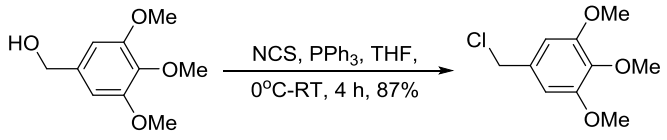
MP: 45.7 - 46.2 °C ($CDCl_3$/petroleum ether) (lit. 45 - 46 °C).[165]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.61 (2H, s, 2 x Ar**H**), 4.64 (2H, s, C**H_2**), 3.87 (6H, s, 2 x C**H_3**), 3.84 (3H, s, C**H_3**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.3 (2 x **C**), 137.3 (**C**), 136.6 (**C**), 103.8 (2 x **C**H), 65.5 (**C**H_2), 60.8 (**C**H_3), 56.0 (2 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 199 $[M+H]^+$ (100%).

5-(Chloromethyl)-1,2,3-trimethoxybenzene (2.35)



2.34

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

2.35

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

To a solution of benzyl alcohol **2.34** (4.20 g, 21.2 mmol) in THF (100 mL) at 0 °C was added *N*-chlorosuccinimide (3.40 g, 25.4 mmol) and PPh_3 (6.67 g, 25.4 mmol). After 4 h at RT, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (0-30% EtOAc in petroleum ether) to give **2.35** as a white solid (4.01 g, 18.5 mmol, 87%).

MP: 60.7 - 61.9 °C ($CDCl_3$/petroleum ether) (lit. 60 - 63).[166]

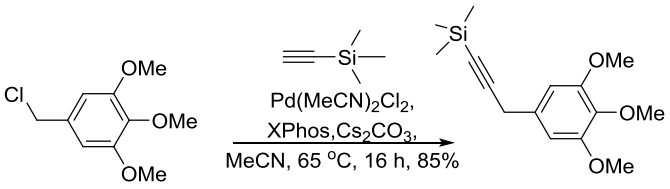
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.62 (2H, s, 2 x Ar**H**), 4.56 (2H, s, C**H_2**), 3.89 (6H, s, 2 x C**H_3**), 3.86 (3H, s, C**H_3**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.4 (2 x **C**), 132.9 (**C**), 130.2 (**C**), 105.7 (2 x **C**H), 60.9 (**C**H_3), 56.1 (2 x **C**H_3), 46.8 (**C**H_2).

LRMS (HPLC-MS; ESI^+): 219 $[M^{37}Cl+H]^+$ (34%), 217 $[M^{35}Cl+H]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{10}H_{13}ClNaO_3$ $[M^{35}Cl+Na]^+$ 239.0445, found 239.0447.

Trimethyl(3-(3,4,5-trimethoxyphenyl)prop-1-yn-1-yl)silane (2.36)



2.35

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

2.36

$C_{15}H_{22}O_3Si$
MW: 278.42

A flask containing benzyl chloride **2.35** (1.2 g, 5.5 mmol), $Pd(MeCN)_2Cl_2$ (86 mg, 0.3 mmol), XPhos (472 mg, 1.0 mmol) and Cs_2CO_3 (1.97 g, 6.1 mmol) was evacuated and filled with Argon in 3 cycles. TMS-acetylene (1.26 mL, 8.8 mmol) and MeCN (15 mL) were then added and the reaction mixture degassed with Argon for 5 minutes. After 16 h at 65 °C, the reaction mixture was cooled

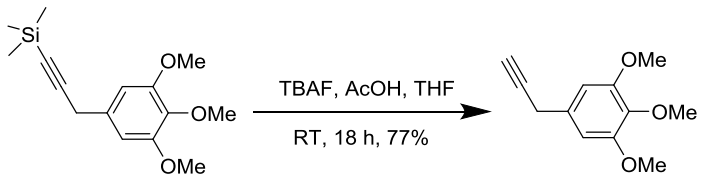
to RT, concentrated *in vacuo* and purified by column chromatography (10-20% Et_2O in petroleum ether) to give **2.36** as a yellow oil (1.30 g, 4.67 mmol, 85%) with physical and spectroscopic data consistent with reported values.[167]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.60 (2H, t, J = 0.9 Hz, 2 x Ar**H**), 3.87 (6H, s, 2 x C**H$_3$**), 3.84 (3H, s, C**H$_3$**), 3.62 (2H, t, J = 0.7 Hz, C**H$_2$**), 0.21 (9H, s, 3 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.2 (2 x **C**), 136.7 (**C**), 131.9 (**C**), 104.9 (**C**), 104.8 (2 x **C**H), 87.4 (**C**), 60.9 (**C**H_3), 56.0 (2 x **C**H_3), 26.3 (**C**H_2), 0.06 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 279 $[M+H]^+$ (100%).

1,2,3-Trimethoxy-5-(prop-2-yn-1-yl)benzene (2.37)



2.36

$C_{15}H_{22}O_3Si$
MW: 278.42

2.37

$C_{12}H_{14}O_3$
MW: 206.24

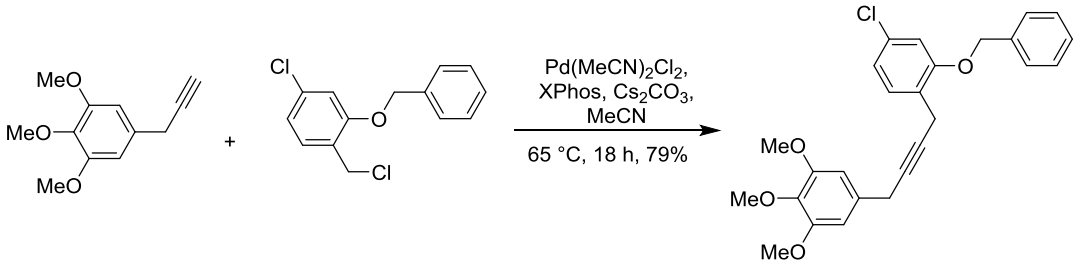
To a solution of alkyne **2.36** (1.12 g, 4.02 mmol) in THF (25 mL) and AcOH (1.15 mL, 20.0 mmol) was added dropwise TBAF (1.0 M in THF; 20.0 mL, 20.0 mmol). After 18 h at RT, the reaction mixture was partitioned between Et_2O (25 mL) and H_2O (25 mL). The aqueous phase was separated and extracted with Et_2O (3 x 25 mL). The organic phases were combined and washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10-20% Et_2O in petroleum ether) provided **2.37** as a yellow oil (641 mg, 3.11 mmol, 77%) with physical and spectroscopic data consistent with reported values.[168]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.59 (2H, t, J = 0.73 Hz, 2 x Ar**H**), 3.87 (6H, s, 2 x C**H$_3$**), 3.84 (3H, s, C**H$_3$**), 3.57 (2H, dt, *J* = 2.7, 1.2 Hz C**H$_2$**), 2.22 (1H, t, *J* = 2.8 Hz, C**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.3 (2 x **C**), 136.8 (**C**), 131.7 (**C**), 104.9 (2 x **C**H), 81.9 (**C**), 70.6 (**C**), 60.9 (**C**H_3), 56.1 (2 x **C**H_3), 26.1 (**C**H_2).

LRMS (HPLC-MS; ESI^+): 207$[M+H]^+$ (100%).

5-(4-(2-(Benzyloxy)-4-chlorophenyl)but-2-yn-1-yl)-1,2,3-trimethoxybenzene (1.154)



2.37

$C_{12}H_{14}O_3$
MW: 206.24

2.11

$C_{14}H_{12}Cl_2O$
MW: 267.15

1.154

$C_{26}H_{25}ClO_4$
MW: 436.93

A flask charged with $Pd(MeCN)_2Cl_2$ (43 mg, 0.17 mmol), XPhos (236 mg, 0.50 mmol) and Cs_2CO_3 (986 mg, 3.03 mmol) was evacuated then filled with Ar in three cycles. Benzyl chloride **2.11** (736 mg, 2.75 mmol) and alkyne **2.37** (567 mg, 2.75 mmol) and MeCN (12 mL) were then added and the reaction mixture degassed with Ar for 5 minutes before The reaction mixture was heated to 65 °C for 18 h. It was then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (30% Et_2O in petroleum ether) afforded the title compound **1.154** (950 mg, 2.17 mmol, 79%) as a yellow oil with physical and spectroscopic data consistent with reported values.[45]

IR ν_{max} (neat, cm^{-1}): 2936 w, 2837 w, 1689 m, 1590 s, 1489 m, 1455 m, 1420 m, 1333 m, 1236 s, 1124 s, 1005 m, 737 m.

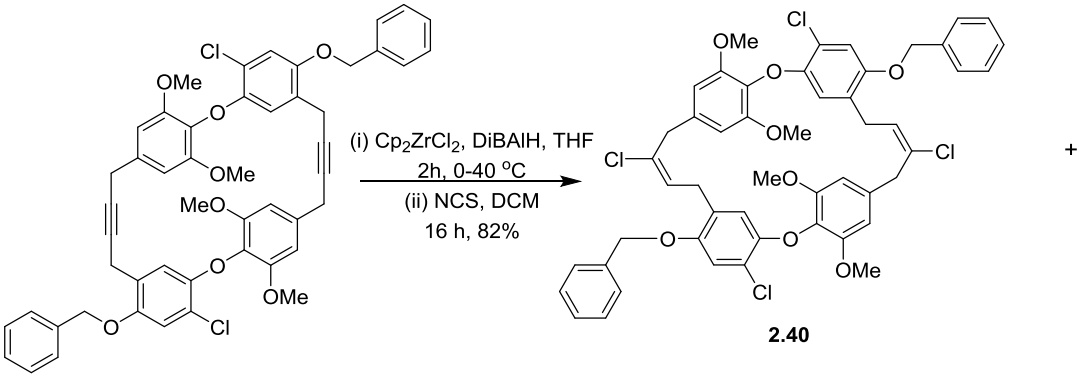
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.50 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.45 - 7.32 (5H, m, 5 × Ar**H**), 6.95 (1H, dd, *J* = 8.1, 2.1 Hz, Ar**H**), 6.92 (1H, d, *J* = 1.8 Hz, Ar**H**), 6.60 (2H, s, 2 × Ar**H**), 5.08 (2H, s, C**H₂**), 3.84 (3H, s, C**H₃**), 3.83 (6H, s, 2 × C**H₃**), 3.64 (2H, d, *J* = 2.1 Hz, C**H₂**), 3.62 (2H, d, *J* = 1.8 Hz, C**H₂**).

^{13}C NMR (100 MHz; $CDCl_3$): δ ppm 156.3 (2 x **C**), 153.2 (**C**), 136.5 (**C**), 136.4 (**C**), 133.0 (**C**), 132.9 (**C**), 129.7 (2 x **C**H), 128.6 (**C**H), 128.1 (2 x **C**H), 127.2 (**C**H), 124.7 (**C**), 120.7 (**C**H), 112.0 (**C**H), 104.8 (2 x **C**H), 80.3 (**C**), 79.6 (**C**), 70.2 (**C**H_2), 60.8 (**C**H_3), 56.0 (2 x **C**H_3), 25.5 (**C**H_2), 19.5 (**C**H_2).

LRMS (HPLC-MS; ESI^+): 439 $[M^{37}Cl+H]^+$ (37%), 437 $[M^{35}Cl+H]^+$ (100%)

HRMS (ESI^+): Calculated for $C_{26}H_{25}ClNaO_4^+$ $[M^{35}Cl + Na]^+$: 459.1334, found: 459.1336.

(9E,23E)-6,20-Bis(benzyloxy)-4,10,18,24-tetrachloro-14,28,29,32-tetramethoxy-2,16-dioxapentacyclo[24.2.2.2^{12,15}.1^{3,7}.1^{17,21}]tetratriaconta-1(28),3(34),4,6,9,12,14,17(31),18,20,23,26,29,32-tetradecaene (2.40) and
(9E,23E)-6,20-Bis(benzyloxy)-4,9,18,24-tetrachloro-14,28,29,32-tetramethoxy-2,16-dioxapentacyclo[24.2.2.2^{12,15}.1^{3,7}.1^{17,21}]tetratriaconta-1(28),3(34),4,6,9,12,14,17(31),18,20,23,26,29,32-tetradecaene (2.41)

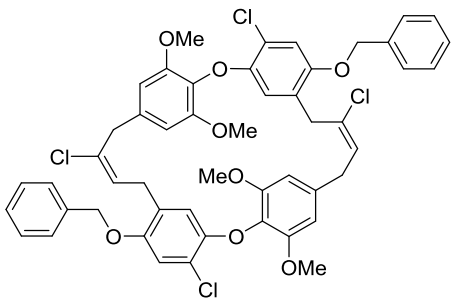


2.1

$C_{50}H_{42}Cl_2O_8$
MW: 841.78

2.40

$C_{50}H_{44}Cl_4O_8$
MW: 914.69



2.41

$C_{50}H_{44}Cl_4O_8$
MW: 914.69

To a flask containing $ZrCp_2Cl_2$ (69 mg, 0.24 mmol) in THF (1 mL) at 0 °C was added DIBAL (1.0 M in hexane, 0.24 mL, 0.24 mmol). After 1 h at 0 °C, the reaction was warmed to RT then macrocycle **2.1** (50 mg, 0.06 mmol) was added. The reaction mixture was heated to 40 °C for 2 h then cooled to RT and a solution of *N*-chlorosuccinimide (16 mg, 0.12 mmol) in DCM (0.5 mL) was added. After 16 h at RT, the reaction mixture was concentrated *in vacuo* and purified by

column chromatography (20-30% EtOAc in petroleum ether) to afford the title compounds **2.40** and **2.41** as a 2:1 mixture of regioisomers in the form of a yellow oil (46 mg, 0.05 mmol, 82%).

Major Isomer **2.40**:

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.53-7.31 (10H, m, 10 x Ar**H**), 7.02 (2H, s, 2 x Ar**H**), 6.34 (2H, s, 2 x Ar**H**), 6.20 (4H, s, 4 x Ar**H**), 5.94 (2H, t, *J* = 8.1 Hz, =C**H**), 5.10 (4H, s, 2 x C**H$_2$**), 3.59 (4H, s, 2 x C**H$_2$**), 3.55 (12H, s, 4 x C**H$_3$**), 3.47 (4H, br d, *J* = 8.1 Hz, 2 x **CH$_2$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 152.8 (4 x **C**), 150.8 (**C**), 148.0 (**C**), 136.6 (**C**), 135.0 (**C**), 133.4 (**C**), 130.1 (**C**), 128.9 (4 x **C**H), 127.9 (2 x **C**H), 127.5 (**C**), 127.4 (4 x **C**H), 126.1 (=**C**H), 119.7 (**C**), 115.0 (**C**H), 113.8 (4 x **C**H), 105.6 (**C**H), 70.8 (2 x **C**H_2), 56.0 (4 x **C**H_3), 40.0 (2 x **C**H_2), 30.0 (2 x **C**H_2).

