Synthesis of Procyanidin Oligomers. Development and Application of Cross-Coupling Reactions using Novel C8-organometallic Derivatives.

A thesis presented for the degree of doctor of philosophy

By

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Contents

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Declaration

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma at any university, and that to the best of my knowledge and belief it does not contain any material previously published or written by another person expect where due reference is made in the text.

Eric G. Dennis

Abstract

This thesis details the evolution of the iterative synthesis of 4→8 linked procyanidin (catechin) oligomers. This was achieved through the novel cross-coupling of a C4-electrophilc catechin species with a C8-organometallic catechin derivative.

Chapter 1 details a short discussion of relevant aspects of flavan-3-ols (catechins) such as nomenclature, reactivity, importance to red wine sensory perception and biological properties. Included is a short review of recent methods in biomimetic-type syntheses of procyanidin oligomers, with particular focus on dimeric and trimeric species.

A model cross-coupling system was developed and discussed in Chapter 2. In this chapter, a metallated 1,3,5-trimethoxybenzene derivative was employed as a C8-organometallic model. Coupling of a variety of metallated 1,3,5-trimethoxybenzenes to benzyl bromide revealed that 2,4,6-trimoxyphenylzinc chloride was readily coupled to this electrophile in moderate to good yields in the presence of numerous palladium catalysts. Following optimisation, the coupling product was obtained in very high yields using Pd(DPEPhos)Cl_2 as a catalyst. This procedure was then extended to the coupling of the organozinc with a variety of substituted benzylic and aryl halides in good to high yields.

The development of a Lewis acid-promoted coupling of a C4-ether with a C8-organometallic towards the synthesis of a 4→8 catechin-catechin dimer is outlined in Chapter 3. Once again, the metallated 1,3,5-trimethoxybenzene derivatives used in Chapter 2 were employed as a C8-organometallic model. The Lewis acid-promoted cross-coupling of a C4-ether with 2,4,6-trimethoxyphenylboronic acid afforded a model pseudo-4→8-dimer in excellent yield with the desired 3,4-*trans* stereochemistry obtained in excellent selectivity. Application of the model cross-coupling conditions using a C8-boronic acid-substituted catechin derivative provided a benzyl-protected catechin-4→8-dimer in consistent 90-95% yields. Debenzylation of the synthesised dimer provided catechin-4α→8-catechin dimer, or natural procyanidin B3. This natural procyanidin dimer was produced in 6 linear steps from (+)-catechin in 54% overall yield.

The synthesis of a boron-protected procyanidin dimer and trimer is presented in Chapter 4. The synthesis of these oligomers was achieved using a C8-boron-protected-C4-ether catechin derivative as a chain extension species. This species could be added to the C8-terminus of a growing oligomer chain in an iterative fashion using a coupling, boron-deprotection strategy. The C4-ether portion of this species selectively reacted with a free C8-boronic *n*-oligomer using the Lewis acid-promoted coupling method developed in Chapter 3 to provide an (*n*+1)-oligomer. Removal of the C8-boron protecting group furnished a free C8-boronic acid oligomer that could undergo further coupling to the chain extension species.

The synthesis of C8-substituted catechin derivatives is discussed in Chapter 5. C8-phenyl substituted catechins were produced in good to excellent yields using Suzuki and Kumada cross-couplings of both C8-boronic acid and C8-iodide-substituted catechins using a variety of palladium catalysts. The synthesis of an 8-8 linked catechin-catechin dimer and C8-alkyl substituted catechin derivatives was attempted using both Suzuki and Kumada methods, but were not successful.

Abbreviations

A number of non-standard abbreviations have been used throughout this thesis. Given here are the abbreviations followed by the systematic or trivial name.

Abbreviation	Standard name
Ac_2O	Acetic Anhydride
Allyl-MgBr	Allylmagnesium Bromide
$B(OMe)_3$	Trimethyl borate, boric acid-trimethyl ester
$BF_3.OEt_2$	Boron Trifluoride diethyl etherate
BnBr	Benzyl Bromide
BnCl	Benzyl Chloride
CaH_2	Calcium Hydride
CD_3CN	1,1,1,-trideuteroacetonitrile
CD_3OD	*O*-deutero, 1,1,1-trideuteromethane
$CDCl_3$	1-deutero-chloroform
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform, 1,1,1-trichloromethane
CsF	Caesium Fluoride
CuCN	Copper-(I)-Cyanide
CuI	Copper-(I)-Iodide
Dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-quinone
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DPEPhos	bis(*o*-diphenylphosphinophenyl)ether
Dppf	1,1′-bis(diphenylphosphino)ferrocene
Et_3N	Triethylamine
EtMgBr	Ethylmagnesium Bromide
EtOAc	Ethyl Acetate

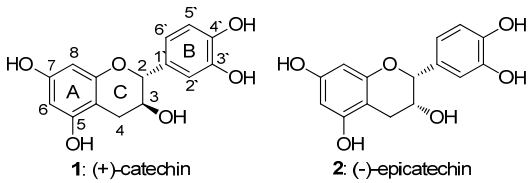
i-PrMgCl	*iso*-propylmagnesium Chloride
K_2CO_3	Potassium Carbonate
K_3PO_4	Potassium Phosphate tribasic
MeI	Iodomethane, methyl iodide
$MgBr_2$	Magnesium Bromide
$MgBr_2.OEt_2$	Magnesium Bromide-diethyl etherate
$MgCl_2$	Magnesium Chloride
MIDA	*N*-methylimidodiacetic acid
Na_2CO_3	Sodium Carbonate
Na_2SO_4	Sodium Sulphate
NaH	Sodium Hydride
NBS	*N*-bromouccinimide
n-BuLi	*n*-Butyllithium
NIS	*N*-iodosuccinimide
$PhB(OH)_2$	Phenylboronic acid
PhBr	Bromobenzene
PhCl	Chlorobenzene
PhI	Iodobenzene
PhMgBr	Phenlymagnesium Bromide
PPh_3	Triphenylphosphine
R_f	Retention factor
rt	Room temperature
Sat. aq. $NaHCO_3$	Saturated aqueous sodium bicarbonate solution
Sat. aq. NH_4Cl	Saturated aqueous Ammonium Chloride solution
t-BuLi	*tert*-Butyllithium
THF	Tetrahydrofuran
$TiCl_4$	Titanium-(IV)-tetrachloride
TMSOTf	Trimethylsilyl-triflate
$ZnCl_2$	Zinc Chloride

Chapter 1: General Introduction and Background.

1.1 Nomenclature and structure of catechin and epicatechin.

(+)-Catechin (**1**) and (-)-epicatechin (**2**) are the trivial names applied to the flavan-3-ols (2*R*, 3*S*)-(+)- and (2*R*, 3*R*)-(-)- isomers of 3,5,7,3′,4′-pentahydroxyflavan respectively (Figure 1).[1]

Figure 1: Catechin and Epicatechin.



These monomeric flavan-3-ols belong to a larger family of naturally occurring flavan compounds that possess the 15 carbon ring structure (Figure 1), with the heterocyclic C-ring fused to the aromatic A-ring, and the aromatic B-ring tethered to the C-ring *via.* the C2 carbon. Convention has dictated each carbon of the flavan skeleton a reference number as shown in Figure 1. Reference to any hydrogens attached to the carbons is through quoting the carbon number, followed by H., i.e. C2-H refers the hydrogen attached to C2.

1.2 Procyanidin (flavan-3-ol) dimers. Nomenclature and structure.

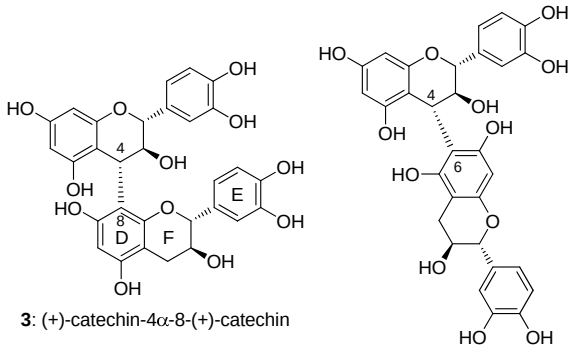
Procyanidin dimers are characterised by two flavan-3-ol monomers linked together by an interflavan bond between C4 of one monomer with either C8 (**3**) or C6 (**4**) of another monomer (Figure 2).

Conventional nomenclature for procyanidin dimers [1] provides the C4-linked monomer first, followed by the C8-linked monomer. The numbering and arrowhead between the two monomers dictates the interflavan linkage. By this convention, catechin-4→8-catechin (**3**) indicates a catechin-catechin dimer linked between C4 and C8 and catechin-4→6-catechin (**4**) describes the catechin-catechin dimer linked between C4 and C6 (Figure 2).

In order to reduce ambiguity of the naming of the A, B and C rings of the monomer units, the A, B, and C designations are usually retained for the upper or top

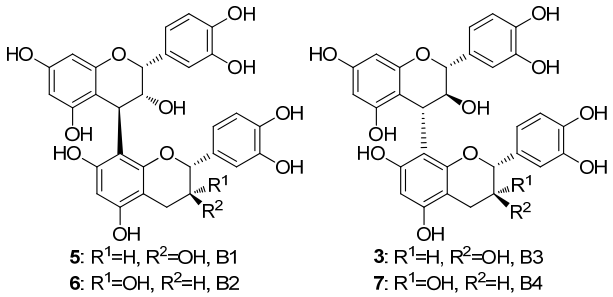
monomer. The A, B, and C rings of the lower or bottom monomer are then designated as the D, E and F rings (Figure 2).

Figure 2: Procyanidin 4→8 and 4→6 dimers.



The four 4→8 dimers composed of catechin and epicatechin monomers are often referred to by their trivial names Procyanidins B1 to B4 (**3**, **5-7**, Figure 3).

Figure 3: **Procyanidins B1 to B4.**



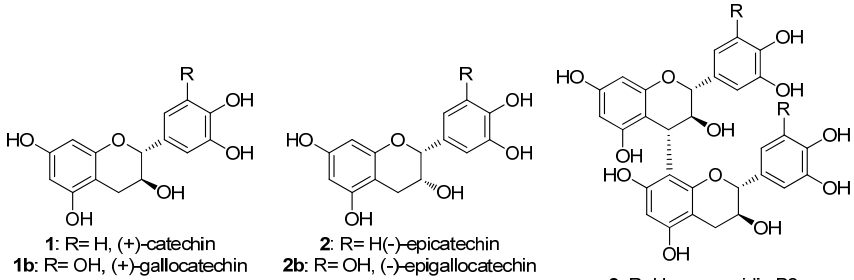
These four dimers all exhibit 3,4-*trans* stereochemistry at the C4 position of the interflavan linkage. Interflavan linkages of proanthocyanidins are named according to the *α*,*β* system, dictated by the C4 stereochemistry of the "top" unit. (*R*) stereochemistry is designated *α* and (*S*) designated *β*. Therefore, a 4→8 interflavan linkage between two epicatechin units (**6**), which exhibits (*S*) stereochemistry at C4, is designated as a 4*β*→8 interflavan bond. (*R*) Stereochemistry at C4, as in **3,** is designated as a 4*α*→8 interflavan bond. Taking all naming conventions into account, **3** is formally known as (+)-catechin-4*α*→8-(+)-catechin and the other dimers are named similarly.[1]

1.2.1 Proanthocyanidins: Procyanidins and prodelphinidins.

The above procyanidin dimers and other procyanidin oligomers belong to the larger family of flavanol oligomers known as proanthocyanidins. The nomenclature of these compounds can be somewhat confusing so the following section has been included to provide some clarity.

Proanthocyanidins, which will be discussed in detail in the next section, are comprised of two groups of flavan-3-ol oligomers/polymers. Proanthocyanidins encompass both the procyanidins (e.g., **3**), and the prodelphinidins (e.g. **3b**). The distinguishing functionality of these two classes is the B-ring hydroxylation pattern. Procyanidin oligomers/polymers are comprised of monomers containing the dihydroxy (catechol) B-ring substitution (e.g. **1, 2**) and prodelphinidin oligomers are characterised by the trihydroxylation (pyrogallol) of the B-ring (e.g. gallocatechins **1b, 2b**) (Figure 4). The procyanidin dimer **3** and prodelphinidin dimer **3b** have been included to further highlight the difference between procyanidins and prodelphinidins (Figure 4).

Figure 4: Monomers comprising procyanidin and prodelphinidin oligomers.



As a consequence, any reference to proanthocyanidins indicates both compound classes are inferred collectively in discussions. Reference to either procyanidins or prodelphinidins infers that particular compound class is being discussed exclusively.

1.3 Proanthocyanidins/tannins in nature.

Proanthocyanidin oligomers and polymers, including the procyanidin dimers B1 to B4, are polyphenolic compounds that are ubiquitous throughout the plant kingdom. They are a group of important secondary metabolites which display numerous biological properties, including protein interactions, chelation of metals and

antioxidant activity, which are involved in numerous protective functions in plants.[2] Tannins, a common name that incorporates many plant polyphenols including proanthocyanidins, are defined as compounds that form stable complexes with proteins and other plant polymers such as polysaccharides. [3] It follows from this broad definition that tannins encompass a wide range of compounds. The name tannin is derived from the tanning of leather, where cow hides are treated with a tannin solution. The resulting protein-tannin interactions form a hardened or leathered hide. There are two subclasses of tannins that are important to grapes and wine; Condensed tannins (Proanthocyanidins) and hydrolysable tannins. Only proanthocyanidins will be discussed in this thesis.[3]

1.3.1 Proanthocyanidins/tannins in grapes and wine.

Tannins play an important role in the perception of sensorial properties in wine, and particularly red wine (Section 1.3.2). Proanthocyanidins are biosynthesised by grapes and are located primarily in the skin, flesh, seed and vine matter. Upon crushing, extraction and fermentation, grape tannins, which are principally comprised of proanthocyanidins, are extracted into a wine "must" (the juice and solids extracted from the grape which is then fermented to produce wine). Importantly, little or no tannin is present in white wine, while tannin-related material is present in red wines in amounts up to 1-2 gL^{-1}.[4] The variations in vinification processes for white and red wines account for these differences. White wines are produced by fermentation of free-run grape juice with little or no pressing of the grape-solid matter and no skin contact during fermentation. As most tannin matter in grapes is located in the grape solids, there is little opportunity to extract tannin matter into white grape juice, and the resulting white wine contains little or no tannin. In contrast, juice from red grapes is allowed some contact time with the grape solids (skins, flesh, seeds and possibly some stem) during fermentation. It follows that tannin matter is extracted into the wine "must" during this time, especially as alcohol content increases. The resulting red wine contains a significant amount of tannin. As a result of these vinification and tannin concentration differences, the sensorial properties, especially colour perception and astringency, of white and red wines are significantly different.[3, 4]

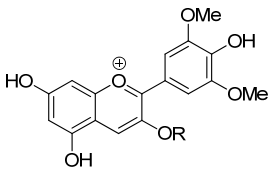
The amount of tannin in a red wine depends on several factors. These include the grape variety used (as different varieties produce differing amounts of

proanthocyanidins), the length of time allowed for contact of the must with grape solids and the amount of mechanical stirring, or "pumping over" of the solids during fermentation.[3] Non-proanthocyanidin tannins can also be added to wines as part of the wine making process or through extraction from oak during oak barrel ageing.[4]

1.3.2 Properties of tannins in wine.

Condensed tannins have been associated with a number of sensorial properties in red wine. The most important of these are astringency and bitterness. Astringency is the drying or puckering sensation of the mouth upon drinking red wine attributed to interactions of tannins with proteins in saliva. This reduces the lubrication of the saliva in the mouth, and hence the drying effect. Condensed tannins present in red wine bind and precipitate the salivary proteins to produce this drying effect.[5] Astringency is often incorrectly associated as a taste perception. Astringency is a global mouth feel perception, and so should not be considered a taste perception. True taste perceptions (e.g. sweet, sour) occur at specific sites of the tongue. The taste sensation of bitterness has also been attributed to proanthocyanidins and is dependent on tannin structure.[4] Condensed tannins also play a major role in the stabilisation of colour of red wine. Anthocyanins, such as 3-O-glycosides of malvidin, (**8**, Figure 5) and anthocyanin-derived pigmented polymers, are principally responsible for the red colour of wine. Pigmented polymers are defined as polymers such as proanthocyanidin polymers which are attached to a pigment (i.e. a coloured molecule, such as **8b**). Anthocyanidins are highly unstable compounds which can undergo bleaching reactions with SO_2 and colour changes with changing pH conditions. Unlike the monomeric anthocyanidins, pigmented polymers are resistant towards pH effects and SO_2 bleaching, and this aids in the stabilisation of colour in red wine.[3] It should be noted there are other anthocyanin monomers present in grapes and wine, but they are of less importance than malvidin-3-O-glycosides in determining the colour of red wines [3, 4] and so will not be discussed.

Figure 5: Malvidin and Malvidin-3-O-glycosides.



8a: R=H, malvidin
8b: R=Gly, malvidin-3-O-glycoside
Gly= glucose, acetylglucose.

1.3.3 Maturation of tannins in grapes and wine.

Condensed tannin composition in wine constantly changes throughout wine-making and ageing. The predominantly flavan-3-ol based proanthocyanidins from grapes that are extracted during fermentation are modified by reactions with other compounds in the must and finished wines, such as acids and aldehydes and other phenolics. They also undergo oxidation in the presence of residual Fe^{2+} and/or oxygen present in wine during the winemaking and ageing process.[2] As tannin composition changes, sensorial properties such as astringency and colour stabilisation are also modified. These compositional changes and how they occur are not well understood. There is also a growing desire to better understand the structure-function relationships in wine tannin composition pertaining to sensorial properties such as astringency and colour stabilisation. For example, do compounds **3** and **4** (Section 1.2, Figure 2) display different astringency or bitterness properties owing to their different interflavan linkage?

1.3.3 Health and other properties of proanthocyanidins.

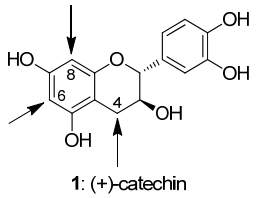
Wine tannins are widely reported to have powerful health benefits, and are implicated in the phenomenon known as the "French Paradox".[3] Regular consumption of red wine by the French has resulted in reduced occurrence of cardiovascular disease despite their diet high in saturated fats. It is believed this effect is due to the antioxidant [6, 7] and free-radical scavenging effect [8, 9] of phenolics and condensed tannins. The health benefits of proanthocyanidins are not limited to wine tannins, as condensed tannins are widespread throughout nature (Section 1.3), being found in many foodstuffs including, but not limited to, cocoa,[10] apples [11] and beer.[12] Many naturally occurring tannins have been shown by *in vitro* assays to have widespread and potentially significant antibacterial,[13] anti-oxidant [6, 7] and radical-scavenging properties.[8, 9] There has also been increasing interest in these compounds

as possible anticancer agents.[14, 15] Also, proanthocyanidin dimers and trimers have been shown to inhibit non-enzymatic browning reactions known as the Maillard Reaction.[16] The Maillard Reaction is important in foodstuffs as an indication of spoilage, as in fruits and beer, or as an ageing factor in increasing flavour complexity and mellowing, as in teas and aged wines. As with wine tannins, studies into structure-function relationships of these important health activities, particularly those pertaining to anticancer properties,[14, 17] are becoming increasingly relevant.

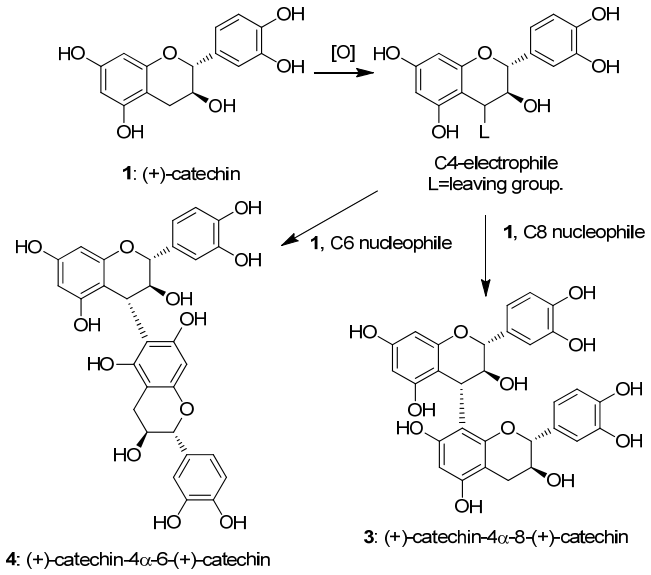
1.3.4 Reactivity of flavan-3-ol monomers and procyanidin oligomers.

As described earlier (Section 1.2), procyanidin dimers possess either 4→6 or 4→8 interflavan linkages. As a consequence, chemical reactions involving flavan-3-ol monomers (e.g. **1**) predominantly occur at the C4, C6 and C8 carbons (Figure 6).[18]

Figure 6: Reactive sites of (+)-catechin.



Scheme 1: C4-oxidation of (+)-catechin (1) and reaction with C6 or C8 to form dimers 3 or 4.

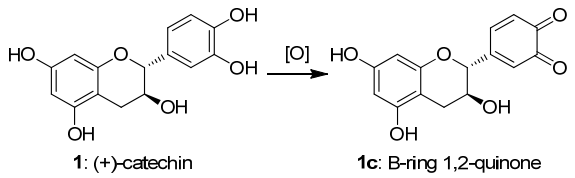


Due to the high electron density of the A-ring, the C6 and C8 positions exhibit nucleophilic behaviour. The C4 position is prone to oxidation which can form C4-

electrophilic species. The reaction of these C4-electrophiles with C6 or C8 of another flavan monomer provides the basis for procyanidin dimer formation (Scheme 1).

Chemical reactions involving the B-ring occurs through oxidation of the B-ring catechol of **1** or pyrogallol ring of **1b** to form 1,2-quinones such as **1c** (Scheme 2).

Scheme 2: Oxidative formation of B-ring 1,2-quinone 1c from (+)-catechin.



While reactions of the B-ring will be not be the focus of this thesis, formation of B-ring 1,2-quinones by oxidation reactions are important in wine [19] and are worth noting in order to provide a more complete overview of flavan-3-ol reactivity.

1.4 Challenges in obtaining tannin material.

In order to investigate structure-function relationships pertaining to condensed tannins, whether that is wine sensory properties or other health-related properties, condensed tannin samples are required. As a result, these compounds must be obtained from some source, usually by isolation from plant material or through synthetic methods. For many of these studies, pure, defined samples of specific proanthocyanidins are a necessity. Traditionally, tannin material has been isolated from plant sources including, but not limited to, teas and cinnamon.[10, 20] However, these isolations can be painstakingly time consuming and purity and reproducibility are often suspect. Also, yields of isolations are often small and information on biological properties is difficult, and sometimes impossible to assimilate on such small samples. In response to this, synthetic methods towards producing these compounds have become more prevalent in the last two decades. Through the tailoring of synthetic methods, pure condensed tannins with defined structure are potentially available in large quantities. Methods of synthesis of procyanidin oligomers will be discussed in Section 1.6.

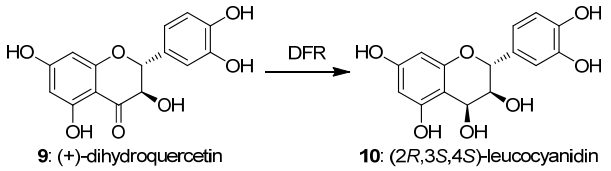
1.5 Biosynthesis of proanthocyanidin oligomers in nature.

Pathways that regulate the biosynthesis of proanthocyanidin oligomers *in vivo* have been the subject of many a study for several decades. Recently, genetic and molecular biology methods have uncovered a series of key enzymes, transcription factors and intracellular transport factors involved in proanthocyanidin biosynthesis.[21, 22, 23]

Despite advances in this field, the exact mechanism for the assembly of proanthocyanidin oligomers from flavan-3-ol monomers *in vivo* remains unclear and is the subject of vigorous debate, which has mainly centred on whether oligomerisation/polymerisation occurs *via.* a complex enzymatic pathway or through direct non-enzymatic condensation.[24]

Following the proposed non-enzymatic condensation biosynthetic pathway, flavan-3,4-diols, or leucocyanidins, act as direct precursors to proanthocyanidin oligomers. Leucocyanidins are biosynthesised by stereospecific reduction of dihydroquercetin precursors mediated by dihydroflavonol 4-reductase (DFR) (Scheme 3).[25]

Scheme 3: Reduction of (+)-dihydroquercetin (9) to leucocyanidin (10).



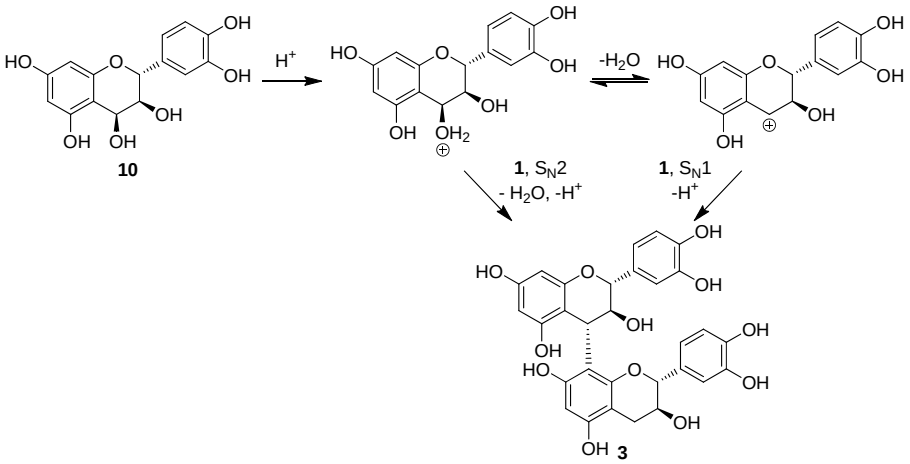
9: (+)-dihydroquercetin **10**: (2*R*,3*S*,4*S*)-leucocyanidin

According to the proposed arguments, non-enzymatic condensation proceeds through acid-catalysed condensation of leucocyanidin **10** with flavan-3-ol monomers or proanthocyanidin oligomers to form extended proanthocyanidin oligomers. As an example, proanthocyanidin B3 (**3**) can be synthesised by acid-catalysed condensation of leucocyanidin **10** with (+)-catechin (**1**) *via*. an electrophilic aromatic substitution (Scheme 4).

Through this acid-catalysed pathway, the natural 3,4-*trans* catechin-catechin dimer **3** is produced through either an S_N1 or S_N2 pathway. Trimers and higher oligomers are formed by this pathway through condensation of leucocyanidins with dimers and higher oligomers in the same manner for the above dimer formation by simply replacing catechin with a higher oligomer. That is, the flavan-3,4-diol precursor

condenses with *n*-oligomers to form (*n*+1)-oligomers in a stepwise fashion. Numerous *in vitro* chemical studies support the viability of such a pathway.[26-28]

Scheme 4: Acid-catalysed condensation of leucocyanidin 10 and (+)-catechin.



In regards to the enzyme-mediated oligomerisation pathway, the final enzymes that may catalyse condensation or oligomerisation steps still remain unknown.[2] No further discussion of the enzyme-mediated pathway is pursued in this thesis.

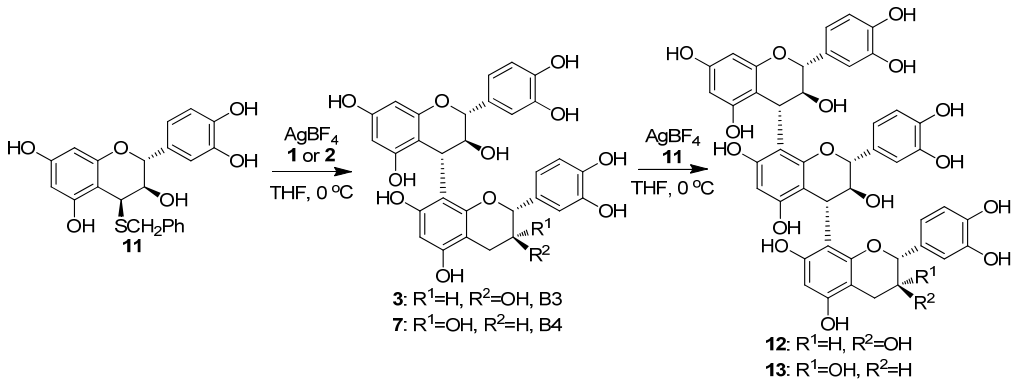
1.6 Biomimetic methods for chemical synthesis of procyanidin oligomers.

As previously stated, synthesis of procyanidin oligomers is desirable in order to investigate biological properties of these molecules (Section 1.4). Since the first reports of procyanidin oligomer synthesis in the mid 1960's,[26, 29] dozens of methods have been employed in their synthesis. Notably, many of these chemical syntheses exploit a biomimetic pathway in order to forge the key interflavan bonds. In light of the sheer number of methods used for procyanidin synthesis, the following review of methods has been limited to discussion of biomimetic-type syntheses that produce predominantly 4→8 interflavan linkages since 1998. In this review, biomimetic-type syntheses are regarded as syntheses that mimic acid catalysed activation of flavan-3,4-diols through the use of C4-leaving groups that can be activated by the addition of an appropriate agent. Only methods pertaining to the synthesis of procyanidins, not prodelphinidins, are discussed. It should be noted, however, that these synthetic strategies may also be applied to synthesis of prodelphinidin oligomers.

1.6.1 Thiophilic Lewis acid activated synthesis of procyanidin dimers and trimers.

In 1998, Steynberg *et al* [30] developed a method for the thiophilic Lewis acid-promoted condensation of 4-benzylsulfanylcatechin **11** with catechin (**1**) or epicatechin (**2**) to form procyanidins B3 (**3**) or B4 (**7**). By further condensation of **3** or **7** with **11** under the same conditions, trimers **12** and **13** were also prepared by this method (Scheme 5).

Scheme 5: Thiophilic Lewis acid promoted condensation of 4-benzylsulfanylcatechin.

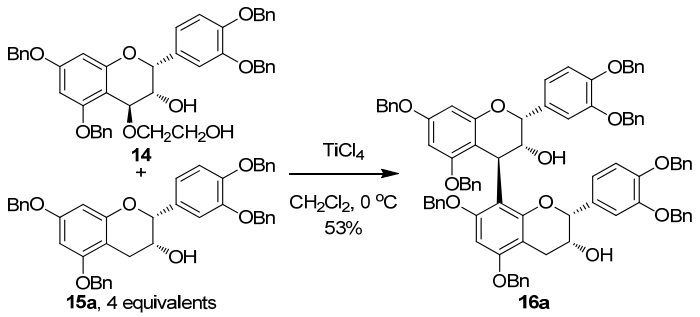


1.6.2 Lewis acid promoted condensation of C4-ether functionalised flavan-3-ols.

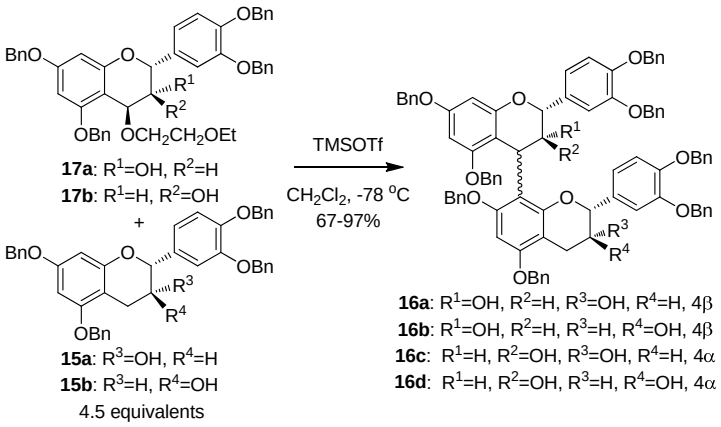
Lewis acid promoted condensation of C4-ethers has become perhaps the most popular method for the synthesis of procyanidin dimers. A notable contribution to this method was by Tückmantel *et al*,[17] who synthesised the benzyl protected procyanidin dimer B2 (**16a**) in good yield (53%) with excellent 3,4-*trans* stereoselectivity by $TiCl_4$ promoted condensation of C4-ether **14** with 4 molar equivalents of protected epicatechin **15a** (Scheme 6). In this condensation, trimer and tetramer products were produced as minor by-products.

The use of the Lewis acid condensation approach was further refined by Saito *et al* in the 3,4-*trans* stereoselective synthesis of procyanidin dimers B1-B4 [16, 31] In this approach, TMSOTf promoted condensation of C4-ethers **17a** or **17b** with 5 molar equivalents of **15a** or **15b** at low temperature produced protected dimers **16a-d** in good to excellent yields (Scheme 7). Notably, no traces of trimer or higher oligomers were produced using this method. The authors attributed this to presence of large molar excesses of nucleophile **15** in the reaction mixture.

Scheme 6: Tückmantel's $TiCl_4$ promoted condensation of C4-ether 14.



Scheme 7: TMSOTf promoted condensation of C4-ether 17.

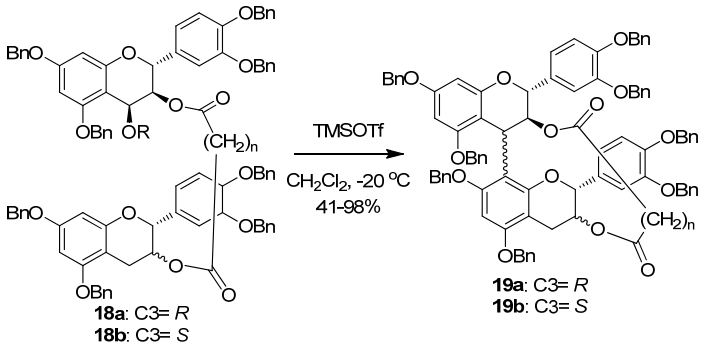


Saito *et al* also applied this coupling strategy in the stepwise synthesis of a number of procyanidin trimers [32] and very recently tetramers, pentamers and hexamers [33] containing a variety of monomer compositions. In their strategy, 1**7a** or **b** was coupled to the C8-terminus of an *n*-oligomer in the presence of TMSOTf to produce an (*n+1*)-oligomer.

1.6.3 Intramolecular Lewis acid promoted condensation procyanidin synthesis.

Along with their intermolecular approach above (Scheme 6), Saito e*t al* also utilised their Lewis acid promoted condensation under intramolecular conditions in an attempt to reduce the molar equivalents of **15** required for selective dimer synthesis. In this approach, the C4-ether and nucleophilic species were linked by an alkyl diester at the C3-oxygens of the two monomers (**18a** and **b**). Condensation was then carried out in the presence of TMSOTf at -20 °C to produce diester dimers **19a** or **19b** in moderate to excellent yields (Scheme 8). Following coupling, the diester linkage was removed by DIBAL reduction.[34, 35]

Scheme 8: Saito *et al* intramolecular Lewis acid promoted dimer formation.

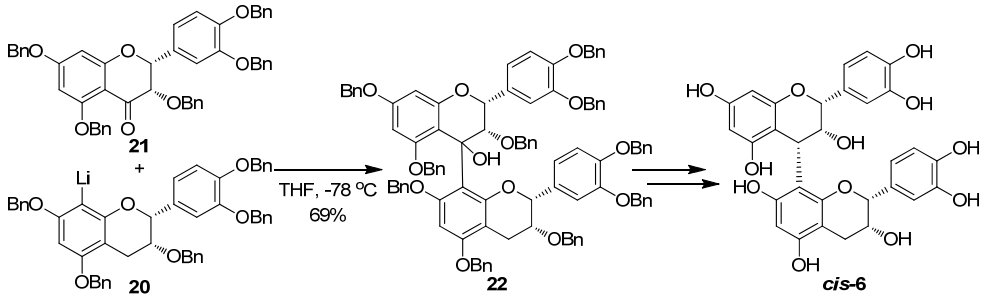


The C4 stereochemistry was controlled by the relative chain lengths of the diester linkage.[36] When short chain diesters were used (*n*= 2, 3) 3,4-*cis* stereoselectivity dominated. As the chain length increased, the relative amount of the 3,4-*trans* product also increased. At diester chain lengths of 6 to 8 (*n*= 6-8), the 3,4-*trans* product was by far the dominant stereoisomer with *n*= 7 being the optimal chain length. With this diester chain length, only traces of the 3,4-*cis* product were observed.

1.6.4 Synthesis of 3,4-cis dimer by addition of C8-organolithium to C4-ketone.

In 2001, Kozikowski *et al* [37] synthesised the unnatural 3,4-*cis* isomer of procyanidin B2 through the addition of C8-organolithium **20** to C4-ketone **21**. Reduction of the resulting alcohol **22** and removal of protecting groups produced 3,4-*cis* B2 (***cis*-6**) (Scheme 9). While not strictly a biomimetic-type synthesis, this method does represent the novel use of a C8-organometallic addition in the synthesis of proanthocyanidin dimers.

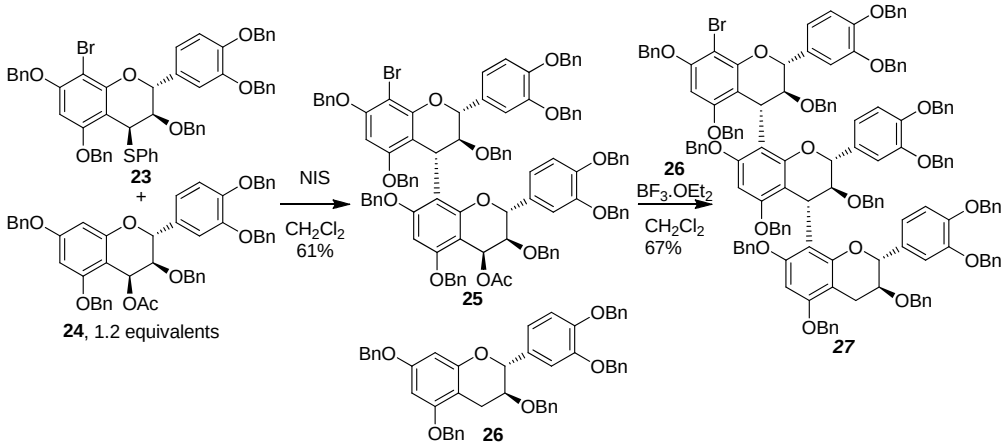
Scheme 9: Kozikowski *et al* synthesis of 3,4-*cis* procyanidin B2 (*cis*-6).



1.6.5 Orthogonal activation strategy in procyanidin dimer and trimer synthesis.

An important biomimetic-type approach to the synthesis of procyanidin dimers and trimers was reported by Ohmori *et al* in 2004.[38] This strategy involved the use of orthogonal C4-leaving groups that could be activated under different conditions. Under thiophilic Lewis acid activation, C4-thioether **23** was coupled to C4-acetate **24** to form dimer **25** in good yield. Importantly, the C-acetate leaving group was not affected by thioether activation. Dimer **25** was then coupled to protected catechin (**26**) to produce trimer **27**, again in good yield and high 3,4-*trans* stereoselectivity (Scheme 10).

Scheme 10: Ohmori *et al* orthogonal activation strategy for dimer and trimer synthesis.



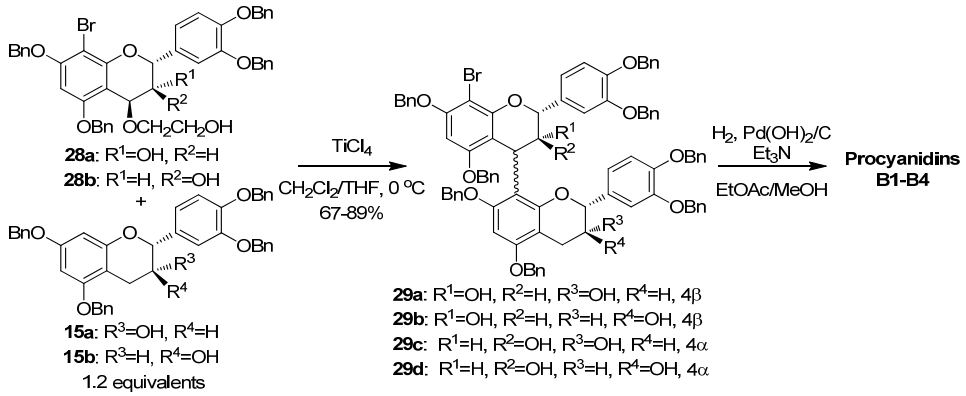
Importantly, the bromide at the C8-terminus of the growing oligomer chain acted as a protecting group, preventing oligomerisation in this direction. As a result, the growing chain was extended in a stepwise, controlled fashion from the C4-terminus of the growing oligomer. No higher oligomeric species were observed in either coupling step. In contrast to Tückmantel *et al* (Scheme 6) or Saito *et al* (Scheme 7) complete condensation of **23** only required a slight molar excess (1.2 equivalents) of the nucleophilic species **24** in order to restrict higher oligomer formation. The C8-bromide protecting group was responsible for this observation by blocking pathways that may lead to higher oligomer formation.

1.6.6 Further approaches to C8-protection in procyanidin dimer synthesis.

Tarascou *et al* [39] also utilised a C8-bromide blocking group for the stereoselective synthesis of proanthocyanidins B1-B4. Each dimer (**29a-d**) was synthesised in good

to excellent yields by $TiCl_4$ promoted condensation of C4-ethers **28a** or **b** with 1.2 equivalents of either **15a** or **b** (Scheme 11). No trimer or higher oligomers were observed by this method.

Scheme 11: Tarascou *et al* stereoselective synthesis of procyanidin dimers 29a-d.



As seen with Ohmori *et al* (Section 1.6.5), the C8-bromide prevented chain extension at the C8-terminus. As a result, only a slight molar excess of nucleophile was required to ensure complete condensation of C4-ethers **28a** and **b**. The native 3,4-*trans* procyanidins B1-B4 were produced from **29a-d** by one-pot debromination/debenzylation by hydrogenation in the presence of Pearlman's catalyst ($Pd(OH)_2/C$ and Et_3N.

1.7 Biological properties of synthetic procyanidins.

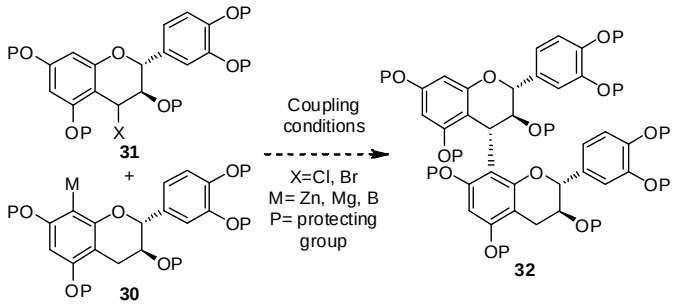
Many synthetic procyanidins have been subjected to *in vitro* biological assays to determine their biological activities. Saito *et al* showed that procyanidin dimers B1-B4 and their peracetate derivatives gave significant inhibitory activity towards the Maillard Reaction.[16] This group also showed these dimers and their C3-O-gallates possess high radical scavenging (antioxidant) activities and potential as DNA polymerase inhibitors.[15] An important study by Kozikowski *et al* [14] showed that epicatechin-based oligomers of varying chain lengths showed inhibitory activity towards cancer cell growth by cell cycle arrest in human breast cancer cells. Importantly the synthetic procyanidin oligomers in these studies showed comparable biological activities to natural samples of the same procyanidins obtained by isolation from plant sources.

Chapter 2: An Organometallic Cross-Coupling Method Towards 4→8 Catechin Dimers: 1,3,5-trimethoxybenzene as a C8 Model System.

2.1 Introduction.

Following the initial literature survey of synthetic methods in 4→8 bond formation of procyanidin dimers, it was noted that little attention had been focussed upon the use of organometallic reagents as nucleophiles for this transformation. The only relevant precedent was reported by Kosikowski *et al*,[37] who used the addition of a C8-organolithium to a C4-ketone derivative to form the epicatechin dimer (***cis*-6**) (Section 1.6.4, Scheme 9). With this in mind, a novel coupling concept involving the use of a C8-organometallic derivative as a directing group in the synthesis of 4→8 catechin-catechin dimers was proposed for investigation. In such a coupling, an appropriate C8-organometallic (or metalloid) **30** could potentially be coupled to a C4-halide **31** to form the desired catechin-catechin dimer **32** (Scheme 1).

Scheme 1: Initial synthetic plan for coupling of 30 with 31 to form dimer 32.



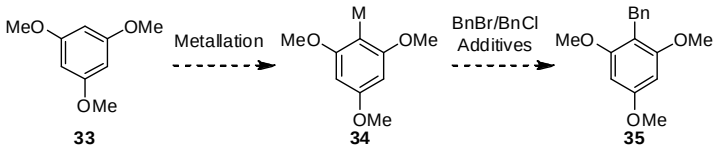
It was thought that such as strategy the may potentially alleviate the necessity to use excess nucleophile in the coupling strategies referred to Sections 1.6.1 and 1.6.2. As nucleophile **30** is activated as the C8-organometallic, coupling of this centre with the C4-halide of **31** should proceed selectively over the C8-centre of **31**. This in turn could reduce the excess nucleophile required to prevent the uncontrolled production of higher oligomers (Section 3.1.2).

Interest in the development of this type of coupling also stemmed from the potential diversity of coupling conditions available. Perhaps most notably, numerous possible metallic/metalloid (M= Li, Mg, Cu, B, Zn, Sn, Si) and halide/leaving group (X= Cl, Br, I, OTf) functionalities could be employed in potential couplings. Also, a great

variety of additives and transition metal catalysts exist as potential coupling aids. As a result, there is a wide scope for optimisation of this 4→8 coupling method.

In order to examine some potentially useful coupling conditions, a model cross-coupling was established (Scheme 2). In this coupling, 1,3,5-trimethoxybenzene (**33**, TMB) was employed as a C8-model compound and benzyl bromide (BnBr) or benzyl chloride (BnCl) as the C4-halide model.

Scheme 2: Model cross-coupling of 1,3,5-trimethoxybenzene 33 and benzyl bromide/chloride.



1,3,5-Trimethoxybenzene possesses the same 1,3,5-oxygen substitution as the A-ring of catechin derivatives. It was also readily available at low cost and possesses simpler ^{1}H and ^{13}C NMR spectral properties compared to that of catechin. These properties endow 1,3,5-trimethoxybenzene as a highly useful C8-model compound. Benzyl bromide or chloride were among the cheapest and most accessible benzylic halides available, and so were a good starting point for a C4-halide model compound.

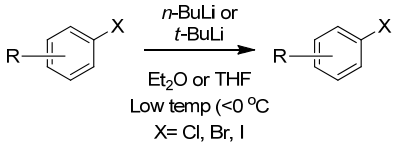
2.1.1 Formation of aryl organometallic species.

Formation of the organometallic derivatives of 1,3,5-trimethoxybenzene (**33**, TMB) was identified as initial issue to be addressed in this model coupling strategy. Accordingly, a short survey of formation methods for aryl organometallics was warranted.

2.1.1.1 Aryl-organolithium species (M=Li).

Organolithium derivatives have been used extensively in synthetic organic chemistry as highly active nucleophilic species in carbon-carbon bond formation [40, 41] and as precursors to other organometallic species.[42, 43] By far the most common method for formation of aryl organolithium species has been through a low-temperature lithium-halogen exchange of an aryl halide using *n*-butyllithium (*n*-BuLi) [45, 46] or *tert*-butyllithium (*t*-BuLi) [46, 47] (Scheme 3).

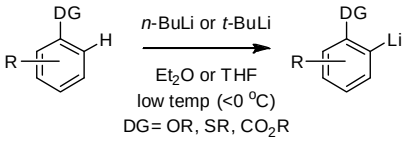
Scheme 3: Low-temperature lithium-halogen exchange of aryl halides using butyl-lithiums.



The low electronegativity (1.0) of lithium compared to carbon (2.5) results in the carbon-lithium bond displaying a high ionic character with high reactivity as either a base or nucleophile. As a practical result, aryl organolithiums are usually prepared *in situ* and used immediately. The high reactivity of these species often dictates the use of low reaction temperatures in the range of 0 ^{o}C to below -100 ^{o}C depending upon the substrate.[40]

Another method for formation of organolithium species is the directed *ortho*-lithiation of benzene derivatives substituted with an appropriate directing group using *n*-BuLi or *t*-BuLi (Scheme 4).

Scheme 4: Formation of organolithiums via directed *ortho*-lithiation.



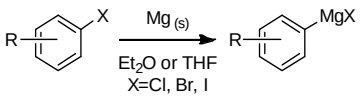
The directed *ortho*-lithiation method requires ortho-substituted heteroatom directing groups (DG) containing lone pair electrons. These include ether (DG=OR), thioether (DG =SR), amine (DG =NR_2), ester (DG =CO_2R) and amide (DG =CO_2NR_2) groups.[40,48] The complexation of the lithium to the heteroatom lone pair electrons provides the activation towards *ortho*-organolithium formation.

2.1.1.2 Aryl-organomagnesium (Grignard) derivatives (M=Mg).

Organomagnesium derivatives were first employed by Victor Grignard in 1900 [49] for nucleophilic additions to carbonyl compounds. Since then organometallic species utilising Mg have generally been referred to as Grignard reagents. These highly reactive species have found many uses in organic chemistry as both bases [50] and nucleophiles.[51, 52]

The most common formation method for Grignard reagents is based on that initially reported by Grignard in 1900.[49] Elemental magnesium directly inserts into the carbon-halogen bond of an aryl halide to produce an arylmagnesium halide (a Grignard reagent, Scheme 5).

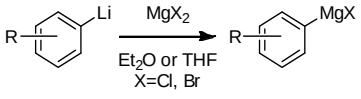
Scheme 5: Direct magnesium insertion into aryl halide.



This insertion is normally carried out using THF or Et_2O as the reaction solvent. Because it is a heterogeneous reaction, initiation of the insertion can be difficult. The application of heat and the addition of iodine or 1,2-dibromoethane can be used to aid activation of the magnesium surface.[53] As a highly reactive species, the Grignard reagent is generally prepared *in situ* and then used immediately upon completion of the magnesium insertion.

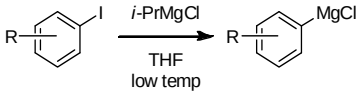
A second applicable method of preparation is through the transmetallation of an appropriate aryllithium derivative. This is performed by the addition of $MgBr_2$ or $MgCl_2$ to a preformed solution of the requisite organolithium in THF or Et_2O [41, 54] (Scheme 6).

Scheme 6: Formation of Grignard reagents by transmetallation of organolithium solutions.



More recently, Knochel *et al* [55] developed a method for the formation of aryl-Grignard reagents by low temperature magnesium-iodine exchange of aryl iodides using isopropylmagnesium chloride (*i*-PrMgCl) in THF (Scheme 7).

Scheme 7: Preparation of Grignard reagents from aryl iodides by *i*-PrMgCl mediated magnesium-iodine exchange.

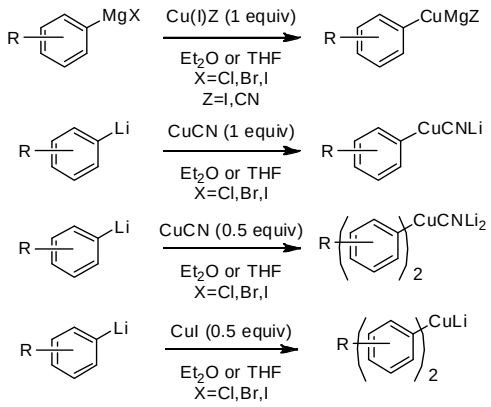


Knochel *et al* reported that the exchange was far more facile using aryl iodides containing electron withdrawing substituents. Preparation of Grignards by this method has more recently been extended to include the use of aryl bromides [56] and halides containing electron donating substituents.[57]

2.1.1.3 Organocopper derivatives (M=Cu).

The use of copper as a reagent in organometallic chemistry dates back to the 1850's. It was the use of this metal in the Ullmann reaction [42, 58] around the turn of the 20th century that brought it to prominence. Since then the use of copper and organocopper reagents (organocuprates) as a catalyst and nucleophiles in cross-coupling chemistry has increased significantly.[42, 59, 60] In comparison to analogous organolithium or Grignard reagents, organocuprate derivatives possess reduced ionic character in the carbon-copper bond. As a result, organocuprates possess greater reaction selectivity and can tolerate a wider range of functional groups than organolithiums or Grignards. An excellent review of organocuprate reactions can be found in Organocopper Reagents.[61]

Scheme 8: Formation of mono and di-aryl cuprates from Grignards or organolithium reagents.

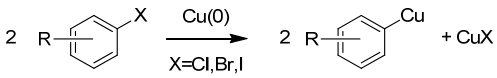


Formation of aryl organocuprates can be achieved by transmetallation of the requisite aryllithium or Grignard reagent by addition of a copper-(I) source, such as copper-(I)-iodide (CuI) or copper-(I)-cyanide (CuCN) to a preformed solution of organolithium or Grignard reagent in THF or Et_2O (Scheme 8). Cuprates formed from a Grignard reagent always form a mono-aryl cuprate species, whereas the organolithium can form either mono-aryl or di-aryl cuprate species. Formation of

higher-order cuprate species using lithium or magnesium to copper transmetallations have also been reported,[62] but will not be discussed here.

Aryl organocopper reagents have also been prepared from aryl halides through direct insertion of active copper-(0) species such as $Cu(PPh_3)_2$ or $Cu(P(Bu)_3)_2$ (Scheme 9).

Scheme 9: Insertion of active copper-(0) species into aryl halides.



The activity of the copper-(0) species and the reactivity of the resulting organocopper reagents are highly dependent upon the ligands complexed to the copper centre.[61]

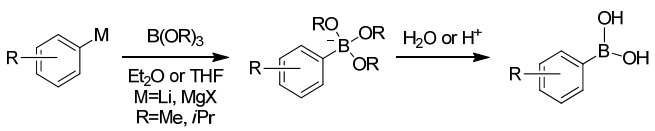
The organocuprates formed by either transmetallation or insertion methods are generally prepared *in situ* and used immediately following formation.

2.1.1.4 Organoboron derivatives (M=B).

Organoboron compounds have been used as nucleophiles in cross-coupling reactions since Brown reported the use of organoboranes in such reactions.[64] Since then, a variety of organoboron compounds such as boronic acids [65, 66] and boronate esters [67] have been employed as nucleophiles.

Aryl-organoboron compounds have generally been limited to boronic acids and boronate esters. Formation of aryl boronic acids containing a vast array of functional groups has been readily achieved through transmetallation of aryllithium or Grignard compounds by addition of a borate ester, such as trimethylborate ($B(OMe)_3$) or triisopropylborate ($B(O\textit{i}\text{-}Pr)_3$), in THF or Et_2O.[42] Hydrolysis of the tetrahedral boronate anion intermediate by addition of water or aqueous acid provides the free boronic acid (Scheme 10).

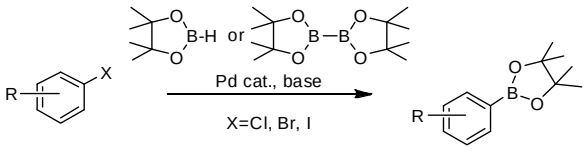
Scheme 10: Formation of boronic acids from organolithium or Grignard reagents by transmetallation and hydrolysis.



Boron is a metalloid element in nature, so the carbon-boron bond possesses a strong covalent character. As a result, aryl boronic acids are readily isolatable, often as crystalline solids which are relatively insensitive to air and moisture. Unlike the air and moisture sensitive organolithium, Grignard and cuprate species discussed above, these boronic acids do not require immediate use after *in situ* preparation. Aryl-boronic acids produced by this method have been reported in good to excellent yields, although these yields are highly dependent upon the substrate.

Aryl boronate esters can be prepared directly from the corresponding aryl halide through the coupling of a diester borane, such as pinacolato-borane, or bis-diester diboron compound, such as bis-pinacolato diboron.[68, 69] Couplings of this type require the use of a palladium catalyst and a base (Scheme 11).

Scheme 11: Direct coupling of diester borane/bisdiester diboron with aryl halide.



Numerous aryl-boronate esters containing a variety of functional groups have been prepared by this method in moderate to excellent yields depending upon substrates.[70-72] Purification of these esters has generally been achieved using chromatographic methods [70, 71] or by distillation.[72]

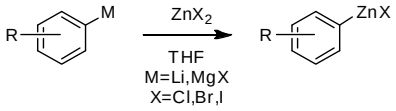
2.1.1.5 Organozinc derivatives (M=Zn).

The use of organozinc reagents in the formation of carbon-carbon bonds has seen increased interest following the successful use of such reagents in the Negishi cross-coupling.[73] Organozinc reagents are far less reactive and show increased thermal stability than corresponding Grignard or cuprate reagents.[43] As a result, a greater reaction selectivity and functional group tolerance is possible using organozincs compared to the less stable Grignards or cuprates.

The most common method for formation of aryl organozincs is *via*. transmetallation of the corresponding organolithium or Grignard reagents by addition of zinc (II) halides, including zinc chloride ($ZnCl_2$), zinc bromide ($ZnBr_2$) or zinc iodide

(ZnI_2).[43, 45, 74] These zinc salts are readily soluble in THF and can be added to a solution of organolithium or Grignard reagent as a solid or as a solution in THF (Scheme 12).

Scheme 12: Formation of organozincs by transmetallation.



The generated aryl organozinc is then used immediately after *in situ* preparation as a solution, usually in THF. The thermal stabilities of aryl organometallics allows for subsequent reactions to be carried out in hot solvent (up to 70 ^{o}C) without decomposition of the reagent.

2.1.2 Transition metal catalysis in cross-coupling reactions.

The subject of transition metal (TM) catalysis in cross-coupling reactions has been well reviewed numerous times [42, 75-77] and an in-depth discussion on the history, development and applications of such reactions is unnecessary. However, numerous references to such reactions are made throughout this thesis. On that basis, a short discussion of the relevant features of TM catalysis in cross-coupling reactions has been included to allow ease of reference to various factors in upcoming discussions.

2.1.2.1 General features of TM catalysis in cross-couplings.

The cross-coupling reactions relevant to this thesis involve the coupling of an organometallic species (R^1-M) with an organohalide or pseudohalide (R^2-X). Such cross-couplings forge a carbon-carbon bond between the two species (R^1-R^2) along with the generation of an inorganic salt (MX, Equation 1).

$R^1\text{-M} + R^2\text{-X} \rightarrow R^1\text{-}R^2 + \text{MX}$ (Equation 1).

Couplings of this type are applicable to a large number of metallic species (M includes Mg, Zn, B, Sn, Si). Numerous halides/pseudohalides (X includes Cl, Br, I, OTf, OTs) can also be incorporated into such a reaction. A diverse range of coupling products is available by such methods. Aryl-aryl, [42] aryl-alkenyl,[78, 79] and alkenyl-alkenyl [80, 81] carbon-carbon bonds have all been formed by these methods to name but a few. The combination of the above factors have proved these

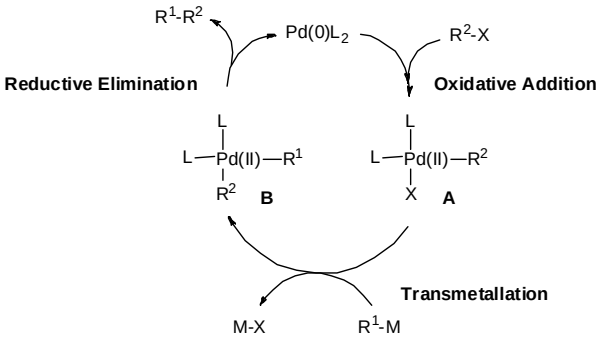
organometallic/halide coupling reactions to be a valuable and versatile tool to the synthetic chemistry community.

The use of TM catalysts, particularly palladium (Pd) [82, 83, 84, 85] or nickel (Ni) [82, 86] reagents can dramatically increase the observed rates and yields of these cross-coupling reactions. A variety of Pd and Ni catalysts have been applied to the cross-coupling of numerous organohalides and organometallic reagents. Historically, a number of named coupling reactions in this field have arisen. The names applied to such reactions are based upon the type of organometallic reagent used and the original author(s). Of particular note are the couplings involving organoboron reagents (the Suzuki-Miyaura or Suzuki reaction),[87] Grignards (the Kumada-Tamao-Corriu or Kumada coupling),[88] organozinc reagents (the Negishi coupling) [73] and organotin reagents (the Stille coupling).[89] At present, references to these named coupling reactions number in the thousands, and have been applied to the formation of most types of carbon-carbon bonds that can be formed within the scope of the organometallic/halide cross coupling protocols. Thus the synthetic power of TM catalysis is well established.

2.1.2.2 The TM catalytic cycle.

Both palladium and nickel reagents catalyse these cross-coupling reactions through a three step catalytic cycle. A typical literature catalytic cycle for Pd is shown below (Figure 1).[75, 76] This cycle can also be applied to Ni by replacement of the Pd centre by this atom.

Figure 1: Catalytic cycle of Pd in organometallic/halide cross coupling reactions.



Initially, a Pd(0) centre attached to two ligands (L=ligand) undergoes oxidative addition into the carbon-halogen bond of the organohalide (R^2-X) to form the tetra-

coordinate Pd(II) complex **A**. Next, transmetallation of the organometallic derivative (R^1-M) to the Pd centre forms complex **B** with the release of the salt M-X. Finally, reductive elimination occurs to restore the original $Pd(0)L_2$ complex along with the release of the cross-coupled product R^1-R^2. The regenerated $Pd(0)L_2$ can now participate in further catalytic cycles.

The catalytic cycle shows the power of Pd or Ni catalysts in terms of increasing yield and reaction rates of these types of couplings. Through binding to the metallic centre of the catalyst, the two reactive centres of the coupling reagents are in close proximity and correct geometry to allow for reductive elimination, and hence the cross-coupling, to proceed.

For most Pd or Ni catalysts, it has been well established that the relative rates of oxidative addition for organic halides increases down the period. That is, in order of fastest to slowest I>Br>Cl>>F.[42, 75, 76] As oxidative addition of the TM catalyst is often the rate-determining step of the catalytic cycle, the choice of halide often plays a key role in the coupling reaction rate. [76] The rate of oxidative addition is also highly dependent upon any substituents on the organic halide. For example, the rate of oxidative addition of aryl halides is increased by the presence of electron withdrawing substituents, with the converse seen for electron donating substituents.[76]

The transmetallation and reductive elimination steps are less important to the context of the discussions presented in this thesis. They are also less well understood than the oxidative addition step. There exists a few references whereby couplings of the same substrates have been carried out using several metal centres,[90, 91] but there is no conclusive evidence that any metal centre is better than another in different situations. The use of bulky ligands on the catalyst centre [84, 91, 92] appears to increase the rate of reductive elimination. Apart from these observations, further discussions of these two steps are beyond the scope of this thesis.

2.1.2.3 Catalysts and catalyst ligands.

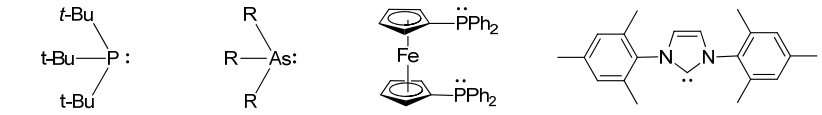
A plethora of different catalysts have been applied to organometallic-organohalide type cross-couplings and as a consequence only Pd catalysts will be discussed here. Certainly the most popular catalyst for such couplings has been tetrakis(triphenylphosphine)Pd(0) ($Pd(PPh_3)_4$).[65-67] In order to allow catalytic

activity, $Pd(PPh_3)_4$ undergoes *in situ* dissociation of two triphenylphosphine ligands to provide a $Pd(0)L_2$ type species, which can undergo oxidative addition and hence exhibits catalytic activity.

While $Pd(PPh_3)_4$ has been popular as a catalyst, it suffers from moisture and air sensitivity which leads to reproducibility and handling issues. Therefore there have been significant efforts to find more effective catalysts that are more easily handled.

Both Pd(0) and Pd(II) catalysts containing a multitude of different ligands have been applied to organometallic-organohalide coupling systems. The ligands attached to the Pd centre play an important role in the activity of the catalyst. Informative discussions of ligand effects can be found in several references and the reader should consult them for detailed information.[42, 76, 91, 93] Monodentate phosphines, such as phenylphosphine or alkylphosphine, are by far the most commonly used ligands for Pd complexes.[65-67, 83, 84] Along with monodentate ligand catalysts like $Pd(PPh_3)_4$, bidentate ligand catalysts, in which the ligand is complexed to the Pd centre through two co-ordination sites, also show activity towards cross-coupling catalysis.[69, 70, 85] Phenylarsene and alkylarsene ligands have also been utilised. [94] More recently Pd complexes containing *N*-heterocyclic carbene ligands have shown excellent activity in the catalytic cycle.[91, 95] Some examples of these different types of ligands are shown below (Figure 2).

Figure 2: Ligands employed in Pd catalysts.



tris(*t*-Bu)phosphine
An alkylphosphine

R= Ar, Alkyl
Arsene ligands

dppf
A bidentate phosphine

I-Mes
An *N*-heterocyclic carbene ligand

The catalytic cycle (Section 2.1.2.2, Figure 1) requires a $Pd(0)L_2$ type catalyst to initiate the cycle. Pd(II) catalysts therefore require reduction to Pd(0) catalysts in order for initiation. This reduction is generally achieved by reaction of the Pd(II) centre with the organometallic coupling partner (R^1-M) in an oxidation-reduction reaction to give the desired Pd(0) species. The homo-coupled product R^1-R^1 is obtained as a byproduct in this reaction (Equation 2).

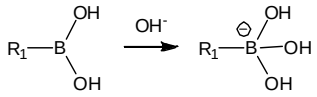
$2R^1\text{-M} + Pd(II)L_2X_2 \rightarrow R^1\text{-}R^1 + Pd(0)L_2 + 2MX$ (Equation 2).

This reduction step is often referred to as the activation step as the inert Pd(II) centre is activated to the catalytically active Pd(0) species.[91, 96]

2.1.2.4 Variations of the catalytic cycle for the Suzuki reaction.

In the cases of the Negishi or Kumada couplings, the metallic species undergoes transmetallation to the Pd centre without the requirement for any additives to induce transmetallation. In contrast, the Suzuki reaction requires the addition of a base in order to activate the boron centre towards transmetallation. Tri-coordinate boron species such as boronic acids or boronate esters are not intrinsically nucleophilic and do not undergo transmetallation to the Pd(II) centre. Therefore the addition of a base, such as NaOH or K_2CO_3, is required to activate the boron centre to the tetracoordiante "boronate" species, which does undergo transmetallation. This is shown in Scheme 13 using OH^- as the base. Both aqueous and anhydrous bases have been successfully applied to Suzuki cross-couplings.

Scheme 13: Activation of a boronic acid to the "boronate" species by hydroxide ion.



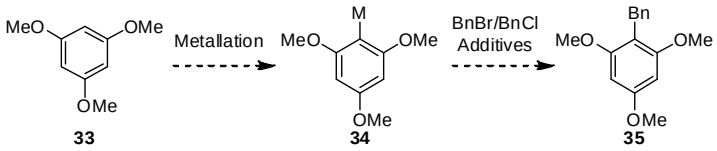
2.1.3 Aims.

The potential cross coupling pathway towards 4→8 dimers (section 2.1) provided a difficult challenge in terms of lack of literature precedents for metallation of the C8-position of catechin derivatives. The overall steric bulk around both the electrophilic and nucleophilic partners also posed further challenges. As a result, the earlier described model cross coupling (Section 2.1, Scheme 2) was established to examine the potential use of various metallic reagents without interference of the steric or electronic issues posed by the catechin derivatives.

Therefore the initial aim of the project was to establish which metallic derivatives of 1,3,5-trimethoxybenzene (**34**) were applicable in the coupling with BnBr or BnCl. The use of any additives such as transition metal catalysts in order to optimise the coupling was also proposed. Thus the aims of this chapter were to establish the

optimal metallic derivatives for performing the model cross-couplings and identify any additives that may optimise the coupling procedure (Scheme 14).

Scheme 14: Proposed model cross-coupling system.



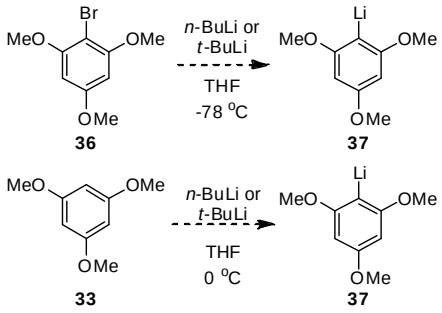
2.2 Results and discussion.

The first task undertaken was to study the formation of a variety of organometallic derivatives of 1,3,5-trimethoxybenzene (**33**, TMB). Only following the successful formation of the organometallics could the coupling of such derivatives with BnBr or BnCl be examined further. The metals (or metalloids) proposed for screening at this point were lithium, magnesium, copper, boron and zinc. The formation and coupling of each of these derivatives are discussed in this order below.

2.2.1 Studies in preparation and coupling of organolithium derivatives (Li-TMB).

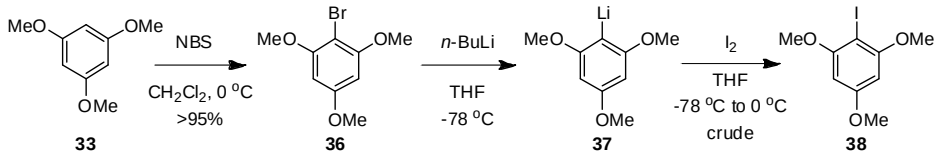
The formation of the organolithium derivative of 1,3,5-trimethoxybenzene (**37**, Li-TMB) was considered first for the model system as it was perhaps the most readily available. After taking into consideration the methods for forming aryllithium reagents (Section 2.1.1.1), two pathways towards the formation of Li-TMB **37** were considered viable. The first method was the low temperature lithium-halogen exchange of 1-bromo-2,4,6-trimethoxybenzene (**36**, Br-TMB) using *n*-butyllithium (*n*-BuLi) or *tert*-butyllithium (*t*-BuLi) as the lithiating agent and THF as the reaction solvent. The second involved the directed *ortho*-lithiation of TMB **33** using *n*-BuLi or *t*-BuLi in THF (Scheme 15).

Scheme 15: Potential methods for formation of Li-TMB 37.



Numerous methods for Li-TMB **37** formation based around these two pathways were examined. In particular the starting material, lithiating agent, solvent and temperature effects were studied. The optimised method for Li-TMB **37** formation was through a slow addition of a slight excess (1.1 equivalents) of *n*-BuLi to a stirred solution of Br-TMB **36** in THF at -78 ^{o}C. Prior to forming Li-TMB **37** using this method, the starting material, Br-TMB **36**, was synthesised by electrophilic aromatic bromination of TMB **33** using 1 equivalent of *N*-bromosuccinimide (NBS) in CH_2Cl_2.[97] Br-TMB was typically prepared in 95% plus yields using 10-15 grams of **33**, after crystallisation of **36** from EtOAc. The activity of Li-TMB **37** formed by the above method was determined by the addition of excess iodine (I_2) to a preformed solution of Li-TMB **37** at -78 ^{o}C and warming to 0 ^{o}C over 1 hour. Aqueous quenching of this reaction provided crude 1-iodo-2,4,6-trimethoxybenzene (**38**, I-TMB) as the sole product (Scheme 16).

Scheme 16: Synthesis of Br-TMB 36, its subsequent lithiation and quenching with I_2.



The product of this reaction was confirmed to be I-TMB **38** by analysis of the crude ^{13}C NMR. A peak at 66.5 ppm was attributed to the *ipso* carbon and matched that reported by Higgs *et al* for the carbon-iodine bond of this compound.[98] Importantly, no peak at 89 ppm in the crude ^{13}C NMR was observed. The absence of this peak indicated no Br-TMB **36** starting material was present, showing that complete bromine to lithium exchange had occurred. This iodine quenching showed that Li-TMB **37** was indeed forming and was reactive towards an electrophile.

During the optimisation of Li-TMB **37** formation, numerous other methods for TMB **33** lithiation were attempted with mixed results. The directed *ortho*-lithiation of **33** (Scheme 15) using *n*-BuLi was not reliably repeatable using 100-200 mg of **33**. Repeatability of lithiation by this method greatly increased with larger reaction scales and was highly useful for forming Li-TMB **37** using gram quantities of TMB **33**. This effect had important implications that will be discussed later. The use of Et_2O as

a reaction solvent was dismissed because TMB **33** or Br-TMB **36** showed poor solubility in this medium. The use of *t*-BuLi also gave successful results, but *n*-BuLi was used as the preferred lithiating agent as it was safer to handle and cheaper.

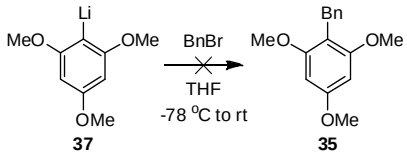
An interesting change was observed upon the addition of *n*-BuLi to Br-TMB **36**. When the reaction was performed at 0.2 M or higher concentration, a white, cloudy precipitate formed approximately 1-5 minutes following completion of the *n*-BuLi addition. The identity of this precipitate was never confirmed, but it was suspected to be lithium bromide (LiBr). This salt was thought to form by the displacement reaction of *n*-BuLi with 1-bromobutane (*n*-BuBr) formed following lithium-bromine exchange (Equation 3). *N*-Octane was also produced in this displacement.

n-BuLi + *n*-BuBr → LiBr + *n*-octane (Equation 3).

Following complete lithium-bromine exchange to form Li-TMB **37**, the excess *n*-BuLi used in the exchange was consumed in this displacement reaction to form LiBr, which precipitated at -78 ^{o}C. Occasionally precipitation did not occur after *n*-BuLi addition. In these cases, the resulting clear, colourless Li-TMB **37** solution formed reacted with electrophiles far less consistently compared to those reactions when a precipitate was observed. This lack of precipitate was often observed when using an old solution of *n*-BuLi, which may have lost some activity over time. This suggested complete lithiation may not have occurred, and so no LiBr precipitate was observed. The precipitation of LiBr was used as an indicator to completion of the lithium-bromine exchange to provide Li-TMB **37**. With confidence that Li-TMB was forming and was reactive towards electrophiles, attention then turned towards the coupling of this species to BnBr.

The coupling of Li-TMB **37** to BnBr was initially attempted by formation of **37** in THF at -78 ^{o}C, followed by addition of BnBr and stirring at this temperature for 4 hours before slow warming to room temperature overnight. Under these conditions, no-cross coupling product was obtained. Only TMB **33** and unreacted BnBr were recovered following aqueous quenching (Scheme 17).

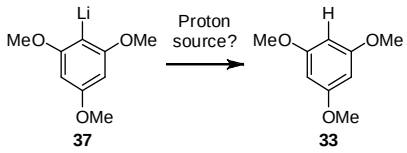
Scheme 17: Failed coupling of Li-TMB 37 with BnBr.



As no Br-TMB **36** was found in the reaction mixture, this result suggested that the Li-TMB **37** was forming prior to the addition of BnBr, but no reaction occurred between the two species. As a result, the addition of water quenched the organolithium to afford TMB **33**. In an effort to affect the coupling, numerous conditions were trialled. These included changing the solvent to THF/Et_2O mixtures, conducting the reaction at -78 ^oC, -40 ^oC or 0 ^oC, and distillation of BnBr over $CaCl_2$ prior to use. In all cases, no coupled product was obtained, with only **33** and BnBr obtained after quenching. While it was unclear why no coupling occurred, it was suspected that the organolithium was quenching *via.* protonation from some unknown source at a temperature lower than what was required for successful reaction with the BnBr (Scheme 18). As a result, the BnBr remained in the reaction mixture unchanged.

So it was concluded that the organolithium Li-TMB **37** was not an appropriate organometallic reagent for the model cross-coupling reaction and attention was then focussed upon the formation and coupling of the Grignard derivative of TMB.

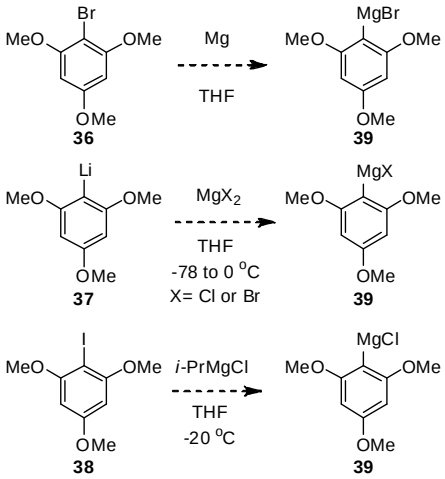
Scheme 18: Deactivation of Li-TMB 37 through protonation.



2.2.2 Studies towards the formation and coupling of Grignard reagents.

Magnesium was the next metal chosen for screening due to its high reactivity and numerous potential pathways for formation (Section 2.1.1.2). Three viable pathways to the formation of the desired Grignard reagent were identified. These were direct insertion of Mg into Br-TMB **36**, transmetallation of Li-TMB **37** using $MgCl_2$ or $MgBr_2$, or through magnesium-halogen exchange of I-TMB **38** using *iso*-propylmagnesium chloride (*i*-PrMgCl) (Scheme 19).

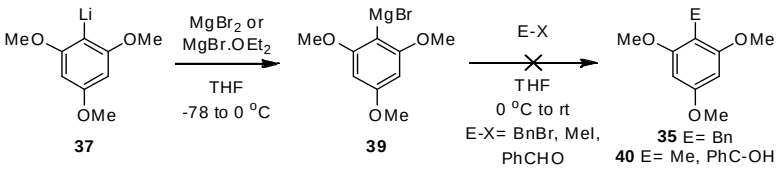
Scheme 19: Potential pathways towards the formation of Grignard reagent 39.



Given that the corresponding Li-TMB **37** had been studied previously (Section 2.2.1), transmetallation of this species to the corresponding Grignard, (**39,** MgBr-TMB), was attempted initially. It was thought the Li-TMB **37** would be readily reactive towards this transmetallation.

Attempts to form Grignard **39** by transmetallation of Li-TMB **37** using $MgCl_2$ were not successful due to the insolubility of $MgCl_2$ in THF at any temperature. $MgBr_2$ and $MgBr_2.OEt_2$ were also employed as the transmetallation salts. When these salts were added to a preformed solution of Li-TMB **37** in THF at -78 ^oC, no dissolution was observed. The Mg salts dissolved upon warming the reaction mixture to *ca*. 0 ^oC, which provided a clear, yellow solution of presumably the desired Grignard. Attempts to couple this suspected Grignard to a variety of electrophiles, including BnBr, methyl iodide (MeI), and benzaldehyde (PhCHO) failed to afford any cross-coupled products. TMB **33** was recovered along with unreacted electrophile (except MeI) following aq. NH_4Cl quenching (Scheme 20).

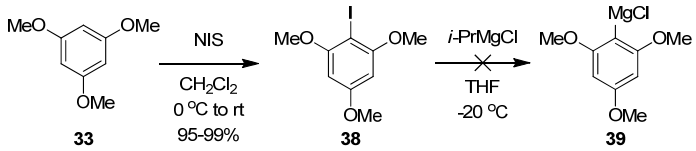
Scheme 20: Attempted formation of Grignard 39 by transmetallation and failed couplings to electrophiles.



It was suspected that the Grignard was not forming under these conditions. Instead Li-TMB **37** was quenching through protonation (Scheme 18) to form TMB **33** during the warming period following addition of the magnesium salt, and the salt dissolved at some point after protonation. As a result, no Grignard was available to participate in coupling with any electrophile. Hence, they were recovered after acidic quenching, except for MeI, which was removed during solvent evaporation.

Access to Grignard **39** was also attempted *via.* a magnesium-halogen exchange of I-TMB **38** using *i*-PrMgCl as conducted by Knochel *et al* (Section 2.1.1.2).[55] In order to investigate this exchange, the starting iodide, I-TMB **38,** was required. This iodide was repeatedly prepared in 10-15 gram quantities in almost quantitative yields through iodination of TMB **33** with one equivalent of *N*-Iodosuccinimide (NIS) in CH_2Cl_2 or acetone (Scheme 21).

Scheme 21: Synthesis of I-TMB (38) and subsequent magnesium-halogen exchange attempts using *i*-PrMgCl.



Initial attempts to produce the desired Grignard **39** *via*. the magnesium-halogen exchange of I-TMB **38** using Knochel's conditions (dropwise addition of 1.05 equivalents of *i*-PrMgCl at -20 ^{o}C in THF) gave no reaction. The starting iodide was recovered almost quantitatively (Scheme 21).

Following the initial result, numerous alterations to the reaction conditions were made in order to achieve the conversion. These included changes of temperature (-78 ^{o}C, -40 ^{o}C, 0 ^{o}C, room temperature, 60 ^{o}C), reaction times (1 hr, 2 hrs, 6 hrs), the use of Br-TMB **36** in place of I-TMB **38**, and the use of ethylmagnesium bromide (EtMgBr) in place of *i*-PrMgCl. In all cases only the starting iodide or bromide was recovered. This lack of reactivity was attributed to the presence of the electron donating methoxy groups around the TMB aromatic core. Numerous works by Knochel [55, 56] and others [57] have suggested that electron donating groups *ortho* and *para* to the halide impede the exchange reaction. The desired magnesium-halogen exchange was prevented by the strongly electron donating methoxy substituents in

the *ortho* and the *para* positions of halides **36** or **38**. As a result, this method for Grignard formation was not considered viable and direct magnesium insertion was attempted to produce the desired Grignard **39**.

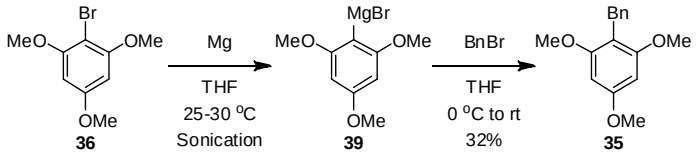
The formation of the Grignard **39** by direct insertion of magnesium into Br-TMB **36** was by far the most direct route to the desired organometallic. Despite this, this method was only used as last resort as it was viewed as the least likely method to succeed due to the electron rich nature of the TMB aromatic core, which greatly reduced the activity of the carbon-bromine bond towards metal insertion. In a final effort to form the Grignard **39**, numerous attempts were made to induce the insertion. Initial attempts at direct insertion using excess magnesium ribbon in THF or THF/Et_2O at room temperature or 70 ^oC, using iodide and/or 1,2-dibromoethane to activate the magnesium, failed to achieve any insertion. In all cases the starting bromide **36** was recovered almost quantitatively following aq. NH_4Cl quenching. This further suggested the TMB aromatic core was too deactivated to allow Mg insertion.