Minor Isomer **2.41**:

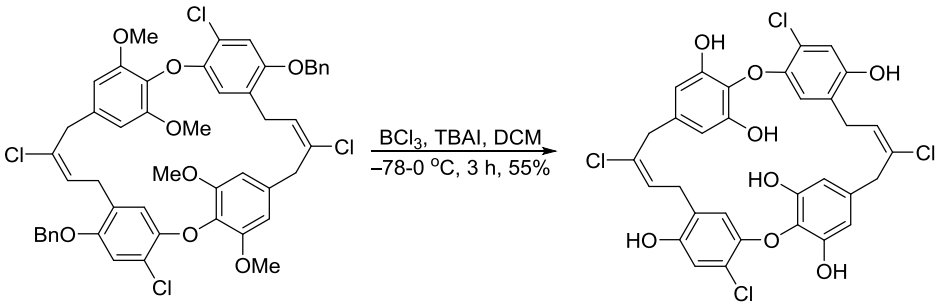
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.53-7.31 (10H, m, 10 x Ar**H**), 7.06 (2H, s, 2 x Ar**H**), 6.41 (2H, s, 2 x Ar**H**), 6.17 (4H, s, 4 x Ar**H**), 5.81 (2H, t, *J* = 7.7 Hz, 2 x =C**H**), 5.09 (4H, s, 2 x C**H$_2$**), 3.81 (2H, br s, C**H$_2$**), 3.62 (12H, s, 4 x C**H$_3$**), 3.50 (2 H br s, C**H$_2$**), 3.21 (4H, br d, *J* = 7.7 Hz, 2 x C**H$_2$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.0 (4 x **C**), 151.0 (**C**), 148.2 (**C**), 136.73 (**C**), 136.70 (**C**), 135.4 (**C**H), 135.2 (**C**H), 134.7 (**C**), 134.43 (**C**), 130.0 (=**C**H), 128.6 (4 x **C**H), 128.10 (2 x **C**H), 127.9 (4 x **C**H), 127.1 (=**C**H), 119.7 (**C**), 114.1 (**C**H), 113.9 (**C**H), 105.6 (4 x **C**H), 70.9 (2 x **C**H_2), 56.3 (4 x **C**H_3), 39.9 (**C**H_2), 36.0 (**C**H_2), 33.2 (**C**H_2), 28.9 (**C**H_2).

LRMS (HPLC-MS, ESI^+): 939 $[M2^{35}Cl2^{37}+Na]^+$ (2%), 937 $[M3^{35}Cl^{37}+Na]^+$ (8%), 935 $[M4^{35}Cl+Na]^+$ (2%).

HRMS (ESI^+): Calculated for $C_{50}H_{44}Cl_4NaO_8$ $[M4^{35}Cl+Na]^+$ 935.1683; found 935.1681.

Chrysophaentin F (1.8)



2.40

$C_{50}H_{44}Cl_4O_8$
MW: 914.69

1.8

$C_{32}H_{24}Cl_4O_8$
MW:678.34

To a solution of **2.40/2.41** (mixture of regioisomers, 40 mg, 0.04 mmol) and TBAI (126 mg, 0.34 mmol) in DCM (4 mL) at -78 °C was added BCl_3 (1.0 M in DCM, 0.53 mL, 0.53 mmol) and the solution stirred for 5 minutes. The solution was warmed to 0 °C and after 4 h, ice (1.0 g) and sat. $NaHCO_3$ (1 mL) were added. The reaction mixture was concentrated *in vacuo* then partitioned between Et_2O (5 mL) and H_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 x 5 mL) then the organic phases were combined and washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20-50% EtOAc in petroleum ether) to provide the title compound **1.8** as a 2:1 mixture of regioisomers, in the form of an off-white solid (15 mg, 0.022 mmol, 55% yield). Further purification by HPLC led to loss of material.

^{1}H NMR (400 MHz; MeOD): δ ppm 6.90 (2H, s, 2 x Ar**H**), 6.42 (2H, s, 2 x Ar**H**), 6.23 (4H, s, 4 x Ar**H**), 5.89 (2H, t, *J* = 8.3 Hz, 2 x =C**H**), 3.53 (4H, br s, 2 x **CH$_2$**), 3.36 (4H, d, *J* = 8.7 Hz, 2 x C**H$_2$**).

^{13}C NMR (101 MHz; MeOD): δ ppm 151.5 (4 x **C**), 151.0 (2 x **C**), 148.5 (2 x **C**), 137.3 (2 x **C**), 134.5 (2 x **C**), 130.2 (2 x **C**), 127.2 (2 x **C**H), 126.9 (2 x **C**), 120.6 (2 x **C**), 117.6 (2 x **C**H), 115.4 (2 x **C**H), 110.3 (4 x **C**H), 40.0 (2 x **C**H_2), 30.9 (2 x **C**H_2).

LRMS (HPLC-MS, ESI^-): 681 $[M-H]^-$ (15%), 679 $[M-H]^-$ (15%), 677 $[M-H]^-$ (100%), 675 $[M-H]^-$ (76%).

Other isomer not characterised due to lack of material.

2-(4-(Benzyloxy)-2-chloro-5-(prop-2-yn-1-yl)phenoxy)-5-(chloromethyl)-1,3-dimethoxybenzene (2.43)

2.25

$C_{28}H_{30}Cl_2O_4Si$
MW:529.53

2.43

$C_{25}H_{22}Cl_2O_4$
MW: 457.35

To a solution of TMS-alkyne **2.25** (100 mg, 0.19 mmol) in THF (5 mL) and AcOH (0.05 mL, 0.94 mmol) was added dropwise TBAF (1.0 M in THF, 0.94 mL, 0.94 mmol). After 18 h at RT, the reaction mixture was diluted with Et_2O (10 mL), washed with brine (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in petroleum ether) afforded the title compound **2.43** as a white solid (78 mg, 0.17 mmol, 90%).

MP: 134.2 - 136.4 °C ($CDCl_3$/petroleum ether).

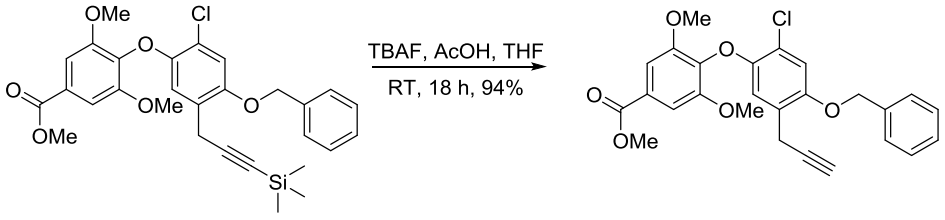
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45-7.31 (5H, m, 5 x Ar**H**), 6.98 (1H, s, Ar**H**), 6.75 (1H, s, Ar**H**), 6.69 (1H, s, Ar**H**), 5.04 (2H, s, C**H$_2$**), 4.60 (2H, s, C**H$_2$**), 3.81 (6H, s, 2 x C**H$_3$**), 3.47 (2H, d, *J* = 2.5 Hz, C**H$_2$**), 2.01 (2H, t, *J* = 2.7 Hz, C**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 153.2 (2 x **C**), 150.1 (**C**), 148.1 (**C**), 136.7 (**C**), 134.5 (**C**), 132.6 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 124.3 (**C**), 120.2 (**C**), 115.4 (**C**H), 113.7 (**C**H), 106.0 (2 x **C**H), 81.1 (**C**), 70.7 (**C**H$_2$), 70.4 (**C**H), 56.5 (2 x **C**H$_3$), 46.5 (**C**H$_2$), 19.6 (**C**H$_2$).

LRMS (HPLC-MS; ESI$^+$): 461 $[M^{37}Cl+Na]^+$ (3%), 459 $[M^{37}Cl^{35}Cl+Na]^+$, $[M^{37}Cl^{35}Cl+Na]^+$ (14%), 457 $[M^{35}Cl+Na]^+$ (21%).

HRMS (ESI$^+$): Calculated for $C_{25}H_{22}Cl_2NaO_4$ $[M^{35}Cl^{35}Cl+Na]^+$, 479.0787, found 479.0784.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(prop-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (2.46)



1.170

$C_{29}H_{31}ClO_6Si$
MW: 539.10

2.46

$C_{26}H_{23}ClO_6$
MW: 466.91

To a solution of TMS-alkyne **1.170** (270 mg, 0.50 mmol) in THF (10 mL) and AcOH (0.14 mL, 2.50 mmol) was added dropwise TBAF (1.0 M in THF, 2.50 mL, 2.50 mmol). After 18 h at RT, the reaction mixture was diluted with Et_2O (20 mL), washed with brine (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5-10% EtOAc in petroleum ether) afforded the title compound **2.46** as a yellow solid (219 mg, 0.47 mmol, 94%).

MP: 157.2 - 159.8 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 3280 s, 2953 w, 2924 w, 2871 w, 2852 w, 1715 s, 1597 m, 1495 m, 1414 m, 1340 s, 1207 s, 1182 s, 1122 s, 990 m, 865 m, 755 m.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.45 - 7.34 (7 H, m, 7 x Ar**H**), 6.98 (1 H, s, Ar**H**), 6.76 (1 H, s, Ar**H**), 5.05 (2 H, s. C**H$_2$**), 3.95 (3 H, s, C**H$_3$**), 3.85 (6 H, s, 2 x C**H$_3$**), 3.47 (2 H, d, *J* = 2.7 Hz, C**H$_2$**), 2.01 (1 H, t, *J* = 2.7 Hz, C**H**).

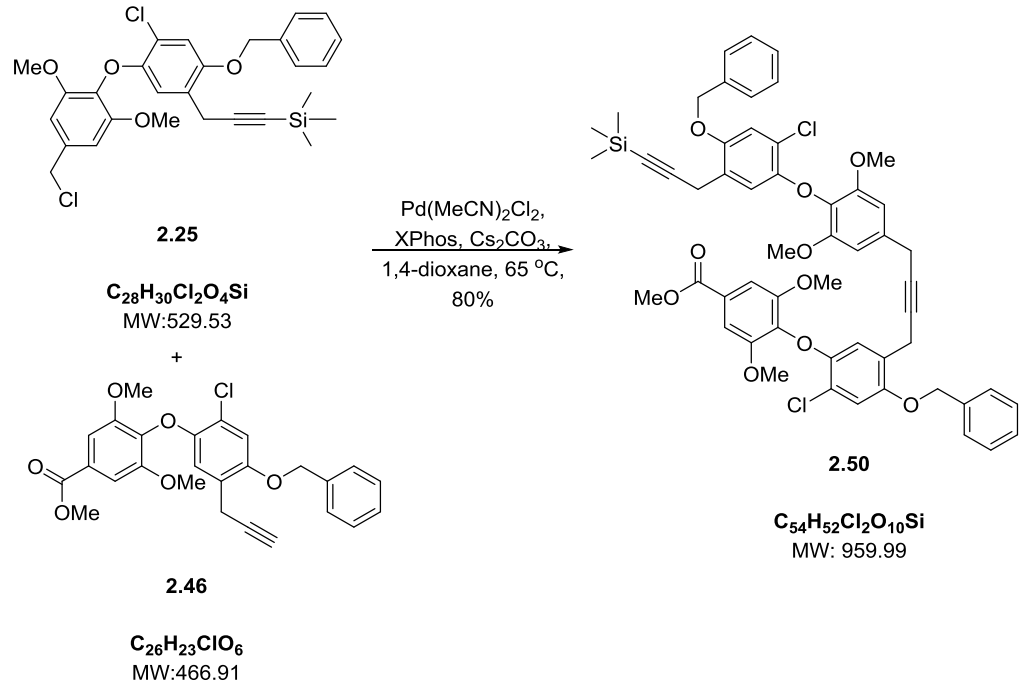
^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 166.6 (**C**O), 153.0 (2 x **C**), 150.8 (**C**), 147.6 (**C**), 136.7 (**C**), 136.6 (**C**), 128.6 (2 x **C**H), 128.1 (**C**H), 127.3 (2 x **C**H), 127.1 (**C**), 124.3 (**C**), 120.6 (**C**), 115.6 (**C**H), 113.7 (**C**H), 107.0 (2 x **C**H), 81.1 (**C**), 70.8 (**C**H_2), 70.5 (**C**H), 56.5 (2 x **C**H_3), 52.4 (**C**H_3), 19.28 (**C**H_2).

LRMS (HPLC-MS; ESI^+): 469 $[M^{37}Cl+H]^+$ (30%), (14%), 467 $[M^{35}Cl+H]^+$ (100%).

489 $[M^{37}Cl+Na]^+$ (1%), (14%), 491 $[M^{35}Cl+Na]^+$ (12%).

HRMS (ESI^+): Calculated for $C_{26}H_{23}ClNaO_6$ $[M^{35}Cl+Na]^+$ 489.1075, found 489.1088.

Methyl 4-(4-(benzyloxy)-5-(4-(4-(benzyloxy)-2-chloro-5-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)but-2-yn-1-yl)-2-chlorophenoxy)-3,5-dimethoxybenzoate (2.50)



A flask charged with alkyne **2.46** (280 mg, 0.60 mmol), benzyl chloride **2.25** (212 mg, 0.40 mmol), $Pd(MeCN)_2Cl_2$ (6 mg, 0.02 mmol), XPhos (34 mg, 0.07 mmol) and Cs_2CO_3 (144 mg, 0.44 mmol) was evacuated and filled with Argon in 3 cycles. The reaction mixture was then heated at 65 °C for 18 h then concentrated *in vacuo*. Purification by column chromatography (10-20% EtOAc in petroleum ether) provided the title compound **2.50** as a pale yellow solid (307 mg, 0.32 mmol, 80%).

MP: 67.4 - 69.1 °C ($CDCl_3$/petroleum ether).

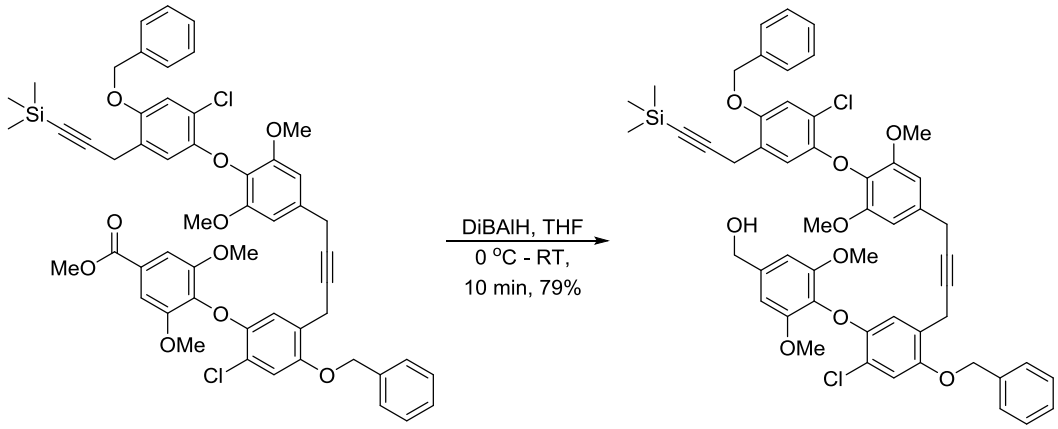
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.44 - 7.32 (12 H, m, 7 x Ar**H**), 6.98 (1 H, s, Ar**H**), 6.96 (1H, s, Ar**H**), 6.79 (1 H, s, Ar**H**), 6.76 (1 H, s, Ar**H**), 5.06 (2 H, s. C**H$_2$**), 5.02 (2 H, s. C**H$_2$**), 3.94 (3 H, s, C**H$_3$**), 3.80 (6 H, s, 2 x C**H$_3$**), 3.70 (6 H, s, 2 x C**H$_3$**), 3.52 (4 H, br s, 2 x C**H$_2$**), 3.48 (2 H, br s, C**H$_2$**), 0.01 (9 H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 166.5 (**C**O), 153.03 (2 x **C**), 152.99 (2 x **C**), 150.8 (**C**), 150.3 (**C**), 148.3 (**C**), 147.6 (**C**), 136.8 (**C**), 136.6 (**C**), 134.4 (**C**), 130.9 (**C**), 128.59 (2 x **C**H), 128.55 (2 x **C**H), 128.1 (**C**H), 127.97 (**C**H), 127.19 (2 x **C**H), 127.17 (2 x **C**H), 125.55 (**C**), 124.45 (**C**), 120.29 (**C**), 120.22 (**C**), 115.86 (**C**H), 114.91 (**C**H), 113.73 (**C**H), 113.57 (**C**H), 106.90 (2 x **C**H), 105.04 (2 x **C**H), 103.50 (**C**), 87.18 (**C**), 80.08 (**C**), 79.58 (**C**), 70.78 (**C**H_2), 70.72 (**C**H_2), 56.45 (2 x **C**H_3), 56.25 (2 x **C**H_3), 52.37 (**C**H_3), 25.22 (**C**H_2), 20.68 (**C**H_2), 19.79 (**C**H_2), -0.13 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 985 $[M^{37}Cl^{37}Cl+Na]^+$ (9%), 983 $[M^{37}Cl^{35}Cl+Na]^+$, $[M^{37}Cl^{35}Cl+Na]^+$ (30%), 981 $[M^{35}Cl+Na]^+$ (35%).