Direct magnesium insertion of Br-TMB **36** was successfully achieved through the application of sonication. Through sonication of a solution of **36** in THF at 25-30 ^oC containing magnesium turnings, a clear, colourless solution of Grignard **39** was obtained.

Addition of one equivalent of BnBr to an aliquot of prepared solution of **39** at 0 ^oC and warming to room temperature over 24 hours afforded the desired cross coupled product 1-benzyl-2,4,6-trimethoxybenzene (**35**, Bn-TMB) in low yield (32%) after SiO_2 purification (Scheme 22).

The use of sonication therefore provided a pathway to the desired Grignard **39** where convectional heating had failed. It was also possible to couple this Grignard to BnBr to afford the model coupling product Bn-TMB **35**, albeit in low yield. No further optimisation of this coupling was conducted, as by the time sonication was investigated as an insertion aid, better results for the model cross-coupling were obtained using other metallic centres.

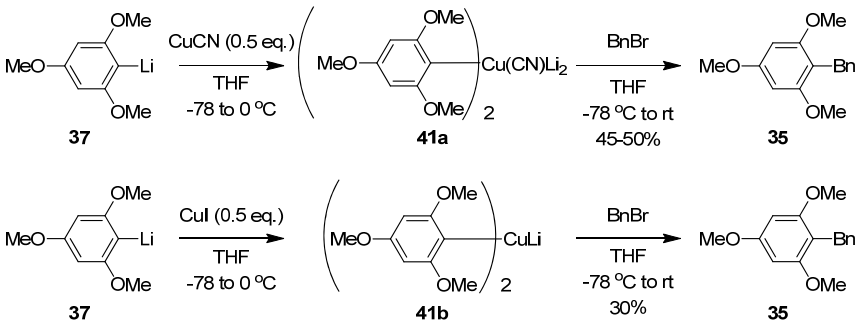
Scheme 22: Magnesium insertion into Br-TMB 36 using sonication and subsequent coupling to BnBr.



2.2.3 Studies in formation and coupling of organocuprate substrates.

As little or no success was achieved in the model cross-coupling reaction using either lithium or magnesium as the metallic centre, copper was investigated as an alternative metal. The desired organocopper reagent could be readily formed from the previously described Li-TMB **37** (Section 2.2.1) using a low temperature transmetallation process by addition of either copper (I) cyanide (CuCN), or copper (I) iodide (CuI) to Li-TMB **37** in THF. Initially, the formation of the diarylcuprate from both copper sources was attempted (Section 2.1.1.3). In order to form the diarylcuprate from either copper source, 0.5 equivalents of the copper (I) reagent was added as a solid to a preformed solution of Li-TMB **37** at -78 °C. At this temperature the copper salts did not dissolve. Upon warming the mixture in an ice bath to 0 °C, the salts dissolved to provide the diarylcuprate species (**41a, b**) as a homogeneous, yellow solution for **41a** and a dark yellow/brown solution for **41b**. The cuprate formed from either source was immediately cooled to -78 °C and one equivalent of BnBr (with respect to the cuprate) was added and the resulting mixture was allowed to warm to room temperature over 4 hours. Following quenching, purification by silica chromatography and concentration, the desired coupling product, Bn-TMB **35**, was obtained as a white, powdery solid (Scheme 23).

Scheme 23: Formation of diarylcuprates 41 from Li-TMB 37 and coupling to BnBr.



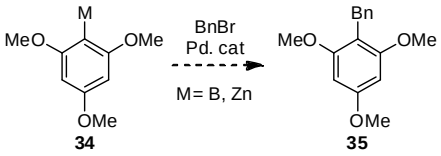
The yield and consistency of coupling was strongly dependent upon the copper salt employed. Using CuCN, coupling yields of 45-50% were repeatedly obtained. In contrast, coupling yields did not exceed 30% for the CuI derived cuprate coupling reactions, and results were highly variable. These repeatability issues were principally attributed to the lower stability and higher hygroscopic nature of the CuI salt compared to CuCN. Considering the relative stabilities, it was not surprising that more consistent and better results were obtained using the CuCN derived cuprate.[61]

While a coupling yield of 45-50% was promising at this point, the use of the diaryl cuprate was not desirable, as only one of the TMB ligands were transferred from the copper complex to the BnBr electrophile. The second TMB ligand was not reactive. This second ligand was surplus to requirements for the coupling and therefore the coupling was viewed as inefficient from an atom economy and purification stand point, as the product required separation from the second TMB unit following quenching. While this was not a significant issue when working with inexpensive TMB derivatives, it was most limiting when considered for the synthesis of 4→8 catechin dimers (Section 2.1). As more expensive and harder to obtain starting materials would be required for the 4→8 dimer, synthesis using the cuprate approach was considered inappropriate for such coupling. With this in mind, the cuprate coupling using the model system was not explored any further. The use of dummy ligands as employed by Lipshutz *et al* [61, 62] was considered. This line of investigation was never examined as it was decided it would be of greater use in the scheme of the model cross-coupling development to explore other metallic centres. As a result, attention turned away from copper as the metallic centre and was focussed upon the use of boron and zinc in conjunction with transition metal catalysts in order to optimise the model coupling system.

2.2.4 Formation of organoboron compounds and Pd-catalysed couplings.

Both arylboron and arylzinc compounds have been shown to undergo cross-couplings to benzylic halides in the presence a variety of Pd (0) and Pd (II) catalysts (Section 2.1.2.1). Given that the direct halide displacement of BnBr using the lithium **37**, magnesium **39** and copper derivatives **41** of TMB failed to give satisfactory results, these more complex Pd-catalysed reactions were considered appropriate alternatives towards the model cross-coupling (Scheme 24).

Scheme 24: Proposed Pd-catalysed model cross-coupling with organoboron or organozinc compounds.

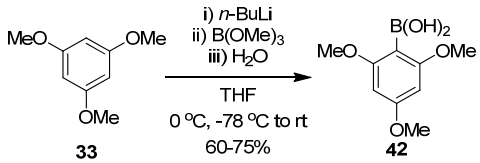


The couplings involving the organoboron derivative **42** were investigated first. This was principally due to a larger number of literature precedents for Suzuki cross-couplings (Section 2.1.2.1) involving arylboronate species with benzylic halides [99-101] compared to that for the analogous Negishi cross-coupling.[83, 102] The wider literature scope for the Suzuki coupling allowed greater capacity for the optimisation of the model coupling system.

Before any Suzuki cross-couplings were attempted, an appropriate organoboron species was required. Arylboronic acids have been used extensively in Suzuki cross-couplings and have been shown to be readily available from aryllithium reagents by transmetallation with trialkyl borate esters (Section 2.1.1.4). This seemed the obvious method to form 2,4,6-trimethoxyphenylboronic acid (**42**, TMB-B(OH)$_2$) as the required starting material, Li-TMB **37**, was readily prepared (Section 2.2.1).

The synthesis of TMB-B(OH)$_2$ **42** required some optimisation. In the optimal procedure, directed *ortho*-lithiation (Section 2.1.1.1) of TMB **33** using *n*-BuLi at 0 ^{o}C in THF for two hours provided the desired organolithium **37**. Transmetallation of **37** through the addition of B(OMe)$_3$ and subsequent hydrolysis with water provided the desired TMB-B(OH)$_2$ **42** in good yields (70-75%) after crystallisation when using 5-15 grams of TMB **33** (Scheme 25).

Scheme 25: Formation of TMB-B(OH)$_2$ 42 from TMB 33 by directed *ortho*-lithiation, transmetallation and hydrolysis.

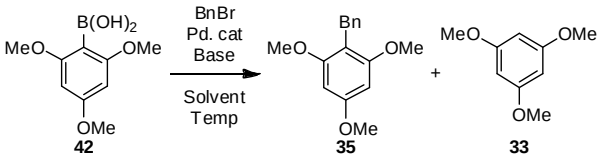


Success of the transmetallation step, and hence the final yield of the boronic acid, was strongly dependent upon the reaction scale. Using either directed *ortho*-lithiation

of TMB **33**, or lithium-bromine exchange of Br-TMB **36** using 100-200 mg of starting material, only traces of boronic acid **42** were detected following hydrolysis. Increasing the scale to *ca*. 1 g gave the boronic acid in low (20-30%) yields after hydrolysis. Further increasing the scale to 5 g and higher provided boronic acid **42** in far more acceptable yields (>60%). As described in section 2.2.1, the formation of Li-TMB **37** by directed *ortho*-lithiation was not reliable at small scales, but worked well when conducted at larger scales. Accordingly, directed *ortho*-lithiation was the preferred method for forming Li-TMB **37** when using 5 grams or more of **33**. Following hydrolysis and concentration, the crude reaction residue contained both the desired boronic acid **42** and TMB **33**, formed by the hydrolysis of any residual Li-TMB **37** that did not undergo transmetallation. TMB-$B(OH)_2$ was readily purified by careful, selective crystallisation from $CHCl_3/Et_2O$ to provide boronic acid **42** as a white, crystalline solid.

With TMB-$B(OH)_2$ **42** routinely available in large quantities, the coupling of this boronic acid with BnBr was attempted under a variety of conditions to determine the potential of the Suzuki coupling protocol for the model system (Scheme 26).

Scheme 26: Suzuki cross-coupling of TMB-$B(OH)_2$ 42 with BnBr.



Using the standard coupling conditions, the base, catalyst, temperature and solvents were varied across numerous couplings. The results of these couplings are shown in Table 1.

Table 1 clearly shows that use of anhydrous base under any conditions (entries 1-6) failed to provide any cross-coupled product. In these cases only TMB **33**, formed by the deboronation of TMB-$B(OH)_2$ **42**, was isolated following quenching. When aqueous basic conditions were employed (entries 7-9), the cross-coupled product **35** was obtained in very low yields. The use of stronger bases in aqueous solution, such as $Ba(OH)_2$ (entry 8), or NaOH (entry 9) resulted in higher coupling yields compared to the weaker base Na_2CO_3 (entry 7). This is consistent with the results of Thompson *et al*,[66] who showed that aryl boronic acids with two *ortho* groups coupled to

electrophiles with improved yields using the stronger base $Ba(OH)_2$, as opposed to the weaker Na_2CO_3. In the cases of entries 6-8, TMB was the major byproduct along with what was assumed to be unreacted BnBr. The presence of BnBr was assumed because a UV active spot developed at the same R_f seen for BnBr through TLC analysis of the crude reaction mixtures. The identity of the compound that gave the TLC spot assumed to be BnBr was never confirmed. The product (**35**, Bn-TMB) was readily isolated from these by-products using silica gel chromatography.

Table 1: Results of Suzuki cross-couplings of TMB-B(OH)$_2$ (42) with BnBr.

Entry [a]	Solvent	Catalyst	Base	Temp (^oC)	Yield of 35 (%) [b]
1	$PhCH_3$	$Pd(OAc)_2/PPh_3$	K_3PO_4	110	0
2	Acetone	$PdCl_2$	K_2CO_3	60	0
3	Acetone	$PdCl_2$	K_2CO_3	rt	0
4	THF	$Pd(PPh_3)_2Cl_2$	CsF	60	0
5	THF	$Pd(PPh_3)_2Cl_2$	NaOH	60	0
6	DME	$Pd(PPh_3)_4$	NaOH	90	0
7	DME/EtOH/H_2O [c]	$Pd(PPh_3)_4$	Na_2CO_3	90	5
8	DME/EtOH/H_2O [c]	$Pd(PPh_3)_4$	$Ba(OH)_2$	90	10
9	DME/EtOH/H_2O [c]	$Pd(PPh_3)_4$	NaOH	90	20

[a]: Standard coupling conditions: 100 µL BnBr, 1.5 equiv. TMB-B(OH)$_2$ **42**, 3 equiv. base, 5 mol% catalyst, 10 mL solvent. All reactions were stirred in the specified solvent for 24 hours at the specified temperature before being cooled to rt and quenched by addition of sat. aq. NH_4Cl.

[b]: Isolated yield following column chromatography. 0% yield indicates no product (**35**) was detected by ^1H NMR analysis of the crude reaction mixture.

[c]: DME (6 mL)/EtOH (3 mL)/H_2O (1 mL).

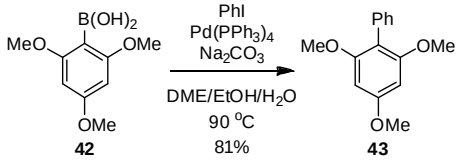
Two possible factors were identified as playing a potential role in hindering the coupling reaction. Firstly, aryl boronic acids containing electron rich substituents, especially in the *ortho* positions, tend to rapidly deboronate under basic conditions.[103] As a result, the amount of boronic acid available for coupling may have been reduced due to this side reaction. As it contained both *ortho* and *para* methoxy groups, TMB-B(OH)$_2$ **42** was an extreme example of an electron rich aryl boronic acid. As a result, **42** may have deboronated at a faster rate than the coupling

reaction proceeded. This pathway was likely in the aqueous coupling reactions (entries 7-9). In these cases, the water and ethanol components of the solvent may have promoted protolytic deboronation of **42**. Secondly, activation of the boronic acid to the "boronate" anion (Scheme 13) appeared to be an issue in the anhydrous coupling reactions (entries 1-6). In the cases of these attempted couplings, the added bases were not soluble and stirred as a suspension in the reaction mixtures. As a result, insufficient base may have been present in the reaction solution to facilitate the activation of **42** to its "boronate" anion. Without this activation, the transmetallation step (Section 2.1.2.2) of the Pd catalytic cycle could not occur, so no coupling product was produced.

In order to show the activity of boronic acid **42** in Suzuki cross-couplings, the coupling of this species with iodobenzene (PhI) was attempted. As a highly active electrophile in Pd-catalysed cross-couplings (Section 2.1.2.2), PhI was employed as an alternate electrophile to BnBr.

This coupling was conducted using $Pd(PPh_3)_4$ as the catalyst, aqueous Na_2CO_3 as the base and DME/EtOH/H_2O as the solvent. The reaction was stirred at 90 ^oC for 16 hours and quenched by the addition of sat. aq. NH_4Cl. Purification through SiO_2 chromatography afforded the desired 2,4,6-trimethoxybiphenyl (**43**, Ph-TMB) in 81% yield as a white, powdery solid following concentration (Scheme 27).

Scheme 27: Suzuki cross-coupling of TMB-B(OH)$_2$ 42 to PhI to provide Ph-TMB (43).



The successful coupling of PhI suggested that the use of BnBr as the electrophile in earlier couplings (Table 1) was also a factor in the poor coupling results obtained in those coupling reactions. It was possible that oxidative addition of the Pd catalyst (Section 2.1.2.2) into BnBr was problematic, or else BnBr was participating in an undetermined side reaction. What ever the case, these issues were not encountered when using PhI as the electrophile. So it seemed issues pertaining to BnBr or base

solubility were responsible for the poor coupling results reported in Table 1, as boronic acid **42** was reactive towards the Pd-catalysed coupling to PhI.

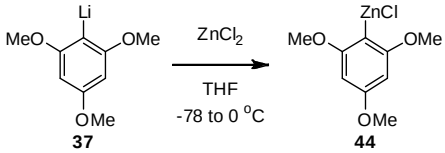
It was concluded that while the Pd-catalysed cross-coupling of TMB-$B(OH)_2$ **42** to BnBr can be achieved in low yields (5-20%) using $Pd(PPh_3)_4$ as a catalyst, the results were not sufficiently satisfactory to be considered further. As a result, attention was turned towards using the organozinc derivative of TMB as the organometallic partner of the model cross coupling.

2.2.5 Application of an organozinc derivative in the model cross coupling.

It appeared likely from the cross-couplings using the boronic acid derivative that the basic conditions required for the Suzuki method were not compatible with BnBr. The requisite organozinc derivative, 2,4,6-trimethoxyphenylzinc chloride (**44**, TMB-ZnCl) seemed a viable alternative to the boronic acid as organozinc derivatives also participate in Pd-catalysed cross-couplings, otherwise known as the Negishi reaction (Section 2.1.2.1). Importantly, organozincs do not require external activation (such as addition of base) to undergo transmetallation to the Pd centre. Accordingly, it was expected the issues encountered with boronic acid **42** should not exist with organozinc **44**.

The formation of TMB-ZnCl **44** was achieved by transmetallation of Li-TMB **37** using $ZnCl_2$ (section 2.1.1.5). To achieve this, a slight excess (1.1 equivalents) of $ZnCl_2$ was added to a pre-prepared Li-TMB **37** solution, either as a solid or as a solution in THF at -78 ^oC. Upon addition of 1 equivalent of $ZnCl_2$, the white LiBr suspension (Section 2.2.1) immediately disappeared, affording a clear, colourless solution of the assumed TMB-ZnCl **44**. This assumed TMB-ZnCl **44** solution was then ready to be used in Negishi cross coupling-reactions (Scheme 28).

Scheme 28: Formation of TMB-ZnCl 44 from Li-TMB 37 by addition of $ZnCl_2$.



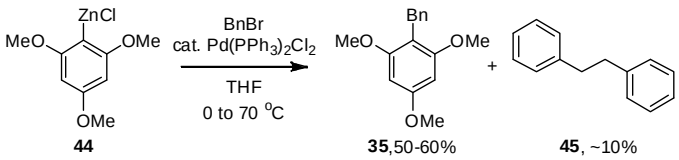
The dissolution of the white LiBr suspension was a useful visual cue for successful transmetallation. When adding the $ZnCl_2$ as solution in THF, the suspension

remained present until one full equivalent of $ZnCl_2$ was added. This provided a useful method for judging the completion of the transmetallation. The rapid transmetallation at -78 ^oC compared to $MgBr_2$ or CuCN was attributed to the solubility of the $ZnCl_2$ in THF compared to the other salts. When used as a solid, the $ZnCl_2$ dissolved immediately upon addition to a solution of Li-TMB **37** at -78 ^oC, and transmetallation took place rapidly. $MgBr_2$ (Section 2.2.2) and CuCN (Section 2.2.3) were not soluble at this temperature, and needed to be warmed in order for transmetallation to take place.

The success of the lithium to zinc transmetallation, and the subsequent coupling reactions to be discussed shortly, were highly dependent upon the quality of $ZnCl_2$ used. After trialling numerous grades, it was found the most consistent results were achieved using anhydrous $ZnCl_2$, purchased from Sigma-Aldrich (product no. 429430) in a sealed ampoule. Upon opening of an ampoule under N_2, the contents were dried *in vacuo* at room temperature for 1-2 hours to ensure complete dryness. The $ZnCl_2$ was then dissolved in sufficient THF to make a 1 M solution, which was stored under N_2 or Ar for up to a month without significant loss of activity.

With TMB-ZnCl **44** successfully prepared, attention turned to coupling this species to BnBr or BnCl. de Lang *et al* [83] had previously reported the use of $Pd(PPh_3)Cl_2$ as a catalyst in the coupling of aryl zinc derivatives with numerous benzylic halides. Accordingly, this catalyst was used in initial coupling attempts. Following formation of TMB-ZnCl (**44**) by the above method, it was then coupled to BnBr using $Pd(PPh_3)Cl_2$ (5 mol%) as the catalyst at 70 ^oC. The catalyst initially remained in suspension upon addition, but heating beyond *ca*. 30 ^oC caused dissolution to give a clear, bright yellow reaction mixture. Following quenching and purification by SiO_2 chromatography, the desired cross-coupled product (**35**, Bn-TMB) was obtained as a white, powdery solid (Scheme 29).

Scheme 29: $Pd(PPh_3)_2Cl_2$ catalysed coupling of TMB-ZnCl 44 with BnBr.



44 **35**,50-60% **45**, ~10%

After optimisation of the coupling, it was found using 1.5 equivalents of TMB-ZnCl **44** with respect to BnBr and 1-2 mol% of catalyst consistently afforded the desired Bn-TMB (**35**) in 50-60% yield as white solid after chromatography.

The yield of Bn-TMB **35** achieved by this method was by far the best obtained for the model cross-coupling. This reaction was, however, hampered by the formation of bi-benzyl (**45**) as a byproduct in *ca*. 10% yields with respect to BnBr. This byproduct was identified by the characteristic CH_2-CH_2 singlet observed at 2.91 ppm in ^{1}H NMR spectra of crude reaction mixtures.[104] This byproduct was readily separated from Bn-TMB **35**, so it posed no purification issues. It did however, account for why yields above *ca*. 60% were never obtained, as the BnBr was being consumed in this side reaction. Accordingly, it was considered a worthwhile task at this point to try to optimise the coupling by attempting to limit the production of this byproduct.

2.2.6 Optimisation of the organozinc model cross coupling.

In an effort to increase the yield of the Negishi cross-coupling, a variety of Pd(0) and Pd(II) catalysts were screened in the cross-coupling reaction. In parallel, benzyl chloride (BnCl) was also used in place of BnBr as the electrophilic coupling partner with some of the catalysts to determine if the nature of the halide had any effect on the reaction. In this catalyst screening, TMB-ZnCl **44** was prepared as a solution in THF, then the electrophile (0.7 equivalents) and the specified catalyst quantity were added and reactions stirred for the specified times and monitored by TLC for halide consumption. Results of these couplings are shown in Table 2.

From Table 2, it was apparent that the catalyst Pd(DPEPhos)Cl_2 (**46**), which contained the bidentate bis(*o*-diphenylphosphinophenyl)ether (DPEPhos) ligand, was by far the most effective catalyst in the cross coupling (entries 6 and 7) when employed at 70 ^{o}C. These conditions provided the desired product Bn-TMB **35** in excellent 85% yield. It was also apparent by comparison of entries 1 with 2, and 6 with 7, that the use of BnBr or BnCl did not affect coupling yields or reaction times. This strongly suggested that the oxidative addition of the catalyst into the benzyl halide was not the rate determining step of the Pd catalytic cycle (Section 2.1.2.2) and the outcomes of the reaction were similar regardless of the halide used. Also of note was that Pd(II) catalysts were generally more effective than the Pd(0) equivalents (compare entry 1 with 3, and 5 with 6). This was likely due to the overall

greater stability and reduced air sensitivity of Pd(II) complexes compared to similar Pd(0) compounds.[76, 77]

Table 2: Results of model system Negishi cross-couplings with various catalysts.

Entry	Electrop-hile	Catalyst	Loading (mol%)	Temp (^{o}C)	Time (hrs)	Yield [a]
1	BnBr	$Pd(PPh_3)_2Cl_2$	1	70	20	60
2	BnCl	$Pd(PPh_3)_2Cl_2$	1	70	20	61
3	BnBr	$Pd(PPh_3)_4$	4	70	20	55
4	BnBr	$Pd(dppf)Cl_2.CH_2Cl_2$ [b]	3	70	48	52
5	BnBr	$Pd(dba)_2$/DPEPhos [c,d]	5	70	2.5	64
6	BnBr	$Pd(DPEPhos)Cl_2$	1	70	1.5	84
7	BnCl	$Pd(DPEPhos)Cl_2$	1	70	1.5	85
8	BnCl	$Pd(DPEPhos)Cl_2$	1	20	48	19

[a]: Isolated yield of Bn-TMB after purification by silica chromatography.

[b]: Dppf= 1,1′-bis(diphenylphosphino)ferrocene.

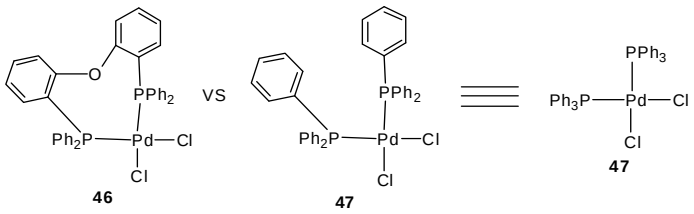
[c]: Dba= dibenzylideneacetone.

[d]: DPEPhos= bis(*o*-diphenylphosphinophenyl)ether.

The increased yield obtained when using $Pd(DPEPhos)Cl_2$ **46** compared to its monodentate ligand equivalent $Pd(PPh_3)_2Cl_2$ (**47**, Figure 3) was due to the fact no bi-benzyl **45** was formed using the bidentate catalyst. As a result, all the halide was available to participate in the cross-coupling reaction and an increased coupling yield was observed. Bi-benzyl **45** was also formed when $Pd(PPh_3)_4$, another monodentate ligand catalyst, was employed in the coupling (entry 3). The coupling yield was also higher when the bidentate ligand DPEPhos was employed (entry 5) when compared to the monodentate ligand catalyst $Pd(PPh_3)_4$ (entry 3). No bi-benzyl **45** was formed in the case of entry 5, and again accounted for the greater yield of Bn-TMB **35** obtained using this catalyst in comparison to $Pd(PPh_3)_4$. Clearly a monodentate *vs.* bidentate ligand effect was evident for the formation of the bi-benzyl byproduct **45**. An in-depth explanation of this ligand effect and how bi-benzyl arises as a byproduct is beyond the scope of this thesis and it is sufficient to state that bi-benzyl **45** is

formed using the monodentate PPh_3 based catalysts, but not when the bidentate DPEPhos based catalysts were used.

Figure 3: Structural comparison of $Pd(DPEPhos)Cl_2$ and $Pd(PPh_3)_2Cl_2$.



The greater effectiveness of the DPEPhos ligand with respect to PPh_3 was not mirrored when the bidentate ligand dppf (Figure 2) was employed (entry 4). This gave a very slow reaction despite the relatively high catalyst loading (3 mol%). Even after 48 hours BnBr was still present. The slow reaction was primarily attributed to the poor catalyst solubility in the reaction mixture. After addition and warming to 70 ^oC, the majority of the catalyst remained as a suspension. So in reality there was a far smaller effective catalyst loading than indicated in the reaction solution. Accordingly, the reaction proceeded slower than anticipated.

The cross-coupling was also attempted at room temperature (*ca*. 20 ^oC) using $Pd(DPEPhos)Cl_2$ in order to investigate the effect of temperature on the coupling reaction (entry 8). The coupling did not proceed efficiently at this temperature and only a 19% coupling yield was obtained. Even with the higher catalyst loading (5 mol%), a large proportion of BnCl was recovered after 48 hours. It was suspected the low yield was a result of poor catalyst solubility at this temperature. At *ca*. 20 ^oC, the $Pd(DPEPhos)Cl_2$ remained as a yellow suspension upon addition to the reaction mixture. Only when the reaction mixture was warmed to *ca*. 30 ^oC and higher did the catalyst dissolve. At this point it was concluded that the use of $Pd(DPEPhos)Cl_2$ was not effective as a catalyst at room temperature. It was later suspected that warming to allow dissolution and then cooling back to room temperature may have improved the efficiency of the reaction at this temperature. However this concept was never examined as the model coupling reactions were almost complete by the time this effect was contemplated.

In summary, the model cross-coupled product Bn-TMB **35** was successfully synthesised in 85% isolated yield *via*. a $Pd(DPEPhos)Cl_2$-catalysed Negishi cross-

coupling of BnCl with TMB-ZnCl **44**. This coupling method represents the highest isolated yield of the desired model coupling product for any of the organometallic species trialled. As a result, formation of the C8-organozinc derivative of catechin was the initial target for a C8-organometallic reagent in the cross couplings towards 4→8 catechin-catechin dimers. The formation and coupling of such a derivative is discussed in Chapter 3.

2.2.7 Extension of the organozinc coupling to other electrophiles.

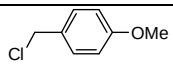
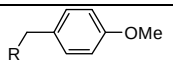
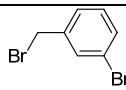
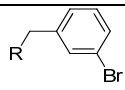
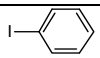
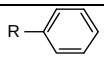
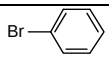
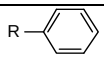
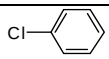
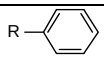
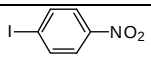
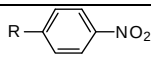
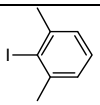
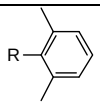
With the success of the Pd(DPEPhos)Cl_2-catalysed cross-coupling of TMB-ZnCl **44** to BnBr and BnCl, attention was focussed upon expanding the scope of the coupling to the use of other benzylic halides and also aryl halides. To achieve this, TMB-ZnCl **44** was coupled to a variety of benzyl and aryl halides containing both electron donating and electron withdrawing substituents. These couplings were carried out using the same reaction conditions as used for the aforementioned couplings of TMB-ZnCl **44** (Section 2.2.6), but with benzyl or aryl halides **48a-h** used in place of BnBr or BnCl. The results of these couplings are shown in Table 3 over page.

The results from Table 3 showed TMB-ZnCl **44** was effectively coupled to a variety of benzyl and aryl halides in moderate to good yields. The successful formation of products **49a** and **49b** indicated that the coupling protocol was applicable to benzylic halides containing both electron donating (entry 1) and electron withdrawing (entry 2) substituents on the aryl ring. These results also showed that the nature of the halide (Cl or Br) did not greatly affect reaction time, as both reactions were complete over similar time periods. This finding supported that found earlier for the couplings of BnBr and BnCl (Section 2.2.6, Table 2).

Interestingly, the coupling of 3-bromo-benzylbromide (entry 2) showed the protocol was selective towards the benzylic halide compared to aryl bromide substituent when the reaction was conducted at 40 ^{o}C. At 70 ^{o}C the benzyl coupled product (**49b**) was formed along with some bis-coupled product (**50**, Figure 4). While the reduced temperature resulted in a reduced coupling yield compared to other benzylic halides used (Section 2.2.6 and entry 1), the 55% isolated yield was quite acceptable considering the difficult nature of the coupling. Notably, this selective coupling of the benzylic bromide over the aryl bromide allowed the possibility for sequential couplings using this protocol. Once the coupling of the benzylic bromide was

complete, a second nucleophile could be added and the temperature increased to 70 ^{o}C, which would promote coupling of the aryl bromide.

Table 3: Pd(DPEPhos)Cl_2 catalysed cross couplings of TMB-ZnCl (44) with various benzylic and aryl halides.

Entry	Halide	Rxn Time (hr) [a]	Product [b]	Yield (%) [c]
1	 **48a**	4	 **49a**	68
2	 **48b**	3 [d]	 **49b**	55
3	 **48c**	5	 **43**	81
4	 **48d**	24	 **43**	77
5	 **48e**	24	 **43**	0
6	 **48f**	6	 **49c**	74
7	 **48g**	4	 **49d**	80
8	 **48h**	24-72	 **49e**	0

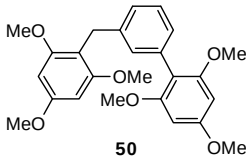
[a]: Reaction conditions: Halide, *ca.* 1 mmol; TMB-ZnCl (**44**), 1.5 equiv.; THF, 4-5 mL; Pd(DPEPhos)Cl_2, 1-2 mol%, 70 ^{o}C. Reactions were monitored by TLC for consumption of halide and quenched after the stated time by addition of dilute aq. HCl.

[b]: R = 2,4,6-trimethoxyphenyl.

[c]: Isolated yields following silica chromatography.

[d]: Conducted at 40 ^{o}C

Figure 4: Bis-coupled product 50 formed in coupling reaction of 3-bromo-benzylbromide.



50

Product **49b**, previously unreported, was identified by a combination of ^{1}H and ^{13}C NMR analysis and HRMS. The ^{1}H NMR singlets at 3.81 ppm (3 protons, *para*-OMe) 3.79 ppm (6 protons, *ortho*-OMe) and 6.16 ppm (2 protons, aromatic) showed that the trimethoxyphenyl portion of the molecule was mono-substituted, presumably at the carbon where the zinc centre had been attached. The key benzylic CH_2 resonances were observed at 3.91 ppm (2 protons) and 28.3 ppm for the ^{1}H and ^{13}C NMR spectra respectively. These shifts were consistent for a CH_2 group attached to two aryl rings. The ^{13}C resonance at 109.6 was assigned to the *ipso* carbon of the TMB moiety, which was consistent with it being attached to an alkyl carbon. HRMS of the product showed the molecular formula of **49b** was $C_{16}H_{17}BrO_3$, which matched that for the proposed structure.

The results of Table 3 also showed that the coupling protocol was applicable to the coupling of aryl halides. Both iodobenzene (**48c**, PhI, entry 3) and bromobenzene (**48d**, PhBr, entry 4) coupled to TMB-ZnCl **44** in good yield to provide Ph-TMB **43**. While comparable coupling yields were obtained using either halide, a far longer reaction time was required for complete consumption of PhBr compared to PhI. This suggested that the nature of the halide played an important role in the coupling of aryl moieties, and that the rate of coupling of the aryl halides was dependent upon the rate of oxidative addition of the Pd catalyst (Section 2.1.2.2) into the carbon-halogen bond. This contrasted the case of the benzylic halides, where the reaction rate was not dependent upon the nature of the halide. In the case of chlorobenzene (**48e**, PhCl, entry 5) no coupling product was obtained. This further suggested the nature of the aryl halide was important in this coupling. The lack of coupling product obtained using PhCl was not surprising, as chlorobenzenes have often been shown to be inert towards oxidative addition unless activated by strong electron withdrawing groups.[76, 105] Oxidative additions of unactivated aryl chlorides have been achieved through the use of highly active phosphine [84] and NHC ligands.[91] It is apparent that

DPEPhos was not sufficiently active as a ligand to allow oxidative addition of Pd(DPEPhos)Cl_2 into chlorobenzene.

The coupling of TMB-ZnCl **44** to substituted aryl halides was also attempted. Under the coupling conditions, aryl iodides containing both electron donating (entry 6) and electron withdrawing groups (entry 7) were successfully coupled in good yields and in reasonable reaction times. The nature of the substituent played an important role in the coupling rate. The electron deficient iodide, 4-iodonitrobenzene (**48g**, entry 7) coupled at a faster rate than the electron rich iodide, 2-iodotoluene (**48f**, entry 6). The effect of the substituent did not greatly affect the yield of the product obtained, as **43**, **49c** and **49d** were all isolated in similar yields.

The previously unreported **49c** was identified through the use of NMR and HRMS. The ^{13}C resonance at 112.1 ppm was assigned to the *ipso* carbon of the trimethoxyphenyl unit, which confirmed it was attached to an aryl group. The ^{13}C resonance corresponding to the carbon attached to iodine of the starting iodide at 101 ppm, [106] had shifted to 138 ppm. This indicated the starting iodide was consumed the new ^{13}C NMR peak was attributed to the *ipso* carbon of the newly formed aryl-aryl bond. Again, the singlets at 3.73 ppm (6 protons, *ortho*-OMe), 3.91 ppm (3 protons, *para*-OMe) and 6.27 ppm (2 protons, aromatics) in the ^{1}H NMR spectrum indicated the presence of the trimethoxyphenyl unit. Finally, the ^{1}H singlet at 2.12 ppm and the ^{13}C resonance at 19.9 ppm were attributed to the toluenyl CH_3 group. HRMS analysis of the product indicated a molecular formula of $C_{16}H_{18}O_3$, which matched that for the expected structure.

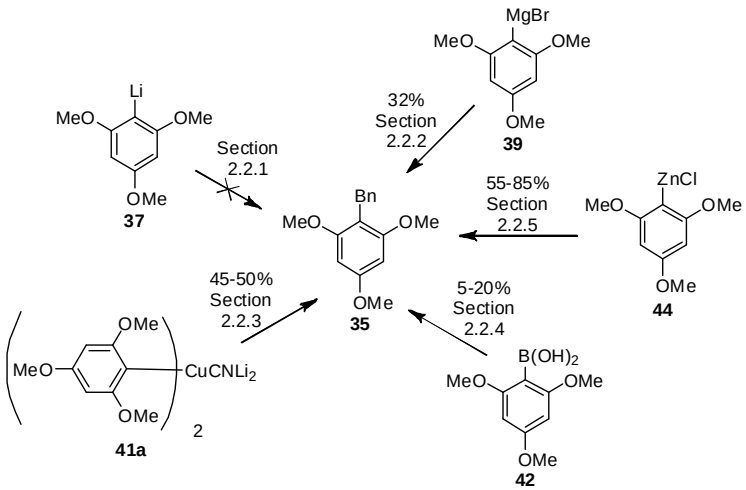
The cross-coupling was also attempted using 2,6-dimethyl-iodobenzene (**48h**, table 3, entry 8) in order to produce the hindered 2′,6′-dimethyl-2,4,6-trimethoxybiphenyl (**49e**). The formation of tetra-*ortho* substituted biaryls *via.* Pd-catalysed cross-couplings has traditionally been very challenging, with relatively few reports of such couplings compared to less hindered biaryls.[84, 91] Accordingly, this potentially challenging coupling was attempted to test the coupling protocol's limits. Unfortunately the coupling of **48h** to TMB-ZnCl **44** using Pd(DPEPhos)Cl_2 was not successful under any coupling conditions. The use of catalyst loading as high as 5 and 10 mol% failed to provide any coupling product. Neither did the use of 1,2-dimethoxyethane (DME) as the reaction solvent at 100 ^{o}C. In most cases, trace

amounts of a product suspected to be **49e** were seen in the NMR spectra of crude reaction mixtures, but never in quantities that could be isolated and identified. As a result, the cross-coupling to form **49e** was not pursued further and this concluded studies of the Pd(DPEPhos)Cl_2 catalysed Negishi couplings of the TMB-ZnCl **44** reagent.

1.3 Conclusions.

The formation of the desired model coupling product, Bn-TMB **35**, was obtained in varying yields using the Grignard (**39**, 32%), organocuprate (**41**, 30-50%), boronic acid (**42**, 5-20%) and organozinc (**44**, 50-85%) derivatives of 1,3,5-trimethoxybenzene (Scheme 30). The optimal condition for the formation of Bn-TMB **35** was a Negishi cross-coupling protocol. This involved the coupling of TMB-ZnCl **44** to either BnBr or BnCl at 70 ^oC using Pd(DPEPhos)Cl_2 as a catalyst and THF as the reaction solvent. Under these conditions, Bn-TMB **35** was obtained in consistent, excellent yields (80-85%) using low catalyst loading (*ca*. 1 mol%). The use of other catalysts for the coupling was explored, but none were as effective as Pd(DPEPhos)Cl_2.

Scheme 30: Review of coupling methods in the formation of Bn-TMB 35.

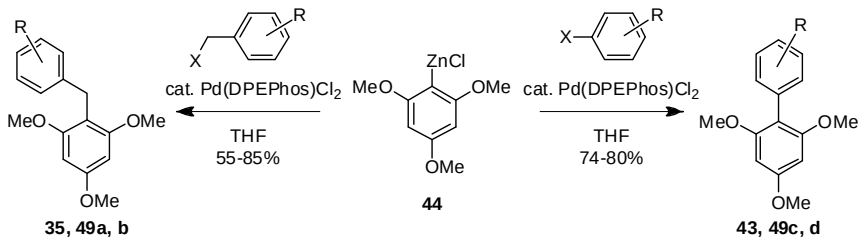


The Negishi cross-coupling protocol was then extended to the coupling of TMB-ZnCl **44** to other benzylic halides and aryl halides to provide a variety of 2,4,6-trimethoxyphenyl derivatives (**49a-d**). Under the established coupling conditions, TMB-ZnCl **44** was successfully coupled to benzyl and aryl halides (**48a-d, f, g**)

containing both electron donating and electron withdrawing substituents in 55-80% yields (Scheme 31).

Unfortunately, this coupling protocol could not be applied the successful coupling of TMB-ZnCl **44** with the hindered 2,6-dimethyl-iodobenzene **48h** in order to form biaryl **49e**. This showed that Pd(DPEPhos)Cl_2 was not effective as a coupling catalyst in the formation of this tetra-*ortho* biaryl.

Scheme 31: Review of Pd(DPEPhos)Cl_2-catalysed coupling of TMB-ZnCl 44 with benzyl and aryl halides.



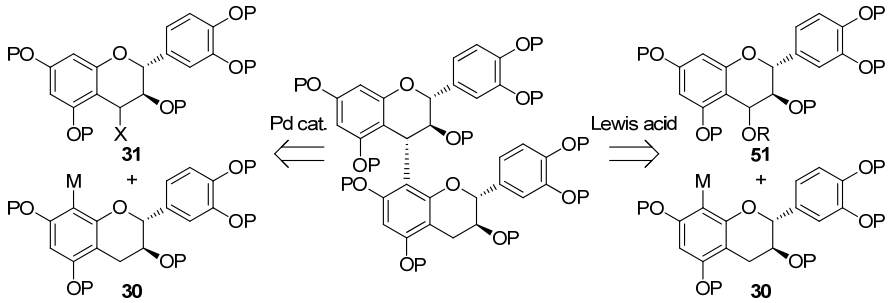
This model system coupling showed the potential for the use of a Negishi cross-coupling in the formation of 4→8 catechin-catechin dimers. If such C8-organozinc derivatives could be prepared, couplings to C4-halide catechin derivatives using the coupling protocol developed in this model system study could be applied to the formation of 4→8 catechin-catechin (or other procyanidin) dimers.

Chapter 3: Couplings of C8-organometallic Derivatives Towards the Synthesis of the catechin-catechin Dimer Procyanidin B3.

3.1 Introduction.

The successful Pd(DPEPhos)Cl_2-catalysed coupling of 2,4,6-trimethoxyphenylzinc chloride (**44**, Section 2.2.5) to BnBr ended the model system studies. From there attention turned towards the application of the developed coupling methods in the synthesis of the key 4→8 interflavan bond of catechin dimers. As little attention had been focussed upon the use of a C8-organometallic derivative as a directing group in this 4→8 bond synthesis, this aspect was considered for further examination. Two potential pathways using this method were identified. The first was a Pd-catalysed cross-coupling of C4-halide **31** with an appropriate C8-organometallic **30** (Section 2.1). The second potential pathway involved the Lewis acid-promoted cross-coupling of C4-ether **51** with C8-organometallic **30**. The retro-synthetic analysis of these potential 4→8 bond formations are shown below (Scheme 1).

Scheme 1: Retro-synthesis of cat-cat 4→8 bond using C4-halide *vs.* C4-ether.

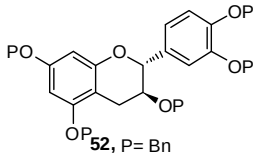


3.1.1 Protection of catechin derivatives.

Numerous synthetic methods towards catechin oligomer synthesis were discussed in Section 1.6. The majority of these methods utilised protecting groups to mask the reactivity of the phenolics and, in some cases the 3-OH hydroxyl groups. Protection of these groups was often necessary to avoid unwanted side reactions during coupling reactions. The use of benzyl ethers (**52**, P= Bn),[107, 108] methyl ethers (**53**, P= Me) [109] or acetyl esters (**54**, P= Ac) [110] as protecting groups have been reported (Figure 1).

The benzyl protecting group has by far been the most popular group for catechin protection for numerous reasons. The protection reaction itself is straight-forward and the protected product(s) can be obtained in high yields.[107] The benzyl ether is also stable to both acidic and basic conditions and can be cleanly removed by hydrogenolysis using Pd/C or $Pd(OH)_2/C$ [31, 39] without degradation of the catechin ring structure.

Figure 1: Protected catechin derivatives 52-54 (P= Bn, Me, Ac).



52, P= Bn
53, P= Me
54, P= Ac

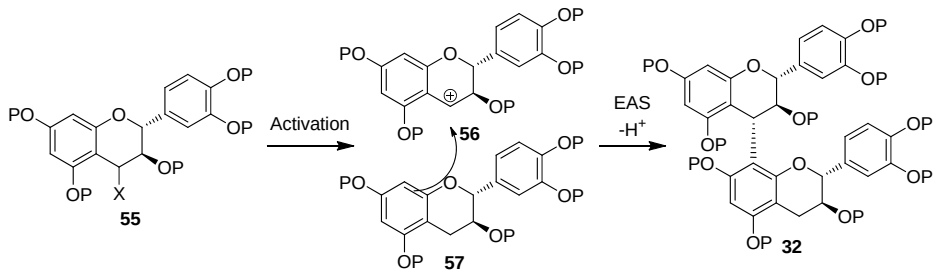
3.1.2 Challenges in 4→8 dimer synthesis.

There are three major components to the selective, iterative synthesis of these catechin oligomers: Control of the 4→8 regiochemical selection, 3,4-*trans* stereochemical selection, and the monodispersive stepwise addition of each monomer. A successful selective synthesis needs to meet all these three requirements. Of these three key requirements, selective stepwise addition of monomers has generally provided the greatest challenge in these types of syntheses. Polydisperse oligomeric products can form readily if the coupling is not strictly controlled. To illustrate this, the synthesis of a catechin-catechin dimer from the C4-electrophilic catechin **55** is presented (Scheme 2). Following activation of the C4-leaving group by addition of an appropriate reagent (e.g. Lewis acid), the generated C4-carbocation **56** is available for nucleophilic attack. In a controlled, stepwise synthesis a nucleophilic C8-catechin **57** undergoes electrophilic aromatic substitution (EAS) at the C4-carbocation to forge the 4→8 bond. Re-aromatisation of this intermediate by loss of H^+ provides the dimer **32**. This pathway, referred to as the "cross" reaction, provides the dimer in a stepwise, controlled manner as desired.

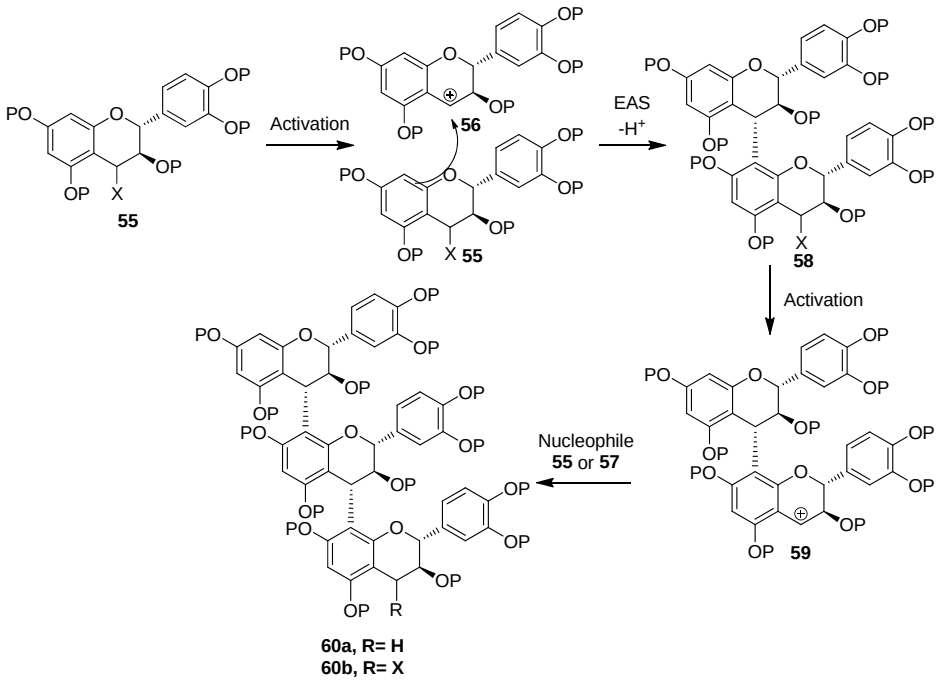
Uncontrolled synthesis of trimer and higher oligomeric products from condensation of C4-electrophile **55** can occur by two pathways. Firstly, the C4-carbocation **56** can undergo condensation with C8 of another C4-electrophile **55** to form dimer **58**. This C4-electrophile containing dimer can then be activated to form C4-carbocation **59**.

This carbocation can undergo further condensations with an available catechin species **57** or C4-electrophile **55** to form trimeric products **60a** or **60b** (Scheme 3). Trimer **60b** can also potentially undergo further condensations following activation to produce tetrameric and higher products. This pathway is referred to the "self" coupling reaction as the C4-electrophile **55** reacts with another monomer of its kind rather than the desired catechin **57**. The "self" reaction pathway is undesirable, as it leads the formation of polydisperse oligomeric products in an uncontrolled manner.

Scheme 2: Activation of catechin C4-electrophile 55 and subsequent condensation reaction to form dimer 32.



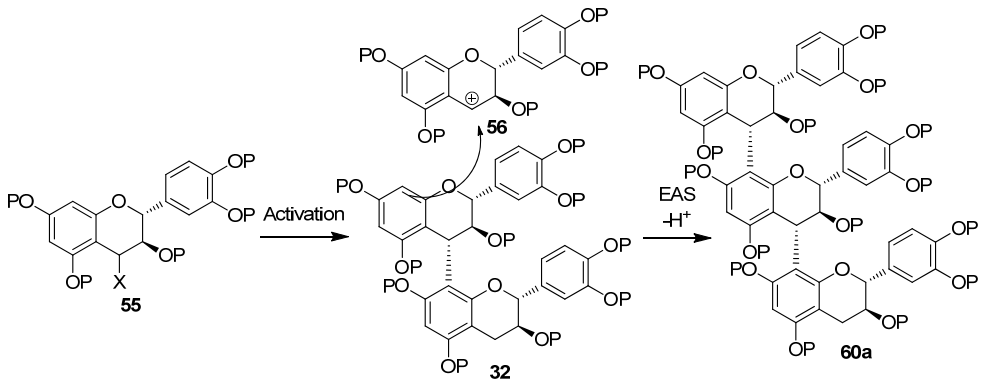
Scheme 3: The "self" reaction pathway to undesired trimeric products 60a and 60b.



The second pathway that leads to the uncontrolled formation of higher oligomeric products involves the dimer **32** that has previously formed under "cross" reaction

conditions. As this dimer **32** is still present in the reaction mixture, the C8 of the top or upper flavan unit is available to undergo condensation with C4-carbocation **56** to form trimer **60a** (Scheme 4).

Scheme 4: Synthesis of trimer 60a by condensation of dimer 32 with C4-carbocation 56.



The trimer produced by this pathway is also available to undergo further condensations with C4-carbocation **56** to form tetrameric products. Generally, by this process *n*-oligomers undergo condensation with a C4-carboation to form (*n*+1)-oligomers. This pathway also leads to the uncontrolled formation of polydisperse oligomers.

As these two pathways lead to uncontrolled oligomerisation products, the major challenge towards the controlled, stepwise synthesis of catechin oligomers is to suppress these uncontrolled pathways to the extent where only the controlled "cross" reaction occurs.

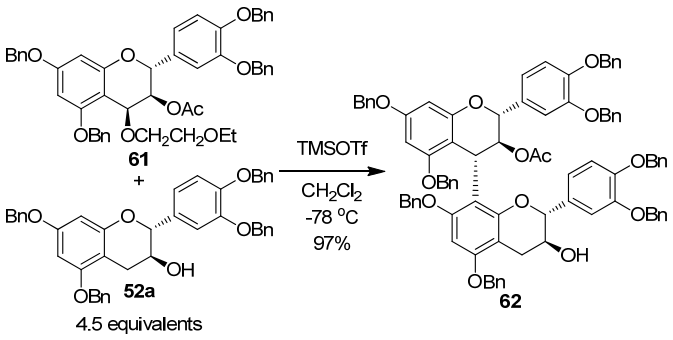
3.1.3 Controlled Lewis acid-promoted cross-couplings in catechin dimer synthesis.

The Lewis acid-promoted cross-coupling method for the formation of catechin derivatives was discussed earlier in section 1.6. The syntheses by Saito (Section 1.6.2), Ohmori (Section 1.6.5) and Tarascou (Section 1.6.6) were identified as controlled, stepwise methods in the formation of catechin oligomers. Accordingly, they warrant further discussion now to highlight the stepwise control of their methods. This chapter will focus upon the use of these technologies in the synthesis of dimeric products, whereas the synthesis of trimers and higher oligomers will be discussed in Chapter 4 (Section 4.1.1).

3.1.3.1 Saito synthesis of catechin dimers.

Saito *et al* [31] synthesised the catechin-catechin dimer **62** using the Lewis acid-promoted cross-coupling of the C4-(2-ethoxyethanol) ether **61** with the nucleophilic species **52a** (TBC). TMSOTf was employed as the Lewis acid activator (Scheme 5). When the nucleophilic species **52a** was used in large excess (4.5 equivalents), the dimer **62** was produced in quantitative yield with excellent 3,4-*trans* selectivity and no trace of trimer or higher oligomers were observed. The use of the large excess of the nucleophilic species was crucial to the selective formation of the dimer. This large excess effectively promoted the desired "cross" reaction over the undesired uncontrolled oligomerisation pathways (Section 3.1.2) by increasing the statistical likelihood of the "cross" reaction to the point where it was the only coupling pathway observed.

Scheme 5: Saito *et al* synthesis of catechin-catechin dimer 62.



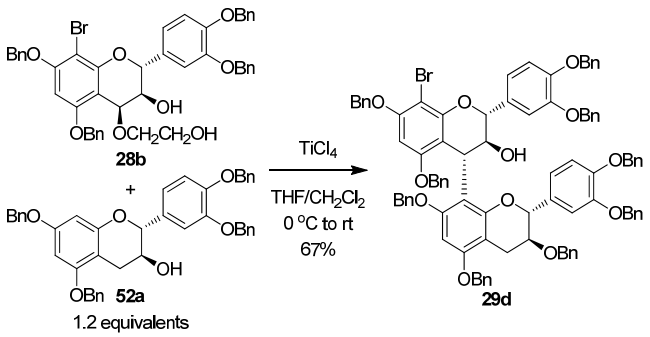
The use of the large excess of TBC **52a** posed a major experimental difficulty. To obtain the pure dimer **62**, separation of this species from the excess monomer **52a** was required. This was not trivial due to the similar polarities of the dimer and monomer products.[111]

3.1.3.2 C8-bromide as blocking group.

Both Ohmori *et al* [38] and Tarascou *et al* [39] employed a C8-bromide as a blocking group in the selective, iterative synthesis of catechin dimers. Although the Ohmori *et al* synthesis preceded that of Tarascou *et al*, it was applied to the synthesis of catechin trimers, and so is more appropriately discussed in greater detail in Chapter 4 (Section 4.1.1.2). Tarascou *et al* used a $TiCl_4$ promoted cross coupling of C4-ether

28b with the C8-nucleophile TBC **52a** to produce the catechin-catechin dimer **29d** in good yield with excellent 3,4-*trans* selectivity (Scheme 6).

Scheme 6: Tarascou *et al* selective catechin-catechin dimer 29d formation.



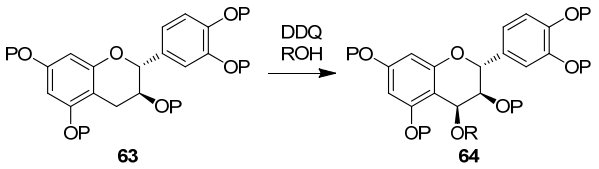
No evidence of trimer or higher oligomers was observed. The key to this selectivity was the incorporation of the C8-bromide functionality on the C4-ether **28b**. This group prevented the formation of higher oligomers by negating the C8-nucleophilicity of C4-ether **28b** and dimer **29d**. As a result, only monomer **52a** reacted with C4-ether **28b** upon $TiCl_4$ activation to afford dimer **29d**. The pathways towards uncontrolled oligomerisation (Section 3.1.2) were suppressed by the C8-bromide blocking group, so only "cross" reaction to dimer **29d** occurred. This principle of blocking C8 reactivity by the incorporation of the C8-bromide applies to both Tarascou's and Ohmori's syntheses.

Employment of this blocking group required the use of only 1.2 equivalents of TBC **52a** to ensure complete consumption of C4-ether **28b**. These almost equimolar conditions provided a great advantage when compared to the Saito *et al* synthesis (Section 3.1.3.1). The separation of the slight excess of monomer from dimer **29d** was much simpler than the separation of the large excess of monomer used by Saito *et al*.

3.1.4 Incorporation of C4-ether functionalities.

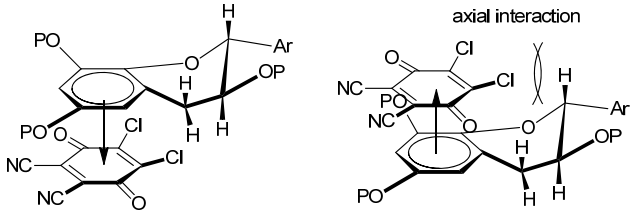
C4-ethers have been used extensively as C4-electrophiles in biomimetic 4→8 procyanidin dimer syntheses (Sections 1.6.2, to 1.6.6, excluding 1.6.4). Production of these C4-ethers has been primarily achieved by the DDQ-promoted oxidation of the C4 position of an appropriately protected catechin derivative **63** in the presence of an appropriate alcohol (Scheme 7).[17, 31, 39]

Scheme 7: Production of C4-ethers 64 through DDQ-promoted oxidation of catechin 63.



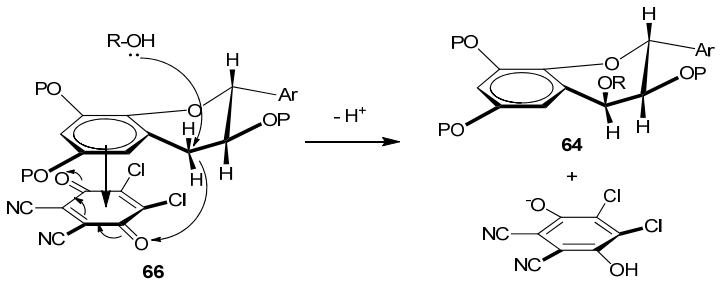
The C4-ethers **64** produced by this method have generally been produced with high 4β stereoselectivity regardless of the stereochemical orientation of the C3-substituent.[31, 112, 113] The origin of this selectivity was proposed by Steenkamp *et al* [113] to be due to π-π stacking interactions of DDQ with the "bottom", or *α*-face of the catechin A-ring to form the complex intermediate **65a** (Figure 2). Stacking of DDQ to the "top" or *β*-face is obstructed due to the presence of the C2-H, which provides unfavourable axial steric interactions with the DDQ substituents (**65b**).

Figure 2: π-π interactions of DDQ to *α* or *β* faces of the catechin A-ring.



After this selective binding of DDQ to the bottom face of the A-ring, selective abstraction of the 4*α*-hydride forms the stable charge transfer species **66**. Nucleophilic attack of the 4*β* face of the resulting C4-carbocation by an alcohol (R-OH) provided the C4*β*-ethers **64** following proton abstraction. Binding of DDQ to the "bottom" or 4*α* face prevented attack of the alcohol at this face (Scheme 8).

Scheme 8: Mechanism of DDQ promoted formation of C4-ether 64.

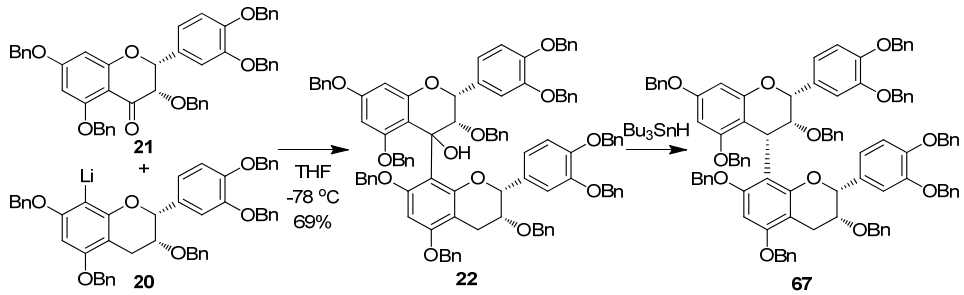


3.1.5 Use of C8-organometallic derivatives in synthesis of 4→8 dimers.

Kozikowski *et al* [37] synthesised the unnatural 3,4-*cis* isomer of procyanidin B2 (***cis*-6**) through the use of a C8-organolithium (section 1.6.4). In this reference, Kozikowski *et al* utilised C8-organolithium **20** in a nucleophilic addition to C4-ketone **21**. Reduction of the produced C4-alcohol **22** provided 3,4-*cis* dimer **67** (Scheme 9). Removal of the benzyl protecting groups provided the unnatural ***cis*-6** procyanidin dimer (Section 1.6.4).

Notably, this is the only literature example of the use of a C8-organometallic species in the synthesis of 4→8 procyanidin dimers. To date, no C8-organometallic derivative has been employed in the synthesis of 3,4-*trans* 4-8 procyanidin dimers.

Scheme 9: Kosikowski *et al* addition of C8-organolithium 20 to C4-ketone 21.



3.1.6 Introduction to ^{11}B NMR.

Boronic acids or esters (Section 2.1.1.4) as C8-organometalloids were identified as potential C8-nucleophiles in the proposed 4→8 coupling schemes (Section 3.1, Scheme 1). As a result, the use of ^{11}B NMR was identified as a potential tool for the characterisation of these compounds and therefore the principles of ^{11}B NMR warranted a short discussion at this time.

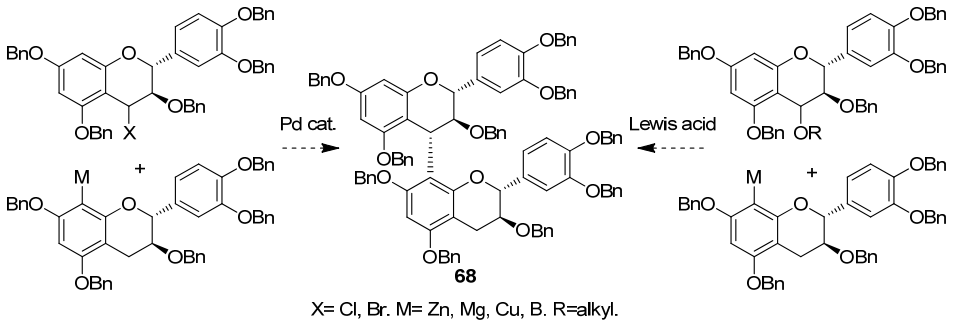
Boron is found in nature as two isotopes, ^{10}B and ^{11}B, with the ^{11}B isotope present in an 80% majority. Both these isotopes possess a nuclear spin, and can therefore be used in NMR spectroscopy. The ^{11}B isotope is most commonly used for boron NMR spectroscopy due to its greater abundance, lower resonance frequency, spin state (3/2), quadrupolar moment and higher magnetic receptivity (16% of ^{1}H) when compared to ^{10}B.[104]

Observations of ^{11}B NMR peaks are usually reported as ppm downfield from $BF_3.OEt_2$ as either an internal or external reference. As with ^{1}H or ^{13}C NMR, the chemical shifts of ^{11}B NMR resonances are related to the electronic configuration of the boron atom. The shift of the ^{11}B resonance provides evidence of the coordination state of the boron atom. Tri-coordinate boron atoms, such as free boronic aids and boronate esters, are generally found in the 25-35 ppm range. In contrast, tetra-coordinate derivatives are usually found in the 10-15 ppm region. As a result, ^{11}B NMR is highly useful in the determination of the coordination state of a boron complex.[104]

3.1.7 Aims.

Two potential pathways towards the controlled, iterative synthesis of 4→8 catechin-catechin dimer **68** were identified earlier (Section 3.1, scheme 1). These were the Pd-catalysed cross-coupling of a C4-halide with a C8-organometallic derivative, and the Lewis acid-promoted coupling of a C4-ether with a C8-organometallic (Scheme 10). Accordingly the 3,4-*trans* 4→8 catechin-catechin dimer **68** was targeted for synthesis by both of these methods. Crucially, access to this dimer **68** would allow synthesis of the natural procyanidin B3 (**3**). As a result, the ultimate aim of this chapter was to synthesise natural procyanidin B3 (**3**) through forging of the key 4→8 interflavan bond of the dimer **68** by one or both of the above methods.

Scheme 10: Coupling of C8-organometallic with C4-halide or C4-ether.



As little attention had been focussed upon the use of C8-organometallics in the synthesis of procyanidin dimers, these pathways were viewed as novel and potentially useful alternatives to current literature methods (Section 1.6).

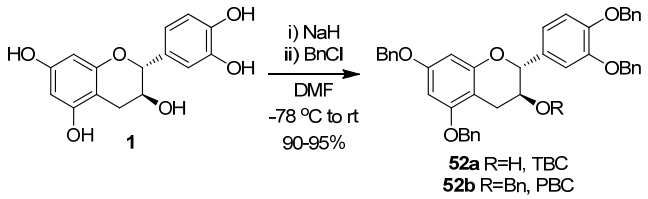
3.2 Results and discussion.

Both pathways shown in Scheme 10 were studied in parallel. Given that the Pd-catalysed cross-coupling of C4-halides to a C8-organometallic directly follows on from the model system studies discussed in Chapter 2 (Sections 2.2.4-2.2.7) the discussions below focus on this pathway first, followed by the Lewis acid-promoted coupling method.

3.2.1 Benzyl-protection of catechin.

Prior to any coupling being attempted, (+)-catechin **1** required protection as the requisite benzyl ethers. The phenolics and, in some cases, the C3-OH group were protected as the benzyl ethers by sequential treatment of **1** with NaH and BnCl. Depending upon the conditions used, either the tetra-benzyl ether **52a** (TBC), or the penta-benzyl ether **52b** (PBC) were produced (Scheme 11).

Scheme 11: Protection of (+)-catechin 1 to provide either TBC 52a or PBC 52b.



The actual conditions used for the benzyl protection of catechin **1** were a slight variation of those used by Mustafa *et al*.[107] According to the method described by Mustafa *et al*, a solution of (+)-catechin (**1**) in DMF was added to a stirring suspension of NaH in DMF. The actual benzylation conditions involved the initial dissolving of **1** in DMF at -78 ^{o}C. Solid NaH was then added to this solution, followed immediately by the addition of neat BnCl. The stirred suspension was then warmed to room temperature and stirred for the times specified below. Under these conditions, it was possible to achieve consistent 90-95% yields of **52a** or **52b** using 1-10 grams of **1**. These yields were in the vicinity of that reported by Mustafa *et al*.[107]

By careful control of the reagents used and reaction times, it was possible to selectively prepare either TBC **52a** or PBC **52b**. The use of 4.25 equivalents of NaH and 4.5 of BnCl with stirring over six hours provided TBC **52a** as the sole product.

The use of 6 equivalents of NaH and 7 of BnCl with stirring over 24 hours afforded PBC **52b** as the major product. In both cases, yields of greater than 90% of the desired products were achieved after purification by silica chromatography.

While DMF was generally the choice of solvent, DMA was also used as an equally effective solvent. When DMA was employed, reaction times and yields were comparable to that achieved with DMF. As DMA froze below -15 ^{o}C, the addition of the NaH and BnCl was conducted at this temperature when using this solvent. It was critical that the solvent, either DMF or DMA, was dry. Any moisture present in the solvent reacted with the NaH, which reduced the amount of NaH available to deprotonate **1**. Given that control of the excess of reagents added was found to be critical, any moisture present in the solvent prevented this control. Accordingly, only anhydrous solvents purchased from Sigma-Aldrich and fitted with a sure-seal were used and yields of the protection carefully monitored. A new bottle of solvent was purchased and used as the yields of protection dropped substantially using an old bottle.

Purification of the protected catechin species **52a** and **52b** was achieved through silica chromatography. It was found that any excess BnCl present in the protected products tended to hamper subsequent reactions, so it was critical to ensure that the BnCl was completely separated from the products at this point.

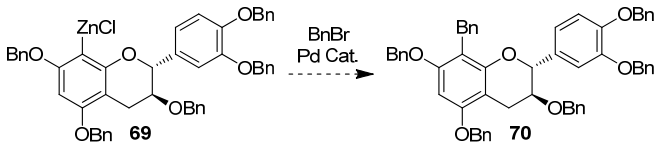
3.2.2 Studies towards Pd-catalysed cross-couplings of C8-organometallic derivatives.

3.2.2.1 C8-metallation studies.

Following on from the success of the Pd-catalysed cross-couplings of the C8-model, 2,4,6-trimethoxyphenylzinc chloride (**44**) set out in Chapter 2 (Sections 2.2.5-2.2.7), the next step was to evaluate the potential of use of C8-organometallic species in cross-couplings towards the synthesis of 4→8 catechin-catechin dimer (**3**) (Section 3.1.7, Scheme 10). Prior to any studies towards the coupling of a C4-halide with a C8-organometallic, the utility of potential C8-organometallics was examined by the Pd-catalysed cross-coupling of the C8-organometallic with BnBr. This coupling allowed for development of a C8-organometallic without any complications of steric

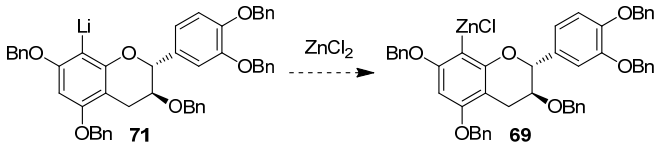
encumbrance of a C4-halide. The formation of the C8-organozinc **69** and its subsequent coupling to BnBr were examined first (Scheme 12).

Scheme 12: Proposed model Pd-catalysed coupling of C8-organozinc 69 to BnBr.



It was envisaged the desired C8-organozinc **69** could be produced from the C8-organolithium **71** through transmetallation by the addition of $ZnCl_2$ (Scheme 13).

Scheme 13: Formation of C8-organozinc 69 from C8-organolithium 71.

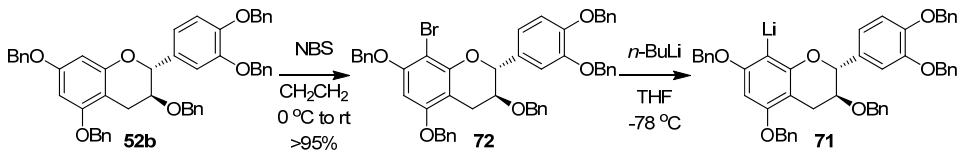


Therefore, the first task in the study of this transmetallation was to produce the desired C8-organolithium derivative **71**.

3.2.2.2 Formation of C8-organolithium derivative 71.

The required C8-organolithium was prepared from PBC **52b** following a slight variation to that reported for the same compound by Kozikowski *et al*.[37] In a two step process, PBC **52b** was initially converted to the C8-bromide (**72**, 8Br-PBC) by selective bromination using NBS, followed by low temperature lithium-halogen exchange using *n*-BuLi in THF to afford the desired C8-organolithium **71** (8Li-PBC, Scheme 14).

Scheme 14: Synthesis of C8-bromide 72 and subsequent conversion to C8-organolithium 71.

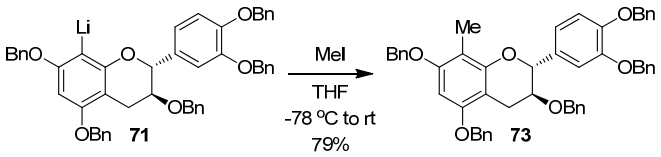


Gram scale synthesis of the C8-bromide **72** was consistently achieved in almost quantitative yields through selective C8-bromination of PBC **52b** using one equivalent of NBS. Following quenching, filtration over SiO_2 and concentration, the desired C8-bromide **72** was isolated as a white, foamy solid.

With the required C8-bromide **72** available, it was converted to the requisite C8-organolithium **71**. This was achieved by the dropwise addition of *n*-BuLi to a stirring solution of the C8-bromide in THF at -78 ^{o}C. The use of *n*-BuLi varied from that reported by Kozikowski *et al*,[37] who used *t*-BuLi as the lithiating agent. The use of *n*-BuLi was preferred as it was less pyrophoric, and so safer to use. Upon addition of *n*-BuLi the clear, colourless solution of the C8-bromide **72** turned a deep yellow/orange colour. This colour change acted as a useful indicator for the formation of the C8-organolithium **71**.

C8-organolithium **71** was too reactive to attempt isolation. In order to establish the formation and reactivity of the organolithium, excess iodomethane (MeI) was added at -78 ^{o}C to trap the newly formed lithium species **71**. Following completion of the reaction, silica chromatography and concentration, the C8-methyl species **73** was isolated in 79 % yield as a white solid (Scheme 15). This successful reaction of the C8-organolithium **71** confirmed that it was indeed forming as desired and was reactive towards electrophiles.

Scheme 15: Synthesis of 73 through trapping of C8-organolithium 71 with MeI.



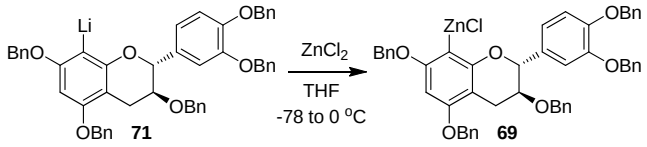
3.2.2.3 Transmetallation of C8-organolithium 71 to C8-organozinc 69.

With C8-organolithium **71** successfully prepared, transmetallation to the desired C8-organozinc **69** was attempted by addition of $ZnCl_2$ to a pre-prepared solution of C8-organolithium **71** in THF at -78 ^{o}C (Scheme 16).

Upon addition of the $ZnCl_2$, either as a solid or as a solution in THF, the deep yellow/orange colour of the C8-organolithium **71** rapidly changed to a pale yellow

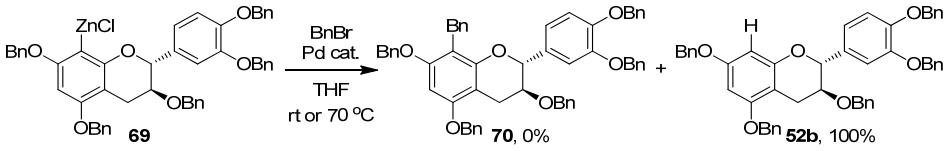
colour. This was seen as somewhat promising, as the colour change may have been indicative of the formation of the C8-organozinc **69**.

Scheme 16: Formation of C8-organozinc 69 from C8-organolithium 71 using $ZnCl_2$.



It was quickly realised the putative C8-organozinc **69** generated could not be coupled to BnBr using any Pd catalyst. The use of $Pd(DPEPhos)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(dppf)Cl_2.CH_2Cl_2$ or $Pd(PPh_3)_4$ in THF at either room temperature or 70 °C failed to provide any cross-coupled product **70**. In all cases, only the starting BnBr and PBC **52b** were recovered following acidic quenching (Scheme 17).

Scheme 17: Attempted cross-couplings of C8-organozinc 69 and recovery of PBC 52b.



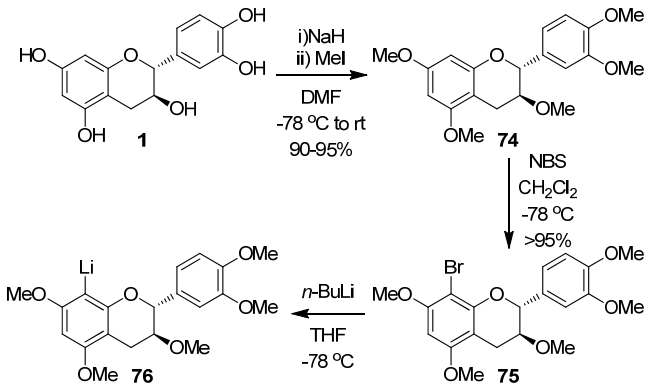
The recovery of PBC **52b** following quenching suggested that one of two things was occurring. Firstly, the transmetallation of the C8-organolithium **71** to the requisite organozinc was not occurring. Thus, upon quenching the organolithium was protonated, forming PBC **52b**. Secondly, C8-organozinc **69** was forming as desired, but was not reactive towards transmetallation to the Pd catalyst (Section 2.1.2.2). It was thought that steric encumbrances of the large *ortho* groups may have prevented the transmetallation from occurring. To test this hypothesis, the requisite penta-methyl ether of (+)-catechin (**1**) was prepared and converted to the C8-organozinc derivative in order to reduce the steric bulk around the C8 centre.

3.2.2.4 Preparation and coupling of a methyl-protected C8-organozinc derivative.

Prior to formation of the methyl-protected C8-organozinc **77**, the corresponding methyl protected C8-organolithium **76** was prepared in 3 steps from (+)-catechin **1**

by methylation of the hydroxyls, followed by selective C8-bromination, then low temperature lithium-halogen exchange using *n*-BuLi (scheme 18).

Scheme 18: 3-step formation of C8-organolithium 76 from (+)-catechin 1.



Penta-O-methyl-catechin (**74**, PMC) was prepared using the same procedure used for the benzyl protection of catechin described earlier (Section 3.2.1), with MeI replacing BnCl as the electrophile. Under these conditions, PMC **74** was prepared using 1-5 grams of **1**. Filtration over silica and concentration provided the desired product **74** as a white solid in *ca*. 90% yields.

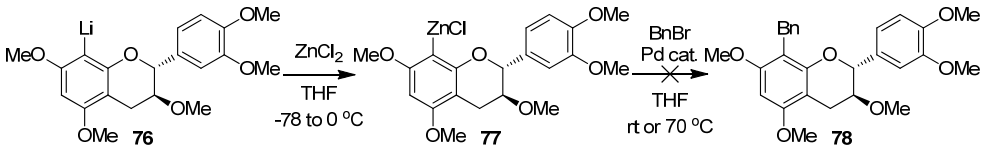
Selective C8-bromination was carried out by the addition of one equivalent of NBS to a stirring solution of PMC **74** in CH_2Cl_2 at -78 ^oC, followed by stirring at this temperature for 4 hours. It was found the temperature of this reaction was critical to ensure that only C8-bromide **75** was formed. Only one product spot was observed by TLC analysis under these conditions. When the reaction was conducted at 0 ^oC, a second product spot, assumed to be the C6-bromide isomer, developed on the TLC. When conducted at -78 ^oC, gram quantities of the desired C8-bromide **75** (8Br-PMC) were obtained consistently in near quantitative as a white solid following quenching and filtration over silica and concentration.

The C8-bromide **75** was converted to the corresponding C8-organolithium **76** by the dropwise addition of *n*-BuLi to a solution of 8Br-PMC **75** in THF at -78 ^oC. Unlike the benzyl-protected analogue **72**, there was no colour change associated with this lithium-halogen exchange. The 8Br-PMC **75** solution remained colourless upon addition of *n*-BuLi. The resulting mixture was allowed to stir for a further 15 minutes at -78 ^oC to provide C8-organolithium **76**.

Following formation of the C8-organolithium **76**, $ZnCl_2$ was immediately added either as a solid or as a solution in THF at -78 ^oC. Stirring at this temperature for 15 minutes, then slow warming to 0 ^oC afforded the assumed C8-organozinc derivative **77**. Unlike the benzyl-protected analogue, there was no colour change associated with this transmetallation. The resulting assumed C8-organozinc **77** existed as a clear, colourless solution.

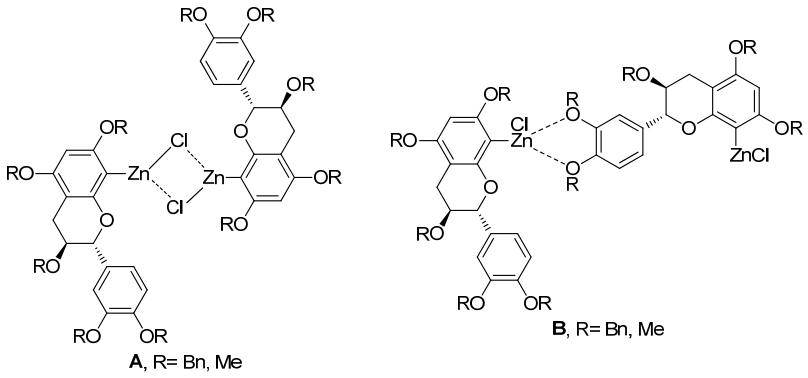
Couplings of C8-organozinc **77** to BnBr were attempted using the catalysts $Pd(DPEPhos)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(dppf)Cl_2.CH_2Cl_2$ or $Pd(PPh_3)_4$ in THF at either room temperature or 70 ^oC. In all these cases, no coupling product was obtained; only BnBr and protonated PMC **74** were recovered from the reaction mixture following acidic quenching (Scheme 19).

Scheme 19: Formation of C8-organozinc 77 from C8-organolithium 76 and failed Negishi cross-couplings with BnBr.



These results mirrored that found for the benzyl-protected analogue. As methyl protected C8-organozinc **77** was significantly less sterically encumbered compared to the benzyl-protected C8-organozinc **69**, it was likely electronic factors were to blame for the lack of coupling rather than sterics. It is probable that one of two things may have occurred. Firstly, the lithium to zinc transmetallation did not take place; instead any residual water in the $ZnCl_2$ quenched the organolithium to provide the C8-protonated materials PBC **52b** or PMC **74**. Secondly, the organozinc derivatives did form, but formed an inactive cluster, which did not participate in the cross coupling reaction. Two possible cluster species are shown below (Figure 3). Firstly, two zinc centres may cluster together to form the dimeric species **A**. Alternatively, the zinc centre of one monomer could coordinate to the B-ring catechol oxygens of an other unit to form the inactive complex **B**.

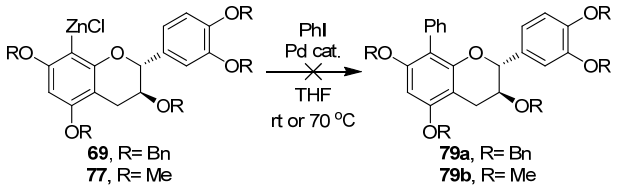
Figure 3: Cluster of C8-organozincs to form inactive dimeric species A and B.



Attempts to break this suspected cluster through the addition of lithium bromide (LiBr) or the use of NMP as a co-solvent were unsuccessful. The use of these additives in the Pd-catalysed cross-coupling of C8-organozinc **77** with BnBr (Scheme 18) failed to provide any cross coupled product **78**. In these cases, only the starting BnBr and PMC **74** were isolated following acidic quenching.

As a last resort, the coupling of both the C8-organozinc derivatives **69** and **77** with iodobenzene (PhI) was attempted using either Pd(DPEPhos)Cl_2 or Pd$(PPh_3)_2Cl_2$ as the catalyst (Scheme 20). As PhI was an active electrophile towards Pd-catalysed cross-couplings (Section 2.2.4), this electrophile was used as a gauge to determine the activity of the C8-organozincs. It was expected that if coupling to the active PhI could not be achieved, then it was unlikely that any couplings using the C8-organozinc species were possible.