HRMS (ESI^+): Calculated for $C_{54}H_{52}Cl_2NaO_{10}Si$ $[M^{35}Cl^{35}Cl+Na]^+$ 981.2599, found 981.2612.

(4-(4-(Benzyloxy)-5-(4-(4-(4-(benzyloxy)-2-chloro-5-(3-(trimethylsilyl)prop-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)but-2-yn-1-yl)-2-chlorophenoxy)-3,5-dimethoxyphenyl)methanol (2.51)



2.50

$C_{54}H_{52}Cl_2O_{10}Si$
MW: 959.99

2.51

$C_{53}H_{52}Cl_2O_9Si$
MW: 931.98

To a solution of ester **2.50** (150 mg, 0.16 mmol) in THF (2 mL) at 0 °C was added dropwise DiBAlH (1.0 M in hexane, 0.34 mL, 0.34 mmol). The reaction mixture was warmed to RT for 10 minutes and MeOH (1 mL) was added. The reaction mixture was then concentrated *in vacuo* and purified

by column chromatography (20-40% EtOAc in petroleum ether) to provide the title compound **2.51** as a pale yellow foam (118 mg, 0.13 mmol, 79%).

MP: 77.9 - 79.3 °C ($CDCl_3$/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.45 - 7.32 (10 H, m, 10 x Ar**H**), 6.99 (1 H, s, Ar**H**), 6.98 (1H, s, Ar**H**), 6.97 (1 H, s, Ar**H**), 6.85 (1H, s, Ar**H**), 6.58 (2 H, s, 2 x Ar**H**), 6.56 (2 H, s, 2 x Ar**H**), 5.05 (2 H, s. C**H$_2$**), 5.03 (2 H, s. C**H$_2$**), 4.64 (2H, s, C**H$_2$**), 3.73 (6 H, s, 2 x C**H$_3$**), 3.65 (6 H, s, 2 x C**H$_3$**), 3.55 (2 H, br s, 2 x C**H$_2$**), 3.52 (4 H, br s, C**H$_2$**), 0.01 (9 H, s, C**H$_3$**).

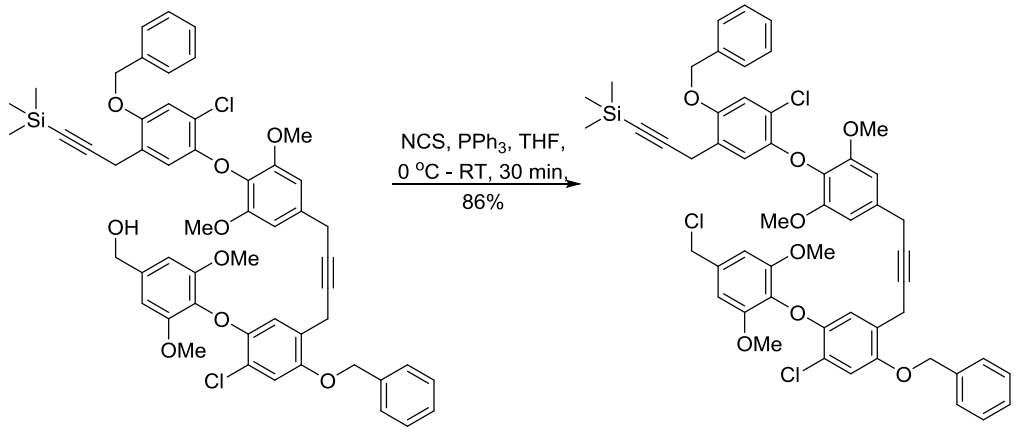
^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 153.2 (2 x **C**), 153.0 (2 x **C**), 150.5 (**C**), 150.4 (**C**), 148.18 (**C**), 148.15 (**C**), 139.0 (**C**), 136.7 (**C**), 135.1 (**C**), 134.7 (**C**), 131.9 (**C**), 130.8 (**C**), 128.57 (2 x **C**H), 128.55 (2 x **C**H), 128.00 (**C**H), 127.97 (**C**H), 127.20 (2 x **C**H), 127.16 (2 x **C**H), 125.4 (**C**), 124.5 (**C**), 120.2 (**C**), 119.9 (**C**), 115.8 (**C**H), 114.8 (**C**H), 113.7 (**C**H), 113.6 (**C**H), 105.00 (2 x **C**H), 104.95 (2 x **C**H), 103.6 (**C**), 87.2 (**C**), 83.6 (**C**), 79.4 (**C**), 70.8 (**C**H$_2$), 70.7 (**C**H$_2$), 65.1 (**C**H$_2$), 56.31 (2 x **C**H$_3$), 56.25 (2 x **C**H$_3$), 25.2 (**C**H$_2$), 20.7 (**C**H$_2$), 19.8 (**C**H$_2$), -0.1 (3 x **C**H$_3$).

LRMS (HPLC-MS; ESI$^+$): 935 $[M^{37}Cl^{37}Cl+H]^+$ (2%), 933 $[M^{37}Cl^{35}Cl+H]^+$, $[M^{37}Cl^{35}Cl+H]^+$ (6%), 931 $[M^{35}Cl+H]^+$ (9%).

973 $[M^{37}Cl^{37}Cl+K]^+$ (5%), 971 $[M^{37}Cl^{35}Cl+K]^+$, $[M^{37}Cl^{35}Cl+K]^+$ (46%), 969 $[M^{35}Cl+K]^+$ (48%).

HRMS (ESI$^+$): Calculated for $C_{53}H_{52}Cl_2NaO_9Si$ $[M^{35}Cl^{35}Cl+Na]^+$ 953.2650, found 953.2673.

(3-(2-(Benzyloxy)-5-(4-(4-(2-(benzyloxy)-4-chloro-5-(4-(chloromethyl)-2,6-dimethoxyphenoxy)phenyl)but-2-yn-1-yl)-2,6-dimethoxyphenoxy)-4-chlorophenyl)prop-1-yn-1-yl)trimethylsilane (2.52)



2.51

$C_{53}H_{52}Cl_2O_9Si$
MW: 931.98

2.52

$C_{53}H_{51}Cl_3O_8Si$
MW: 950.42

To a solution of benzyl alcohol **2.51** (50 mg, 0.05 mmol) in THF (2 mL) at 0 °C was added PPh_3 (16.9 mg, 0.06 mmol) and *N*-chlorosuccinimide (8.6 mg, 0.06 mmol). The reaction mixture was warmed to RT for 30 minutes, then concentrated *in vacuo*. Purification by column chromatography (0-20% EtOAc in petroleum ether) afforded the title compound **2.52** as a pale yellow solid (44 mg, 0.046 mmol, 86%).

MP: 72.1 - 74.9 °C ($CDCl_3$/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.46 - 7.31 (10 H, m, 10 x Ar**H**), 6.98 (1 H, s, Ar**H**), 6.97 (1H, s, Ar**H**), 6.81 (1 H, s, Ar**H**), 6.78 (1H, s, Ar**H**), 6.64 (2 H, s, 2 x Ar**H**), 6.57 (2 H, s, 2 x Ar**H**), 5.05 (2 H, s. C**H$_2$**), 5.03 (2 H, s, C**H$_2$**), 4.57 (2H, s, C**H$_2$**), 3.75 (6 H, s, 2 x C**H$_3$**), 3.9 (6 H, s, 2 x C**H$_3$**), 3.55 - 3.49 (6 H, m, 3 x C**H$_2$**), 0.01 (9 H, s, C**H$_3$**).

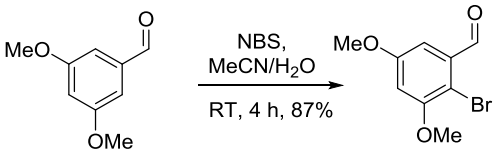
^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 153.4 (2 x **C**), 153.1 (2 x **C**), 150.7 (**C**), 150.4 (**C**), 148.4 (**C**), 148.0 (**C**), 136.9 (**C**), 136.8 (**C**), 135.1 (**C**), 134.7 (**C**), 132.7 (**C**), 131.0 (**C**), 128.69 (2 x **C**H), 128.65 (2 x **C**H), 128.13 (**C**H), 128.07 (**C**H), 127.30 (2 x **C**H), 127.28 (2 x **C**H), 125.6 (**C**), 124.6 (**C**), 120.4 (**C**), 120.1 (**C**), 115.6 (**C**H), 115.0 (**C**H), 113.8 (**C**H), 113.7 (**C**H),

106.0 (2 x **C**H), 105.2 (2 x **C**H), 103.6 (**C**), 87.3 (**C**), 80.2 (**C**), 79.8 (**C**), 70.8 (**C**H_2), 70.7 (**C**H_2), 56.5 (2 x **C**H_3), 56.4 (2 x **C**H_3), 46.8 (**C**H_2), 25.3 (**C**H_2), 20.9 (**C**H_2), 19.9 (**C**H_2), -0.1 (3 x **C**H_3).

LRMS (HPLC-MS; ESI^+): 975 $[M^{37}Cl^{37}Cl+Na]^+$ (37%), 973 $[M^{37}Cl^{35}Cl+Na]^+$, $[M^{37}Cl^{35}Cl+Na]^+$ (68%), 971 $[M^{35}Cl^{35}Cl+Na]^+$ (75%).

6.3 Chrysophaentin A

2-Bromo-3,5-dimethoxybenzaldehyde (3.8)



3.7

$C_9H_{10}O_3$
MW: 166.18

3.8

$C_9H_9BrO_3$
MW: 245.07

To a solution of 3,5-dimethoxybenzaldehyde (1.00 g, 6.02 mmol) in MeCN (8 mL) and H_2O (2 mL) was added *N*-bromosuccinimide (1.18 g, 6.62 mmol). After 4 h at RT the reaction mixture was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous phase extracted with EtOAc (3 x 10 mL) then the organic phases were combined and washed with H_2O (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5-10% EtOAc in petroleum ether) to give the title compound **3.8** as an off-white solid (1.28 g, 5.23 mmol, 87%) with physical and spectroscopic data consistent with reported values.[169]

MP: 110.1 - 111.4 °C ($CDCl_3$/petroleum ether) (lit. 110 - 112 °C).[170]

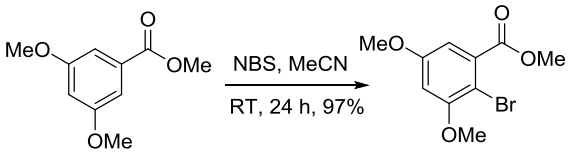
IR ν_{max} (neat, cm^{-1}): 3077 w, 2976 w, 2943 w, 2838 w, 1673 s, 1584 s, 1456 m, 1447 s, 1392 m, 1333 s, 1291 s, 1200 m, 1159 s, 1077 m, 1021 s, 918 m, 832 m, 600 s.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 10.43 (1H, s, C**H**O), 7.06 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.73 (1H, d, *J* = 2.8 Hz, Ar**H**), 3.93 (3H, s, C**H$_3$**), 3.86 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 192.1 (**C**HO), 160.0 (**C**), 157.1 (**C**), 134.7 (**C**), 109.1 (**C**), 105.9 (**C**H), 103.4 (**C**H), 56.6 (**C**H_3), 55.8 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 247 $[M^{81}Br+H]^+$ (99%), 245 $[M^{79}Br+H]^+$ (100%).

Methyl 2-bromo-3,5-dimethoxybenzoate (3.9)



3.11

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

3.9

$C_{10}H_{11}BrO_4$
MW: 275.10

To a solution of methyl 3,5-dimethoxybenzoate (5.00 g, 25.5 mmol) in MeCN (30 mL) was added *N*-bromosuccinimide (4.54 g, 25.5 mmol) at 0 °C and the reaction mixture was stirred at RT for 24 h. H_2O (100 mL) and EtOAc (100 mL) were then added and the aqueous phase extracted with EtOAc (3 x 100 mL). The organic phases were combined and washed with H_2O (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (0-10% EtOAc in petroleum ether) provided the title compound **3.9** as a white solid (6.82 g, 24.8 mmol, 97%) with physical and spectroscopic data consistent with reported values.[171]

MP: 56.5 - 57.4 °C ($CDCl_3$/petroleum ether) (lit. 57 - 59).[172]

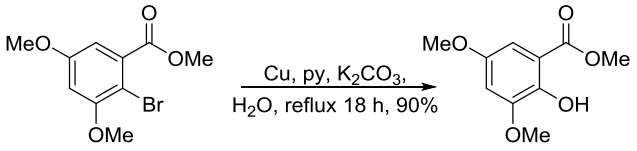
IR ν_{max} (neat, cm^{-1}): 3007 w, 2964 w, 2943 w, 2843 w, 1723 m, 1673 m, 1582 s, 1455 s, 1431 s, 1332 s, 1201 s, 1154 s, 1021 s, 855 m, 816 m, 641 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.81 (1H, d, *J* = 2.7 Hz, Ar**H**), 6.59 (1H, d, *J* = 2.7 Hz, Ar**H**), 3.94 (3H, s, C**H$_3$**), 3.89 (3H, s, C**H$_3$**), 3.83 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 167.2 (**C**), 159.6 (**C**), 157.2 (**C**), 134.8 (**C**), 106.1 (**C**H), 102.4 (**C**H), 55.6 (**C**H$_3$), 55.7 (**C**H$_3$), 52.7 (**C**H$_3$).

LRMS (HPLC-MS; ESI^+): 277 $[M^{81}Br+H]^+$ (95%), 275 $[M^{79}Br+H]^+$ (100%).

Methyl 2-hydroxy-3,5-dimethoxybenzoate (3.5)



3.9

$C_{10}H_{11}BrO_4$
MW: 275.10

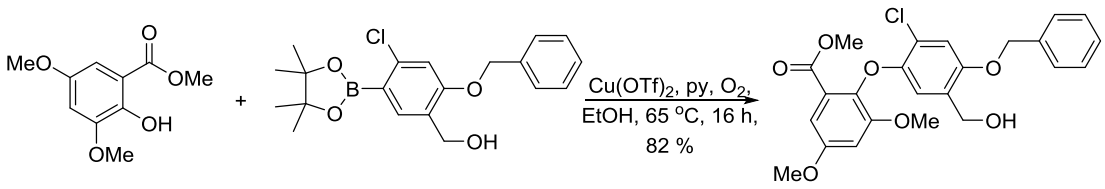
3.5

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

A suspension of aryl bromide **3.9** (275 mg, 1.00 mmol), Cu powder (13 mg, 0.2 mmol) and K_2CO_3 (138 mg, 1.00 mmol) and pyridine (0.08 mL, 1.00 mmol) in H_2O (5 mL) was heated at reflux for 18 h then cooled to RT. The reaction mixture was acidified with conc. HCl and diluted with EtOAc (10 mL). The aqueous phase was separated and extracted with EtOAc (3 x 10 mL). The organic phases were combined and washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (0-10% EtOAc in petroleum ether) to provide the title compound **3.5** as a white solid (192 mg, 0.90 mmol, 90%) with physical and spectroscopic characteristics corresponding to reported values.[173]

MP:	89.7 - 92.3 °C (EtOAc) (lit. 91-92 °C).[174]
IR ν_{max} (neat, cm^{-1}):	3210 br s, 2958 w, 2940 w, 1672 s, 1590 m, 1448 s, 1436 s, 1333 m, 1321 m, 1200 s, 1160 s, 1066 s, 1050 s, 860 m, 782 m.
^{1}H NMR (400 MHz; $CDCl_3$):	δ ppm 10.65 (1H, s, O**H**), 6.85 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.70 (1H, d, *J* = 2.8 Hz, Ar**H**), 3.97 (3H, s, C**H$_3$**), 3.89 (3H, s, C**H$_3$**), 3.79 (3H, s, C**H$_3$**).
^{13}C NMR (101 MHz; $CDCl_3$):	170.6 (**C**), 151.8 (**C**), 149.3 (**C**), 147.1 (**C**), 106.8 (**C**H), 101.1 (**C**H), 56.2 (**C**H$_3$), 55.7 (**C**H$_3$), 52.4 (**C**H$_3$).
LRMS (HPLC-MS; ESI^+):	213 $[M+H]^+$ (100%). 235 $[M+Na]^+$ (31%).

Methyl 2-(4-(benzyloxy)-2-chloro-5-(hydroxymethyl)phenoxy)-3,5-dimethoxybenzoate (3.14)



3.5

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

1.160

$C_{20}H_{24}BClO_4$
MW: 374.67

3.14

$C_{24}H_{23}ClO_7$
MW: 458.89

A flask containing a suspension of phenol **3.5** (106 mg, 0.5 mmol), boronic ester **1.160** (187 mg, 0.5 mmol), $Cu(OTf)_2$ (36 mg, 0.1 mmol) and powdered 4 Å molecular sieves (106 mg) in EtOH (8 ml) was placed under a slight positive pressure of oxygen before pyridine (0.3 mL, 3.75 mmol) was added. The reaction mixture was heated to 65 °C for 16 h then concentrated *in vacuo*. Purification by column chromatography (10-30% EtOAc in petroleum ether) provided the title compound **3.14** as an off white solid (189 mg, 0.41 mmol, 82%).

MP: 106.8 - 108.1 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 3502 br s, 3269 br s, 2948 w, 1692 m, 1602 m, 1487 m, 1467 m, 1359 m, 1208 s, 1190 s, 1051 s, 963 m, 757 m.

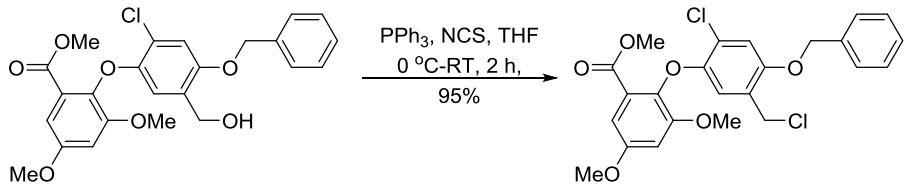
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.42-7.32 (5H, m, 5 x Ar**H**), 7.02 (1H, s, Ar**H**), 6.98 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.72 (1H, d, *J* = 2.8 Hz, Ar**H**), 6.49 (1H, , Ar**H**), 5.04 (2H, s, C**H$_2$**), 4.53 (2H, s, C**H$_2$**), 3.85 (3H, s, C**H$_3$**), 3.745 (3H, s, C**H$_3$**), 3.738 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 165.8 (**C**), 157.0 (**C**), 154.0 (**C**), 150.7 (**C**), 148.8 (**C**), 137.3 (**C**), 128.9 (**C**), 128.7 (2 x **C**H), 128.2 (**C**H), 127.4 (2 x **C**H), 125.9 (**C**), 120.8 (**C**), 114.4 (**C**H), 114.0 (**C**H), 105.2 (**C**H), 104.9 (**C**H), 70.9 (**C**H_2), 61.2 (**C**H_2), 56.4 (**C**H_3), 55.8 (**C**H_3), 52.4 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 483 $[M^{37}Cl+Na]^+$ (33%), 481 $[M^{35}Cl+Na]^+$ (76%).

HRMS (ESI^+): Calculated for $C_{24}H_{23}ClNaO_7$ $[M^{35}Cl+Na]^+$ 481.1035, found 481.1025.

Methyl 2-(4-(benzyloxy)-2-chloro-5-(chloromethyl)phenoxy)-3,5-dimethoxybenzoate (3.4)



3.14

$C_{24}H_{23}ClO_7$
MW: 458.89

3.4

$C_{24}H_{22}Cl_2O_6$
MW: 477.33

To a solution of benzyl alcohol **3.14** (528 mg, 1.15 mmol) in THF at 0 °C was added PPh_3 (362 mg, 1.38 mmol) and *N*-chlorosuccinimide (184 mg, 1.38 mmol). The reaction mixture was warmed to RT for 2 h then concentrated *in vacuo*. Purification by column chromatography (0-10% EtOAc in petroleum ether) to provide the title compound **3.4** as a white solid (520 mg, 1.09 mmol, 95%).

MP: 114.5 - 115.9 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2947 w, 2842 w, 1732 m, 1711 m, 1601 m, 1485 s, 1435 s, 1396 s, 1335 s, 1285 m, 1261 m, 1205 s, 1188 s, 1050 m, 1004 m, 864 w.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.49-7.35 (5H, m, 5 x Ar**H**), 7.06 (1H, s, Ar**H**), 7.03 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.76 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.53 (1H, s, Ar**H**), 5.11 (2H, s, C**H$_2$**), 4.52 (2H, s, C**H$_2$**), 3.90 (3H, s, C**H$_3$**), 3.79 (3H, s, C**H$_3$**), 3.78 (3H, s, C**H$_3$**).

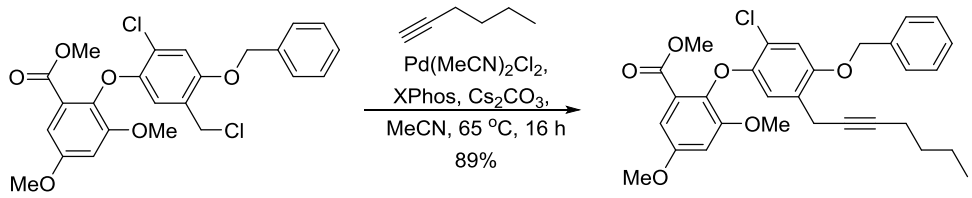
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 165.7 (**C**O), 157.1 (**C**), 153.9 (**C**), 150.9 (**C**), 148.7 (**C**), 137.1 (**C**), 136.5 (**C**), 128.6 (2 x **C**H), 128.1 (**C**H), 127.3 (2 x **C**H), 125.9 (**C**), 125.3 (**C**), 122.4 (**C**), 116.1 (**C**H), 114.6 (**C**H), 105.2 (**C**H), 104.9 (**C**H), 71.1 (**C**H_2), 56.4 (**C**H_3), 55.7 (**C**H_3), 52.3 (**C**H_3), 41.1 (**C**H_2).

LRMS (HPLC-MS; ESI^+): 479 $[M^{37}Cl+H]^+$ (76%), 477 $[M^{35}Cl+H]^+$ (100%).

501 $[M^{37}Cl+Na]^+$ (34%), 499 $[M^{35}Cl+Na]^+$ (81%).

HRMS (ESI^+): Calculated for $C_{24}H_{22}Cl_2NaO_6$ $[M^{35}Cl^{35}Cl+Na]^+$ 499.0686, found 499.0683.

Methyl 2-(4-(benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (3.15)



3.4

$C_{24}H_{22}Cl_2O_6$
MW: 477.33

3.15

$C_{30}H_{31}ClO_6$
MW: 523.02

A flask containing benzyl chloride **3.4** (500 mg, 1.05 mmol), XPhos (90 mg, 0.19 mmol), Cs_2CO_3 (376 mg, 1.16 mmol) and $Pd(MeCN)_2Cl_2$ (16 mg, 0.06 mmol) was evacuated and filled with argon in 3 cycles. 1-hexyne (0.18 mL, 1.57 mmol) and MeCN (5 mL) were then added and the reaction mixture degassed with Ar for 5 minutes before heating to 65 °C for 16 h. The reaction mixture was then concentrated *in vacuo* and then purified by column chromatography (5-10% EtOAc in petroleum ether) to provide the title compound **3.15** as a yellow oil (490 mg, 0.94 mmol, 89%).

IR ν_{max} ($CDCl_3$, cm^{-1}): 2956 w, 2935 w, 1731 m, 1600 m, 1483 m, 1353 m, 1206 s, 1064 m, 771 m.

^{1}H NMR (400 MHz; MeCN-d_3): δ ppm 7.48-7.34 (5H, m, 5 x Ar**H**), 7.07 (1H, s, Ar**H**), 6.96 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.88 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.70 (1H, t, *J* = 0.9 Hz, Ar**H**), 5.08 (2H, s, C**H$_2$**), 3.84 (3H, s, C**H$_3$**), 3.75 (3H, s, C**H$_3$**), 3.69 (3H, s, C**H$_3$**), 3.39 (2H, td, *J* = 2.7 Hz, 0.6 Hz, C**H$_2$**), 2.04 (2H, tt, J = 7.0 Hz, 2.5 Hz, C**H$_2$**), 1.30-1.23 (4H, m, 2 x C**H$_2$**), 0.85 (3H, t, *J* = 7.1 Hz, C**H$_3$**).

^{13}C NMR (101 MHz; MeCN-d_3): δ ppm 166.3 (**C**), 158.5 (**C**), 155.0 (**C**), 151.4 (**C**), 149.6 (**C**), 138.20 (**C**), 137.3 (**C**), 129.6 (2 x **C**H), 129.1 (**C**H), 128.6 (2 x **C**H), 127.4 (**C**), 127.1 (**C**), 119.8 (**C**), 115.7 (**C**H), 115.0 (**C**H), 106.5 (**C**H), 105.3 (**C**H), 84.6 (**C**), 77.3 (**C**), 71.7 (**C**H_2), 57.3 (**C**H_3), 56.7 (**C**H_3), 52.9 (**C**H_3), 31.9 (**C**H_2), 22.7 (**C**H_2), 20.1 (**C**H_2), 18.8 (**C**H_2), 13.8 (**C**H_3).

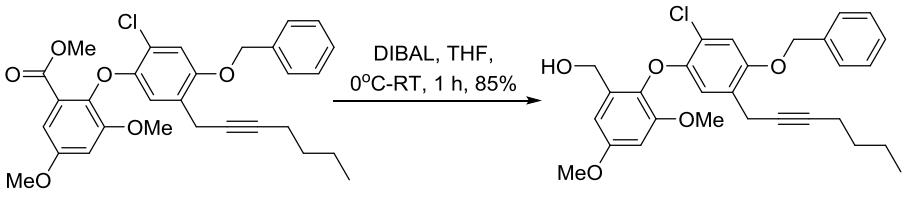
LRMS (HPLC-MS; ESI^+): 525 $[M^{37}Cl+H]^+$ (37%), 523 $[M^{35}Cl+H]^+$ (100%).

547 $[M^{37}Cl+Na]^+$ (24%), 545 $[M^{35}Cl+Na]^+$ (56%).

HRMS (ESI^+): Calculated for $C_{30}H_{32}ClO_6$ $[M^{35}Cl+H]^+$ 523.1882 found 523.1894.

Calculated for $C_{30}H_{31}ClNaO_6$ $[M^{35}Cl+Na]^+$ 545.1701 found 545.1714.

(2-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (3.16)



3.15

$C_{30}H_{31}ClO_6$
MW: 523.02

3.16

$C_{29}H_{31}ClO_5$
MW: 495.01

To a solution of ester **3.15** (189 mg, 0.36 mmol) in THF (5 mL) at 0 °C was added dropwise DIBAL (1.0 M in hexane, 0.76 mL, 0.76 mmol). The reaction mixture was warmed to RT for 1 h then MeOH (1 mL), sat. Rochelle's salt (5 mL) and EtOAc (5 mL) were added. The aqueous phase separated and then extracted with EtOAc (3 x 5 mL). The organic phases were combined and washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc in petroleum ether) to furnish the title compound **3.16** as a pale yellow solid (170 mg, 0.34 mmol, 85%).

MP: 82.7 - 84.1 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 3514 br, 2932 w, 2872 w, 1732 w, 1711 w, 1602 m, 1487 m, 1463 m, 1390 w, 1200 s, 1151 m, 1038 m, 865 m, 836 m.

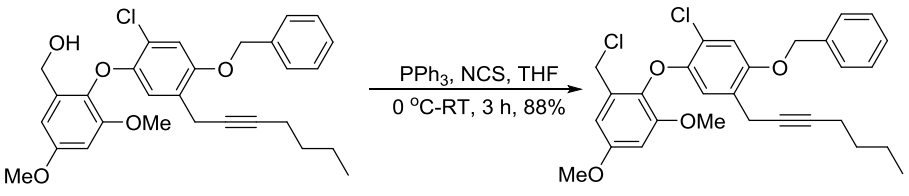
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.45-7.32 (5H, m, 5 x Ar**H**), 6.96 (1H, s, Ar**H**), 6.78 (1H, s, Ar**H**), 6.63 (1H, d, *J* = 2.8 Hz, Ar**H**), 6.53 (1H, d, *J* = 2.9 Hz, Ar**H**), 5.03 (2H, s, C**H$_2$**), 4.60 (2H, d, *J* = 5.9 Hz, C**H$_2$**), 3.84 (3H, s, C**H$_3$**), 3.77 (3H, s, C**H$_3$**), 3.44 (2H, t, *J* = 2.0 Hz, C**H$_2$**), 2.11-2.02 (2H, m, C**H$_2$**), 1.96 (1H, t, *J* = 6.4 Hz, O**H**), 1.39-1.15 (4H, m, 2 x C**H$_2$**), 0.87 (3H, t, *J* = 7.1 Hz, C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 157.1 (**C**), 153.1 (**C**), 150.6 (**C**), 147.8 (**C**), 136.7 (**C**), 135.5 (**C**), 134.8 (**C**), 128.6 (2 x **C**H), 128.0 (2 x **C**H), 127.2 (2 x **C**H), 126.2 (**C**), 119.3 (**C**), 115.0 (**C**H), 113.5 (**C**H), 103.6 (**C**H), 99.8 (**C**H), 83.3 (**C**), 76.4 (**C**), 70.7 (**C**H_2), 61.0 (**C**H_2), 56.1 (**C**H_3), 55.6 (**C**H_3), 31.0 (**C**H_2), 21.9 (**C**H_2), 19.6 (**C**H_2), 18.3 (**C**H_2), 13.5 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 519 $[M^{37}Cl+Na]^+$ (27%), 517 $[M^{35}Cl+Na]^+$ (61%).

HRMS (ESI^+): Calculated for $C_{29}H_{31}ClNaO_5$ $[M^{35}Cl+Na]^+$, 517.1752, found 517.1747.

2-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-1-(chloromethyl)-3,5-dimethoxybenzene (3.3)



3.16

$C_{29}H_{31}ClO_5$
MW: 495.01

3.3

$C_{29}H_{30}Cl_2O_4$
MW: 513.46

To a solution of alcohol **3.16** (170 mg, 0.34 mmol) in THF at 0 °C was added PPh_3 (107 mg, 0.41 mmol) and *N*-chlorosuccinimide (54 mg, 0.41 mmol). The reaction mixture was warmed to RT for 3 h then concentrated *in vacuo* and purified by column chromatography (0-10% EtOAc in petroleum ether) to provide the title compound **3.3** as a pale yellow solid (153 mg, 0.30 mmol, 88%).

MP: 75.9 - 77.0 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2957 w, 2929 w, 2871 w, 1605 m, 1489 s, 1394 w, 1361 w, 1208 s, 1159 m, 1151 m, 1052 m, 831 w, 771 m, 693 m, 684 m.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.48-7.31 (5H, m, 5 x Ar**H**), 6.97 (1H, s, ArH), 6.80 (1H, s, Ar**H**), 6.64 (1H, d, *J* = 2.8 Hz, Ar**H**), 6.54 (1H, d, *J* = 2.8 Hz, Ar**H**), 5.03 (2H, s, C**H$_2$**), 4.58 (2H, s, C**H$_2$**), 3.84 (3H, s, C**H$_3$**), 3.74 (3H, s, C**H$_3$**), 3.45 (2H, t, *J* = 2.1

Hz, C**H₂**), 2.09-2.04 (2H, m, C**H₂**), 1.36-1.26 (4H, m, 2 x C**H₂**), 0.87 (3H, t, *J* = 6.9 Hz, C**H₃**).