Scheme 20: Attempted couplings of C8-organozincs 69 and 77 with iodobenzene (PhI).



In the cases of the attempted coupling using both the benzyl and methyl-protected organozinc derivatives, only starting PhI along with either PBC **52b** or PMC **74** were recovered after acid quenching. No trace of any coupled product was observed by ^{1}H NMR analysis of crude reaction mixtures. These results mirrored those found for the BnBr couplings, so it was suspected that the formation and/or reactivity issues of the

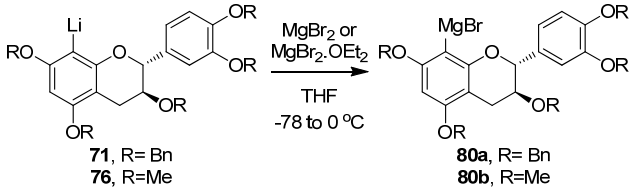
C8-organozinc derivatives described previously were indeed the primary barriers towards the cross-couplings of these species. As a result, it was concluded that the C8-organozinc derivatives **69** and **77** were not worth pursuing in Pd-catalysed cross-couplings. Instead further C8-organometallic species were considered for the cross-coupling to BnBr and ultimately for the use in 4→8 dimer synthesis.

3.2.2.5 Preparation and couplings of C8-Grignard derivatives.

Given the failed couplings of the C8-organozinc derivatives **69** and **77**, it was determined that a C8-organomagnesium, or C8-Grignard, derivative was a viable C8-organometallic alternative. The reactivity of the carbon-magnesium bond compared to that of the carbon-zinc bond could potentially overcome some of the formation and reactivity issues seen with the organozinc derivatives.

The C8-Grignard derivatives of both PBC (**80a**) and PMC (**80b**) were prepared by initial formation of the corresponding C8-organolithiums **71** or **76** as solutions in THF (Sections 3.2.2.2, 3.2.2.4), followed by transmetallation by addition of either solid $MgBr_2$ or $MgBr_2.OEt_2$ at -78 ^oC. At this temperature, the added salt remained as a suspension. Slow warming of the solution to 0 ^oC over 30 minutes saw the salts dissolve completely to provide the assumed C8-Grignards **80a** and **80b** as solutions in THF (Scheme 21).

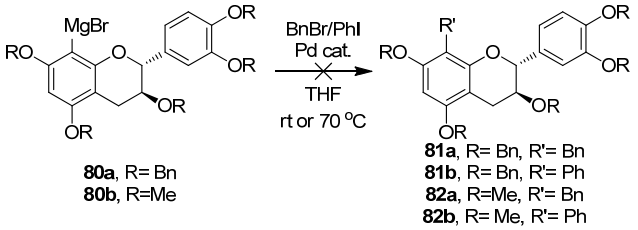
Scheme 21: Attempted formation C8-Grignard derivatives 80a and 80b from C8-organolithiums 71 and 76.



These lithium to magnesium transmetallations showed similar colour changes to that observed for the corresponding lithium to zinc transmetallations. In the case of the benzyl-protected analogue **80a**, the deep yellow/orange colour of C8-organolithium **71** solution changed to a pale yellow colour upon dissolution of the magnesium salt. No colour change was observed with the methyl-protected analogue. The putative solution of Grignard **80b** was clear and colourless. These colour changes were sighted regardless of the magnesium salt used.

The Pd-catalysed Kumada couplings [88] of the C8-Grignard derivatives **80a** and **80b** with both BnBr and PhI were attempted using either $Pd(DPEPhos)Cl_2$ or $Pd(PPh_3)_2Cl_2$ as the catalyst in THF at both room temperature and 70 ^oC for 24-72 hours. In all cases, no trace of any coupling product was observed by ^1H NMR analysis of reaction mixtures following quenching and extraction. Only the starting halide and PBC **52b** or PMC **74** were recovered (Scheme 22).

Scheme 22: Attempted Pd-catalysed coupling of C8-Grignards 80a and 80b with BnBr or PhI.



These results, along with those found with the corresponding organozinc derivatives, suggested that the failed couplings were likely due to issues related to the transmetallation of the organolithium species, as this step was common to the formation of both organometallics. A major issue that was never overcome was the fact that the generated organometallics were too reactive to isolate, so required formation *in situ*, followed by immediate use. This issue made it difficult to track problem steps in the coupling process. Since the C8-Grignard could not be successfully generated, this species was not considered further as a C8-organometallic reagent.

With the failure of the C8-organozinc and C8-Grignard derivatives, the use of copper as the C8-organometallic was posed as an alternative. As generation of the C8-organocopper species would have also required the transmetallation an appropriate organolithium species, it was conceived the same issues observed for the earlier transmetallations would likely affect this lithium to copper transmetallation also. On top of this, the coupling of organocuprate **41a** to BnBr (Section 2.2.3) provided the desired coupling product **35** in only moderate 45-50% yields. As a result, the C8-organocopper derivative was not considered a viable option. This concluded the studies towards the coupling of the Pd-catalysed cross-couplings of a C8-organometallic derivative to BnBr as a model towards the cross-coupling of a C8-

organometallic to a C4-halide. As model system studies towards the Lewis acid-promoted cross-couplings of a C4-ether were showing some promise by this time, these couplings became the major focus for the synthesis of the 4→8 dimer. As a result, the Pd-catalysed C4-halide coupling approach was abandoned and the formation of the C4-halide was no longer applicable.

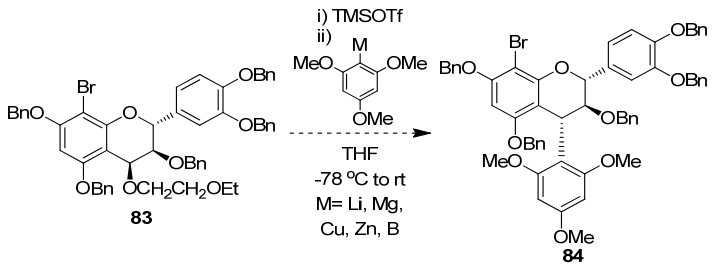
3.2.3 Studies towards the Lewis acid-promoted cross-coupling of a C4-ether with a C8-organometallic derivative.

As described earlier (Section 3.1.7, Scheme 10), the Lewis acid-promoted coupling of a C4-ether with a C8-organometallic derivative was also identified as a potential pathway towards the synthesis the targeted 3,4-*trans* catechin-catechin dimer **68** (Scheme 1). Accordingly, this pathway was examined in parallel to the Pd-catalysed couplings towards the 4→8 dimer **68**.

3.2.3.1 Model system studies in the Lewis acid-promoted coupling.

To determine the viability of this coupling pathway, a new model system was established (Scheme 23). As the formation of several metallated 1,3,5-trimethoxybenzene derivatives were available through methods previously discussed (Chapter 2, Sections 2.2.1-2.2.5), rapid screening of these organometallic species in the Lewis acid-promoted coupling to C4-ether **83** (8Br-4EE-PBC) was possible.

Scheme 23: Proposed Model system TMSOTf-promoted cross-coupling of C4-ether 83 to metallated-1,3,5-trimethoxybenzenes.



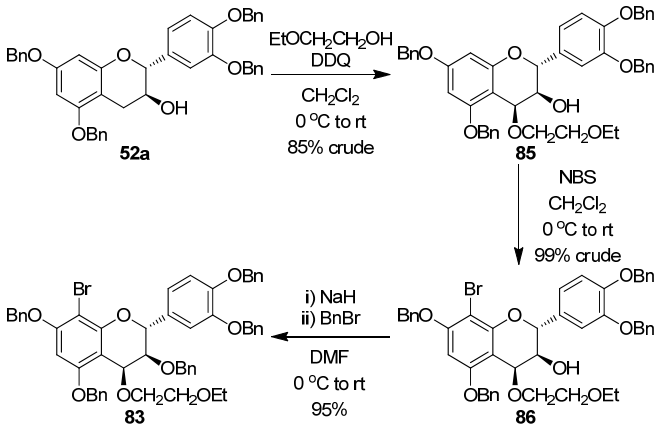
The use of TMSOTf as the Lewis acid and 8Br-4EE-PBC **83** was employed as the preferred Lewis acid/C4-ether combination for the coupling studies. The use of this combination by Saito *et al* [31] provided excellent coupling yields and 3,4-*trans* selectivity when applied to their synthesis of the catechin-catechin dimer **62** (Section 3.1.3.1). The C8 bromide, as used by Ohmori *et al* and Tarascou *et al* (Section

3.1.3.2), was incorporated into the C4-ether to block the "self" reaction pathway (Section 3.1.2) and prevent higher oligomer formation. Finally, the C3-OH was protected as the benzyl ether in order to prevent any potential side reactivity of the organometallic derivative with this hydroxyl.

3.2.3.2 Preparation of the C4-ether 83 (8B-4EE-PBC).

Prior to the attempt of any coupling reaction, the desired C4-ether **83** (8Br-4EE-PBC) was synthesised in three steps from the already available TBC **52a** (Scheme 24).

Scheme 24: Preparation of 8Br-4EE-PBC 83 from TBC 52a.



The C4-ether **85** (4EE-TBC) was prepared using the method described by Saito *et al*.[31] DDQ-promoted C4-oxidation of TBC **52a** in the presence of excess 2-ethoxyethanol provided the desired C4-ether **85** in 85% crude yield following filtration over SiO_2. This C4-ether did contain a small number of indentified impurities. Attempts to crystallise the product using the conditions reported by Saito *et al* resulted in co-crystallisation of the impurities. C4-ether **85** was found to be very insoluble in most solvent systems except CH_2Cl_2 or $CHCl_3$. The material tended to crystallise out of solution at the top of a column when silica gel chromatography was attempted using hexane-based solvent systems. CH_2Cl_2 or $CHCl_3$-based solvent systems, while preventing crystallisation of the product, failed to effectively separate the product from the impurities. As a result, the obtained crude orange solid was used in the following steps without further purification.

The selective C8-bromination of this crude C4-ether **85** was achieved in almost quantitative crude yield by treatment of this ether with one equivalent of NBS in

CH_2Cl_2 at 0 ^oC for 2 hours. The crude material from this reaction (**86**, 8Br-4EE-TBC) was subsequently used in the C3-OH benzyl-protection with no further treatment.

Benzyl protection of the C3-OH of 8Br-4EE-TBC **86** was achieved by deprotonation of the alcohol using NaH and subsequent trapping with BnBr. This afforded the desired 8Br-4EE-PBC **83** in 90-95% yields over two steps from **85** (4EE-PBC) as a foamy white solid after purification. Incorporation of the benzyloxy group at C3 greatly improved the solubility of this material compared to 4EE-TBC **85**. As a result, the impurities carried through from the oxidation reaction were removed using silica chromatography without any crystallisation of the material on the column. As a number of impurities were present, the purification of 8Br-4EE-PBC **83** was difficult. Through the use of a gradient solvent system, the desired material was obtained as a white foamy solid. Rigorous purification of this material at this stage was critical, as subsequent reactions were severely hampered by the presence of any impurities. This three step conversion of TBC **52a** to 8Br-4EE-PBC **83** was carried out multiple times using 1-5 gram quantities. The reported yields were consistently obtained regardless of reaction scale.

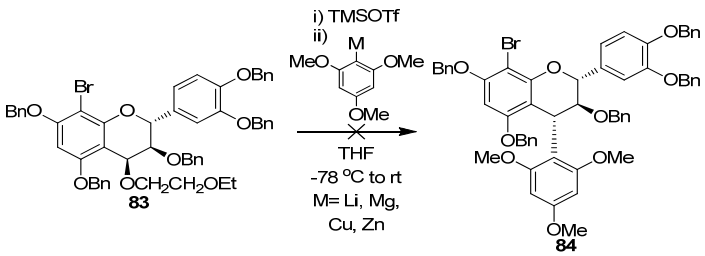
The identity of 8Br-4EE-PBC **83** was confirmed by the use of ^1H and ^{13}C NMR, along with HRMS. The protons resonances corresponding to C4 and the ether groups were still present and found at the similar shifts to the 4EE-TBC **85** starting material. The singlet at 6.22 ppm (1 proton) of the ^1H NMR and the peak at 92.6 ppm of the ^{13}C NMR spectra confirmed the presence of the C8-bromide. The C6 and C8 doublets observed at 6.27 and 6.27 ppm in the ^1H NMR spectrum of the starting 4EE-TBC **85** had collapsed to a singlet, confirming that either C6 or C8 was substituted. The C6-H singlet at 6.22 ppm confirmed the C8-substitution, as the C8-H singlet of the alternative C6-bromide isomer would be expected to be seen upfield at 6.0-6.1ppm.[37, 114] The C3-benzyloxy group was confirmed by the presence of two doublets at 4.06 and 4.22 ppm in the ^1H NMR spectrum, which corresponded to the diastereotopic CH_2 protons of the benzyl group. HRMS of the product afforded the molecular formula $C_{54}H_{51}BrO_8$, which corresponded to that of the expected structure.

3.2.3.3 Model Lewis acid-promoted cross-couplings of 8Br-4EE-PBC 83 to metallated-1,3,5-trimethoxybenzenes.

With pure 8Br-4EE-PBC **83** available in gram quantities, the model Lewis acid-promoted cross-coupling studies commenced. The first task was to determine what, if any, organometallic species were applicable to this coupling.

Initial studies were conducted using the organolithium **37** (Li-TMB) and Grignard **39** (MgBr-TMB) derivatives. In both cases, TMSOTf was added to a stirring solution of 8Br-4EE-PBC **83** in THF at -78 ^{o}C, upon which the clear, colourless solution of C4-ether **83** turned deep purple. A solution of the organometallic (prepared as per Sections 2.2.1 or 2.2.2) in THF was immediately added at this temperature (Scheme 25). Following quenching, ^{1}H NMR analysis of the crude mixtures obtained from these couplings showed complex mixtures of products were present. From these results, it was concluded that the organolithium and Grignard derivatives were too reactive to obtain a selective reaction with C4-ether **83**. Further studies involving these metals were abandoned in favour of less reactive organometallics.

Scheme 25: Attempted cross-coupling of 8Br-4EE-PBC 83 with TMB-organometallics.



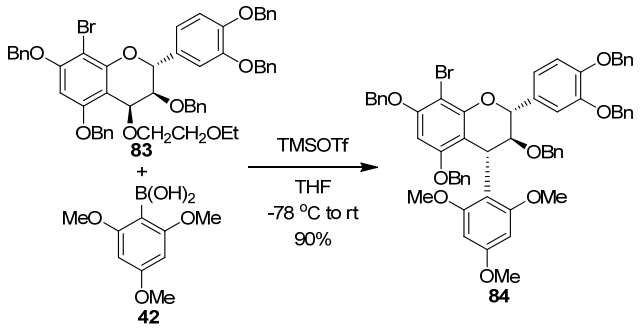
The organocopper **41a** and organozinc **44** (TMB-ZnCl) derivatives were considered as potential coupling partners due to their reduced reactivity compared to the organolithium and Grignard reagents. Again, TMSOTf was added at -78 ^{o}C to a stirring solution of 8Br-4EE-PBC **83** in THF, which provided the same colourless to purple colour change seen above. A preformed solution of organocopper **41a** or organozinc **44** (prepared as per Sections 2.2.3 or 2.2.5) was immediately added at this temperature (scheme 25). In both cases no coupling product was obtained. The starting C4-ether **83** was recovered after aqueous quenching, along with TMB **33**. This suggested that the either these organometallics were not sufficiently reactive to

perform the required C4-substitution, or the organometallics were compromised during transfer and addition to the ether/Lewis acid solution. With that, both the organocopper and organozinc derivatives were not considered further in Lewis acid-promoted cross-coupling.

3.2.3.4 Lewis acid-promoted cross-couplings of 8Br-4EE-PBC 83 to 2,4,6-trimethoxyphenylboronic acid (42).

With the failed couplings using the *in situ* generated organometallic species, attention turned towards the use of 2,4,6-trimethoxyphenylboronic acid (**42**) in the coupling reaction. The use of this organometalloid species possessed an advantage compared to the other organometallic derivatives used. As it was isolatable, there was no question over of its identity and correct formation. Since **42** was already available in large quantities, the Lewis acid-promoted model coupling was attempted (Scheme 26).

Scheme 26: TMSOTf-promoted coupling of 8Br-4EE-PBC 83 to TMB-B(OH)$_2$ 42.



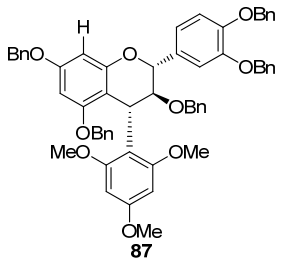
As TMB-B(OH)$_2$ **42** was available as the free boronic acid, it was added to the 8Br-4EE-PBC **83** solution prior to Lewis acid addition. To this solution, TMSOTf was added dropwise at -78 ^{o}C, resulting in an immediate colour change from colourless to deep purple as the Lewis acid complexed with the C4-oxygen. Following quenching, this coupling consistently furnished desired pseudo-dimer **84** (8Br-4TMB-PBC) in 75-85% yield as a white, foamy solid following purification by silica chromatography when conducted using *ca*. 50-100 mg scale of C4-ether **83**. This yield increased to 90% when conducted using 200 mg of **83**. These results suggested that the coupling yield increased with scale. No evidence of any higher oligomer was

obtained, suggesting that the C8-bromide of **83** was preventing any such side reactivity (Section 3.2.3.1).

Only 1.1 equivalents of boronic acid **42** were required for complete consumption of C4-ether **83**. This slight excess represents the smallest excess of nucleophile required for a Lewis acid-promoted coupling to a C4-ether. As the excess nucleophile required separation from the pseudo-dimer product **84,** the smaller the excess, the easier the separation, and so this reduced excess possessed an advantage over other coupling methods discussed previously (section 3.1.3). In this coupling, the excess boronic acid was recovered post-reaction as TMB **33**. This showed that under either the reaction or quenching conditions, boronic acid **42** was protonated to form **33**.

The excess of **33** was readily separated from the coupled product by silica chromatography. The actual pseudo-dimer product 8Br-4TMB-PBC **84** obtained was a 90:10 mixture of two products which were initially thought to be the two C4-isomers. However, upon closer examination of the ^{1}H NMR spectrum, the minor product was actually found to be the C8-H material **87** (4TMB-PBC), which may have been present due to incomplete bromination of 4EE-TBC **85** (Section 3.2.3.2) or arose from debromination of 8Br-4EE-PBC **83** or 8Br-4TMB-PBC **84** during the coupling reaction. The C6 and C8 doublets at 6.12 and 6.16 ppm integrated for 0.1 protons in comparison to the major product confirmed the presence of this product (Figure 4). Attempts to separate the two species **84** and **87** using silica chromatography were fruitless.

Figure 4: The minor isomer found in the coupling, 4TMB-PBC 87.

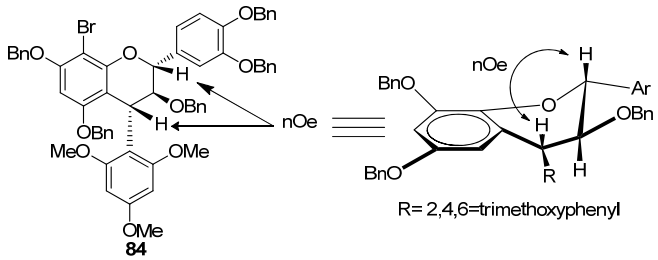


87

The use of 1D and 2D NMR experiments along with HRMS confirmed the identity of the major product as the desired 3,4-*trans*, or 4*α* pseudo-dimer **84** (8Br-4TMB-PBC). The proton resonances due to the C4-ether alkyl groups were no longer present, confirming that the C4-ether had been consumed. The ^{13}C resonance of C4

had shifted from 71.8 ppm in the starting ether **83** to 36.4 ppm in the product **84**. This shift was consistent with C4 being attached to a phenyl group. The C4-H doublet at 4.85 ppm and the large $J^{3,4}$ coupling constant of 10 Hz was consistent with the C4-H being in the pseudo-axial, or 4*β* position. As a consequence, the trimethoxyphenyl substituent was assumed to be orientated in the desired 4*α* position. The use of a ROESY experiment confirmed this stereochemistry. This experiment showed a strong nOe correlation between C2-H (4.68 ppm) and C4-H (4.85 ppm), which confirmed these two protons were on the same side of the C-ring. As a consequence, C4-H of the major product **84** was confirmed to be in the 4*β* orientation. This showed that the desired 3,4-*trans*, or 4*α* isomer was obtained (Figure 5). The stereochemistry of the minor product **87** could not be determined due to the fact it could not be separated from **84**. As a result, the diastereoselectivity of the reaction could not be absolutely determined. As the major product **84** was present in *ca.* 90%, it was possible to state that the diastereoselectivity of the reaction was at least 90%. It is worthwhile to note at this point that it is not unreasonable to expect that the stereochemistry of the minor product **84** would also be predominantly 4*α*. This assumption will be expanded upon in discussions pertaining to the mechanism and stereoselectivity of the developed coupling reaction, which are located in section 3.2.4.7.

Figure 5: Confirmation of 3,4-*trans* stereochemistry of 84 using a ROESY experiment.



The presence of the trimethoxyphenyl unit was confirmed by the broad singlets at 6.04 and 5.98 ppm (1 proton each), along with 3.82, 3.47 and 3.36 ppm (3 protons each). These signals were due to the presence of the aromatic and methoxy protons of this unit respectively. The broadness of the 6.04, 5.98, 3.47 and 3.3.6 ppm signals was thought to be due to the restricted rotation of this substituent around the C4-TMB pseudo-interflavan bond. HRMS analysis of the product confirmed the

molecular formula $C_{59}H_{53}BrO_9$ matched that of the expected structure. Accordingly, the major product was identified as the 3,4-*trans* pseudo-dimer 8Br-4TMB-PBC **84**.

With the successful Lewis acid-promoted cross-coupling of 8Br-4EE-PBC **84** with TMB-$B(OH)_2$ **42** to afford the desired 3,4-*trans* pseudo-dimer **84** in excellent yield and stereo-selectivity, the model cross-couplings were complete. Attention then turned towards the elucidation of the mechanism of this coupling and the application of these methods to the formation of the desired catechin-catechin dimer **68**.

3.2.4 Studies towards the elucidation of the mechanism of the Lewis acid-promoted cross-coupling reaction.

The Lewis acid-promoted cross-coupling of C4-ether **83** with boronic acid **42** described above (Section 3.2.3.3) was without literature precedent. As a result an investigation towards the elucidation of the mechanism of this coupling was carried out.

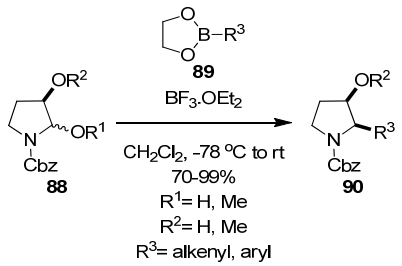
3.2.4.1 Initial mechanistic considerations.

The mechanism of the so-called biomimetic pathways (Section 1.6) towards the synthesis of 4→8 interflavan bonds proceeded *via.* an initial Lewis acid-promoted activation of some C4-electrophile, followed by electrophilic aromatic substitution of the C8-H of another catechin moiety (Section 3.1.2). The mechanism of the developed coupling (Section 3.2.3.4) compared to these biomimetic-type methods was complicated by the use of the boronic acid derivative; as such species are not intrinsically nucleophilic. Perhaps the greatest question in determining the mechanism became was the boronic acid activated to the nucleophilic "boronate" anion during the coupling, and if so what was providing that activation?

As already described (Section 2.1.2.4), the successful application of boronic acids in Suzuki cross coupling reactions required the presence of a base. The base activated the boronic acid to the "boronate" anion, which was supposedly the active nucleophile in transmetallation of the metalloid to the Pd centre. Two other nucleophilic additions of boronic acid derivatives supported this activation to the "boronate" anion as a key requirement for nucleophilic activity of these species.

Batey *et al* [115] reported the Lewis acid-promoted addition of alkenyl and aryl boronate esters **89** to *N*-acyliminium ions (Scheme 27). This reaction represents the closest precedent to the Lewis acid-promoted cross-coupling described in Section 3.2.3.4.

Scheme 27: Batey *et al* Lewis acid-promoted addition of alkenyl and aryl boronate esters 89 to *N*-acyliminium ions.



In this reaction, Batey *et al* claimed that the presence of the C3-OR group of **88** was critical to the success of the reaction. Presumably, complexation of the boron centre of boronate ester **89** to this oxygen atom completed the required activation to the "boronate" anion nucleophilic species. This species then underwent nucleophilic addition of the *N*-acyliminium ion generated by the addition of the Lewis acid to produce the coupled products **90**.

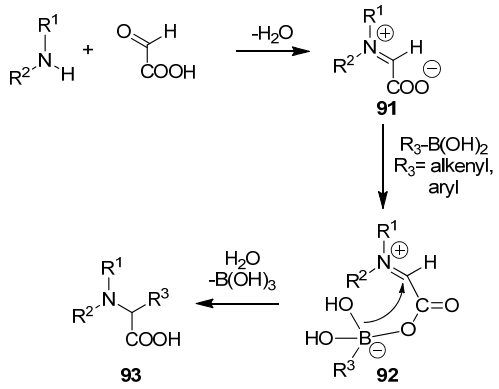
The final example of nucleophilic addition of boronic acids was the Petasis reaction.[116] This reaction involved the addition of boronic acids to *α*-iminocarboxylate species. The synthesis of *α*-amino acids *via*. the Petasis reaction was reviewed by Kaiser *et al*.[117] A useful discussion of the mechanism of this reaction was presented in this review.

The activation of the boronic acid to the "boronate" anion was achieved through intramolecular complexation of the carboxylate anion of the generated *α*-iminocarboxylate species **91** (Scheme 28) to provide complex **92**. Once activated as the "boronate" anion, the carbon attached to boron underwent intramolecular nucleophilic attack at the *α*-imine carbon to produce the desired *α*-amino acids **93**.

In each example above, activation of the boronic acid derivatives to their corresponding "boronate" anion complex was a critical prerequisite for the nucleophilic activity of such species. Armed with this knowledge, it was assumed that such activation of 2,4,6-trimethoxyphenylboronic acid (**42**) was required to

provide nucleophilic activity of this species in the Lewis acid-promoted cross-coupling with C4-ether **83** (8Br-4EE-PBC).

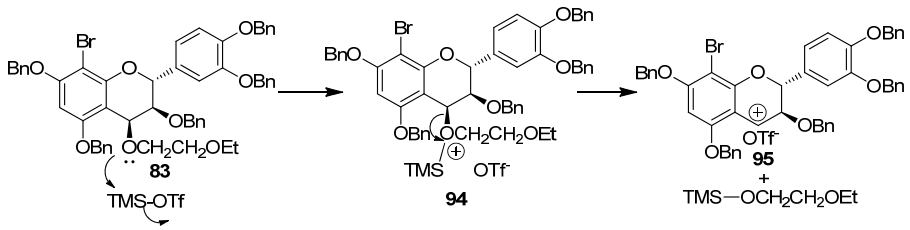
Scheme 28: Mechanism of the synthesis of functionalised *α*-amino acids *via*. nucleophilic addition of boronic acids (the Petasis reaction).



3.2.4.2 Step 1: Lewis acid-promoted activation of C4-ether.

The first mechanistic step of the Lewis acid-promoted coupling of C4-ether **83** (8Br-4EE-PBC) with boronic acid **42** was the initial complexation of the Lewis acid to the C4-oxygen to create the necessary C4-electrophilic species **94** (Scheme 29). The deep purple colour developed upon addition of the Lewis acid to C4-ether **83** was assumed to be due to this complexation. The nature of the C4-electrophilic species as either a C4-oxonium species **94** or a full C4-carbocationic species **95** was not clear. The nature of the species may have implications in the stereoselectivity of the nucleophilic addition; but this will be discussed in due course.

Scheme 29: Lewis acid-promoted activation of C4-ether 83.

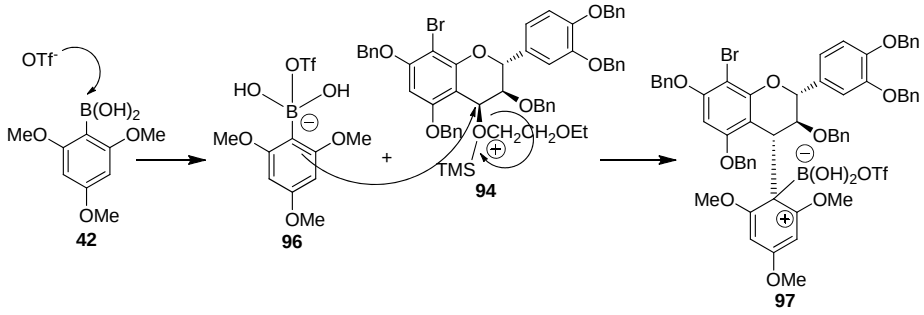


3.2.4.3 Step 2: Nulceophilic addition of boronic acid 42 to C4-electrophilic species.

The second step of the coupling reaction involved the proposed activation of boronic acid **42** to its requisite "boronate" anion, followed by nucleophilic attack at the C4-

electrophilic centre (Schemes 30 and 31). Two potential pathways for the activation of boronic acid **42** to its "boronate" anion were identified. First, the generated triflate (OTf^-) anion complexed to the vacant p-orbital of the boronic acid to form the "boronate" species **96**, which then acted as the nucleophilic species in the formation of the pseudo 4→8 bond (scheme 30).

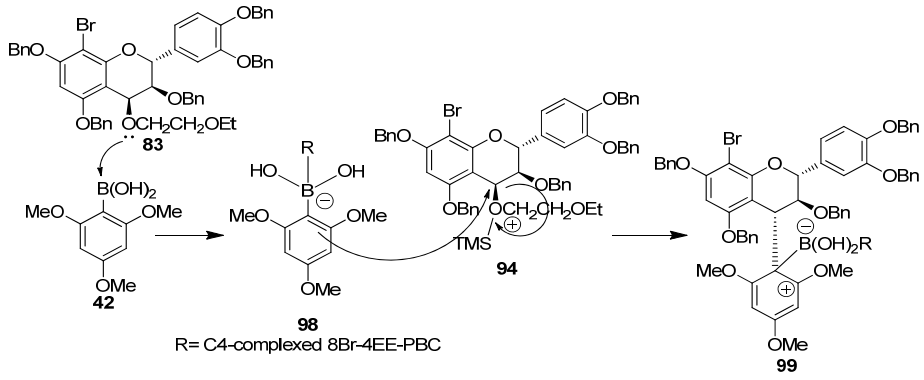
Scheme 30: Activation of boronic acid 42 by triflate anion and subsequent pseudo 4→8 bond formation.



The second pathway involved the complexation of the vacant boron p-orbital to the C4-oxygen of an inactivated C4-ether **83** (8Br-4EE-PBC). This formed the activated "boronate species **98**, which then underwent nucleophilic addition with the C4-electrophilic species **94** (Scheme 31).

The trimethylsilyl ether of 2-ethoxyethanol ($TMS\text{-}OCH_2CH_2OEt$) produced was never isolated in any reaction. However, carrying out the reaction in an NMR tube and subsequent *in situ* ^1H and ^{13}C NMR experiments confirmed its formation as the reaction proceeded.

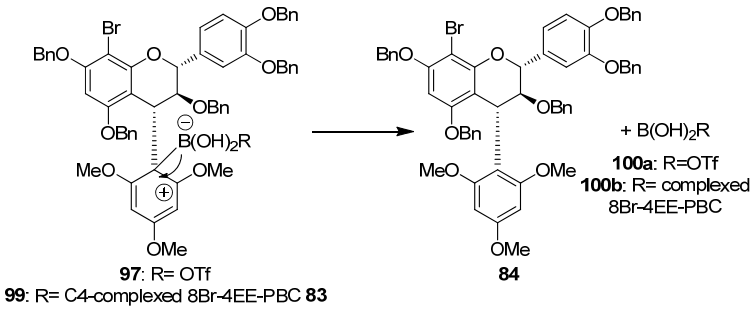
Scheme 31: Activation of boronic acid 42 by complexation of C4-ether 83 and subsequent carbon-carbon bond formation.



3.2.4.4 Step 3: Rearomatisation to provide pseudo 4→8 dimer 84.

The final step of the mechanism by either of the above proposed pathways involved the rearomatisation of the trimethoxybenzene derivative through the loss of the boron derivative attached to the *ipso* carbon (Scheme 32). Pseudo-dimer **84** was produced as a result, along with the requisite boric acid derivatives **100a** or **100b**. The identity of these boric acid derivatives is assumed. No attempts to determine their identity were carried out. Following quenching, no boron containing species were found in the crude reaction mixture after extraction into organic solvent and concentration, which suggests any boron containing compounds partitioned into the aqueous phase.

Scheme 32: Rearomisation of intermediates 97 and 99 to provide pseudo-dimer 84.



In both pathways, an S_N2-type addition has been assumed, which provides the obtained 4*α* stereochemistry of the pseudo 4→8 bond. The stereochemical considerations of this bond formation will be discussed in detail shortly.

3.2.4.5 Studies towards determination of mechanistic pathway.

It was clear from the two proposed mechanisms for activation of boronic acid **42** that the first was specific towards the use of TMSOTf as the Lewis acid (Scheme 30). The second, however, could potentially be applied to the use of other Lewis acids and may also require only catalytic quantities of Lewis acid for complete coupling (Scheme 31). Accordingly, the cross-coupling of 8Br-4EE-PBC **83** to boronic acid **42** was carried out using either stoichiometric or catalytic quantities of TMSOTf, $BF_3.OEt_2$ or $TiCl_4$ as the Lewis acid in a variety of solvents (Table 1). In all reactions, the Lewis acid was added to a stirred solution of C4-ether **83** and boronic acid **42** at the specified temperature, and then stirred at the specified temperatures for the quoted time frames, followed by quenching with sat. aq. $NaHCO_3$.

Table 1: Lewis acid-promoted cross-coupling of C4-ether 83 with boronic acid 42 using stoichiometric or catalytic quantities of Lewis acid.

Entry	Lewis acid (equiv)	Solvent	Temp (^oC)	Time (hrs)	% conv. [a]	% yield [b]
1	None (control)	THF	rt	24	0	0
2	TMSOTf (1.1)	THF	-78 to rt	3	100	80-90
3	TMSOTf (1.1)	CH_2Cl_2	-78 to rt	3	100 [c]	0
4	TMSOTf (0.2)	THF	-78 to rt	24	100	75
5	TMSOTf (0.2)	THF/$PhCH_3$	-78 to rt	24	100	n.d. [e]
6	TMSOTf (0.2)	$PhCH_3$	0 to rt	24	100	n.d.
7	$BF_3.OEt_2$ (1.1)	THF	-78 to rt	3	0	0
8	$BF_3.OEt_2$ (1.1)	CH_2Cl_2	-78 to rt	3	100 [b]	0
9	$BF_3.OEt_2$ (1.1)	$PhCH_3$	0	2	100	65
10	$BF_3.OEt_2$ (0.2)	$PhCH_3$	0 to rt	24	100	60
11	$TiCl_4$ (0.2)	THF	0 to rt	24	100	n.d.
12 [d]	TMSOTf (0.2)	THF	-78 to rt	24	100	70

[a]: Conversion of starting C4-ether **83** determined by ^1H NMR analysis of crude reaction mixtures.

[b]: Isolated yield of pseudo-dimer **84** following silica chromatography.

[c]: No coupling product was found, oligomeric products of unknown composition were formed.

[d]: 1,3,5-trimethoxybenzene (**33**) was used as the nucleophile instead of boronic acid **42**.

[e]: n.d. indicates that the crude reaction mixture was analysed by ^1H NMR and showed complete conversion of C4-ether **83** to pseudo-dimer **84**, but isolation was not conducted.

It was immediately apparent all three Lewis acids surveyed effectively promoted the coupling reaction when employed in stoichiometric or catalytic quantities. Also, the %-conversion of C4-ether **83** and the isolated yields of pseudo-dimer **84** were comparable using either catalytic or stoichiometric treatments, with longer reaction times required for the catalytic reactions. Importantly, entry 1 shows that some quantity of Lewis acid is required to promote the coupling. The stirring of a C4-ether **83**/ boronic acid **42** solution in THF for up to 24 hours afforded no reaction. TLC analysis of the reaction mixture at regular intervals indicated both starting materials were present unaltered. The coupling also proceeded in all solvent mixtures apart

from CH_2Cl_2 (entries 2 and 5) regardless of the Lewis acid employed. In the cases of entries 2 and 5, several unidentified products formed. ^{1}H NMR analysis of the crude mixtures of these reactions showed a multitude of peaks in the 5-7 ppm range, which suggested that uncontrolled oligomer formation had occurred. The formation of these products could be attributed to the poor solubility of boronic acid **42** in CH_2Cl_2. Without this species available in solution, side reactions to form oligomeric products dominated. Also, the use of THF in conjunction with $BF_3.OEt_2$ gave no reaction (entry 7). It was not clear why this lack of reactivity was observed, but it was possibly attributed to the irreversible complexation of THF with the Lewis acid rather than any incompatibility of the coupling partners with the Lewis acid. Finally, the coupling reaction was also successful using 1,3,5-trimethoxybenzene (**33**) as the nucleophilic species instead of boronic acid **42** (entry 12) in the presence of a catalytic quantity of Lewis acid. This provided pseudo-dimer **84** in comparable yield to that obtained in the coupling using **42** as the nucleophile (entry 4). The implications of this result will be discussed in the next section. Importantly, the pseudo-dimer product of this coupling showed identical ^{1}H and ^{13}C NMR spectral properties to the pseudo-dimer **84** formed by coupling of boronic acid **42**. This proved the same product **84** was produced from the coupling of either **33** or **42** to 8Br-4EE-PBC **84** as should be expected.

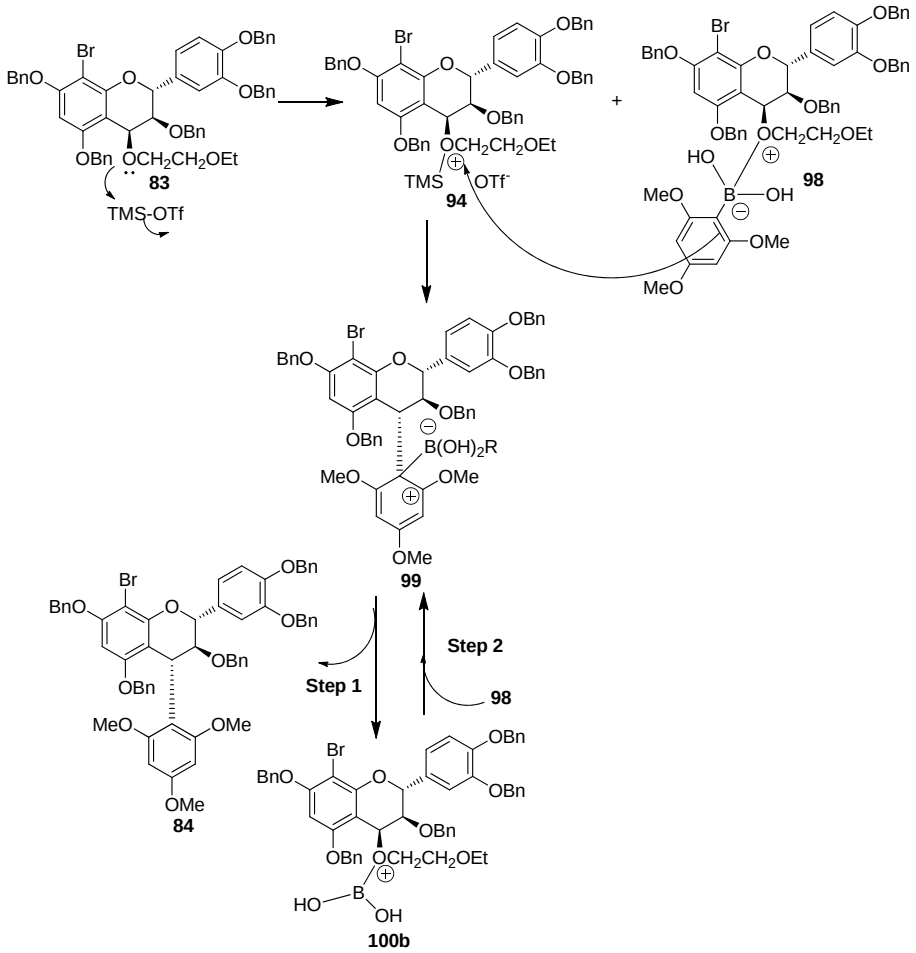
3.2.4.6 Proposed mechanism for catalytic Lewis acid-promoted coupling.

It was clear from Table 1 that the general mechanism for the catalytic Lewis acid-promoted coupling of C4-ether **83** and boronic acid **42** proposed in Scheme 31 was in operation rather than the specific triflate anion activation mechanism proposed in Scheme 30. To account for the catalytic nature of the coupling, the following extension of the Lewis-acid promoted coupling proposed in Scheme 31 was suggested (Scheme 33).