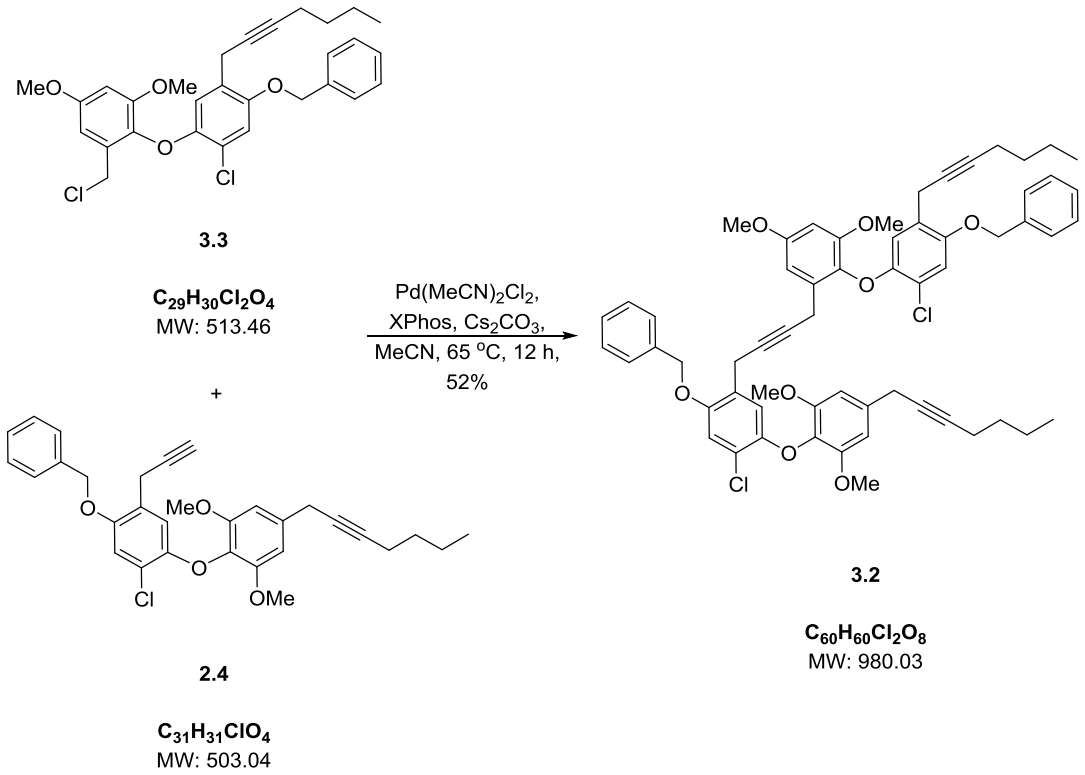
^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 157.5 (**C**), 153.1 (**C**), 150.6 (**C**), 148.1 (**C**), 136.8 (**C**), 135.5 (**C**), 132.1 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 126.0 (**C**), 119.5 (**C**), 115.5 (**C**H), 113.5 (**C**H), 104.9 (**C**H), 100.9 (**C**H), 83.2 (**C**), 76.4 (**C**), 70.7 (**C**H_2), 56.2 (**C**H_3), 55.6 (**C**H_3), 40.7 (**C**H_2), 31.0 (**C**H_2), 21.9 (**C**H_2), 19.6 (**C**H_2), 18.3 (**C**H_2), 13.5 (**C**H_3).

LRMS (HPLC-MS; ESI^+): 517 $[M^{37}Cl^{37}C+H]^+$ (10%), 515 $[M^{35}Cl^{37}C+H]^+$, $[M^{35}Cl^{37}C+H]^+$ (53%), 513 $[M^{35}Cl^{35}C+H]^+$ (68%).

539 $[M^{37}Cl^{37}C+Na]^+$ (13%), 537 $[M^{35}Cl^{37}C+Na]^+$, $[M^{35}Cl^{37}C+Na]^+$ (21%), 535 $[M^{35}Cl^{35}C+Na]^+$ (32%).

HRMS (ESI^+): Calculated for $C_{29}H_{30}Cl_2NaO_4$ 535.1413 $[M^{35}Cl+Na]^+$, found 535.1410.

2-(4-(Benzyloxy)-2-chloro-5-(hept-2-yn-1-yl)phenoxy)-1-(4-(2-(benzyloxy)-4-chloro-5-(4-(hept-2-yn-1-yl)-2,6-dimethoxyphenoxy)phenyl)but-2-yn-1-yl)-3,5-dimethoxybenzene (3.2)



A flask charged with benzyl chloride **3.3** (102 mg, 0.20 mmol), alkyne **2.4** (100 mg, 0.20 mmol), $Pd(MeCN)_2Cl_2$ (3 mg, 0.01 mmol), XPhos (17 mg, 0.04 mmol) and Cs_2CO_3 (72 mg, 0.22 mmol) was evacuated and filled with Ar in 3 cycles. MeCN (1 mL) was added and the reaction mixture degassed with Ar for 5 minutes before heating to 65 °C for 12 h. The reaction mixture was then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (100% $CHCl_3$) afforded the title compound **3.2** as a pale yellow oil (101 mg, 0.10 mmol, 52%).

IR ν_{max} ($CDCl_3$, cm^{-1}): 2956 w, 2931 w, 2871 w, 1597 m, 1490 s, 1462 m, 1391 m, 1204 s, 1128 s, 997 w, 771 m, 734 m, 697 m.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.44-7.32 (10 H, m, 10 x Ar**H**), 6.95 (2H, s, 2 x Ar**H**), 6.76 (1H, s, Ar**H**), 6.72 (1H, s, Ar**H**), 6.66 (1H, d, *J* = 2.8 Hz, Ar**H**), 6.60 (2H, s, 2 x Ar**H**), 6.47 (1H, d, *J* = 2.9 Hz, Ar**H**), 5.02 (2H, s, C**H$_2$**), 5.01 (2H, s, C**H$_2$**), 3.76 (3H, s, C**H$_3$**), 3.72 (6H, s, 2 x C**H$_3$**), 3.70 (3H, s, C**H$_3$**), 3.51 (2H, t, *J* = 2.6 Hz, C**H$_2$**), 3.45 (2H, t, *J* = 2.3 Hz, C**H$_2$**), 3.42 (4H, t, *J* = 2.3 Hz, 2 x C**H$_2$**), 2.24 (2H, tt, *J* = 6.8, 2.4 Hz, C**H$_2$**), 2.05 (2H, m, C**H$_2$**), 1.56 - 1.46 (4H, m, 2 x C**H$_2$**), 1.33-1.29 (4H, m, 2 x C**H$_2$**), 0.92 (3H, t, *J* = 3.4 Hz, C**H$_3$**), 0.85 (3H, t, *J* = 3.4 Hz, C**H$_3$**).

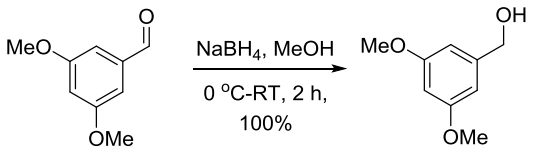
^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 153.1 (2 x **C**), 153.0 (**C**), 150.47 (**C**), 150.45 (**C**), 148.2 (**C**), 147.6 (**C**), 136.80 (**C**), 136.76 (**C**), 135.3 (**C**), 134.8 (**C**), 131.9 (**C**), 131.1 (**C**), 128.53 (2 x **C**H), 128.51 (2 x **C**H), 128.0 (**C**H), 127.9 (**C**H), 127.18 (2 x **C**H), 127.15 (2 x **C**H), 126.1 (**C**), 125.5 (**C**), 119.9 (**C**), 119.4 (**C**), 115.8 (**C**H), 115.0 (**C**H), 113.7 (**C**H), 113.5 (**C**H), 105.0 (**C**H), 104.5 (**C**H), 98.7 (**C**H), 83.3 (**C**), 83.1 (**C**), 80.4 (**C**), 78.7 (**C**), 77.3 (**C**), 76.4 (**C**), 70.8 (**C**H$_2$), 70.7 (**C**H$_2$), 56.2 (2 x **C**H$_3$), 56.1 (**C**H$_3$), 55.3 (**C**H$_3$), 31.1 (**C**H$_2$), 31.0 (**C**H$_2$), 25.3 (**C**H$_2$), 22.0 (**C**H$_2$), 21.9 (**C**H$_2$), 19.72 (**C**H$_2$), 19.69 (**C**H$_2$), 19.6 (**C**H$_2$), 18.5 (**C**H$_2$), 18.3 (**C**H$_2$), 13.6 (**C**H$_3$), 13.5 (**C**H$_3$).

LRMS (HPLC-MS; ESI^+): 1005 $[M^{37}Cl^{37}C+Na]^+$ (25%), 1003 $[M^{35}Cl^{37}C+Na]^+$, $[M^{35}Cl^{37}C+Na]^+$ (64%), 1001 $[M^{35}Cl^{35}C+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{60}H_{60}Cl_2NaO_8$ 1001.3557 $[M^{35}Cl^{35}Cl+Na]^+$, found 1001.3538.

6.4 Chrysophaentin E

(3,5-Dimethoxyphenyl)methanol (4.3)



3.7

$C_9H_{10}O_3$
MW: 166.18

4.3

$C_9H_{12}O_3$
MW: 168.19

To a solution of 3,5-dimethoxybenzaldehyde (3.32 g, 20.0 mmol) in MeOH (30 mL) at 0 °C was added $NaBH_4$ (1.51 g, 40.0 mmol). After 2 h at RT, H_2O (5 mL) was added and the reaction mixture was filtered over a pad of silica, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **4.3** as a white solid (3.36 g, 20.0 mmol, 100%) with spectroscopic and physical properties consistent with reported values.[165]

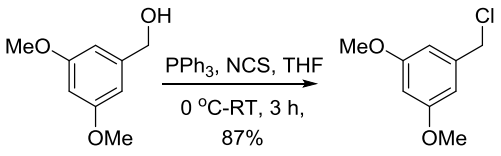
MP: 52.4 - 53.9 °C ($CDCl_3$/petroleum ether) (lit. 52 - 54°C).[165]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.54 (2H, d, *J* = 2.3 Hz, 2 x Ar**H**), 6.40 (1H, t, *J* = 2.3 Hz, Ar**H**) (2H, d, *J* = 5.9 Hz, C**H$_2$**), 3.81 (6H, s, 2 x C**H$_3$**), 1.70 (1H, t, *J* = 6.1 Hz, O**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 161.0 (2 x **C**), 143.4 (**C**), 104.6 (2 x **C**H), 99.7 (**C**H), 65.4 (**C**H$_2$), 55.3 (2 x **C**H$_3$).

LRMS (GC-MS; EI): 168 $[M]^{+\bullet}$ (94%), 151 $[M\text{-}OH]^{+\bullet}$ (40%).

1-(Chloromethyl)-3,5-dimethoxybenzene (4.4)



4.3

$C_9H_{12}O_3$
MW: 168.19

4.4

$C_9H_{11}ClO_2$
MW: 186.64

To a solution of benzyl alcohol **4.3** (1 g, 5.95 mmol) in THF at 0 °C was added *N*-chlorosuccinimide (953 mg, 7.13 mmol) and PPh_3 (1.87 g, 7.13 mmol). The reaction mixture was warmed to RT. After 3 h, it was concentrated *in vacuo* and purified by column chromatography (0-60% $CHCl_3$ in petroleum ether) to give the title compound **4.4** as a white solid (967 mg, 5.18 mmol, 87%) with spectroscopic and physical data consistent with reported values.[175]

MP: 45.9 - 47.2 °C ($CDCl_3$/petroleum ether) (lit. 46-48 °C).[175]

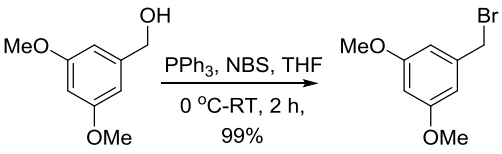
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.55 (2H, d, *J* = 2.3 Hz, 2 x Ar**H**), 6.42 (1H, t, *J* = 2.3 Hz, Ar**H**), 4.53 (2H, s, C**H$_2$**), 3.81 (6H, s, 2 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 160.9 (2 x **C**), 139.5 (**C**), 106.5 (2 x **C**H), 100.5 (**C**H), 55.4 (2 x **C**H_3), 46.3 (**C**H_2).

LRMS (GC-MS; EI): 188 $[M^{37}Cl]^{+\bullet}$ (59%), 186 $[M^{35}Cl]^{+\bullet}$ (96%)

151 $[M\text{-}OH]^{+\bullet}$ (100%).

1-(Bromomethyl)-3,5-dimethoxybenzene (1.86)



4.3

$C_9H_{12}O_3$
MW: 168.19

1.86

$C_9H_{11}BrO_2$
MW: 231.09

To a solution of benzyl alcohol **4.3** (500 mg, 2.97 mmol) in THF (10 mL) at 0 °C was added *N*-bromosuccinimide (635 mg, 3.57 mmol) and PPh_3 (936 mg, 3.57 mmol). The reaction mixture was warmed to RT. After 2 h, it was then concentrated *in vacuo* and purified by column chromatography (50-60% $CHCl_3$ in petroleum ether) to give the title compound **1.86** as a white

solid (678 mg, 2.93 mmol, 99%) with physical and spectroscopic data consistent with reported values.[165]

MP: 75.4 - 77.2 °C ($CDCl_3$/petroleum ether) (lit. 76 - 78).[165]

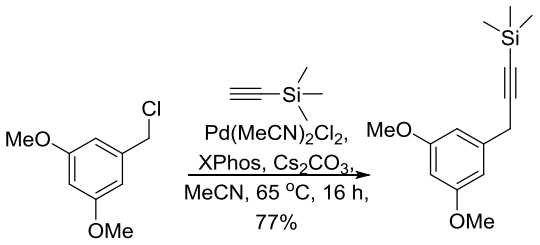
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.55 (2H, d, *J* = 2.2 Hz, 2 x Ar**H**), 6.40 (1H, t, *J* = 2.3 Hz, Ar**H**), 4.43 (2H, s, C**H$_2$**), 3.81 (6H, s, 2 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 160.9 (2 x **C**), 139.7 (**C**), 107.0 (2 x **C**H), 100.6 (**C**H), 55.4 (2 x **C**H_3), 33.6 (**C**H_2).

LRMS (GC-MS; EI): 230 $[M^{79}Br]^{+\bullet}$ (54%), 232 $[M^{81}Br]^{+\bullet}$ (56%).

151 $[M\text{-}OH]^{+\bullet}$ (100%).

(3-(3,5-Dimethoxyphenyl)prop-1-yn-1-yl)trimethylsilane (1.87)

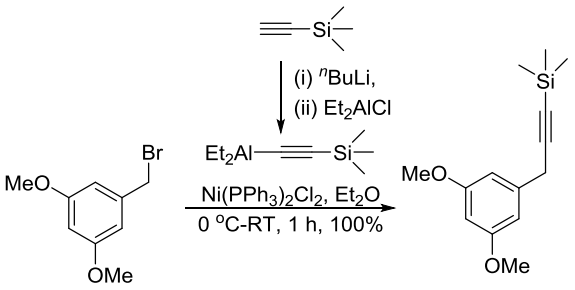


4.5 **1.87**

$C_9H_{11}BrO_2$ **$C_{14}H_{20}O_2Si$**
MW: 231.09 MW: 248.40

A flask containing benzyl chloride **4.5** (500 mg, 2.68 mmol), XPhos (229 mg, 0.48 mmol), Cs_2CO_3 (961 mg, 2.95 mmol) and $Pd(MeCN)_2Cl_2$ (42 mg, 0.16 mmol) was evacuated and filled with Ar in 3 cycles. MeCN (5 mL) and TMS-acetylene (0.59 mL, 4.29 mmol) were then added and the reaction mixture degassed with Ar for 5 minutes. The reaction mixture was heated to 65 °C for 16 h then concentrated *in vacuo* and purified by column chromatography (0-10% Et_2O in petroleum ether) to provide the title compound **1.87** as a pale yellow oil (512 mg, 2.06 mmol, 77%).

Alternatively,



1.86

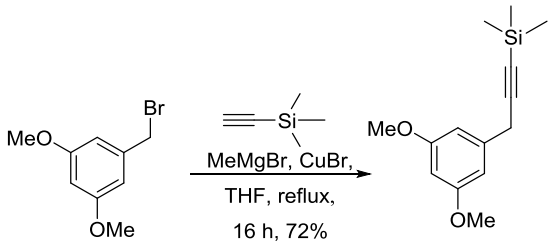
$C_9H_{11}BrO_2$
MW: 231.09

1.87

$C_{14}H_{20}O_2Si$
MW: 248.40

To a solution of TMS-acetylene (0.60 mL, 4.33 mmol) in Et_2O (20 mL) at 0 °C was added dropwise ^{n}BuLi (2.5 M in hexanes, 1.73 mL, 4.33 mmol). After 1 h at 0 °C, Et_2AlCl (1.0 M in hexanes, 4.33 mL, 4.33 mmol) was added and after 20 minutes the reaction was allowed to warm to RT. After 2 h, $Ni(PPh_3)_2Cl_2$ (85 mg, 0.13 mmol) was added followed, after 15 minutes, by benzyl bromide **1.86** (500 mg, 2.16 mmol). After a further 1 h, NH_4Cl (5 mL) was added, then the aqueous phase was separated and extracted with Et_2O (3 x 20 mL). The organic phases were combined and washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (100% petroleum ether) provided the title compound **1.87** as an orange oil (537 mg, 2.16 mmol, 100%).

Alternatively,



1.86

$C_9H_{11}BrO_2$
MW: 231.09

1.87

$C_{14}H_{20}O_2Si$
MW: 248.40

To a solution of TMS-acetylene (0.83 mL, 1.50 mmol) in THF (6 mL) at 0 °C was added dropwise MeMgBr (3.0 M in Et_2O, 2.00 mL, 6.00 mmol). The reaction mixture was then warmed to RT and CuBr (215 mg, 1.50 mmol) was added. After a further 30 minutes benzyl bromide **1.86** (347 mg, 1.50 mmol) was added and the reaction mixture was heated at reflux for 16 h. NH_4Cl (5 mL) was added and the aqueous phase separated and extracted with Et_2O (3 x 5 mL). The organic phases

were combined and washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound **1.87** as a pale yellow oil (268 mg, 1.08 mmol, 72%) with physical and spectroscopic data consistent with reported values.[2]

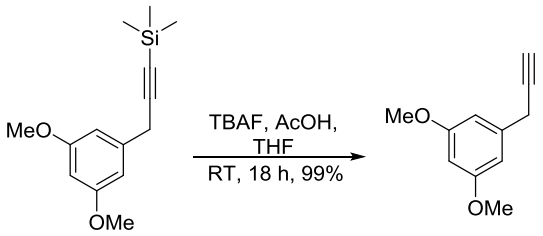
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.54 (2H, d, *J* = 2.2 Hz, 2 x Ar**H**), 6.35 (1H, t, *J* = 2.3 Hz, Ar**H**), 3.80 (6H, s, 2 x C**H$_3$**), 3.61 (2H, s, C**H$_2$**), 0.20 (9H, s, 3 x C**H$_3$**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 160.8 (2 x **C**), 138.7 (**C**), 105.9 (2 x **C**H), 104.0 (**C**), 98.7 (**C**H), 87.1 (**C**), 55.3 (2 x **C**H_3), 26.3 (**C**H_2), 0.1 (3 x **C**H_3).

LRMS (GC-MS; EI): 248 $[M]^{+\bullet}$ (97%).

232 $[M\text{-}CH_3]^{+\bullet}$ (100%).

1,3-Dimethoxy-5-(prop-2-yn-1-yl)benzene (1.83)



1.87

$C_{14}H_{20}O_2Si$
MW: 248.40

1.83

$C_{11}H_{12}O_2$
MW: 176.22

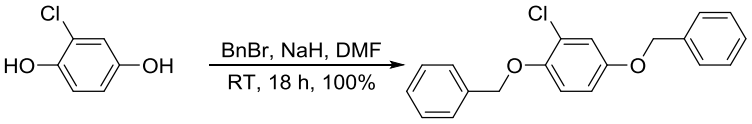
To a solution of TMS-protected alkyne **1.87** (250 mg, 1.01 mmol) in THF (5 mL) and AcOH (0.23 mL, 4.03 mmol) was added TBAF (1M in THF, 4.03 mL, 4.03 mmol). After 18 h at RT, the reaction mixture was diluted with Et_2O (10 mL), washed with brine (2 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (0-10% EtOAc in petroleum ether) provided the title compound **1.83** as a colourless oil (174 mg, 0.99 mmol, 99%) with physical and spectroscopic data consistent with reported values.[2]

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.53 (2H, d, *J* = 2.3 Hz, 2 x Ar**H**), 6.36 (1H, t, *J* = 2.3 Hz, Ar**H**), 3.80 (6H, s, 2 x C**H$_3$**), 3.56 (2H, d, *J* = 2.7 Hz, C**H$_2$**), 2.20 (1H, t, *J* = 2.8 Hz, C**H**).

^{13}C NMR (101 MHz; $CDCl_3$): δ ppm 160.9 (2 x **C**), 138.3 (**C**), 105.9 (2 x **C**H), 98.7 (**C**H), 81.7 (**C**/**C**H), 70.6 (**C**/**C**H), 55.3 (2 x **C**H_3), 25.0 (**C**H_2).

LRMS (GC-MS; EI): 175 $[M]^{+\bullet}$ (100%).

2-Chloro-1,4-dibenzyoxybenzene (4.10)



1.125 **4.10**

$C_6H_5ClO_2$ MW: 144.55 **$C_{20}H_{17}ClO_2$** MW: 324.80

To a solution of chlorohydroquinone **1.125** (100 mg, 0.69 mmol) and benzyl bromide (0.21 mL, 1.66 mmol) in DMF (5 mL) was added NaH (60% dispersion in mineral oil, 68 mg, 1.73 mmol). After 18 h at RT, H_2O (50 mL) and Et_2O (15 mL) were added. The organic phase washed with brine (3 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (100% petroleum ether) provided the title compound **4.10** as a white solid (224 mg, 0.69 mmol, 100%) with physical and spectroscopic data consistent with reported values.[176]

MP: 69.4 - 70.9 °C (EtOAc) (lit. 68 - 69).[176]

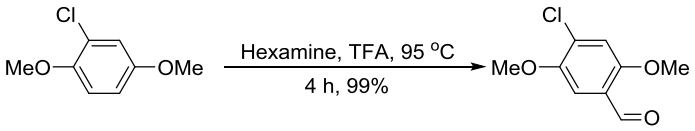
IR ν_{max} (neat, cm^{-1}): 3063 w, 3038 w, 2912 w, 2860 w, 1573 w, 1497 s, 1453 s, 1380 m, 1275 m, 1222 s, 1207 s, 1051 m, 1014 s, 840 m, 733 s, 694 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.47-7.34 (10H, m, 10 x Ar**H**), 7.07 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.90 (1H, d, *J* = 9.1 Hz, Ar**H**), 6.80 (1H, dd, *J* = 9.2 Hz, 2.8 Hz, Ar**H**), 5.10 (2H, s, C**H$_2$**), 5.01 (2H, s, C**H$_2$**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 153.4 (**C**), 148.7 (**C**), 136.8 (**C**), 136.7 (**C**), 128.6 (**C**H), 128.5 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 127.5 (**C**H), 127.2 (**C**H), 124.2 (**C**), 117.2 (**C**H), 115.9 (**C**H), 113.9 (**C**H), 71.9 (**C**H_2), 70.7 (**C**H_2).

LRMS (GC-MS; EI): 326 $[M^{37}Cl]^{+\bullet}$ (2%), 324 $[M^{35}Cl]^{+\bullet}$ (8%).

4-Chloro-2,5-dimethoxybenzaldehyde (1.84)



1.90

$C_8H_9ClO_2$
MW: 172.61

1.84

$C_9H_9ClO_3$
MW: 200.62

To a solution of chlorobenzene **1.90** (1.73 g, 10.0 mmol) and hexamethylenetetramine (1.41 g, 10.0 mmol) was added dropwise TFA (17 mL). The mixture was heated at 95 °C for 4 h. The hot reaction mixture was then poured into 100g of crushed ice and $NaHCO_3$ (16.82 g, 20.0 mmol) was then added portionwise over 2 h resulting in a yellow gelatinous precipitate. This was filtered through a pad of celite and washed with H_2O (3 x 50 mL). The solid was then dissolved in Et_2O (50 mL) and the resulting solution was washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound **1.84** as a white solid (1.99 g, 9.92 mmol, 99%) with physical and spectroscopic data consistent with reported values.[2]

MP: 113.5 - 114.0 °C ($CDCl_3$/petroleum ether) (lit. 112 - 114 °C).[177]

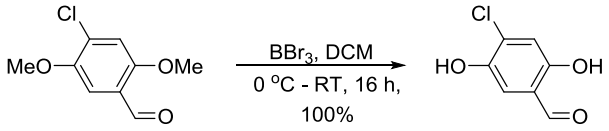
IR ν_{max} (neat, cm^{-1}): 2943 w, 2876 w, 2854 w, 1665 m, 1602 w, 1498 s, 1462 s, 1441 m, 1387 s, 1270 m, 1212 s, 1183 m, 1026 s, 976 m, 866 m, 725 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.40 (1 H, s, C**H**), 7.39 (1 H, s, Ar**H**), 7.07 (1 H, s, Ar**H**), 3.91 (6 H, s, 2 x C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 188.6 (**C**HO), 156.2 (**C**), 149.5 (**C**), 130.6 (**C**), 123.5 (**C**), 114.6 (**C**H), 110.1 (**C**H), 56.6 (**C**H$_3$), 56.4 (**C**H$_3$).

LRMS (GC-MS; EI): 202 $[M^{37}Cl]^{+\bullet}$ (72%), 200 $[M^{35}Cl]^{+\bullet}$ (100%).

4-Chloro-2,5-dihydroxybenzaldehyde (4.11)



1.84

$C_9H_9ClO_3$
MW: 200.62

4.11

$C_7H_5ClO_3$
MW: 172.56

To a solution of methyl ether **1.84** (750 mg, 3.74 mmol) in DCM (30 mL) at 0 °C was added dropwise BBr_3 (1M in DCM, 9.35 mL, 9.35 mmol). The reaction mixture was then warmed to RT and after 16 h, $NaHCO_3$ (5 mL) was then added dropwise. The reaction mixtiure was then neutralised with 1M HCl, then the aqueous phase was extracted with DCM (3 x 30 mL). The organic phases were combined and washed with H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound **4.11** as a pale brown solid (645 mg, 3.74 mmol, 100%) with physical and spectroscopic data consistent with reported values.[178]

MP: 174.2 - 175.8 °C (DCM) (lit. 172 - 174 °C DCM).[178]

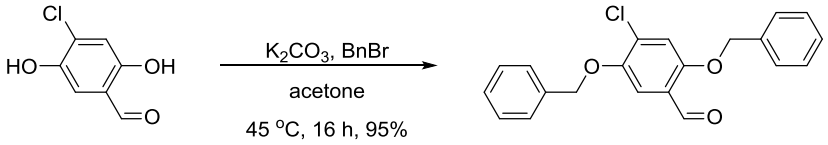
IR ν_{max} (neat, cm^{-1}): 3303 br, 3056 br s, 2876 w, 1644 m, 1621 m, 1568 m, 1474 s, 1450 s, 1351 w, 1234 s, 1145 s, 1015 s, 867 m.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.64 (1 H, s, O**H**), 9.83 (1 H, s, C**H**O), 7.20 (1 H, s, Ar**H**), 7.04 (1 H, s, Ar**H**), 5.31 (1 H, s, O**H**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 195.5 (**C**HO), 155.3 (**C**), 144.7 (**C**), 129.6 (**C**), 119.9 (**C**), 118.8 (**C**H), 118.0 (**C**H).

LRMS (GC-MS; EI): 173 $[M^{37}Cl]^{+\bullet}$ (40%),171 $[M^{35}Cl]^{+\bullet}$ (100%).

2,5-Bis(benzyloxy)-4-chlorobenzaldehyde (4.12)



4.11

$C_7H_5ClO_3$
MW: 172.56

4.12

$C_{21}H_{17}ClO_3$
MW: 352.81

To a solution of hydroquinone **4.12** (600 mg, 3.48 mmol) in acetone (30 mL) was added K_2CO_3 (2.40 g, 17.4 mmol) and benzyl bromide (0.91 mL, 7.65 mmol). The reaction mixture was heated to 45 °C for 16 h then the acetone was removed *in vacuo*. The resulting residue partitioned between EtOAc (30 ml) and H_2O (30 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (2-25% EtOAc in petroleum ether) to afford the title compound **4.12** as a white solid (1.27 g, 3.32 mmol, 95%).

MP: 147.2 - 148.7 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 3033 w, 2853 w, 1701 w, 1682 s, 1600 w, 1575 w, 1496 m, 1484 m, 1452 m, 1380 s, 1267 m, 1219 s, 1204 s, 1013 s, 732 s, 695 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.44 (1H, s, C**H**O), 7.49-7.46 (3H, m, 3 x Ar**H**), 7.44-7.32 (8H, m, 8 x ArH), 7.17 (1H, s, Ar**H**), 5.152 (2H, s, C**H$_2$**), 5.149 (2H, s, C**H$_2$**).

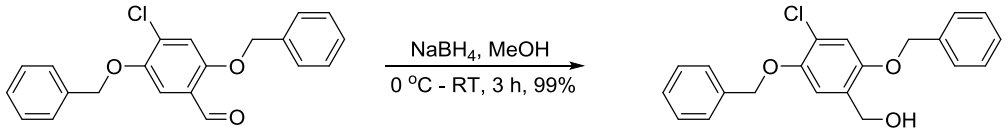
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 188.4 (**C**HO), 155.5 (**C**), 148.9 (**C**), 136.1 (**C**), 135.6 (**C**), 131.3 (**C**), 128.8 (**C**H), 128.6 (**C**H), 128.5 (**C**H), 128.1 (**C**H), 127.5 (**C**H), 127.3 (**C**H), 124.1 (**C**), 116.1 (**C**H), 112.0 (**C**H), 71.5 (**C**H_2), 71.35 (**C**H_2).

LRMS (HPLC-MS, ESI^+): 355 $[M^{37}Cl+H]^+$ (38%), 353 $[M^{35}Cl+H]^+$ (100%).

377 $[M^{37}Cl+Na]^+$ (2%), 375 $[M^{35}Cl+Na]^+$ (9%).

HRMS (ESI^+): Calculated for $C_{21}H_{17}ClNaO_3^+$ $[M^{35}Cl+Na]^+$ 375.0758, found 375.0766.

(2,5-Bis(benzyloxy)-4-chlorophenyl)methanol (4.13)



4.12

$C_{21}H_{17}ClO_3$
MW: 352.81

4.13

$C_{21}H_{19}ClO_3$
MW: 354.83

To a solution of benzaldehyde **4.12** (1.00 g, 2.83 mmol) in methanol (30 mL) at 0 °C was added portionwise $NaBH_4$ (533 mg, 14.1 mmol). The reaction mixture was warmed to RT and after 3 h acetone (3 mL) was added. The mixture was partitioned between EtOAc (30 mL) and H_2O (30 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 x 30 mL) and the organic phases were combined and washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound **4.13** as a white solid (998 mg, 2.81 mmol, 99%) with physical and spectroscopic characteristics consistent with reported values.[135]

MP: 114.6 - 115.4 °C ($CDCl_3$/petroleum ether) (lit. 113.5 - 114.5 °C).[135]

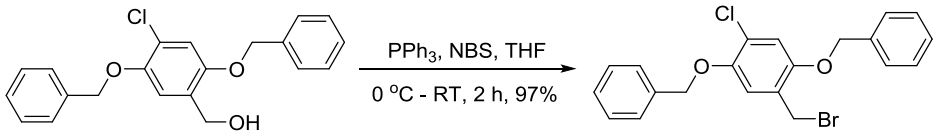
IR ν_{max} (neat, cm^{-1}): 3320 br s, 3033 w, 2875 w, 1735 w, 1497 s, 1453 m, 1382 s, 1221 m, 1196 s, 1043 m, 1007 s, 862 m, 729 s, 695 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.50-7.46 (2H, m, 2 x Ar**H**), 7.43-7.31 (8H, m, 2 x Ar**H**), 7.04 (1H, s, Ar**H**), 7.02 (1H, s, Ar**H**), 5.12 (2H, s, C**H$_2$**), 5.06 (2H, s, C**H$_2$**), 4.67 (2H, d, *J* = 6.4 Hz, C**H$_2$**), 2.10 (1H, t, *J* = 6.5 Hz, O**H**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 150.7 (**C**), 148.6 (**C**), 136.7 (**C**), 136.3 (**C**), 129.1 (**C**), 128.7 (**C**H), 128.5 (**C**H), 128.3 (**C**H), 128.0 (**C**H), 127.4 (**C**H), 127.3 (**C**H), 122.7 (**C**), 115.5 (**C**H), 114.4 (**C**H), 71.9 (**C**H_2), 71.0 (**C**H_2), 61.3 (**C**H_2).