Following an initial Lewis acid-promoted coupling to produce intermediate **99**, rearomatisation of **99** provided pseudo-dimer **84** and complex **100b** (step 1). This boric acid complex provided another C4-electrophilic site, which underwent nucleophilic addition with another molecule of complex **98** (step 2). This addition provided a further molecule of intermediate **99**, which could undergo further rounds of steps 1 and 2 until all the C4-ether **83** was consumed. This mechanism accounted

for the use of catalytic quantities of Lewis acid in the coupling reaction. While Schemes 31-33 show only TMSOTf as the Lewis acid, it is clear from Table 1 that either $BF_3.OEt_2$ or $TiCl_4$ could also promote the initial formation of intermediate **99**.

Scheme 33: Catalytic cycle for C4-ether 83/boronic acid 42 condensation.

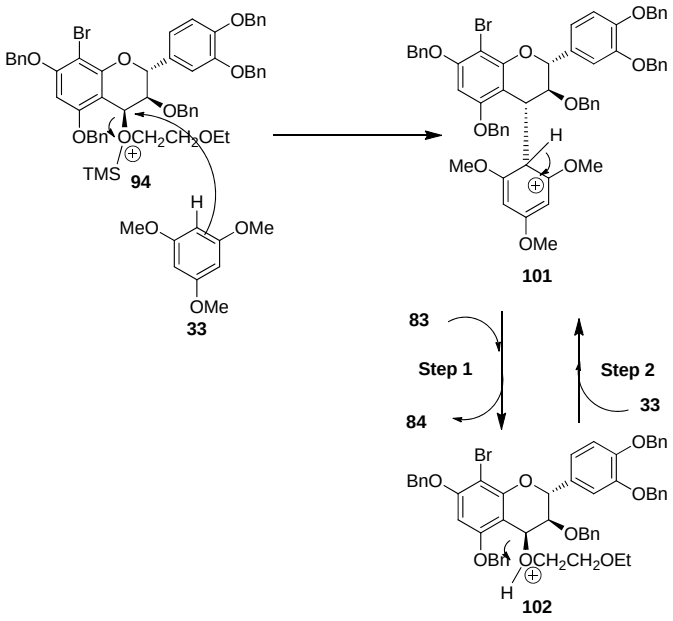


From Table 1, entry 1 it was apparent that boronic acid **42** was not sufficiently Lewis acidic to promote the formation of an appropriate C4-electrophilic species. So in order to start the catalytic cycle, the addition of a catalytic or trace quantity of a strong Lewis acid was required to promote the initial activation of C4-ether **83** and hence promote the coupling. The rearomatisation of the intermediate **99** was the critical step of the coupling as the generated boric acid species **100b** was sufficiently electrophilic to allow a further coupling event at C4 of this species.

The catalytic coupling of C4-ether **83** with TMB **33** (Table 1, entry 12) was proposed to follow a similar, but modified catalytic cycle. Following formation of C4-

electophilic species **94**, it undergoes nucleophilic attack by **33** *via.* an electrophilic aromatic substitution pathway (Scheme 34).

Scheme 34: Proposed catalytic cycle for Lewis acid-promoted coupling of C4-ether 83 with 1,3,5-trimethoxybenzene (33).



Rearomatisation of the generated intermediate **101** through proton abstraction by the C4-oxygen of 8Br-4EE-PBC **83** provided the pseudo dimer product **84** (step 1). The generated C4-electrophilic species **102** then underwent nucleophilic attack by TMB **33** to provide a further round of intermediate **101** (step 2). The regeneration of **101** established a catalytic cycle of steps 1 and 2. Like the proposed boronic acid coupling cycle above, the addition of a trace quantity of strong Lewis acid TMSOTf was essential in order to form the necessary intermediate **101** required to promote catalytic activity. This electrophilic aromatic substitution type reaction is very reminiscent of the 4→8 oligomer syntheses by Saito *et al* (Section 1.6.2), Tückmantel *et al* (Section 1.6.2), Ohmori *et al* (Section 1.6.5) and Tarascou *et al* (Section 1.6.6). It is therefore highly likely that these types of electrophilic aromatic substitution-type catechin oligomer formations would proceed in the presence of catalytic quantities of Lewis acid-promoters.

It should be stressed that these are only proposed mechanisms for the Lewis acid-prompted coupling of 8Br-4EE-PBC **83** with either TMB-B(OH)$_2$ **42** or TMB **33**. Detailed mechanistic studies were considered too time consuming for the project and

so were not carried out. A few experiments were identified as potentially useful for elucidation of the mechanism and identification of reaction intermediates. *In situ* ^{1}H and ^{11}B NMR experiments may help to identify the intermediates formed during the coupling reaction. Also, ^{11}B NMR analysis of the aqueous phase post quenching may give some insight into the fate of any boron-containing compounds.

3.2.4.7 Stereochemical considerations of Lewis acid-promoted coupling.

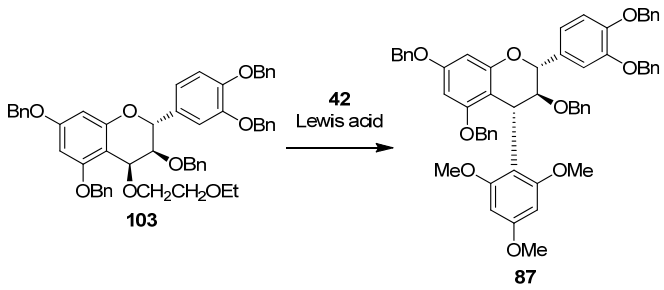
It was identified in Scheme 29 that the coupling of the C4-electrophilc species could proceed by nucleophilic attack of oxonium species **94** or C4-carbocationic species **95**. Nucleophilic attack of the two species would be indicative of S_N2 or S_N1-type displacements, respectively. As determined in section 3.2.3.4, only the 4*α* isomer of pseudo-dimer **84** was produced in the coupling reaction. This suggested that the reaction proceeded by the S_N2 pathway proposed in Schemes 30 and 31. The 4*β* stereochemistry of the C4-oxonium ion dictated nucleophilic attack from the *α*-face to provide the 4*α*-pseudo-dimer product **84**. The S_N1 pathway could not be ruled out though. The orientation of the C3-subsituent of C4-carbocation **95** may have blocked nucleophilic attack at the *β*-face of the carbocation. If this was the case the desired 4*α*-pseudo dimer product would also be produced selectively. There was no method to determine which pathway the reaction followed, but the end result was the same. The desired 4α, or 3,4-*trans* product **84** was produced.

In the Lewis acid-promoted couplings presented in Table 1, the 4*α*-psuedo-dimer **84** was obtained regardless of the Lewis acid and solvent employed. The stereochemical outcome of the coupling was also unaffected whether stoichiometric or catalytic quantities of Lewis acid were employed. On top of this, the 4*α*-isomer of **84** was produced using either boronic acid **42** or TMB **33** as the nucleophile, which indicated that the nature of the nucleophile did not play a role in the stereoselectivity of the coupling. These factors indicated that only the C4-ether **83** played a role in the stereochemical selectivity of the reaction.

The same batch of 8Br-4EE-PBC **83** was used for all the couplings presented in Table 1. Interestingly, ^{1}H NMR analysis of the crude materials of couplings that provided pseudo dimer **84** showed the same 90:10 product ratio of pseudo-dimer **84** (8Br-4TMB-PBC) to the by-product **87** (4TMB-PBC, Section 3.2.3.4, Figure 4). This suggested 4TMB-PBC **87** formed from reaction of C4-ether **103** (4EE-PBC) with

boronic acid **42** rather than by debromination of either 8Br-4EE-PBC **83** or 8Br-4TMB-PBC **84** under the Lewis acidic conditions (Scheme 35).

Scheme 35: Formation of by-product 4TMB-PBC 87 from 4EE-PBC 103.



It was suspected the presence of 4EE-PBC **103** was due to incomplete C8-bromination in the formation of C4-ether **83** (8Br-4EE-PBC, Section 3.2.3.2). This was confirmed by ^{1}H NMR analysis of the residual C4-ether **83** used in the coupling reactions, which showed the presence of an impurity (~10%). The C6-H and C8-H doublets of this impurity at 6.23 and 6.27 ppm, respectively, indicated the presence of the non-brominated impurity **103**.

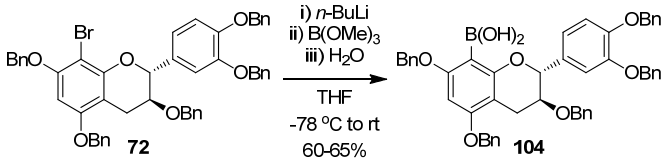
With these observations, the mechanistic studies of the Lewis acid-promoted cross-couplings were concluded. The proposed mechanism was not further investigated as the development of the coupling towards the formation of 4→8 catechin-catechin was considered of more significance in terms of the project aims.

3.2.5 Formation of a catechin C8-boronic acid derivative.

Following from the successful model cross-coupling of 8Br-4EE-PBC **83** with boronic acid **42** (Section 3.2.3.4), the next logical step was to examine the use of this novel coupling in the formation of the desired 4→8 catechin-catechin dimer **68**. In order to examine the Lewis acid-promoted cross-coupling towards this dimer, the requisite C8-boronic acid derivative was required.

The synthesis of C8-boronic acid **104** (PBC-B(OH)$_2$) was achieved through lithium-halogen exchange of 8Br-PBC **72** using *n*-BuLi, followed by transmetallation using B(OMe)$_3$ and hydrolysis with water (Scheme 36).

Scheme 36: Formation of the C8-boronic acid 104 (PBC-B(OH)$_2$) from 8Br-PBC (72).



Initial attempts to form C8-boronic acid **104** using *ca.* 50-100 mg of 8Br-PBC **72** gave no desired product, affording only protonated PBC **52b**. This indicated that the C8-organolithium **71** was forming, but transmetallation did not occur at this small scale. The organolithium was then quenched upon addition of water to give PBC **52b**. The reasoning for the lack of transmetallation was not clear, but this did mirror the results found for the formation of TMB-B(OH)$_2$ **42** (section 2.2.4). Increasing the scale of the reaction to 0.5 mmol (*ca*. 400 mg of 8Br-PBC **72**) solved this transmetallation issue. Below this scale, no boronic acid was ever isolated. At this scale, the desired C8-boronic acid **104** was consistently isolated in 40-50% yield following silica chromatography. A steady increase in the isolated yield of the boronic acid was observed with increasing reaction scale. When conducted using 2-3 grams of the starting 8Br-PBC **72**, the product **104** was isolated in good yields (60-65%).

Interestingly, the use of a 4:1 THF/Et$_2$O mixture as the reaction solvent was found to be beneficial when the reaction was conducted at *ca.* 0.5 mmol scale. At this scale, the use of only THF as the solvent gave somewhat unpredictable results and product yields varied by up to 20%. Using the optimised solvent mixture this unpredictability was eliminated, and yields of 40-50% were consistently achieved. This effect was not seen at gram scales, and the isolated yield of C8-boronic acid **104** did not vary greatly regardless of whether THF only or THF/Et$_2$O was employed as the solvent. As a consequence, THF only was used as the preferred solvent when conducting the larger scale metallations for no other reason than for simplicity in preparation of the reaction.

Purification of C8-boronic acid **104** was achieved using silica chromatography. This use of silica chromatography in the isolation of boronic acids is unusual, as generally most can be purified by crystallisation and are often reported to be sensitive to silica

chromatography. Attempts to crystallise boronic acid **104** were not successful, with the product generally remaining in solution. Through the use of the silica gel column the major byproduct, PBC **52b**, eluted first, followed by a small amount (*ca*. 5-10%) of an unidentified byproduct. Finally, the boronic acid was eluted. Following concentration, C8-boronic acid **104** was obtained as a white foamy solid.

A combination of ^{1}H, ^{13}C and ^{11}B NMR, along with HRMS confirmed the structure of the C8-boronic acid **104** (PBC-$B(OH)_2$). The characteristic singlet at 6.27 ppm in the ^{1}H NMR was attributed to the C6-H, which confirmed that C8 was indeed substituted as the boronic acid. The remaining ^{1}H peaks were observed at the shifts expected for penta-benzylated catechin derivatives. The ^{13}C spectrum showed a 5-10 ppm downfield shift of the C7, C5 and C8a in the 155-165 ppm region compared to the starting bromide. This was attributed to the boron group at C8 providing an electron withdrawing effect, which reduced the electron density of the A-ring. As a result, these carbon resonances were shifted downfield. The C8 carbon itself was not present in the spectrum. This was due to quadrupolar relaxation of the carbon attached to boron and has been reported as a common effect seen for carbon-boron bonds.[118] The remaining ^{13}C peaks were not greatly affected by the presence of the boron group, and the observed shifts were consistent with that seen for penta-benzylated catechin derivatives. The ^{11}B NMR spectrum of the compound showed a broad peak at 29.1 ppm, which was consistent with that seen for free boronic acids.[104, 118] As this was the first time ^{11}B NMR had been utilised, a short discussion of running and interpreting ^{11}B NMR has been included in the next section. HRMS analysis of the product gave a molecular formula of $C_{50}H_{45}BO_8$, which was consistent with that of the expected structure.

3.2.6 ^{11}B NMR: Establishment of method and interpretation of spectra.

As ^{11}B NMR was a useful tool for characterisation of boron containing species, this technique was used to characterise PBC-$B(OH)_2$ **104** as the free boronic acid beyond any doubt. A broad peak at 29.1 ppm in the ^{11}B NMR spectrum of this compound was observed, which was in the range of chemical shifts expected for that of the tri-coordinate boronic acid species (Section 3.1.6).

The establishment of the ^{11}B NMR experiment was met with some difficulty. Initial attempts to run ^{11}B NMR spectra in $CDCl_3$ using regular pyrex NMR tubes using

$BF_3.OEt_2$ as an external standard in a coaxial insert gave no clear peaks beyond that seen for the sharp $BF_3.OEt_2$ reference peak. The use of quartz tubes in conjunction with $CDCl_3$ as the NMR solvent also gave the same result. Switching the NMR solvent to CD_3CN provided the key to gaining a clear ^{11}B NMR signal. The use of either quartz or pyrex tubes provided clear ^{11}B NMR signals when employing this solvent. Quartz tubes were used preferentially due to the lower boron content of these tubes compared to pyrex. Using a quartz tube and CD_3CN as the NMR solvent with $BF_3.OEt_2$ as an external standard in a coaxial insert, boronic acid PBC-$B(OH)_2$ **104** showed a broad ^{11}B NMR peak at the reported shift.

The observed boronic acid peak was very broad (*ca.* 1000 Hz) at 30 ^oC. This peak broadness was due to the fast relaxation of the boron centre *via.* quadrupolar interactions. Boron nuclei have been reported to relax in 10^{-3} to 10^{-2} seconds following excitation.[104] Conversely, boron atoms in symmetrical environments, such as $BF_3.OEt_2$, relax at much slower rate. As a result, the ^{11}B NMR peak due to $BF_3.OEt_2$ was much sharper compared to boronic acid **104**. As the boron nuclei relaxes very fast after excitation, a short acquisition time (0.1-0.2 s) and relaxation delay (0.1-0.2 s) were employed as the acquisition parameters for the ^{11}B NMR experiment.

In response to the broadness of the ^{11}B NMR peak of PBC-$B(OH)_2$ **104**, the NMR experiment was conducted at progressively higher temperatures. As the temperature increased, the ^{11}B peak became progressively sharper. After some experimentation, 60 ^oC was found to be the optimal temperature, providing a balance between the peak broadness and the volatility of the CD_3CN solvent. The optimised ^{11}B NMR experiment was established using CD_3CN as the solvent in a quartz tube with a coaxial insert containing the external reference $BF_3.OEt_2$ at 60 ^oC using the above acquisition parameters.

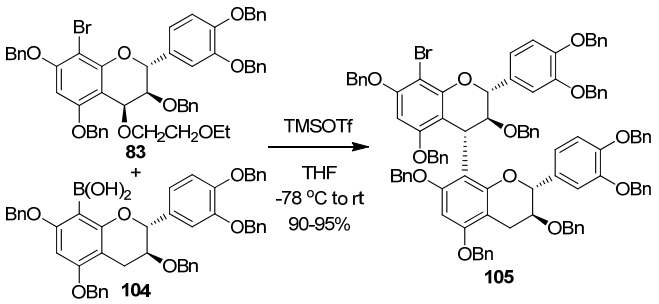
In the ^{11}B NMR spectrum of PBC-$B(OH)_2$ **104**, a sharp peak at *ca.* 20 ppm was observed. This peak was attributed to the presence of boric acid ($B(OH)_3$) as an impurity. The chemical shift of this peak was consistent with that reported for boric acid,[119] and the sharp peak observed was consistent with a boron centre in a symmetrical environment. This boric acid impurity was attributed to a small amount of decomposed boronic acid and/or hydrolysed $BF_3.OEt_2$ in the NMR sample.

3.2.7 Extension of the Lewis acid cross coupling to catechin-catechin dimer formation.

With the successful gram scale synthesis and structural determination of the desired C8-boronic acid **104**, attention turned to the use of this compound in the Lewis acid-promoted cross-coupling in the synthesis of the catechin-catechin dimer **105**. TMSOTf promoted coupling of 8Br-4EE-PBC **83** with C8-boronic acid **104** using the initially developed stoichiometric Lewis acid conditions in THF (Section 3.2.3.4) furnished the desired dimer (Scheme 37).

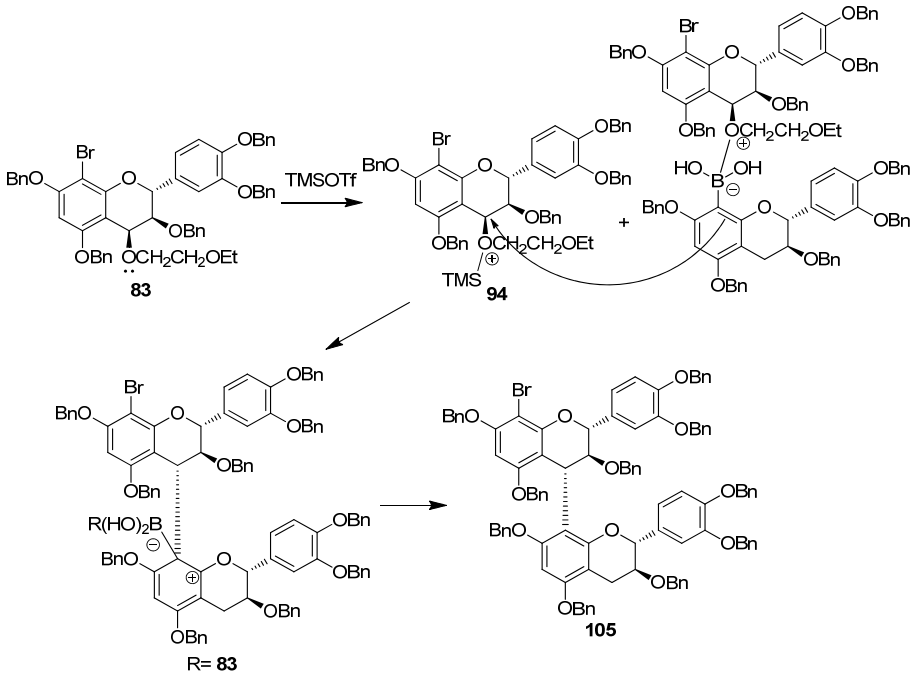
Under these coupling conditions, the desired 3,4-*trans*, 4→8 linked dimer **105** (8Br-PBC-PBC) was synthesised in good to excellent yields following purification when boronic acid **104** (PBC-B$(OH)_2$) was employed in 1.1 equivalents excess compared to C4-ether **83**. The actual isolated yield of the product depended strongly upon the scale of the reaction. When using 50-100 mg of C4-ether **83**, coupling yields of 75-80% were generally achieved. This yield gradually increased to 90-95% when the coupling was carried out at gram scales. The origin of this scaling effect is unknown, but considering that possible future uses of these compounds for sensory analysis and model ferments would require large quantities of such materials, the greater efficiency of the process at larger scale would certainly facilitate the access to gram-scale quantities of procyanidin oligomers. Importantly, there was no evidence of the formation of trimer or higher oligomeric species. This showed that the C8-bromide of 8Br-4EE-PBC **83** was performing its desired function as a blocking group (Section 3.2.3.1).

Scheme 37: Synthesis of catechin-catechin dimer 105 by Lewis acid-promoted cross-coupling of C4-ether 83 and C8-boronic acid 104.



It was inferred that the mechanism for this coupling should mirror that proposed for the formation of the model system pseudo-dimer **84** (8Br-4TMB-PBC). That is, boronic acid **104** complexed with the C4-oxygen of C4-ether **83**, activating the boronic acid to the "boronate" anion species which was the active nucleophile. Complexation of the Lewis acid with the C4-oxygen of C4-ether **83** activated C4 towards nucleophilic attack (compound **94**). The activated boronic acid then nucleophilically attacked the activated C4 species **94** from the *α* face to forge the key 3,4-*trans* 4→8 interflavan bond. Rearomatisation of the A-ring of the "lower" unit (D-ring) by loss of the borate ester resulted in the desired dimer **105** product (Scheme 38). Notably, both the 4*α* selectivity and reaction time for dimer **105** formation were the same as that observed for the model pseudo-dimer **84** formation. These results strongly suggested that the greater steric bulk of the C8-boronic acid **104** compared to TMB-$B(OH)_2$ **42** did not affect the selectivity or the coupling rate to any noticeable extent. The use of catalytic quantities of Lewis acid was never attempted for this coupling as the slower coupling rate observed using catalytic quantities was not desirable. It can be inferred though that use of catalytic quantities of Lewis acid should be applicable to dimer **105** formation.

Scheme 38: Proposed mechanism for the formation of dimer 105 from C4-ether 83.



Silica gel chromatography was employed in the purification of 8Br-PBC-PBC **105**. Following quenching, the crude reaction mixture contained both the desired dimer **105** and a small amount of PBC **52b**, formed by deboronation of excess boronic acid **104**. The two compounds showed very similar R_f values in all TLC solvents analysed. The presence of the C8-bromide of the dimer **105** did provide a small polarity difference between the two products. Through the use of a large silica column (*ca*. 50 times volume by mass) the two compounds were separated. After concentration, 8Br-PBC-PBC **105** was isolated in the above yields (75-95%) as a white foamy solid. Attempts to purify the dimer by crystallisation proved futile due to the amorphous nature of the solid.

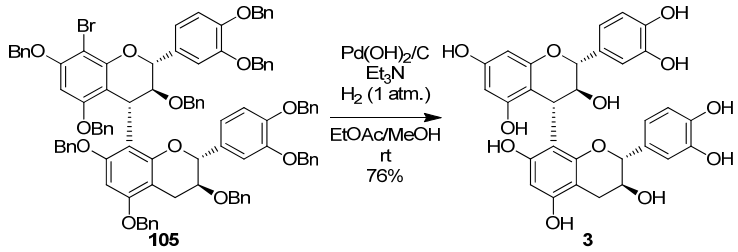
The identity and stereochemistry of the product **105** (8Br-PBC-PBC) was confirmed by the use of 1D and 2D ^{1}H and ^{13}C NMR analysis combined with HRMS analysis. Interpretation of both the ^{1}H and ^{13}C NMR spectra was complicated by restricted rotation around the 4→8 bond. This restriction gave rise to two rotational isomers that showed similar, but sufficiently different NMR spectra to result in numerous overlapping regions which made peak identification difficult. The ^{1}H resonances for the C2-H and C4-H of the "top" catechin unit were identified at 4.65 ppm and 4.89 ppm, respectively. This was consistent with the shifts for these protons seen in the model pseudo-dimer **84** (8Br-4TMB-PBC). In an analogous ROESY experiment used for the stereochemical determination of pseudo-dimer **84** (Section 3.2.3.4), an nOe correlation was seen between the C2-H and C4-H protons of the "top" flavan unit. This confirmed that these two protons were on the same side of the C-ring and it followed the desired 4α, or 3,4-*trans* isomer was obtained. For the ^{13}C spectrum, the key C4 peaks of the two flavan units were observed at 36.5 ppm and 27.5 ppm respectively. The first resonance was consistent with that expected to be found for the C4 of the 4→8 bond.[31, 38, 39] The second correlated with that expected for the CH_2 group of the C4 carbon of the "bottom" catechin unit. HRMS analysis of the product gave the molecular formula $C_{100}H_{85}BrO_{12}$, which was consistent with that of the proposed structure.

With success of the novel Lewis acid cross coupling in the synthesis of 3,4-*trans*, 4→8 dimer 8Br-PBC-PBC **105**, attention then turned towards the deprotection of this compound to complete the synthesis of the targeted procyanidin B3 (**3**).

3.2.8 Formation of procyanidin B3 through removal of protecting groups.

Removal of the benzyl and C8-bromide protecting groups from dimer **105** (8Br-PBC-PBC) was attempted in order to show that the dimer synthesised by this method was indeed identical to natural procyanidin B3 (**3**). Several hydrogenolysis methods using catalytic Pd/C or $Pd(OH)_2/C$ have been reported for the benzyl deprotection of catechin oligomers.[17, 31, 39] Tarascou *et al* [39] method reported that both the C8-bromide and the benzyl groups were removed in one step using Pearlman's catalyst ($Pd(OH)_2/C$) in the presence of triethylamine (Et_3N) under an atmosphere of H_2 in an EtOAc/MeOH solvent mixture. Using such conditions, Tarascou *et al* reported almost quantitative yields of the free phenolic procyanidin dimers (**B1-B4**) from their protected analogues (Section 1.6.6). Accordingly, deprotection of dimer 8Br-PBC-PBC **105** was attempted using these conditions (Scheme 39).

Scheme 39: Deprotection of dimer 8Br-PBC-PBC 105 to provide procyanidin B3 (3).



Following overnight hydrogenolysis using these conditions, the desired deprotected procyanidin B3 (**3**) was isolated in 76% yield as a yellow solid following filtration over silica gel and concentration. This yield was not optimised and was significantly lower than that reported by Tarascou *et al*. Importantly, characterisation of the product by melting point, ^1H and ^{13}C NMR and optical rotation analysis confirmed that the synthesised procyanidin was indeed the desired (+)-catechin-4α→8-(+)-catechin dimer, or natural procyanidin B3 (**3**). The melting/decomposition point of 216-221 ^oC was in good agreement with that reported by Tarascou *et al* (218-220 ^oC).[39] Both the ^1H and ^{13}C NMR, along with the optical rotation of the product correlated with that reported by Saito *et al* for procyanidin B3 (**3**).[16, 31]

With the successful removal of the bromide and benzyl protecting groups of dimer 8Br-PBC-PBC **105**, the desired procyanidin B3 (**3**) was obtained. This showed that

the developed Lewis acid-promoted cross-coupling of C8-boronic acid **104** with C4-ether **83** was applicable to the formation of the key 4→8 interflavan bond. On top of this, the coupling selectively formed the desired 3,4-*trans* product. With that, the study towards the dimer system was completed using this novel approach. Focus then shifted to the further development of this novel coupling procedure in the iterative synthesis of catechin trimers and higher oligomers.

3.3 Conclusions.

The use of a C8-organometallic derivative in the synthesis of the 4→8 bond of catechin-catechin dimer was realised by the development of the novel cross-coupling of C8-boronic acid **104** with C4-ether **83**. Earlier attempts to use either C8-oganozinc (**69** or **77**) or C8-Grignard (**80a** or **80b**) derivatives in Pd-catalysed cross-couplings to organic halides were not successful. The air and moisture sensitivity of these derivatives, which made isolation impossible, was a major drawback to the use of these organometallics in the Pd-catalysed coupling method.

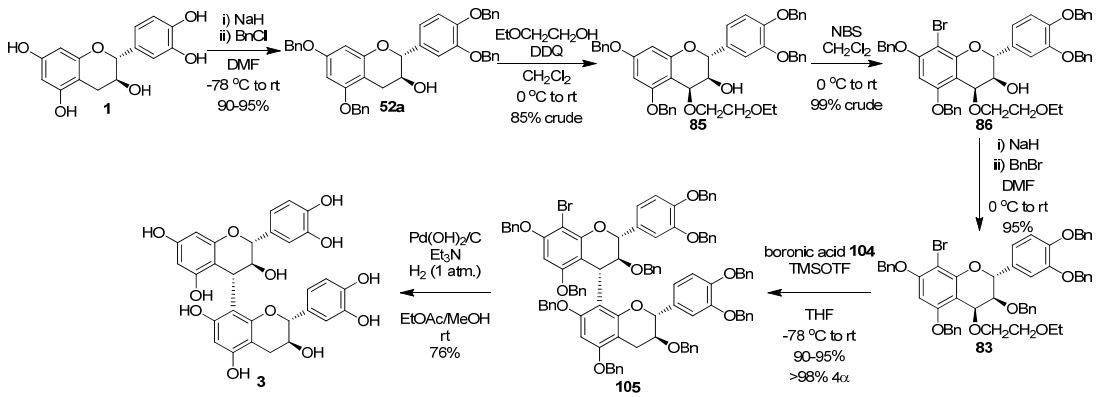
The attempted model Lewis acid-promoted cross-coupling of the C4-ether **83** with several metallated 1,3,5-trimethoxybenzene derivatives revealed that boronic acid **42** was applicable to this coupling method. Using this boronic acid, the TMSOTf-promoted coupling to C4-ether **83** was achieved in good to excellent yields to provide pseudo-dimer **84** (8Br-4TMB-PBC). As added benefits, the boronic acid was readily isolatable on a large scale and easily characterised. This contrasted with the other organometallics, which all required preparation *in situ*, followed by immediate use. Accordingly, there was no doubt that formation of the boronic acid had occurred. The use of a ROESY NMR experiment determined that the pseudo-dimer **84** (8Br-4TMB-PBC) formed by this method exhibited the desired 3,4-*trans* stereochemistry. Following this, ^{1}H NMR showed the 4α selectivity of the cross coupling was >98%.

A mechanistic study of this Lewis acid-promoted cross-coupling of boronic acid **42** showed that the reaction was also applicable to other Lewis acids using stoichiometric or catalytic quantities in several solvents. The general mechanism proposed meant the activation of the boronic acid to the nucleophilic “boronate” anionic species was achieved through complexation of the free p-orbital of the boronic acid with the C4-oxygen of C4-ether **84** (Section 3.2.4).

Following on from the model system, the developed Lewis acid-promoted cross-coupling conditions were applied to the successful gram-scale synthesis of catechin-catechin dimer **105** (8Br-PBC-PBC) in 90-95% yields. Prior to this coupling, gram quantities of C8-boronic acid **104** derivative was prepared in moderate yields (50-65%) from the C8-bromide **72** (8Br-PBC, Section 3.2.5). The same ROESY NMR experiment used for the model dimer demonstrated that the 4→8 bond of dimer **105** exhibited the desired 3,4-*trans* stereochemistry. This stereoselectivity showed that the coupling developed could potentially be applied to the synthesis of other 3,4-*trans* procyanidins.

Finally, removal of the bromide and benzyl protecting groups of dimer **105** (8Br-PBC-PBC) provided the targeted free phenolic (+)-catechin-4α→8-(+)-catechin, or natural procyanidin B3 (**3**). The synthesis of this dimer was achieved from (+)-catechin (**1**) in 6 linear steps in good 50-55% overall yield (Scheme 40).

Scheme 40: Summary of synthesis of procyanidin B3 (3) from (+)-catechin 1 *via.* the key 4→8 bond forming Lewis acid-promoted cross-coupling of C4-ether 83 with C8-boronic acid 104.



Chapter 4: Extension of the Lewis Acid-Promoted Cross-Coupling Method Towards the Iterative Synthesis of Catechin Oligomers.

4.1 Introduction.

With the successful application of the Lewis acid-promoted cross-coupling of C4-ether **83** and C8-boronic acid **104** in the synthesis of catechin-catechin dimer procyanidin B3 (**3**), attention turned to the use of this coupling protocol in the synthesis of the analogous 4→8 catechin trimer and higher oligomers. Particular attention was focussed on the development of an iterative coupling strategy in the synthesis of these higher oligomers.

4.1.1 Iterative synthetic strategies in the synthesis of trimers and higher oligomers.

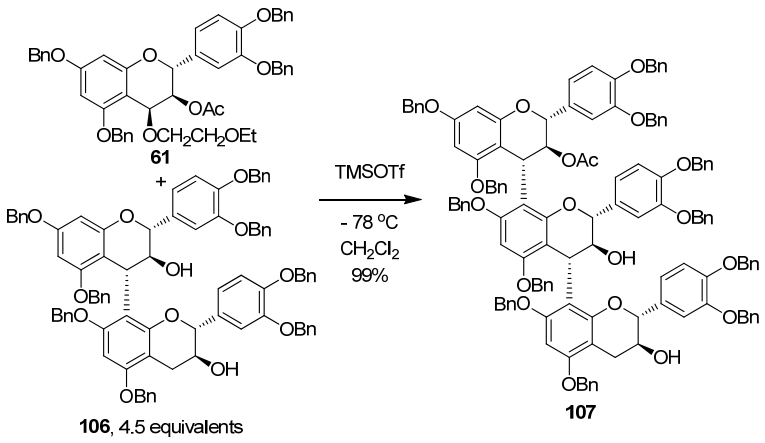
Synthetic methods towards procyanidin trimers and higher oligomers are fewer in number than their dimer counterparts. This is not surprising as the greater complexity of trimers and higher oligomers compared to dimers render them more difficult targets. Two notable methods towards synthetic trimers and higher oligomers by Saito *et al* and Ohmori *et al* were introduced in Chapter 1 (Sections 1.6.2 and 1.6.5). As both of these methods were useful in the iterative synthesis of trimers and higher oligomers, they warrant further discussion in this context.

4.1.1.1 Extension of Saito *et al* method to synthesis of procyanidin trimers and higher oligomers.

Saito *et al* [32] reported the iterative synthesis of several procyanidin trimers. These syntheses involved the use of previously synthesised dimers (Section 3.1.3.1) as nucleophiles in the TMSOTf-promoted coupling of C4-ether **61**. As an example, coupling of C4-ether **61** using dimer nucleophile **106** provided the requisite trimer **107** without any trace of higher oligomers when dimer nucleophile **106** was used in 4.5 equivalents excess (Scheme 1).

Again, the requirement for the large excess of nucleophilic dimer species was a major drawback to this method for the same reasons as stated in section 3.1.3.1. In particular, the issues of separation of the excess dimer from the trimeric products by silica chromatography were even more acute than the separation of the dimeric and monomeric species (Section 3.1.3.1).[111]

Scheme 1: Iterative synthesis of trimer from dimer using Saito *et al* methods.



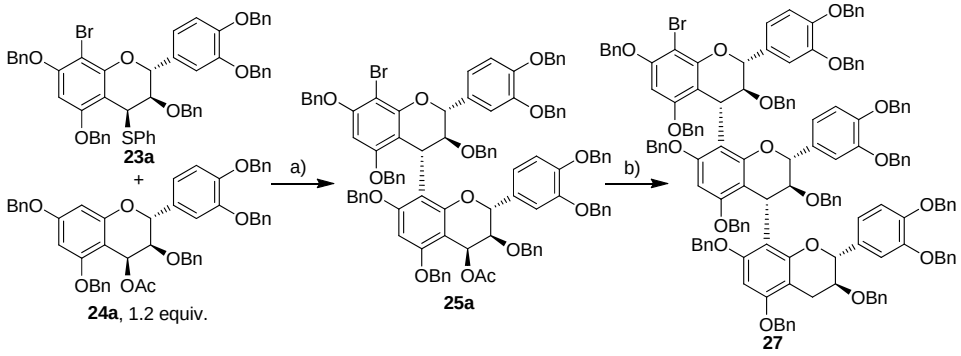
More recently, Saito and co-workers have extended this coupling strategy to the iterative synthesis of tetramer, pentamer and hexamer oligomers.[33] As with the dimer and trimer syntheses a large excess of the *n*-oligomeric nucleophile was used in the selective formation of (*n+1*)-oligomers through coupling to C4-ether **61**. The separation issues discussed above are the major drawback to this method.

4.1.1.2 Ohmori *et al* orthogonal activation strategy towards trimer synthesis.

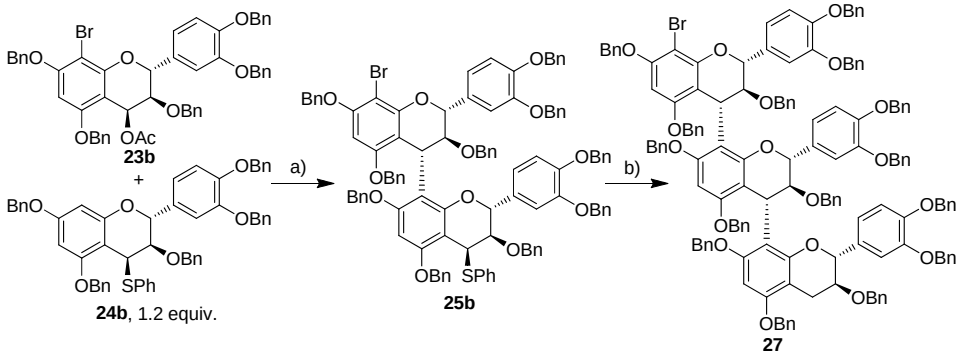
An extremely elegant and powerful iterative synthetic strategy was reported in 2004 by Ohmori e*t al*.[38] This synthesis employed the use of a C8-bromide as a blocking group to suppress uncontrolled oligomerisation (Sections 3.1.2, 3.1.3.2). This blocking group was used in conjunction with an orthogonal activation strategy employing alternate C4-electrophiles in the synthesis of the catechin dimers **25a** and **25b** and trimer **27**. The C4-SPh and C4-OAc were activated as leaving groups under soft (NIS) and hard ($BF_3.OEt_2$) Lewis acid conditions, respectively. This orthogonal activation strategy was employed to selectively promote the iterative synthesis of first the dimeric species **25a** and **25b**, and then the trimeric species **27** (Scheme 2). The C8-bromide blocking group effectively forced the extension of the oligomer chain to proceed in a "downward" direction from the C4-terminus.

Using this method, the dimeric and trimeric species were obtained in good yields with high 4α-stereoselectivity. This strategy was considered as the benchmark in the iterative synthesis of catechin oligomers.

Scheme 2: Ohmori *et al* synthesis of dimeric and trimeric catechins using an orthogonal activation strategy.



Conditions: a) NIS, -30 ^{o}C, CH_2Cl_2, b) PBC **52b** (1.2 equivalents), $BF_3.OEt_2$, -30 ^{o}C, CH_2Cl_2.



Conditions: a) $BF_3.OEt_2$, -30 ^{o}C, CH_2Cl_2 b) PBC **52b** (1.2 equivalents), NIS, -30 ^{o}C, CH_2Cl_2.

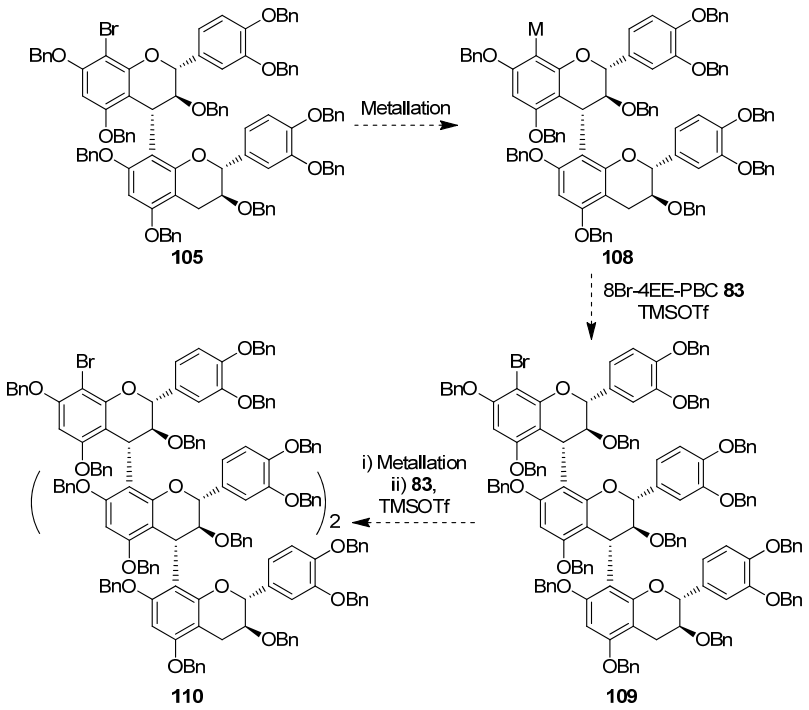
Two drawbacks to this synthetic method were identified for potential improvement in the iterative synthesis of catechin oligomers. Firstly, the synthesis of two extender species **24a** and **24b** were required in order to satisfy the orthogonal activation strategy. This aspect will be further discussed shortly. Secondly, the synthesis of C4-SPh **24a** required the use of thiophenol (PhSH), a highly noxious compound. So any synthesis that avoided the use of this compound would be beneficial to the chemist performing the synthesis.