HRMS (APPI): Calculated for $C_{21}H_{19}ClO_3$ $[M^{35}Cl]^{+\bullet}$ 354.1017, found 354.1012.

4-Chloro-2,5-dibenzyloxy benzyl bromide (4.14)



4.13

$C_{21}H_{19}ClO_3$
MW: 354.83

4.14

$C_{21}H_{18}BrClO_2$
MW: 417.73

To a solution of benzyl alcohol **4.13** (150 mg, 0.42 mmol) in THF (5 mL) at 0 °C was added PPh_3 (133 mg, 0.51 mmol) and *N*-bromosuccinimide (90 mg, 0.51 mmol). The reaction mixture was awrmed to RT for 2 h then concentrated *in vacuo* and purified by column chromatography (silica; 0-5% Et_2O in petroleum ether) to afford the title compound **4.14** as a white solid (170 mg, 0.41 mmol, 97%) with physical and spectroscopic properties consistent with reported values.[135]

MP: 121.1 - 122.1 °C ($CDCl_3$/petroleum ether) (lit. 121 - 122 °C).[135]

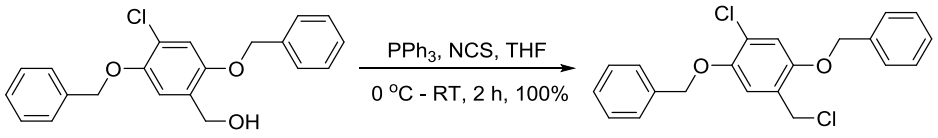
IR ν_{max} (neat, cm^{-1}): 3064 w, 3033 w, 2876 w, 1582 w, 1498 s, 1454 w, 1389 s, 1297 s, 1223 s, 1202 s, 1044 w, 1013 s, 856 m, 731 s, 692 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.50-7.32 (10H, m, 10 x Ar**H**), 7.01 (2H, s, 2 x Ar**H**), 5.11 (2H, s, C**H₂**), 5.10 (2H, s, C**H₂**), 4.53 (2H, s, C**H₂**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 151.0 (**C**), 148.4 (**C**), 136.7 (**C**), 136.4 (**C**), 128.7 (**C**H), 128.6 (**C**H), 128.13 (**C**H), 128.06 (**C**H), 127.4 (**C**H), 127.3 (**C**H), 125.8 (**C**), 124.6 (**C**), 117.4 (**C**H), 115.1 (**C**H), 72.0 (**C**H_2), 71.1 (**C**H_2), 28.3 (**C**H_2).

HRMS (APPI): Calculated for $C_{21}H_{18}BrClO_2$ $[M^{79}Br^{35}Cl]^{+\bullet}$ 416.0173; found 416.0169.

4-Chloro-2,5-dibenzyloxy benzyl chloride (4.15)



4.13

$C_{21}H_{19}ClO_3$
MW: 354.83

4.15

$C_{21}H_{18}Cl_2O_2$
MW: 373.27

To a solution of benzyl alcohol **4.13** (500 mg, 1.41 mmol) in THF (10 mL) at 0 °C was added PPh_3 (517 mg, 1.97 mmol) and *N*-chlorosuccinimide (351 mg, 1.97 mmol). The reaction mixture was warmed to RT for 2 h, then concentrated *in vacuo* and purified by chromatography (2-15% EtOAc in petroleum ether) to afford the title compound **4.15** as a white solid (526 mg, 1.41 mmol, 100%) with physical and spectroscopic characteristics consistent with reported values.[135]

MP: 115.8 - 116.6 °C ($CDCl_3$/petroleum ether) (lit. 115.5 - 116.5 °C).[135]

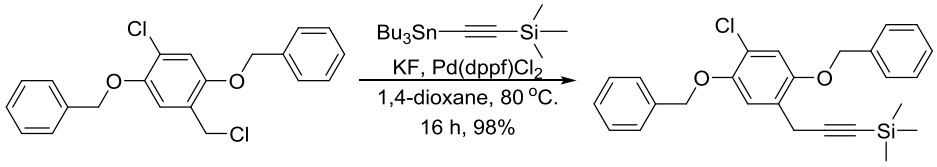
IR ν_{max} (neat, cm^{-1}): 3064 w, 3033 w, 2876 w, 1584 w, 1500 s, 1454 m, 1390 s, 1297 w, 1260 w, 1222 s, 1206 s, 1012 s, 857 s, 729 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.50-7.34 (10H, m, 10 x Ar**H**), 7.06 (1H, s, Ar**H**), 7.03 (1H, s, Ar**H**), 5.12 (2H, s, C**H$_2$**), 5.08 (2H, s, C**H$_2$**), 4.63 (2H, s, C**H$_2$**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 150.8 (**C**), 148.5 (**C**), 136.5 (**C**), 136.4 (**C**), 128.64 (**C**H), 128.56 (**C**H), 128.13 (**C**H), 128.05 (**C**H), 127.34 (**C**H), 127.30 (**C**H), 125.6 (**C**), 124.3 (**C**), 117.1 (**C**H), 115.0 (**C**H), 72.0 (**C**H_2), 71.1 (**C**H_2), 41.1 (**C**H_2).

HRMS (APPI): Calculated for $C_{21}H_{18}Cl_2O_2$ $[M^{35}Cl^{35}Cl]^{+\bullet}$ 372.0678, found 372.0680.

(3-(2,5-Bis(benzyloxy)-4-chlorophenyl)prop-1-yn-1-yl)trimethylsilane (4.16)



4.15

$C_{21}H_{18}Cl_2O_2$
MW: 373.27

4.16

$C_{26}H_{27}ClO_2Si$
MW: 435.04

A flask charged with benzyl chloride **4.15** (500 mg, 1.34 mmol), Pd(dppf)Cl_2 (39 mg, 0.05 mmol) and KF (311 mg, 5.36 mmol) was evacuated and filled with argon in 3 cycles. Organostannane **2.21** (778 mg, 2.01 mmol) and 1,4-dioxane (5 mL) were then added and the reaction mixture degassed with argon for 5 minutes. The reaction mixture was heated at 80 °C for 16 h. RM was then concentrated *in vacuo* and purified by column chromatography (silica:K_2CO_3 9:1,[112] 100% petroleum ether) to afford the title compound **4.16** as a white solid (571 mg, 1.31 mmol, 98%).

MP: 101.7 - 103.1 °C ($CDCl_3$/petroleum ether).

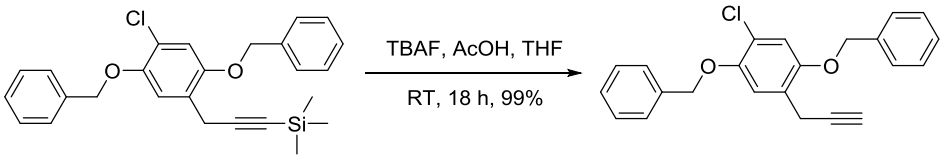
IR ν_{max} ($CDCl_3$, cm^{-1}): 3064 w, 3033 w, 2955 w, 2873 w, 2173 w, 1499 s, 1454 m, 1385 m, 1221 s, 1202 s, 1013 s, 856 m, 732 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.50-7.47 (2H, m, 2 x Ar**H**), 7.43-7.32 (8H, m, 8 x Ar**H**) 7.29 (1H, s, Ar**H**), 6.96 (1H, s, Ar**H**), 5.14 (2H, s, C**H$_2$**), 5.03 (2H, s, C**H$_2$**), 3.62 (2H, s, C**H$_2$**), 0.21 (9H, 3 x C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 150.3 (**C**), 148.4 (**C**), 136.8 (**C**), 136.7 (**C**), 128.6 (**C**H), 128.5 (**C**H), 128.02 (**C**H), 127.95 (**C**H), 127.3 (**C**H), 127.2 (**C**H), 124.8 (**C**), 121.6 (**C**), 124.3 (**C**), 116.0 (**C**H), 114.0 (**C**H), 103.7 (**C**H), 71.7 (**C**H_2), 70.8 (**C**H_2), 20.8 (**C**H_2), 0.11 (3 x **C**H_3).

HRMS (APPI): Calculated for $C_{26}H_{27}ClO_2Si$ $[M^{35}Cl]^{+\bullet}$ 434.1463; found 434.1470.

3-(2,5-Bis(benzyloxy)-4-chlorophenyl)prop-1-yne (4.2)



4.16

$C_{26}H_{27}ClO_2Si$
MW: 435.04

4.2

$C_{23}H_{19}ClO_2$
MW: 362.85

To a solution of TMS-alkyne **4.16** (571 mg, 1.32 mmol) in THF (5 mL) and AcOH (0.38 mL, 6.56 mmol) was added dropwise TBAF (1.0 M in THF, 6.56 mL. 6.56 mmol). After 18 h, the reaction mixture was diluted with Et_2O (20 mL), washed with brine (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (0-5% EtOAc in petroleum ether) provided the title compound **4.2** as a white solid (472 mg, 1.30 mmol, 99%).

MP: 77.0 - 78.3 °C ($CDCl_3$/petroleum ether).

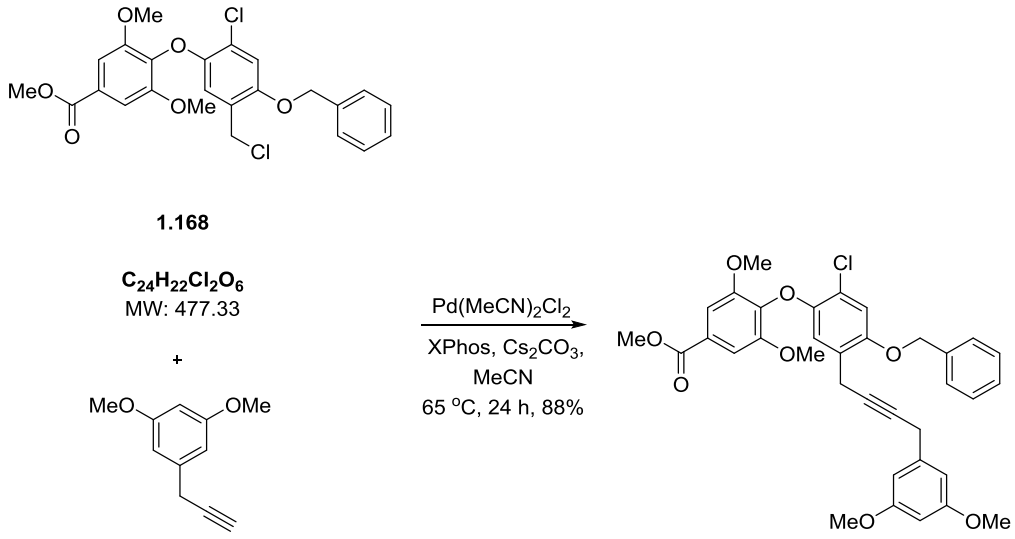
IR ν_{max} (neat, cm^{-1}): 3285 s, 3064 w, 3033 w, 2916 w, 2888 w, 2120 w, 1501 s, 1453 m, 1415 m, 1383 m, 1211 s, 1199 s, 1021.6 s, 846 m, 733 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.49 (2H, d, 2 x Ar**H**), 7.44-7.30 (8H, m, 8 x Ar**H**) 7.26 (1H, s, Ar**H**), 6.97 (1H, s, Ar**H**), 5.14 (2H, s, C**H$_2$**), 5.03 (2H, s, C**H$_2$**), 3.58 (2H, d, *J* = 2.7 Hz C**H$_2$**), 2.19 (1H, t, *J* = 2.7 Hz, C**H**).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 150.3 (**C**), 148.5 (**C**), 136.8 (**C**), 136.6 (**C**), 128.6 (**C**H), 128.5 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 127.4 (**C**H), 127.3 (**C**H), 124.4 (**C**H), 121.8 (**C**), 124.3 (**C**), 116.2 (**C**H), 114.0 (**C**H), 81.2 (**C**), 72.0 (**C**H_2), 71.0 (**C**H), 70.9 (**C**H_2), 19.4 (**C**H_2).

HRMS (APPI): Calculated for $C_{23}H_{19}ClO_2$ $[M^{35}Cl]^{+\bullet}$ 362.1068; found 362.1065.

Methyl 4-(4-(benzyloxy)-2-chloro-5-(4-(3,5-dimethoxyphenyl)but-2-yn-1-yl)phenoxy)-3,5-dimethoxybenzoate (4.17)



A flask charged with benzyl chloride **1.168** (200 mg, 0.42 mmol), XPhos (36 mg, 0.08 mmol), Cs_2CO_3 (151 mg, 0.46 mmol), and $Pd(MeCN)_2Cl_2$ (6.5 mg, 0.03 mmol) was evacuated and filled with argon in 3 cycles. MeCN (1 mL) and alkyne **1.83** (89 mg, 0.50 mmol) were then added. The reaction mixture was then heated to 65 °C and stirred for 24 h then concentrated *in vacuo* and purified by column chromatography (100% $CHCl_3$) to afford the title compound **4.17** as a pale yellow solid (229 mg, 0.37 mmol, 88%).

MP: 130.9 - 132.4 °C ($CDCl_3$/petroleum ether).

IR ν_{max} ($CDCl_3$, cm^{-1}): 2949 w, 2838 w, 2360 w, 2158 w, 1719 m, 1597 m, 1498 s, 1462 m, 1341 m, 1215 s, 1208 s, 1130 s, 998 w, 759 m.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.44-7.30 (7H, m, 7 x Ar**H**), 6.97 (1H, s, Ar**H**), 6.79 (1H, s, Ar**H**), 6.40 (2H, d, *J* = 2.2 Hz, 2 x Ar**H**), 6.31 (1H, t, *J* = 2.2 Hz, Ar**H**), 5.05 (2H, s, C**H$_2$**), 3.93 (3H, s, C**H$_3$**), 3.79 (6H, s, 2 x C**H$_3$**), 3.74 (6H, s, 2 x C**H$_3$**), 3.50 (2H, t, *J* = 2.0 Hz, C**H$_2$**), 3.41 (2H, t, *J* = 2.0 Hz, C**H$_2$**).

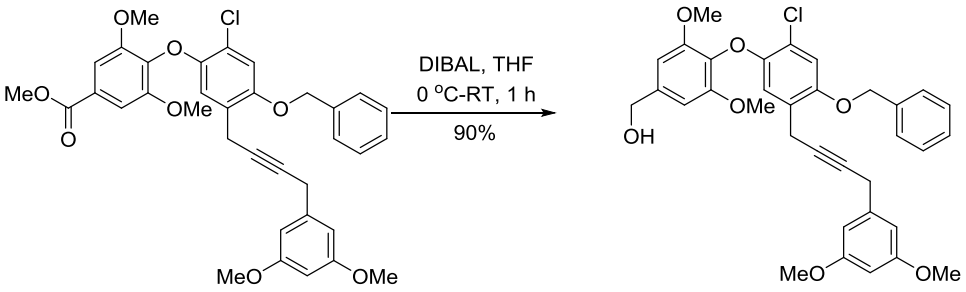
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 166.5 (**C**O), 160.8 (2 x **C**), 153.0 (2 x **C**), 150.8 (**C**), 147.6 (**C**), 145.6 (**C**), 139.2 (**C**), 136.7 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 127.1 (**C**), 125.6 (**C**), 120.1 (**C**), 115.7 (**C**H), 113.6 (**C**H), 106.9 (2 x **C**H), 105.8 (2 x **C**H), 98.4 (**C**H), 80.0 (**C**), 79.5 (**C**), 70.8 (**C**H_2), 56.4 (2 x **C**H_3), 55.2 (2 x **C**H_3), 52.3 (**C**H_3), 25.1 (**C**H_2), 19.8 (**C**H_2).

LRMS (HPLC-MS, ESI^+): 619 $[M^{37}Cl+H]^+$ (34%), 617 $[M^{35}Cl+H]^+$ (82%).

641 $[M^{37}Cl+Na]^+$ (26%), 639 $[M^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{35}H_{33}ClNaO_8$ 639.1746 $[M^{35}Cl+Na]^+$, found 639.1756.

(4-(4-(Benzyloxy)-2-chloro-5-(4-(3,5-dimethoxyphenyl)but-2-yn-1-yl)phenoxy)-3,5-dimethoxyphenyl)methanol (4.18)



4.17

$C_{35}H_{33}ClO_8$
MW: 617.09

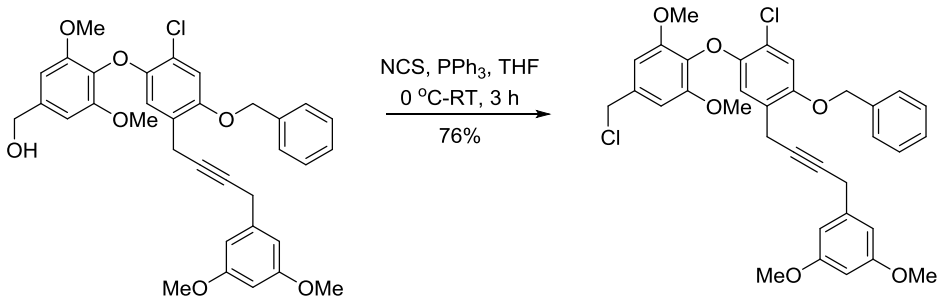
4.18

$C_{34}H_{33}ClO_7$
MW: 589.08

To a solution of ester **4.17** (140 mg, 0.23 mmol) in THF (2 mL) at 0 °C was added dropwise DIBAL (1.0 M in hexanes, 0.5 mL, 0.50 mmol). The reaction mixture was warmed to RT for 1 h then MeOH (2 mL), sat. Rochelle's salt (5 mL) and EtOAc (5 mL) were added. The aqueous phase was separated, extracted with EtOAc (3 x 10 mL). The organic phases were then combined and washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (30-50% EtOAc in petroleum ether) to provide the title compound **4.18** as a pale yellow foam (122 mg, 0.21 mmol, 90%).

MP:	106.2 - 108.0 °C ($CDCl_3$/petroleum ether).
IR ν_{max} (neat, cm^{-1}):	3547 br, 3003 w, 2938 w, 2839 w, 1597 s, 1493 s, 1462 s, 1421 m, 1217 s, 1206 s, 1153 m, 1129 s, 1064 m, 829 m.
^{1}H NMR (400 MHz, $CDCl_3$):	δ ppm 7.44-7.30 (5H, m, 5 x Ar**H**), 6.97 (1H, s, Ar**H**), 6.82 (1H, s, Ar**H**), 6.59, (2H, s, 2 x Ar**H**), 6.40 (2H, d, *J* = 2.3 Hz, 2 x Ar**H**), 6.34 (1H, t, *J* = 2.2 Hz, Ar**H**), 5.04 (2H, s, C**H$_2$**), 4.60 (2H, d, *J* = 6.2 Hz, C**H$_2$**), 3.75 (6H, s, C**H$_3$**), 3.74 (6H, s, 2 x C**H$_3$**), 3.51 (2H, t, *J* = 1.8 Hz C**H$_2$**), 3.44 (2H, t, *J* = 2.1 Hz C**H$_2$**), 1.88 (1H, t, *J* = 6.1 Hz, O**H**).
^{13}C NMR (100 MHz, $CDCl_3$):	δ ppm 160.7 (2 x **C**), 153.3 (2 x **C**), 150.5 (**C**), 148.1 (**C**), 139.5 (**C**), 138.8 (**C**), 136.8 (**C**), 131.8 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 125.4 (**C**), 119.8 (**C**), 115.4 (**C**H), 113.6 (**C**H), 106.0 (2 x **C**H), 103.7 (2 x **C**H), 98.4 (**C**H), 79.8 (**C**), 79.7 (**C**), 70.8 (**C**H_2), 65.4 (**C**H_2), 56.3 (2 x **C**H_3), 55.3 (2 x **C**H_3), 25.2 (**C**H_2), 19.7 (**C**H_2).
LRMS (HPLC-MS, ESI^+):	613 $[M^{37}Cl+H]^+$ (16%), 611 $[M^{35}Cl+H]^+$ (47%).
HRMS (ESI^+):	Calculated for $C_{34}H_{33}ClNaO_7$ 611.1816 $[M^{35}Cl+Na]^+$, found 611.1807.

2-(4-(Benzyloxy)-2-chloro-5-(4-(3,5-dimethoxyphenyl)but-2-yn-1-yl)phenoxy)-5-(chloromethyl)-1,3-dimethoxybenzene (4.19)



4.18

$C_{34}H_{33}ClO_7$
MW: 589.08

4.19

$C_{34}H_{32}Cl_2O_6$
MW: 607.52

To a solution of alcohol **4.18** (100 mg, 0.17 mmol) in THF (3 mL) at 0 °C was added PPh_3 (53 mg, 0.20 mmol) and *N*-chlorosuccinimide (27 mg, 0.20 mmol). The reaction mixture was warmed to RT for 3 h then concentrated *in vacuo*. Purification by column chromatography (0-10% EtOAc in petroleum ether) yielded the title compound **4.19** as a white solid (79 mg, 0.13 mmol, 76%).

MP: 116.7 - 118.0 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 2935 w, 2840, 1596 s, 1493 s, 1462 s, 1421 s, 1392 m, 1244 m, 1209 m, 1192 m, 1123 s, 1065 m, 997 m, 832 m, 701 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.46 - 7.30 (5H, m, 5 x Ar**H**) 6.96 (1H, s, Ar**H**) 6.79 (1H, s, Ar**H**) 6.63 (2H, s, 2 x Ar**H**) 6.43 (2H, d, *J* = 2.1 Hz, 2 x Ar**H**) 6.33 (1H, t, *J* = 2.2 Hz, Ar**H**) 5.04 (2H, s, C**H$_2$**) 4.53 (2H, s, C**H$_2$**) 3.75 (6H, s, 2 x C**H$_3$**) 3.75 (6H, s, 2 x C**H$_3$**) 3.51 (2H, br t, *J* = 2.1 Hz, C**H$_2$**) 3.43 (2H, t, *J* = 2.5 Hz, C**H$_2$**).

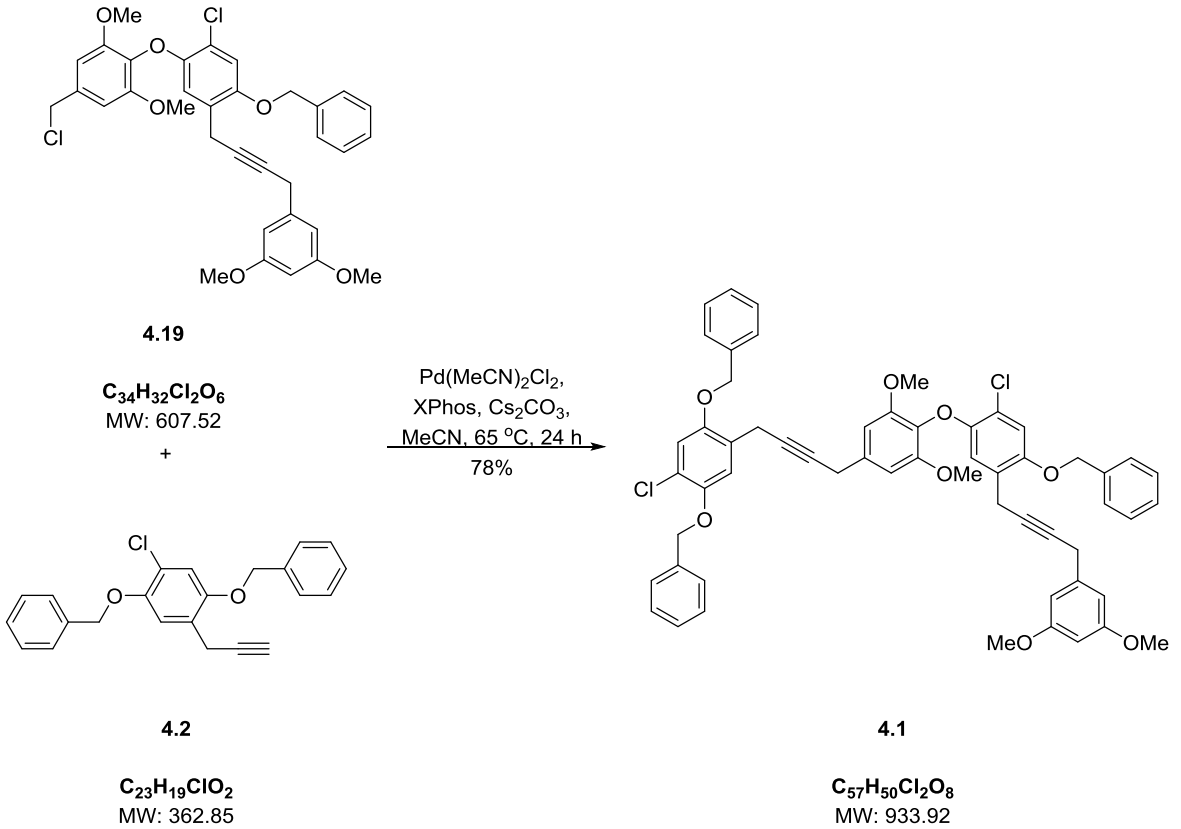
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 160.8 (2 x **C**), 153.3 (2 x **C**), 150.6 (**C**), 147.9 (**C**), 139.5 (**C**), 136.8 (**C**), 136.0 (**C**), 132.6 (**C**), 128.6 (2 x **C**H), 128.0 (**C**H), 127.2 (2 x **C**H), 119.8 (**C**), 119.2 (**C**), 115.4

(**C**H), 113.6 (**C**H), 106.0 (2 x **C**H), 105.9 (2 x **C**H), 98.4 (**C**H), 80.1 (**C**), 79.5 (**C**), 70.8 (**C**H_2), 56.4 (2 x **C**H_3), 55.3 (2 x **C**H_3), 46.6 (**C**H_2), 25.1 (**C**H_2), 19.8 **C**H_2).

LRMS (HPLC-MS, ESI^+): 609 $[M^{37}Cl+H]^+$ (70%), 607 $[M^{35}Cl+H]^+$ (100%). 631 $[M^{37}Cl+Na]^+$ (74%), 629 $[M^{35}Cl+Na]^+$ (95%).

HRMS (ESI^+): Calculated for $C_{34}H_{32}Cl_2NaO_6$ $[M^{35}Cl^{35}Cl+Na]^+$ 629.1456, found 629.1468.

2-[4-(Benzyloxy)-2-chloro-5-[4-(3,5-dimethoxyphenyl)but-2-yn-1-yl]phenoxy]-5-{4-[2,5-bis(benzyloxy)-4-chlorophenyl]but-2-yn-1-yl}-1,3-dimethoxybenzene (4.1)



4.19

$C_{34}H_{32}Cl_2O_6$
MW: 607.52

+

4.2

$C_{23}H_{19}ClO_2$
MW: 362.85

4.1

$C_{57}H_{50}Cl_2O_8$
MW: 933.92

A flask charged with benzyl chloride **4.19** (250 mg, 0.41 mmol), alkyne **4.2** (298 mg, 0.82 mmol) XPhos (35 mg, 0.07 mmol), Cs_2CO_3 (147 mg, 0.45 mmol), and $Pd(MeCN)_2Cl_2$ (6.4 mg, 0.02 mmol) was evacuated and filled with argon in 3 cycles. MeCN (1 mL) was then added and the reaction mixture was heated to 65 °C for 24 h. The crude mixture was concentrated *in vacuo* and purified by column chromatography (100% $CHCl_3$) to afford the title compound **4.1** as a pale yellow solid (300 mg, 0.32 mmol, 78%).

MP: 68.7 - 69.9 °C ($CDCl_3$/petroleum ether).

IR ν_{max} (neat, cm^{-1}): 3063 w, 3032 w, 2935 w, 2837 w, 1596 s, 1492 s, 1453 s, 1419 w, 1329 w, 1203 s, 1191 s, 1152 m, 1126 s, 1024 m, 734 s, 695 s.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.43 - 7.31 (15 H, m, 15 x Ar**H**), 7.24 (1H, s, Ar**H**), 6.96 (2H, s, 2 x Ar**H**), 6.77 (1H, s, Ar**H**), 6.61 (2H, s, 2 x Ar**H**), 6.40 (2H, d, *J* = 2.3 Hz, 2 x Ar**H**), 6.29 (1H, t, *J* = 2.3 Hz, Ar**H**), 5.05 (2H, s, C**H₂**), 5.03 (2H, s, C**H₂**), 5.02 (2H, s, C**H₂**), 3.70 (6H, s, 2 x C**H₃**) 3.70 (6H, s, 2 x C**H₃**) 3.61 (2H, br d, *J* = 1.3 Hz, C**H₂**), 3.60 (2H, br d, *J* = 1.8 Hz, C**H₂**), 3.44 (2H, t, *J* = 2.2 Hz, C**H₂**) 3.38 (2H, t, *J* = 2.1 Hz, C**H₂**).

^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 160.8 (2 x **C**), 153.2 (2 x **C**), 150.5 (**C**), 150.4 (**C**), 148.5 (**C**), 148.2 (**C**), 136.83 (**C**), 136.79 (**C**), 136.6 (**C**), 134.9 (**C**), 134.7 (**C**), 131.3 (**C**), 128.6 (2 x **C**H), 128.53 (2 x **C**H), 128.46 (2 x **C**H), 128.1 (**C**H), 127.92 (**C**H), 127.89 (**C**H), 127.4 (2 x **C**H), 127.23 (2 x **C**H), 127.18 (2 x **C**H), 125.6 (**C**), 125.5 (**C**), 121.8 (**C**), 119.8 (**C**), 116.5 (**C**H), 115.5 (**C**H), 114.0 (**C**H), 113.7 (**C**H), 105.9 (2 x **C**H), 105.3 (2 x **C**H), 98.3 (**C**H), 80.3 (**C**), 79.9 (**C**), 79.64 (**C**), 79.62 (**C**), 72.1 (**C**H_2), 70.81 (**C**H_2), 70.77 (**C**H_2), 56.3 (2 x **C**H_3), 55.2 (2 x **C**H_3), 25.5 (**C**H_2), 25.1 (**C**H_2), 19.8 (**C**H_2), 19.7 (**C**H_2).

LRMS (HPLC-MS, ESI^+): 959 $[M^{37}Cl^{37}Cl+Na]^+$ (10%), 957 $[M^{35}Cl^{37}Cl+Na]^+$, $[M^{37}Cl^{35}Cl+Na]^+$ (80%), 955 $[M^{35}Cl^{35}Cl+Na]^+$ (100%).

HRMS (ESI^+): Calculated for $C_{57}H_{51}Cl_2O_8$ $[M^{35}Cl+H]^+$ 933.2940 found 933.2956.

Calculated for $C_{57}H_{50}Cl_2NaO_8$ $[M^{35}Cl+Na]^+$ 955.2773, found 955.2775.

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