4.1.2 Aims.

Given that the benchmark Ohmori *et al* [38] synthesis involved the extension of the growing oligomer chain from the C4-terminus, it was decided that a complementary iterative synthetic strategy would be highly useful and worthy of further investigation. In other words, an iterative strategy involving the extension of the growing chain from the C8-terminus was considered for further development. To achieve this, the synthesis of trimeric **109** and tetrameric species **110** through the use

of the Lewis acid-promoted coupling developed in Chapter 3 (Section 3.2.7) was targeted (Scheme 3).

Scheme 3: Metallation of dimer 105 (8Br-PBC-PBC) and subsequent coupling to C4-ether 83 (8Br-4EE-PBC) to give trimer 109 and repeated metallation and coupling to tetramer 110.



The critical factor noted in the extension of this Lewis acid-promoted coupling to higher oligomers was gaining access to the C8-organometallic derivatives of dimer **108** and higher oligomers. The C8-metallated dimer **108** was potentially available by metallation of the C8-bromide **105** (8Br-PBC-PBC). If this metallation could be achieved, then the C8-metallated dimer could be coupled to the C4-ether **83** (8Br-4EE-PBC) to provide trimer **109**.

Metallation of this C8-brominated trimer **109** and further Lewis acid-promoted coupling to C4-ether **83** could furnish the tetramer **110**. Conceivably repeated metallation of C8-brominated *n*-oligomers and Lewis acid-promoted couplings to 8Br-4EE-PBC **83** would furnish (*n*+1)-oligomers in an iterative fashion by extension from the C8-terminus of the growing chain. On top of this, the proposed strategy required only one chain extension species, C4-ether **83**. As a consequence, this strategy would alleviate the necessity for the synthesis of two chain extender species

as was required by Ohmori *et al* [38] in their orthogonal activating strategy discussed earlier (Section 4.1.1.2).

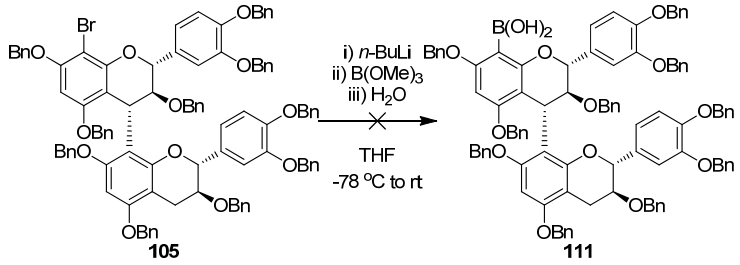
4.2 Results and Discussions.

4.2.1 Studies towards metallation of 8Br-PBC-PBC 105.

With the above strategy in mind for the formation of higher oligomers, metallation of dimer **105** (8Br-PBC-PBC) was attempted. Since C8-boronic acid **104** was successfully employed in the 4→8 Lewis acid-promoted cross-coupling (Section 3.2.7), it was logical to attempt the conversion of this bromide to the corresponding dimeric C8-boronic acid **111** (8B$(OH)_2$-PBC-PBC).

This bromide to boronic acid conversion was attempted using the low temperature lithiation with *n*-BuLi, transmetallation with $B(OMe)_3$ and hydrolysis method employed in the formation of the analogous monomeric C8-boronic acid **104** (Scheme 4).

Scheme 4: Formation of PBC-PBC-B$(OH)_2$ 111 from C8-bromide dimer 105.

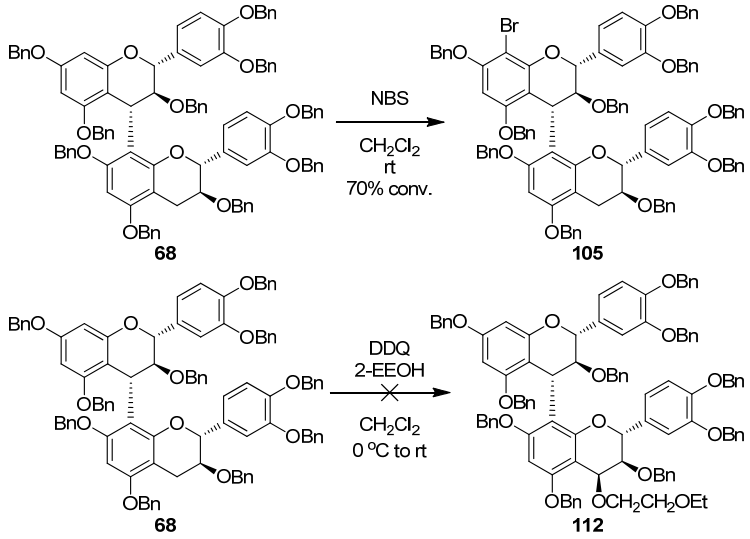


Initial attempts to form boronic acid **111** were conducted at *ca*. 0.5 mmol, the critical scale for the monomeric species noted earlier (Section 3.2.5). At this scale, no boronic acid product was obtained. TLC and ^{1}H NMR analysis of the crude reaction mixture showed that only the C8-protonated dimer **68** (PBC-PBC) had formed. This result indicated that lithiation had occurred, but the transmetallation to boron did not. Upon hydrolysis, the organolithium species was quenched to the C8-H product **68**. To further assess this scaling effect, the reaction was attempted again using one gram of the starting bromide **105**. In this case the same result was found. Only the C8-H product **68** was obtained.

It was clear there was more than a scaling issue for this transmetallation step. It was probable the larger size of the dimer compared to the monomeric C8-boronic acid

104 (PBC-B(OH)$_2$) was contributing to the lack of lithium-boron transmetallation observed. Also, in earlier unreported works,[120] it was noted that the C8-bromination or the DDQ promoted C4-oxidation of dimer **68** (PBC-PBC, Scheme 5) was far more difficult to achieve compared to the analogous reactions using the monomeric species. Conversion of the dimer **68** to C8-bromide **105** (8Br-PBC-PBC) did not proceed beyond ca. 70% by ^{1}H NMR analysis, even with reaction times of 48 hours. The DDQ promoted C4-oxidation of dimer **68** in the presence of 2-ethoxyethanol (2-EEOH) failed to provide any trace of the C4-ether **112**.

Scheme 5: Attempted C8-bromination and C4-oxidation of dimer 68 (PBC-PBC).



These results, along with the failed bromide to boronic acid conversion results, suggested that the larger size and different molecular shape of the dimeric species compared to the requisite monomers played a significant role in the hindrance of the reactivity of the dimeric species.

With this discovery, the conversion of the dimeric C8-bromide **105** (8Br-PBC-PBC) to the dimeric C8-boronic acid **111** (8B(OH)$_2$-PBC-PBC) was abandoned. It was clear that major functional group changes using the dimeric species were difficult at best, if not impossible. Assumingly, similar functional group conversions using trimer and higher oligomeric species would also be hindered significantly, probably to a greater extent than the dimer due to their increased molecular sizes.

Accordingly, the iterative synthetic strategy of Scheme 3 was no longer considered viable as the key dimeric C8-organometallic reagent **111** could not be produced from the dimeric C8-bromide **105**. Another strategy to build the dimeric C8-organometallic was required.

4.2.2 Boron masking strategies and their application to catechin oligomer synthesis.

An important lesson was learned from the failure of the dimeric C8-boronic acid formation, major functional group interconversions were not effective using dimeric species and it was unlikely this would change for trimers and higher oligomers. To overcome this, the establishment of a method that incorporated the major C8-halide to C8-organometallic conversions at the monomeric stage was a critical factor in the application of the developed Lewis-acid promoted cross-coupling reaction in an iterative synthetic strategy towards trimeric and higher catechin oligomers.

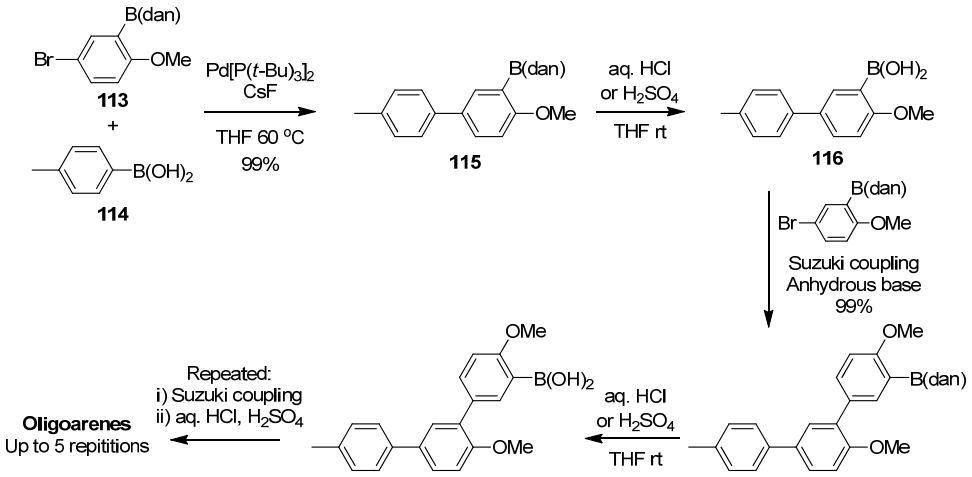
4.2.2.1 Boron masking strategies in the synthesis of oligoarenes.

In 2007, two independent papers were published involving the iterative synthesis of oligoarenes using Suzuki-Miyaura couplings of boron-protected (or masked) haloboronic acid building blocks. Noguchi *et al* [121] employed the use of the 1,8-diaminonapthalene (dan) protecting group in the masking of arylbromoboronic acid derivatives, such as compound **113**. Using this boron-masking group, **113** was coupled to aryl boronic acid **114** under anhydrous basic Suzuki coupling conditions to provide biaryl **115** in good yield. Notably, only coupling of the free boronic acid **114** to the aryl bromide was observed. The dan masking group effectively prevented reactivity at the boron centre of **113**. Treatment of **115** with dilute HCl or H_2SO_4, revealed the free boronic acid **116**. Noguchi *et al* then proceeded to apply these coupling and demasking steps to various masked arylbromoboronic acid species in an iterative fashion in order to build oligoarenes (Scheme 6).

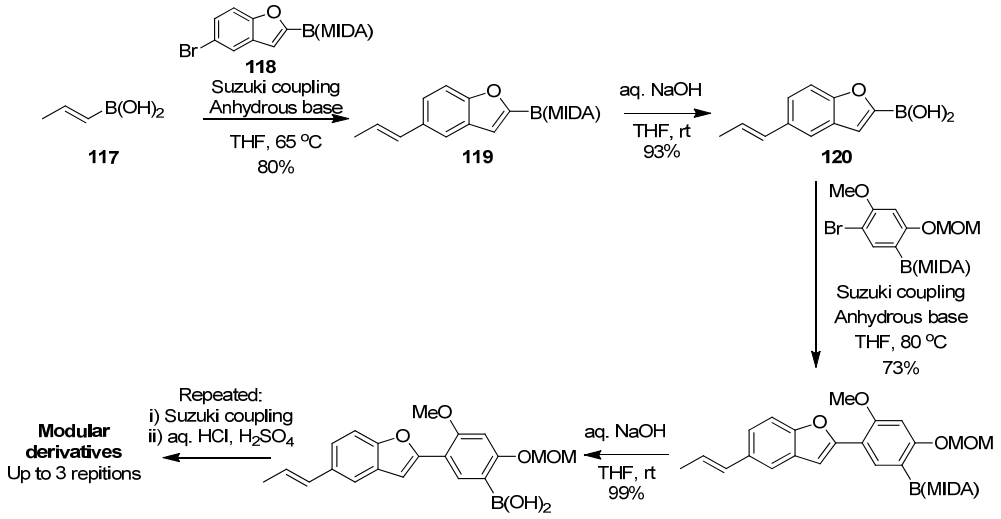
In a similar strategy, Gillis *et al* [118] employed *N*-methylimidodiacetic acid (MIDA) as a boron masking group. In this case, the masked arylbromoboronic acid **118** was coupled to alkenyl boronic acid **117** under anhydrous basic Suzuki coupling conditions. Selective coupling of the bromide with the free boronic acid was achieved to produce the coupled product **119**. Demasking of **119** through treatment

with dilute aqueous NaOH provided the free boronic acid **120**. Sequential coupling and demasking steps were then employed in an iterative fashion in order to produce the modular oligoarene derivatives (Scheme 7).

Scheme 6: Noguchi *et al* selective coupling of free boronic acids using the dan masking group and iterative oligoarene synthesis *via.* sequential coupling and demasking steps.



Scheme 7: Gillis *et al* application of iterative coupling and demasking strategy in oligoarene synthesis.



The key to the success of the selective couplings of the free boronic acid derivatives was the reduced Lewis acidity of the masked boronic acids compared to the free boronic acid species. In Section 3.2.4 it was noted that in order for a boronic acid to act as a nucleophile, it must be activated to the anionic "boronate" species *via.* complexation of an available oxygen lone electron pair with the vacant Lewis acidic

p-orbital of the boron atom. The function of the masking groups was to reduce this Lewis acidity of the boron centre. In the case of the dan group, Lewis acidity was reduced by back-donation of the lone pair electrons of the nitrogen atoms of the dan group into the empty boron p-orbital. The MIDA group achieved the reduced Lewis acidity through complexation of the lone pair electrons of the nitrogen atom of the MIDA group to produce an sp^3 hybridised boron centre. With the reduced Lewis acidity of these boron masked groups, base promoted activation to the "boronate" anion species was significantly hindered. Accordingly, addition of base to the reaction mixtures selectively activated the free boronic acid species over the masked boronic acids, which in turn led to selective coupling of the free boronic acid with the aryl bromide.

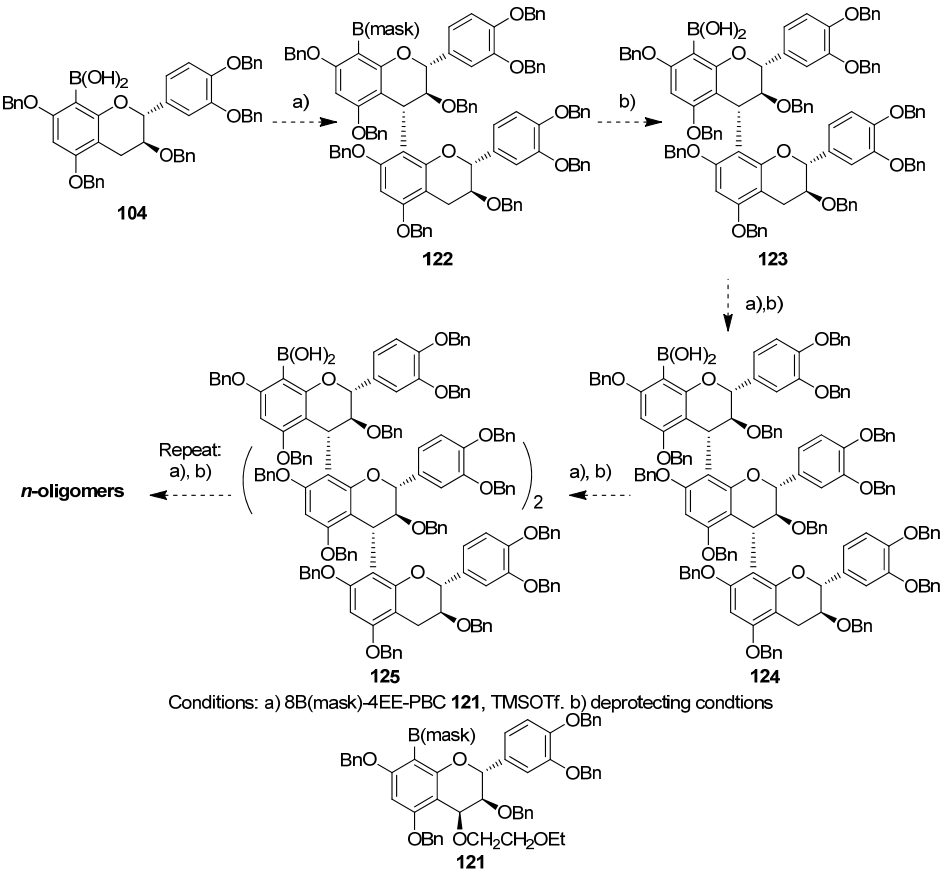
These selective, iterative coupling strategies were considered in the development of an iterative synthesis of catechin oligomers.

4.2.2.2 Boron masking strategies in the iterative synthesis of catechin oligomers.

In order to apply a boron masking strategy towards the iterative synthesis of catechin oligomers, the following coupling strategy was proposed (Scheme 8).

Using this strategy, the C8-boron masked C4-ether **121** (8B(mask)-4EE-PBC) could conceivably be sequentially added to the C8-terminus of a growing *n*-oligomer chain to form (*n*+1)-oligomers. The success of this strategy depended strongly upon three key questions. Firstly, could an appropriate masked C8-boronic acid-C4-ether (8B(mask)-4EE-PBC, **121)**, moiety be constructed? Two, what protecting groups could be employed to effectively mask the boron atom of this species? Finally, could the boron masking strategy be applied to the Lewis-acid promoted 4→8 cross-coupling reaction and would the protecting group be effective in preventing reactivity at the boron centre of 8B(mask)-4EE-PBC **121**? In order to successfully apply this strategy towards the iterative synthesis of catechin oligomers, affirmative responses to these questions were required.

Scheme 8: Iterative coupling scheme using boron masking in the iterative synthesis of catechin oligomers.



4.2.3 Synthesis of the C8-masked boron C4-ether "chain extension" unit.

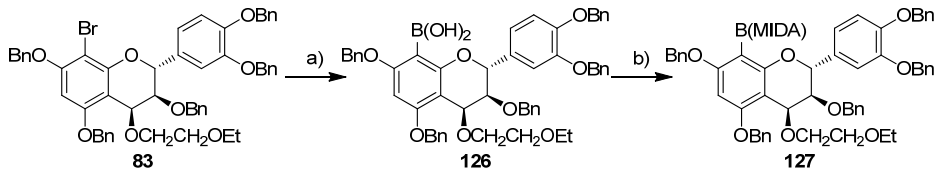
Of these key questions, the first that required addressing was the construction of the masked C8-boronic acid-C4-ether **121** (8B(mask)-4EE-PBC). Without the successful construction of this unit, no couplings towards dimer and higher oligomers were possible. Given that this unit could conceivably be coupled to the C8-terminus of growing oligomer chain, this protected moiety is often referred to as the "chain extension" unit in the following discussions.

The first task was to select an appropriate boron masking agent for the "chain extension" unit. Both the dan and MIDA groups (Section 4.2.2.1) were initially considered for this assignment. The dan group was quickly ruled out due to the difficulties found working with it. 1,8-Diaminonaphthalene exists as a purple solid that tended to leave residues on labware, which could not be completely removed even with soaking in conc. HCl. In contrast, the MIDA group was a white, powdery

solid that readily dissolved in acetone or water and left no residues on labware. Due to the comparative ease of workability of the MIDA group over the dan group, the MIDA group was employed as the boron masking agent of choice for the coupling studies which follow.

The MIDA masked "chain extender" unit **127** (8B(MIDA)-4EE-PBC) was synthesised in two steps from the previously prepared C4-ether **83** (8Br-4EE-PBC) by formation of the boronic acid **126** (8B$(OH)_2$-4EE-PBC), followed by boron protection using MIDA in the presence of CaH_2 (Scheme 9).

Scheme 9: Synthesis of MIDA masked "chain extender" species 127 from C4-ether 83.



a) i) *n*-BuLi, ii) $B(OMe)_3$, iii) H_2O. THF, -78 °C to rt, 50-55%
b) MIDA, CaH_2, $PhCH_3$/DMSO, 120 °C, 75-80%

4.2.3.1 Formation of boronic acid precursor 126.

The synthesis of C8-boronic acid **126** (8B$(OH)_2$-4EE-PBC) from the corresponding C8-bromide **83** (8Br-4EE-PBC) was performed using the same low temperature lithium-halogen exchange with *n*-BuLi, transmetallation with $B(OMe)_3$ and hydrolysis process that was used for the synthesis of C8-boronic acid **104** (8B$(OH)_2$-PBC, Section 3.2.5). The scaling issues observed for the synthesis of PBC-B$(OH)_2$ **104** were also noted for the formation of 8B$(OH)_2$-4EE-PBC **126**. No boronic acid product was formed when the reaction was performed using quantities smaller than 0.5 mmol of the starting bromide. Only the C8-H species **103** (4EE-PBC, Section 3.2.4.7, Scheme 35) was recovered in these cases. Increasing the reaction scale to 0.5 mmol and higher afforded the boronic acid in increasing yields up to 50-55% following silica chromatography when performed using 1-2 grams of 8Br-4EE-PBC **83**. The purity of the staring bromide was critical to the success of this reaction. If the starting bromide was not rigorously purified (Section 3.2.3.2), the isolated yield of boronic acid **126** was generally reduced to 10-30% depending upon purity of bromide **83**. This suggested that the by-products present in bromide **83** were involved

in some side reaction(s) that ultimately resulted in the reduced yield of boronic acid **126**.

The only significant by-product of the reaction was the C8-H species **103**. The potential for the Lewis acidic $B(OMe)_3$ to complex to the C4-ethoxyethanol was noted prior to attempting the formation of boronic acid **126**. If this occurred, then uncontrolled oligomerisations were possible as side reactions. No higher oligomeric products were observed for this reaction. This suggested that either the $B(OMe)_3$ did not possess sufficient Lewis acidity to effect the complexation with the C4-oxygen, or it selectively reacted with the C8-organolithium species. Early reactions were trialled using only a slight excess (1.2-1.3 equivalents) of $B(OMe)_3$. Later reactions using a larger excess of $B(OMe)_3$ (*ca*. 2 equivalents) were also attempted. Both reaction conditions provided the boronic acid product **126** in similar yield with no evidence of oligomeric products. It was therefore likely that the $B(OMe)_3$ was not sufficiently Lewis acidic to complex with the C4-oxygen, or the THF solvent complexed the excess $B(OMe)_3$ in preference to the C4-oxygen. Since the smaller excess was employed with highly reproducible results, these conditions were used preferentially for the synthesis of 8B$(OH)_2$-4EE-PBC **126**.

Like its analogue **104** (PBC-B$(OH)_2$), C8-boronic acid **126** (8B$(OH)_2$-4EE-PBC) could not be crystallised and purification of this species was carried out using silica chromatography. Using this method, C8-boronic acid **126** was separated from the C8-H by-product **103** (4EE-PBC) and a small amount (*ca*. 5%) of an unknown by-product. Following separation and concentration, the white, foamy solid C8-boronic acid **126** was obtained. Occasionally, the boronic acid was isolated as an off-white or slightly yellow solid. The origins of these colourations were unknown, but they did not greatly affect the subsequent boron-masking step. Consistent results in the protection of the boronic acid were achieved regardless of colouration of C8-boronic acid **126** (Section 4.2.3.2).

Characterisation of C8-boronic acid **126** (8B$(OH)_2$-4EE-PBC) was achieved by analysis of ^{1}H, ^{13}C and ^{11}B NMR spectra along with HRMS. The key ^{1}H NMR C6-H singlet had shifted downfield slightly from 6.22 ppm in the starting bromide **83** to 6.26 ppm, indicating that C8 was substituted. The presence of the ether C4-ether group was confirmed by the C4-H doublet located at 4.85 ppm, along with the ether

chain CH_2 multiplets at 3.45, 3.65, 3.81 and 4.01 ppm and the CH_3 triplet at 1.16 ppm. The $J^{3,4}$ coupling constant of the C4-H doublet was 3 Hz. This small coupling constant suggested that C4-H was in the 4*α* orientation. It followed that the C4-ether was in the 4β orientation. The orientation of this ether was therefore not affected by the boronation reaction. The ^{13}C NMR spectrum showed a downfield shift of the C5, C7 and C8a carbon resonances of 5-10 ppm to 160-165 ppm compared to the starting bromide. This phenomenon was also seen with the analogous C8-boronic acid **104** (PBC-$B(OH)_2$) and was indicative of the presence of the sp^2 boron atom at C8. The C8 resonance was not observed due to quadrupolar relaxations through the neighbouring boron centre.[118] The C4 resonance at 71.8 ppm was indicative of the presence of the C4-ether group at this centre. The peaks at 69.8, 67.5, 66.3 and 15.2 ppm were assigned to the ether chain carbons. So it was concluded the C4-ether was still attached. The ^{11}B NMR spectrum displayed a broad peak centred at 29.5 ppm. This shift was consistent with the presence of a boronic acid.[104, 118] Finally, HRMS confirmed the molecular formula of the product as $C_{54}H_{53}BO_{10}$, which was consistent with that expected for 8$B(OH)_2$-4EE-PBC **126**.

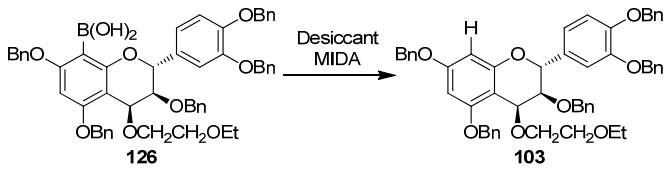
4.2.3.2 Synthesis of MIDA masked "chain extension" species 127 from C8-boronic acid 8$B(OH)_2$-4EE-PBC 126.

The formation of the "chain extension" species required the protection or masking of the boronic acid **126** (8$B(OH)_2$-4EE-PBC) as the MIDA ester **127** (8B(MIDA)-4EE-PBC) (Scheme 9). This protection reaction required significant optimisation in order to gain the desired product. The original masking reaction reported by Gillis *et al* [118] involved refluxing a boronic acid and MIDA in benzene/DMSO (10:1) with azeotropic removal of water using a Dean and Stark apparatus. Using this method or refluxing in the presence of desiccants such as $MgSO_4$ or 4Å molecular sieves failed to produce any protected species. The only product obtained using this method was the C8-H material **103** (4EE-PBC). Protolytic deboronation of the starting boronic acid **126** afforded this product (Scheme 10).

Since the neutral desiccation methods failed to produce any MIDA masked product, the basic desiccant CaH_2 was employed. The desired "chain extender" unit **127** was produced in 75-80% isolated yields when a large excess CaH_2 (*ca.* 10 equivalents) was employed using toluene/DMSO (10:1) at 120 ^oC. Under these conditions, similar

yields of 8B(MIDA)-4EE-PBC **127** were obtained using both small (~50 mg) and larger (>1 g) quantities of the starting boronic acid **126** (8B$(OH)_2$-4EE-PBC, Scheme 9).

Scheme 10: Failed MIDA protections of boronic acid 126 to afford C8-H species 103.



The success of the CaH_2 was assumed to be due to its greater capacity to react with and remove water quickly compared to the use of neutral desiccants. As a result, the esterification of 8B$(OH)_2$-4EE-PBC **126** proceeded with far greater efficiency in the presence of CaH_2.

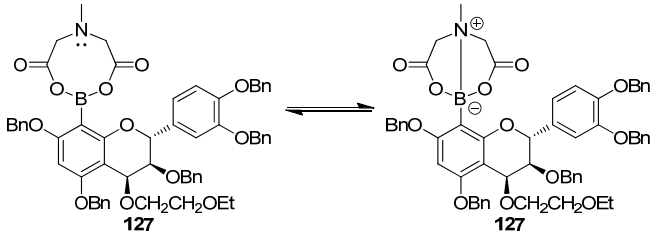
The original Gillis e*t al* [118] procedure utilised benzene/DMSO (10:1) as the reaction solvent at 80 ^oC. These conditions were used initially and provided the desired product 8B(MIDA)-4EE-PBC **127** in 70% yield. By changing the solvent to toluene/DMSO (10:1) and increasing the temperature to 120 ^oC, the yield of the esterified product was increased to *ca.* 80%. The increased yield of the reaction was attributed to the improved solubility of the starting boronic acid **126** (8B$(OH)_2$-4EE-PBC) in toluene compared to benzene. The higher temperature also allowed for faster esterification. The use of ~10% DMSO was critical to ensure the complete solubility of the free acid MIDA starting material. The solubility of this free acid in benzene or toluene alone was very poor.

The isolation of the protected product **127** (8B(MIDA)-4EE-PBC) was fairly straightforward after some initial optimisation. The reaction mixture was filtered over celite to remove the excess CaH_2 and other insoluble material. The filter cake was then washed with CH_2Cl_2 several times. The use of CH_2Cl_2 or $CHCl_3$ here was critical. The product **127** showed good solubility in these chlorinated solvents, but exhibited poor solubility in other common extraction solvents such as EtOAc or Et_2O. The organic extracts were then washed with several portions of water or brine to remove the bulk of the DMSO. Removal of the DMSO at this stage was important.

Large quantities of DMSO present in the crude mixture after concentration greatly affected isolation of the product using silica chromatography.

The C8-H material **103** (4EE-PBC) was the sole by-product of the reaction. Separation of this by-product and the "chain extension" product **127** was very straight forward. The MIDA masked product was zwitterionic in nature due to complexation of the nitrogen lone pair with the vacant p-orbital of the boron centre (Figure 1). This zwitterionic product **127** was far more polar than the C8-H by-product **103**, so separation required only filtration over a silica plug. After concentration, the "chain extender" product **127** (8B(MIDA)-4EE-PBC) was isolated as a white, amorphous solid.

Figure 1: 8B(MIDA)-4EE-PBC 127 as a zwitterionic species.



Spectral analysis using ^{1}H, ^{13}C and ^{11}B NMR and HRMS confirmed the identity of the "chain extension" moiety **127** (8B(MIDA)-4EE-PBC). In the ^{1}H NMR spectrum, the singlet at 2.46 ppm (3 protons) was attributed to the N-CH_3 group of the MIDA protecting group. The CH_2 resonances for this unit were also present between 3.2 and 3.6 ppm, but overlapping of these signals with those of the CH_2 groups of the ether chain prevented absolute assignment of these peaks. The presence of ether CH_2 peaks in this region suggested that the ether was still attached at C4. The C4-H peak at 4.80 ppm (one proton) confirmed C4 was still attached to the ether oxygen. Interestingly, this peak was observed as a broad singlet rather than the doublet reported for the starting boronic acid **126**. Several peaks in both the ^{1}H and ^{13}C NMR spectra exhibited this broadening. This peak broadening was thought to be attributed to the zwitterionic nature of the compound, so the small $J^{3,4}$ doublet (*ca.* 3 Hz) of the C4-H was broadened sufficiently to become an apparent singlet. The C6-H singlet shifted upfield from 6.26 ppm in starting boronic acid **126** (8B$(OH)_2$-4EE-PBC) to 6.17 ppm in the product. This shift suggested that the boron centre was indeed complexed to the MIDA nitrogen lone pair. As the zwitterionic complex, the electron withdrawing

character of the boron centre was reduced compared to the free boronic acid. The induction of the A-ring electrons by the empty p-orbital of the free boronic acid (Section 3.2.5) was not possible with the MIDA protected species. As a result, the C6-H singlet was observed at the upfield shift. The key ^{13}C NMR peaks for the MIDA group were observed at 167.9 ppm for the ester carbonyls (two signals), 63.0 and 62.6 ppm for the CH_2 groups and 46.9 ppm for the N-CH_3. These shifts were in the vicinity of the ^{13}C NMR shifts reported for the MIDA protecting group by Gillis *et al*.[118] The C4 peak was observed at 70.2 ppm, which confirmed the ether was still attached. As with the other boron containing compounds, the C8 resonance was not observed.[118] The ^{11}B NMR spectrum of the product displayed a broad peak at 12.7 ppm. This shift was consistent with the ^{11}B shifts reported for the MIDA protected boronic acids by Gillis *et al*.[118] HMRS analysis confirmed the molecular formula as $C_{59}H_{58}BNO_{12}$, which corresponded with that for the expected structure of 8B(MIDA)-4EE-PBC **127**.

Apart from being the critical "chain extension" unit, the synthesis of the 8B(MIDA)-4EE-PBC **127** was also important as the crucial bromide to boron functional group conversion was achieved at the monomeric stage (Sections 4.2.3, Scheme 9). This meant that this functional group change did not need to take place at the troublesome dimer stage (Section 4.2.1). With this critical species prepared in gram quantities, attention then turned towards the coupling and demasking steps required for the application of the proposed method (Section 4.2.2.2, Scheme 8) in the synthesis of catechin oligomers.

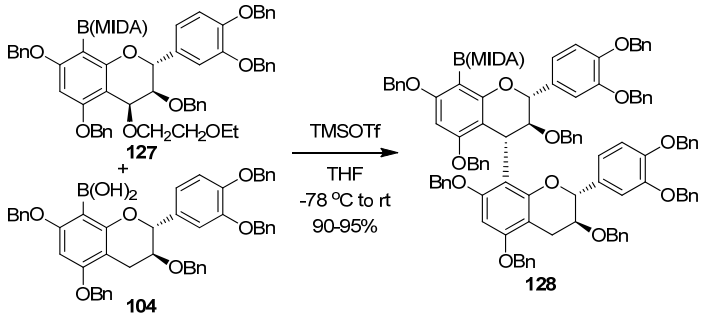
4.2.4 Application of the "chain extension" species to the Lewis acid-promoted coupling.

Following the successful synthesis of the key "chain extension" species **127** (8B(MIDA)-4EE-PBC), the next logical step was to attempt the Lewis acid-promoted coupling of this species with C8-boronic acid **104** (PBC-$B(OH)_2$) to produce the C8-MIDA-capped dimer **128** (8(MIDA)-PBC-PBC). Using the earlier developed TMSOTf-promoted coupling (Section 3.2.7), the desired catechin-catechin dimer **128** was synthesised in good to excellent yield. Complete conversion of the "chain extender" unit **127** was achieved using only 1.1 equivalents excess of

C8-boronic acid **104**. No evidence of any trimer or higher oligomeric products was observed in the reaction mixture (Scheme 11).

Like the earlier Lewis acid-promoted cross-coupling of 8Br-4EE-PBC **83** to PBC-$B(OH)_2$ **104** (Section 3.2.7) the coupling yield of this reaction was highly scale-dependent. Using small quantities (~50 mg) of 8B(MIDA)-4EE-PBC **127**, coupling yields of 8B(MIDA)-PBC-PBC **128** were in the vicinity of 75-80% following purification by silica chromatography. The coupling yield steadily increased to 90-95% when conducted using gram scales of the "chain extender" unit **127**.

Scheme 11: Lewis acid-promoted coupling of "chain extender" species 127 with boronic acid 104 to form dimer 128.



Through the use of silica chromatography, the dimer product **128** (8B(MIDA)-PBC-PBC) was readily isolated. The only reaction by-product was PBC **52b**, which resulted from deboronation of the excess C8-boronic acid **104**. The zwitterionic B-MIDA containing dimer **128** was far more polar than the PBC by-product **52b**, so the two species were easily separated using silica gel. Following elution from the silica column and concentration, the desired dimer **128** was obtained as a white, amorphous solid in the yields reported above.

Analysis of the dimer product 8B(MIDA)-PBC-PBC **128** by ^{1}H and ^{13}C NMR was complicated by two issues. Firstly, rotational atropisomerism around the 4→8 interflavan bond gave rise to two isomeric products. Secondly, the large, predominantly hydrophobic nature of the molecule hindered the removal of grease and aliphatic solvents, particularly hexanes, from the product. Vigorous drying *in vacuo* at room temperature or at *ca.* 50 ^{o}C and freeze drying failed to remove significant quantities of the solvents. Washing a solution of the dimer **128** in acetonitrile with hexanes to remove grease and accumulated solvents was also

attempted. This also failed to remove the accumulated impurities. As a result, the ^{1}H NMR spectrum showed several aliphatic C-H peaks in the 1-3 ppm region and the ^{13}C NMR spectrum showed similar aliphatic solvent signals around 10-30 ppm. These solvent peaks made it difficult to characterise the material fully by ^{1}H and ^{13}C NMR, as there were some overlapping product and solvent signals that couldn't be fully resolved. There were however, numerous key peaks in both spectra which allowed identification of the product when combined with the ^{11}B NMR and HRMS data obtained for the material.

The key ^{13}C NMR signals C4 and C8 peaks of the interflavan bond were observed at 36.7 and 112.6 ppm respectively, which closely matched the resonances observed for the 4→8 carbons of the previously synthesised dimeric analogue **105** (8Br-PBC-PBC, Section 3.2.7). As with previously synthesised C8-boron containing compounds, the C8 peak of the upper unit was not seen due to its attachment to the boron atom.[118] The ^{13}C NMR signals for the MIDA group resonated at 167.9-167.8, 63.15-63.10 and 46.9 ppm for the carbonyls, CH_2 groups and the N-CH_3, respectively. The ^{1}H NMR signal for the N-CH_3 group was seen as a large singlet at 2.37 ppm. The CH_2 groups of the MIDA group expected at ~3.5 ppm could not be assigned with complete certainty as they overlapped with a large number of peaks in the 3-5.5 ppm region relating to C2-H, C3-H, C4-H and the benzyl CH_2 resonances. Two singlets observed at 6.22 and 6.12 ppm corresponded to F6-H and C6-H of the major rotational isomer, respectively. Outside of the MIDA group and solvent signals, both the ^{1}H and ^{13}C NMR spectra compared closely to that of the earlier reported dimer **105** (Section 3.2.7). As a result, the ^{1}H and ^{13}C NMR data strongly suggested the synthesised product was the desired 8B(MIDA)-PBC-PBC **128**. ^{11}B NMR of the product showed a broad peak at 13.5 ppm. This shift was consistent with that expected for the tetra-coordinate MIDA protected boron atom.[118] Finally, HRMS confirmed the molecular formula of the compound as $C_{105}H_{92}BNO_{16}$, which matched that expected for the desired product. As a result, the product was confidently characterised as the desired dimer **128**.

The 3,4-stereochemistry of the interflavan bond was not confirmed at this point, but was inferred from earlier results that it should exhibit the desired 3,4-*trans* stereochemistry. Both the earlier reported pseudo-dimer **84** (8Br-4TMB-PBC, Section 3.2.3.4) and dimer **105** (8Br-PBC-PBC, Section 3.2.7) were confirmed as the

3,4-*trans* products. Since the same TMSOTf-promoted coupling reaction of the C4-ether **83** was used in this reaction, it was reasonable to assume this coupling should proceed *via.* the same mechanism to provide the 3,4-*trans* product (Section 3.2.4).

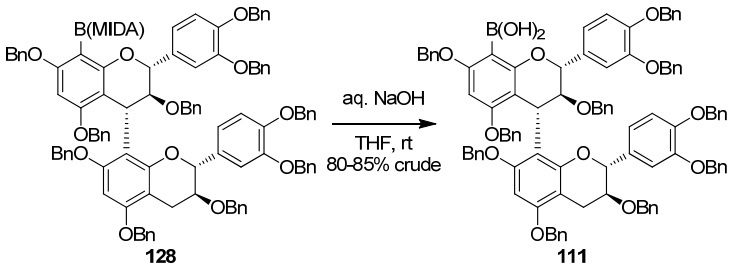
Notably, the lack of any trimer or higher oligomeric by-products proved the MIDA protecting group achieved the function for which it was employed. It prevented any coupling of this boron centre. The reduced Lewis acidity of the boron centre by complexation of the MIDA nitrogen atom blocked reactivity at this site. Selective coupling of the C4-ether **127** (8B(MIDA)-4EE-PBC) with the free C8-boronic acid **104** (PBC-B$(OH)_2$) was achieved to provide the desired dimer **128** (8B(MIDA)-PBC-PBC). With this dimer in hand, attention turned towards the removal of the MIDA protecting group and the subsequent trimer formation.

4.2.5 Removal of the MIDA protecting group from dimer 128.

The removal of the MIDA protecting group of dimer **128** (8B(MIDA)-PBC-PBC) to release the free boronic acid **111** (8B$(OH)_2$-PBC-PBC) was of vital importance in the scheme of the coupling strategy towards higher oligomers. If this free boronic dimer **111** could not be obtained, then the trimer and subsequent oligomers would not be accessible. Gillis *et al* [118] reported the facile removal of the MIDA group from small aromatic and alkenyl moieties by stirring the protected MIDA esters in THF in the presence of either dilute aq. NaOH or sat. aq. $NaHCO_3$ at room temperature. Removal of the MIDA group under these conditions required 10 minutes and 6 hours, respectively. Since NaOH required a shorter reaction time, deprotection of dimer **111** (8B(MIDA)-PBC-PBC) was attempted using this base.

To effect the deprotection, 1M aq. NaOH was added to a solution of dimer **128** (8B(MIDA)-PBC-PBC) in THF. Vigorous stirring of the reaction was critical in order to ensure mixing of the organic and aqueous phases. Almost complete deprotection was obtained after two hours (Scheme 12). The longer reaction time required to complete MIDA removal using aq. NaOH compared to that reported by Gillis *et al* [118] for smaller, less hindered systems was likely as a result of the greater steric bulk around the boron centre.

Scheme 12: MIDA deprotection of dimer 128 to provide free boronic acid dimer 111.



A small amount of an unidentified by-product was formed in this deprotection that spotted on the TLC slightly above the boronic acid at R_f= 0.9. This by-product spot ran close to the boronic acid using several TLC solvents, so separation of this byproduct was not attempted at this stage. Filtration of the product mixture over silica gel provided the desired free boronic acid **111** (8B$(OH)_2$-PBC-PBC) along with the by-product in 80-85% crude yields. The yield of the deprotection was consistent regardless of scale. The crude boronic acid **111** was used immediately in the Lewis acid-promoted coupling with the "chain extender' unit **127** (8B(MIDA)-4EE-PBC) in order to access the trimeric oligomer. HRMS analysis of a sample of crude boronic acid **111** confirmed the molecular formula of the compound as $C_{100}H_{87}BO_{14}$.

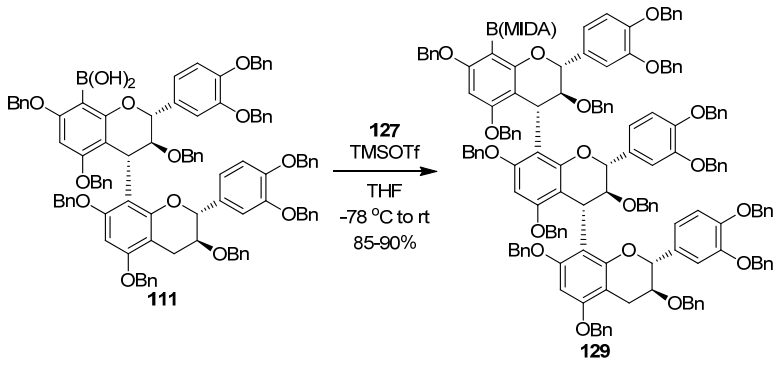
4.2.6 Extension of the Lewis acid-promoted cross-coupling to trimer synthesis.

With the crude free boronic acid dimer **111** (8B$(OH)_2$-PBC-PBC) available, the Lewis acid-promoted coupling to a further "chain extender" unit **127** (8B(MIDA)-4EE-PBC) was attempted in order to construct the trimer **129** (8B(MIDA)-PBC-PBC-PBC). Employing the same Lewis acid-promoted cross-coupling conditions as used for dimer **128** (8B(MIDA)-PBC-PBC) synthesis (Section 4.2.4), the desired trimer **129** was produced in very good yields (85-90%). Similar coupling yields were obtained when both small (*ca*. 20 mg) and larger (*ca*. 100 mg) quantities of the starting "chain extender' unit **127** were employed (Scheme 13).

The reaction was sluggish at -78 ^oC, but the slow warming to room temperature over 3-4 hours showed steady disappearance of the starting material spots by TLC analysis and the corresponding appearance of the product spot at R_f= 0.15. Quenching of the reaction was achieved by addition of sat. aq. $NaHCO_3$ followed by

stirring for 5 minutes. The by-product from the crude boronic acid dimer **111** (8B(OH)$_2$-PBC-PBC) mixture was still present at R_f= 0.9 (Section 4.2.5).

Scheme 13: Synthesis of trimer 129 *via*. coupling of "chain extender" unit 127 with free boronic acid dimer 111.

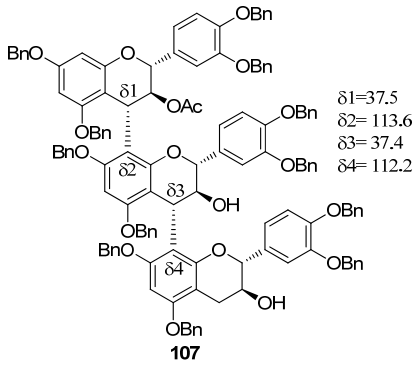


Isolation of the trimer product **129** (8B(MIDA)-PBC-PBC-PBC from this by-product was readily achieved by filtration over silica gel. The presence of the zwitterionic B-MIDA group once again provided a large polarity difference between the trimer product **129** and the unknown by-product from the demasking step (Section 4.2.5) and dimer **68** (PBC-PBC), which was produced from deboronation of excess dimeric boronic acid **111**. Separation of trimer **129** from these by-products was straightforward through filtration over a short plug of silica. Following concentration, the trimer product **129** was obtained in 85-90% yields as a white, amorphous solid.

As with the corresponding dimer **128** (8B(MIDA)-PBC-PBC), full characterisation of the trimer **129** (8B(MIDA)-PBC-PBC-PBC) by ^{1}H and ^{13}C NMR was complicated by rotational isomerism around the two interflavan bonds (a total of 4 atropisomers were possible) and aliphatic impurities arising from grease and aliphatic solvents that was trapped in the molecular network of the trimer **129** during isolation and silica chromatography. Removal of the residual solvents by drying *in vacuo* at room temperature or at 50 ^{o}C, or by freeze drying, was not successful. Washing a solution of the trimer **129** in acetonitrile with hexanes also proved futile in the removal of the aliphatic impurities. Accordingly, the 1-3 ppm region of the ^{1}H NMR spectrum and the 10-40 ppm region of the ^{13}C NMR spectrum were obscured by resonances of these aliphatic impurities. The key ^{13}C NMR C4 and C8 peaks for the two 4→8 interflavan bonds were observed at 36.7, 36.9 and 112.6, 112.8 ppm, respectively.

The chemical shift of these C4 and C8 peaks closely matched those reported for the related catechin trimer **107** (Figure 2) synthesised by Saito *et al* (37.4 and 37.5 ppm for C4 and 112.2 and 113.6 ppm for C8).[36] This strongly suggested that the PBC-4→8-PBC-4→8-PBC trimer had been synthesised. The ^{13}C NMR peaks at 167.8-167.9, 61.3 and 47.0 ppm confirmed the presence of the B-MIDA group in the product. ^{11}B NMR of the product displayed a broad peak at 13.7 ppm. This shift was consistent with that expected for the tetra-coordinate B-MIDA group.[118] The ^{11}B NMR peak of trimer **129** was far broader than the related B-MIDA species **127** (8B(MIDA)-4EE-PBC) and **128** (8B(MIDA)-PBC-PBC). Assuming this broadening was related to molecular size, this suggested the ^{11}B NMR method for characterisation of the oligomeric species may be limited to the smaller oligomeric species. HRMS analysis of the product afforded a molecular formula of $C_{155}H_{134}BNO_{22}$, which matched that expected for the trimer product **129** (8B(MIDA)-PBC-PBC).

Figure 2: Catechin trimer 107 synthesised by Saito *et al* [36] and C4, C8 ^{13}C NMR assignments.



As with the analogous dimer **128** (Section 4.2.4), the 3,4-stereochemistry of the new 4→8 interflavan bond was not confirmed, but inferred as the 3,4-*trans* isomer for the same reasons as described in Section 4.2.4. While absolute identification of the trimer **129** (8B(MIDA)-PBC-PBC) was not possible due to the difficulties described, the spectral data of the product was consistent with that expected for the trimeric product. Ideally, trimer **129** could have been characterised by removal of the boron and benzyl protecting group to reveal the free phenolic trimer. The NMR spectra of the synthetic free phenolics trimer could then be compared to that reported for the

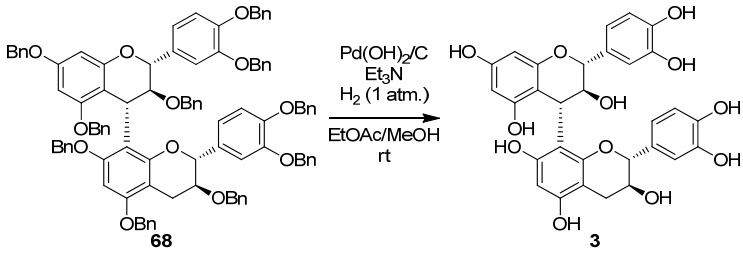
compound in the literature. However, material constraints on trimer **129** did not allow this path to be further examined.

Importantly, the Lewis acid-promoted cross-coupling was applicable to the synthesis of both the dimeric **128** and trimeric **129** catechin oligomers. Similar coupling yields and reaction times were achieved in the synthesis of both these oligomers. So the coupling reaction appeared to be independent of the size of the nucleophilic boronic acid component of the coupling. Also, the "chain extension" unit **127** (8B(MIDA)-4EE-PBC) was performing its desired function to add a further catechin unit to the C8-terminus of a growing oligomer chain in an iterative fashion. Now that the first steps in the iterative synthesis towards *n*-oligomers had been adequately dealt with, the further extension of the strategy towards the synthesis of the tetrameric species was investigated.

4.2.7 Absolute characterisation of dimer 128 (8B(MIDA)-PBC-PBC).

In the formation of trimer **129** (8B(MIDA)-PBC-PBC-PBC) from the dimeric boronic acid **111** (8B$(OH)_2$-PBC-PBC), the excess boronic acid **111** used in the coupling reaction (Section 4.2.6, Scheme 14) was isolated from the reaction mixture as dimer **68** (PBC-PBC). Deprotection of the benzyl groups of this species using the same conditions as described for the deprotection of dimer **105** (Section 3.2.8, Scheme 39) provided procyanidin dimer B3 (**3**, Scheme 14).

Scheme 14: Debenzylation of dimer 68 to provide procyanidin B3 (3).



The synthesis of natural procyanidin B3 (**3**) from dimer **68** (PBC-PBC) confirmed the characterisation of dimers **128** (8B(MIDA)-PBC-PBC) and **111** (8B$(OH)_2$-PBC-PBC) as the 3,4-*trans* isomers. As dimer **68** was derived from **111**, which was in turn derived from **128**, all three species must possess the 3,4-*trans* stereochemistry observed in natural procyanidin B3 (**3**). This confirmed the coupling of 8B(MIDA)-

4EE-PBC **127** and PBC-B(OH)$_2$ **104** was 3,4-*trans* selective as assumed earlier (Section 4.2.4).

4.2.8 Further extension of the coupling strategy towards tetramer synthesis.

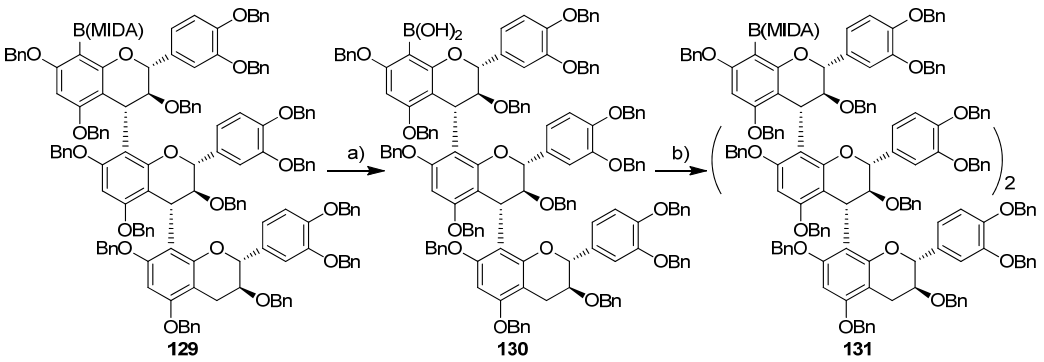
By the time that the tetramer synthesis was attempted, supplies of the crucial "chain extender" species **127** (8B(MIDA)-4EE-PBC) were running very low and the time and effort required to synthesise more of this material was considered too prohibitive at the late stage of the project. As a result, the synthesis of the tetrameric species **131** (8B(MIDA)-PBC-PBC-PBC-PBC) was only attempted using a small *ca.* 20-50 mg quantity of the "chain extender" unit **127**.

Initially, the protected trimer **129** (8B(MIDA)-PBC-PBC-PBC) was treated with aq. NaOH to provide the free boronic acid trimer **130** (8B(OH)$_2$-PBC-PBC-PBC). This deprotection behaved in much the same way that the deprotection of dimeric species **128** did (Section 4.2.5). Following filtration of the reaction mixture over silica gel, the crude boronic acid **130** was obtained as a white, amorphous solid in 79% crude yield. The crude boronic acid **130** was then used immediately in the Lewis acid-promoted coupling with the "chain extender" unit **127** (Scheme 15).

The Lewis acid-promoted coupling towards the tetramer was initially attempted using *ca.* 50 mg of the starting "chain extender" unit **127**. Using a stoichiometric amount of Lewis acid, the reaction was followed by TLC analysis (EtOAc/Hexanes 1:1). Promisingly, a spot developed at R_f= 0.15, the R_f value expected for that of the MIDA masked tetrameric species **131**. Isolation of this product by silica chromatography gave what was thought to be the tetramer in 81% yield. However, identification of the product by spectral methods failed to afford any definitive results. ^{1}H and ^{13}C NMR spectral analysis was hampered by the previously discussed issues of rotational isomerism and aliphatic impurities and attempts to gain a HRMS of the product failed to provide accurate enough results to adequately report the product as the tetramer. As a result, the product obtained was tentatively designated as the tetramer **131** (8B(MIDA)-PBC-PBC-PBC-PBC) by the location of the TLC spot for this product. This product spot corresponded well to the TLC spots seen for the dimeric **128** and trimeric **129** analogues. It should be noted here that removal of the MIDA protecting group of the putatively synthesised **131** or complete removal of the boron group may have aided in obtaining cleaner NMR spectra and more

accurate HRMS data. It was however, not possible to pursue this pathway due to the small quantities of the putative tetramer **131** being available.

Scheme 15: Deprotection of trimer 129 and subsequent coupling to "chain extension" unit 127 to produce tetramer 131.



Conditions: a) aq. NaOH, THF, rt, 75-79% crude, b) **127**, TMSOTf, THF, -78 °C to rt.

A second attempt at the synthesis of tetramer **131** using *ca*. 20 mg of the starting "chain extender" unit was conducted using another batch of the free boronic acid trimer **130** (8B(OH)$_2$-PBC-PBC-PBC). Unfortunately, no spot at R_f= 0.15 developed. This suggested that the reaction was incredibly sluggish due to the steric hindrance of the large boronic acid trimer **130** or the solvent impurities present in the boronic acid **130** hampered the reaction. The addition of a further two equivalents of Lewis acid failed to provide any tetramer product. The reaction was quenched and ^{1}H NMR analysis of the crude reaction residue suggested that uncontrolled oligomerisation had occurred. This was attributed to the additional Lewis acid participating in undesired side reactions.

At this point, no further "chain extender" unit was available. As a result, the product obtained in the first reaction could only be speculated as the tetramer **131** (8B(MIDA)-PBC-PBC-PBC-PBC) and the result of this coupling was not repeatable on a small scale. It was not possible to further investigate this result due to time and material constraints. The "gut feeling" was the product was indeed the tetramer, but this requires further clarification through a repeated synthesis on larger scales.

The material constraints brought an end to the study towards the iterative synthesis of catechin oligomers. At this point, further development of the Lewis acid-promoted coupling method was abandoned in favour of investigating further uses of the C8-boronic acid derivative **104** (PBC-B(OH)$_2$), which are discussed in Chapter 5.

4.3 Conclusions

In this chapter, the Lewis acid-promoted cross-coupling developed for the formation of catechin-catechin dimer **105** (8Br-PBC-PBC) (Section 3.2.7) was further investigated towards the iterative synthesis of catechin trimers and higher oligomers.

Initially, the formation of the dimeric boronic acid species **111** (8B$(OH)_2$-PBC-PBC) was attempted by metallation of the previously synthesised C8-bromide dimer **105** (8Br-PBC-PBC). This transformation was unsuccessful due to difficulties in performing functional group changes using dimeric species. As a result, performing the major bromide to boron functional group change at the monomer stage was identified as a key step in the successful implementation of an iterative method towards the synthesis of catechin oligomers.

The use of boron masking or protecting groups, such as that employed by Noguchi *et al* [121] and Gillis *et al*, [118] were considered for potential use in the iterative synthesis of the catechin oligomers. In order to extend the masking concept to the iterative coupling of catechin oligomers, the key "chain extension" unit **127** (8B(MIDA)-4EE-PBC) was synthesised from the previously prepared C4-ether **83** (8Br-4EE-PBC). This species was crucial for two reasons. Firstly, the vital C8-bromide to boron conversion was performed at the monomer stage. Secondly, this species could be potentially added to the C8-terminus of a growing *n*-oligomer chain in an iterative fashion.

The Lewis acid-promoted coupling developed in Chapter 3 (Sections 4.2.7) was applied to the coupling of the "chain extender" unit with C8-boronic acid **104** (PBC-B$(OH)_2$). This coupling provided the 4→8 dimer **128** (8B(MIDA)-PBC-PBC) with no evidence of any trimer or higher oligomer being formed. This showed that the MIDA protecting group was performing its desired task and prevented coupling at this boron centre, which led to selective dimerisation. Gram quantities of dimer **128** were synthesised using this method in excellent coupling yields (90-95%).

Removal of the MIDA group through treatment of dimer **128** (8B(MIDA)-PBC-PBC) with dilute aq. NaOH revealed the free boronic acid dimer **111** (8B$(OH)_2$-PBC-PBC) in good 80-85% crude yield. This was coupled to further "chain extension" unit **127** to produce trimer **129** (8B(MIDA-PBC-PBC-PBC) in very good

yields (85-90%). This central result proved that the developed coupling/demasking strategy was applicable to the synthesis of both dimeric and trimeric species. Also, the "chain extension" unit was added to the C8-terminus of a growing oligomer chain in an iterative fashion as designed.

Notably, 8B(MIDA)-4EE-PBC **127** was the only "chain extension" species required in this iterative oligomer synthesis. This alleviated the requirement for the synthesis of two chain extender species, which was essential to Ohmori *et al* [38] in the orthogonal activation strategy in the iterative synthesis of catechin oligomers (Section 4.1.1.2).

The extension of the method towards the synthesis of the tetrameric species **131** (8B(MIDA)-PBC-PBC-PBC-PBC) was attempted. A promising TLC spot developed in the first attempt to form this species, but the reaction product could not be definitively identified. A second attempt to form this species gave a complex mixture of oligomeric products. Accordingly, the putative tetrameric product requires resynthesis on a larger scale in order to ascertain that the product obtained was indeed the tetramer **131** and validate the method.

Ready access to an LC-MS was not available during the synthesis of these higher oligomers. Access to such an analytical tool would have without doubt aided the complete characterisation of the higher oligomers synthesised. It is highly recommended that should the above results be revisited at some stage, access to such an instrument would be invaluable.

The repeated success of the Lewis acid-promoted cross-coupling of the "chain extension" species **127** in the synthesis of dimer **128** (8B(MIDA)-PBC-PBC) and trimer **129** (8B(MIDA-PBC-PBC-PBC) suggested that the coupling/deprotection strategy developed may be applicable to the synthesis of *n*-oligomers of any chain length. Before this can be ascertained beyond doubt issues pertaining to the characterisation of the oligomers and the repeatability of the tetramer **131** synthesis need to be resolved.

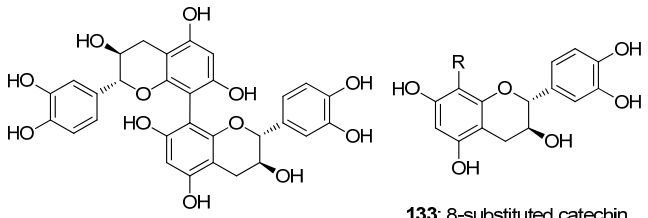
Chapter 5: Expanding the Scope of C8-organometallics. Suzuki and other Palladium-Catalysed Cross-Couplings Towards C8-substituted Catechins.

5.1 Introduction.

With the successful application of C8-boronic acid **104** (PBC-B$(OH)_2$) and its MIDA protected analogue **127** (8B(MIDA)-4EE-PBC) in the iterative synthesis of 4→8 catechin oligomers (Sections 3.2.7, 4.2.4, 4.2.6), attention then turned towards other potential uses for boronic acid **104**. Ideally, boronic acid **104** could be applied to the synthesis of several substituted catechin derivatives by varying reactants and reaction conditions. The synthetic value of boronic acid **104** would be greatly increased if such pathways could be achieved.

One obvious use for C8-boronic acid **104** was its application in palladium-catalysed Suzuki cross-couplings (Section 2.1.2.1) with organic halides. Using C8-boronic acid **104** in a Suzuki coupling method, 8-8 catechin-catechin dimer **132** and C8-substituted catechin derivatives **133** were targeted for synthesis (Figure 1).

Figure 1: 8-8 catechin dimer and 8-substituted catechins.



132: 8-8 catechin-catechin dimer.

133: 8-substituted catechin
R= aryl, vinyl, alkyl

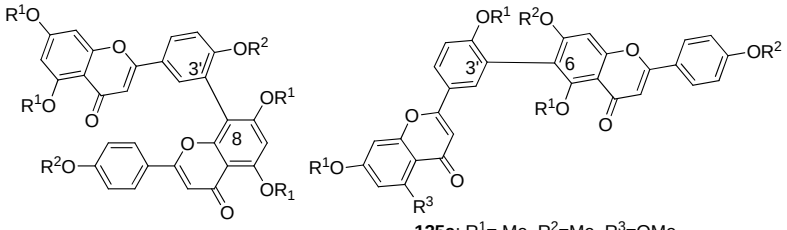
5.1.1 Uses of boronic acids in synthesis of catechin derivatives and related compounds.

Both biflavonoid derivatives and C8-aryl and alkenyl substituted catechin derivates have been prepared using Suzuki coupling protocols.

5.1.1.1 Syntheses of biflavonoid derivatives *via*. Suzuki cross-couplings.

The biflavonoid derivatives below **134a, b** and **135a-c** (Figure 2) have all been synthesised using a Suzuki coupling method. In all these cases, the Suzuki coupling was employed to forge the interflavonoid bond.

Figure 2: Biflavonoid compounds available from Suzuki cross-couplings.



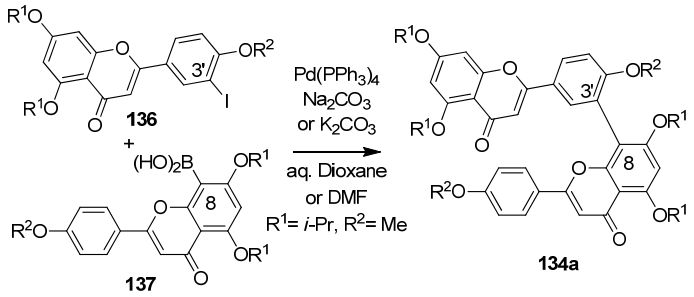
134a: R^1= *i*-Pr, R^2=Me
134b: R^1= H, R^2=Me, isoginketin

135a: R^1= Me, R^2=Me, R^3=OMe
135b: R^1= Me, R^2= CF_2H, R^3= H
135c: R^1= H, R^2= H, R^3= OH, robustaflavone

Flavonoids are related to procyanidins in the fact that they share the same 15 carbon A, C, B ring structure.[3] Their distinguishing feature compared to catechin is the C-ring enone depicted in Figure 2. Biflavonoids are formed by the linkage of two flavonoid monomers, generally between the C3′ and C8 or C6 carbon centres.[3]

Four notable references have employed a Suzuki coupling protocol in the synthesis of biflavonoid derivatives. The 3′→8 biflavonoid **134a** was successfully achieved independently by Muller *et al*,[122] and Mao *et al*.[123] In both cases a C8-boronic acid (**137**) and a C3′-iodide (**136**) were synthesised and then coupled using a Suzuki protocol to produce biflavonoid **134a** (Scheme 1).

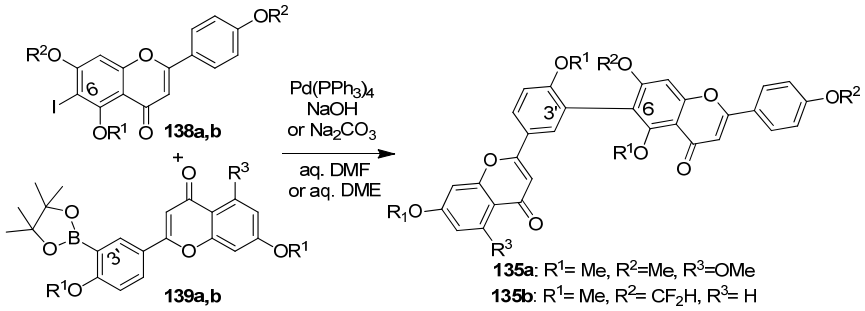
Scheme 1: Muller *et al* and Mao *et al* synthesis of biflavonoid 134a through coupling of flavonoid C8-boronic acid 137 and C3′-iodide 136.



Muller *et al* [122] synthesised biflavonoid **134a** in 91% yield using $Pd(PPh_3)_4$ as the catalyst and Na_2CO_3 as the base in refluxing aqueous dioxane. Mao *et al* [123] employed the same catalyst in the presence of anhydrous K_2CO_3 in DMF at 100 ^oC to provide biflavonoid **134a** in 60% yield. Removal of the isopropyl protecting groups by Mao *et al* afforded the natural biflavonoid isoginkgetin **134b**, a known active ingredient in herbal medicines.[125]

In the other two references referred to above, Zembower *et al* [125] and Zheng *et al* [126] synthesised the 3′→6 biflavonoids **135a-b** via the Suzuki coupling of C3′-boronate esters **138a-b** and C6-iodides **139a-b** (Scheme 2).

Scheme 2: Zembower *et al* and Zheng *et al* syntheses of 3′→6 biflavonoids 135a and 135b *via*. Suzuki cross-couplings.



Zembower *et al* [125] synthesised biflavonoid **135a** in 50% yield using $Pd(PPh_3)_4$ as the catalyst and NaOH as the base in aqueous DMF at 80 ^oC. Removal of the methyl protecting groups of biflavonoid **135a** provided the naturally occurring robustaflavone **135c**, a potential anti-hepatitis B agent.[127]

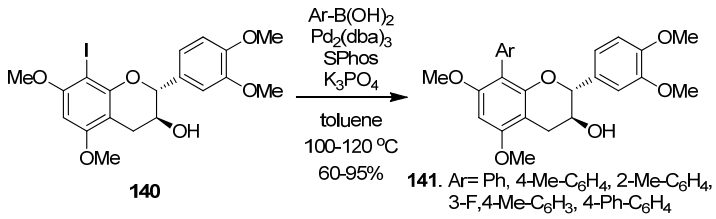
Zheng *et al* [126] synthesised the *gem*-difluoromethylenated biflavonoid **135b** in 33% yield using $Pd(PPh_3)_4$ as the catalyst in aqueous DME at 80 ^oC in the presence of Na_2CO_3. The *gem*-difluoromethylene groups were introduced in an attempt to improve the anti-cancer activity of the biflavonoid **135a** compared to its naturally occurring parent biflavonoid.[8, 128, 129]

5.1.1.2 Suzuki cross-couplings involving catechin derivatives.

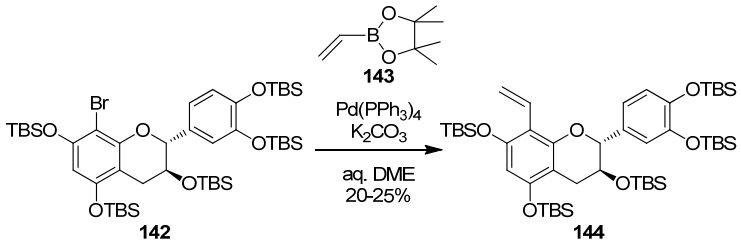
The synthesis of C8-aryl and C8-vinyl catechin derivatives using Suzuki coupling protocols have been recently reported independently by Bernini *et al* [130] and Cruz e*t al*,[131] respectively. In the case of Bernini *et al*,[130] a variety of C8-aryl catechin and epicatechin derivatives were produced in good to excellent yield (60-95%) through the coupling of C8-iodide **140** with an appropriate aryl boronic acid using the $Pd_2(dba)_3$/SPhos catalytic system in the presence of anhydrous K_3PO_4 in refluxing toluene (Scheme 3). The C8-aryl epicatechin derivatives were prepared in similar fashion from the analogous C8-iodinated epicatechin derivative.

C8-vinyl catechin **144** was synthesised by Cruz *et al* [131] through a Suzuki cross-coupling of C8-bromide **142** with the pinacol ester of vinyl boronic acid (**143**, Scheme 4).

Scheme 3: Bernini *et al* synthesis of C8-aryl substituted catechins 141.



Scheme 4: Synthesis of C8-vinyl catechin 144 by Cruz *et al*.



This synthesis afforded the desired C8-vinyl product **144** in low yields (20-25%). Despite the low yield, it did provide an example of the use of a boronate ester in the Suzuki cross-coupling of catechin derivatives.

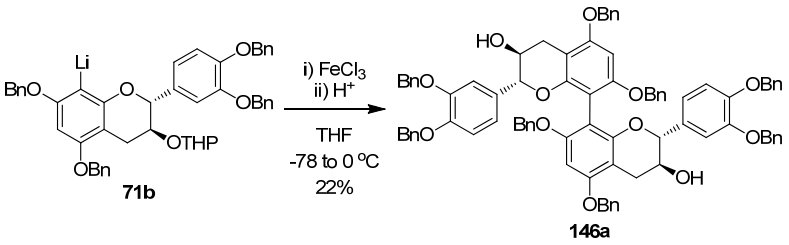
Both these examples highlighted the use of a C8-halide being coupled to a boronic acid. There still existed the potential to develop a complimentary synthesis of these C8-substituted catechin through the coupling of the previously encountered C8-catechin boronic acid **104** (PBC-$B(OH)_2$, Section 3.2.5), with various organic halides.

5.1.2 Kozikowski et al synthesis of 8-8 dimer.

Kozikowski *et al* [114] reported the synthesis of 8-8 dimer **146a** in 22% yield by oxidative homo-coupling of C8-organolithium derivative **71b** by addition of excess Iron(III) Chloride ($FeCl_3$, Scheme 5).

This synthetic method showed that the synthesis of an 8-8 dimer was possible and provided a useful platform to build on for the synthesis of 8-8 dimer **132** by cross-coupling or homo-coupling methods to be discussed shortly.

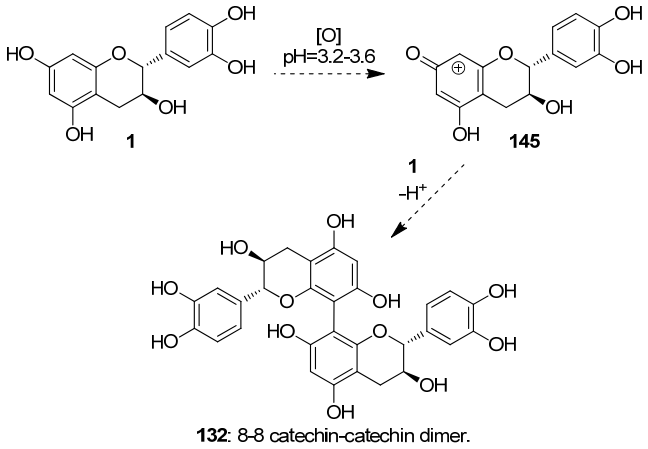
Scheme 5: Kozikowski *et al* synthesis of 8-8 dimer 146a through $FeCl_3$ promoted oxidative homo-coupling of C8-organolithium 71b.



5.1.3 Aims.

Two major synthetic focuses for a Suzuki cross-coupling of C8-boronic acid **104** were identified in Section 5.1. The first and major focus for this chapter was the synthesis of the 8-8 catechin-catechin dimer **132** (Figure 1). The second was the production of a variety of C8-substituted catechin derivatives **133** using both C8-boronic acid and C8-halide reactants.

Scheme 6: Possible oxidative coupling of catechin derivative in wine to form 8-8 dimers.



The 8-8 dimer **132** was chosen as the major focus for two reasons. Firstly, synthesis of the target imposed numerous challenges and was deemed a highly demanding, but achievable target. Kosikowski *et al* [119] (Section 5.1.2) had synthesised 8-8 dimer **146a** in 22% yield, so there was reasonable scope to improve on this yield. Secondly, related 8-8 dimers are potentially formed in wine through oxidative couplings of catechin derivatives (Scheme 6). So if 8-8 dimer **132** can be synthesised, then it could be used as an analytical standard to determine the presence of the compound in grapes or wine. It should be noted that this oxidation scheme is speculative. The B-

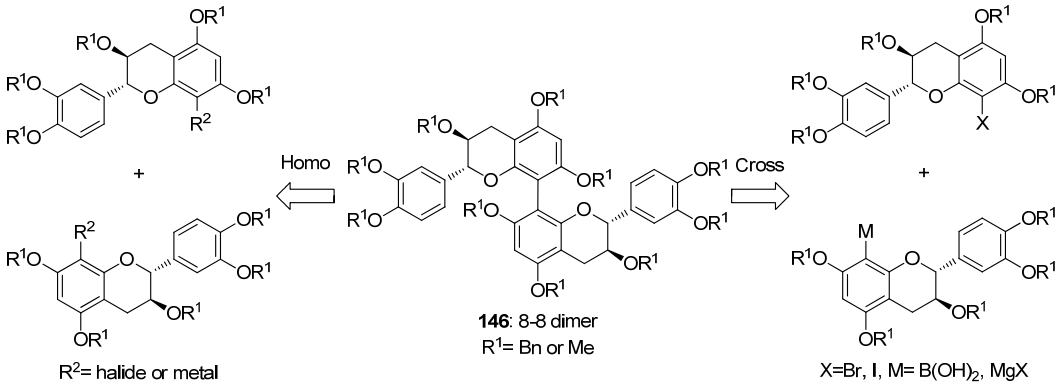
ring is usually noted as the site of oxidation of flavan monomers (Section 1.3.4, Scheme 2), but it is conceivable that oxidation could take place in the A-ring. As the biaryl 8-8 dimer **132** would be expected to have very different chemical and physical properties to 4→8 linked catechin oligomers, it would also be highly useful in structure-function relationship studies, particularly in the field of medicinal chemistry and health.

The most direct route to the synthesis of 8-8 dimer **146** involved the coupling of two catechin moieties at their C8-carbons. In such a coupling, both steric and electronic challenges were identified. Sterically, the synthesis of such a compound from monomer starting materials demanded the production of the 8-8 biaryl bond. This required the formation of a biaryl containing four large *ortho* substituents. As described in Chapter 2 (Section 2.2.7), the synthesis of such hindered biaryls has traditionally been difficult. The electronic challenges of this synthesis arose from the electron rich nature of the catechin A-ring. The 1,3,5 oxygenation of the A-ring rendered the C8 position resistant towards nucleophilic substitution,[40, 75] which will be shown in due to course to be an essential step in any coupling. Both these steric and electronic challenges needed to be overcome in order to successfully construct the 8-8 dimer.

Two possible synthetic strategies were considered in the construction of 8-8 dimers **146b-c**. It was envisaged the aryl-aryl bond could be formed either by an Ullmann-type homo-coupling of a C8-halide or C8-organometallic, or *via*. a cross-coupling of a C8-organometallic derivative with a C8-halide (Scheme 7). It should be noted at this point that the use of both benzyl and methyl protected catechin moieties was considered.

The cross-coupling pathway was chosen as the preferred synthetic method due to its versatility in potential extension to dimers containing different flavan derivatives, such as epicatechin (**2**) or the gallocatechins (**1b, 2b**). The homo-coupling method was limited to the synthesis of 8-8 dimers containing the same flavan unit due to the nature of the coupling. Use of the cross-coupling method provided the possibility to alter both the organometallic and halide derivatives to other flavan units, thus opening the opportunity to synthesise other 8-8 linked dimers of different monomer composition.

Scheme 7: Retro-synthetic analysis of 8-8 dimers 146 formation by either cross or homo-coupling pathways.



The synthesis of C8-aryl and alkyl substituted catechin derivatives was also targeted. Development of syntheses towards these molecules will be discussed in due course.

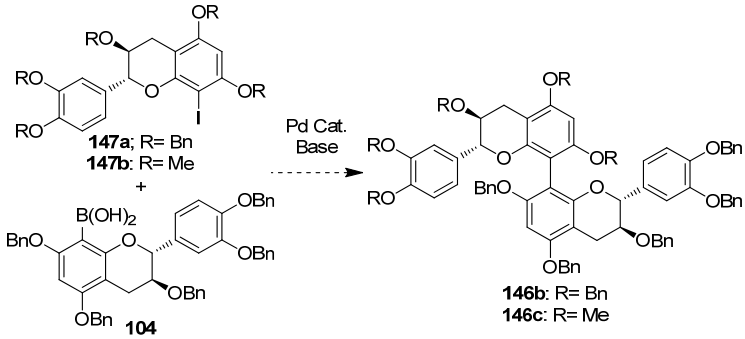
5.2 Results and discussions.

As the primary target of this chapter, the synthesis of 8-8 dimers **146b** or **146c** was attempted using a cross-coupling method (Scheme 7).

5.2.1 Suzuki couplings towards 8-8 dimers 146b and 146 c.

With the C8-boronic acid **104** (Section 3.2.5), and the C8-iodides **147a** (I-PBC) [39] and **147b** (I-PMC) [110] previously synthesised or available through literature methods, a Suzuki cross-coupling pathway was considered for the synthesis of 8-8 dimers **146b** and **146c**. The large literature base for the formation of aryl-aryl bonds *via*. the Suzuki method (Sections 2.1.2.1, 2.2.4), along with the versatility of the reaction in terms of varying base, catalyst and solvent used allowed for great scope in optimisation of the coupling (Scheme 8).

Scheme 8: Proposed Suzuki cross-coupling towards 8-8 dimers 146b and 146c.



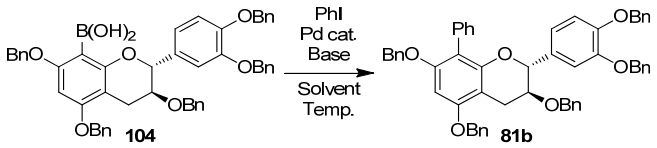
5.2.2 Model cross-couplings.

Given the cross-coupling towards 8-8 dimer **146b** or **146c** was deemed potentially problematic due to steric and electronic issues, two model cross-couplings were developed to determine the respective suitability of C8-boronic acid **104** and C8-iodies **147a** and **147b** derivatives in Suzuki cross-couplings.

5.2.2.1 Model system 1: Coupling of boronic acid 104 (PBC-B(OH)$_2$) to iodobenzene.

The first model system involved the Suzuki coupling of C8-boronic acid **104** (PBC-B(OH)$_2$) to iodobenzene (PhI). As discussed in Chapter 2 (Sections 2.2.4, 2.2.7), iodobenzene was found to be highly active in the Pd-catalysed cross-couplings to boronic acid **42** (TMB-B(OH)$_2$) and organozinc **44** (TMB-ZnCl). Accordingly, this electrophile was deemed to be a useful gauge for the utility of **104** (PBC-B(OH)$_2$) under Suzuki cross-coupling conditions. The cross-coupling of boronic acid **104** to PhI was subsequently attempted (Scheme 9).

Scheme 9: Model Suzuki coupling of PBC-B(OH)$_2$ 104 to iodobenzene (PhI).



This coupling was achieved using a variety of catalysts and bases to provide biaryl **81b** (8Ph-PBC) in good to excellent yields using *ca.* one mmol of PhI. Results of these cross couplings are shown in Table 1.

Entries 1-5 of Table 1 showed that the phosphine-ligand catalysts used in Chapter 2 (Sections 2.2.4, 2.2.6) were successfully applied to this cross-coupling using numerous bases in THF. As a starting point, the so called "standard", or common, Suzuki conditions of Pd(PPh$_3$)$_4$ with aqueous Na_2CO_3 in THF [67] was applied (entry 1). These conditions afforded the desired coupling product **81b** in reasonable yield (60%). Deboronation of the boronic acid derivative to form PBC **52b** was the major side reaction of this coupling. Deboronation of aryl boronic acids containing electron donating substituents has been shown to occur rapidly under aqueous basic

conditions (Section 2.2.4).[104] Accordingly, couplings involving the use of anhydrous bases were studied exclusively following this result.

Table 1: Cross-coupling of PBC-B(OH)$_2$ 104 to PhI under various Suzuki conditions.

Entry [a]	Catalyst	Base	Solvent	Temp. (^{o}C)	Yield (%) [b]
1	$Pd(PPh_3)_4$	Na_2CO_3	THF/H_2O	60	60
2	$Pd(PPh_3)_2Cl_2$	CsF	THF	60	70
3	$Pd(PPh_3)_2Cl_2$	NaOH	THF	60	80
4	Pd(DPEPhos)Cl_2	CsF	THF	60	90
5	Pd(DPEPhos)Cl_2	NaOH	THF	60	95
6	PEPPSI-IPr	CsF	THF	60	80
7	PEPPSI-IPr	K_2CO_3	Dioxane	80	80
8	PEPPSI-IPr	CsF	Dioxane	80	90
9	PEPPSI-IPr	NaOH	Dioxane	80	95
10	PEPPSI-IPr	CsF	THF	rt	0

[a]: Reaction conditions: PhI, (~1 mmol); PBCB(OH)$_2$ **104**, 1.3 equiv.; base, 4 equiv.; catalyst, 3 mol%; solvent, 5 mL. Reactions were stirred overnight at the specified temperature.

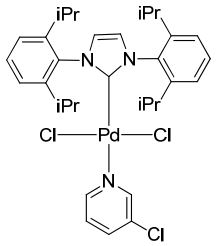
[b]: Isolated yield following column chromatography.

The Pd (II) catalysts $Pd(PPh_3)_2Cl_2$ and Pd(DPEPhos)Cl_2 were also trialled for their suitability (entries 2-5). Higher coupling yields were obtained when the strong base NaOH (entries 3 and 5) was employed in comparison to the weaker base CsF [132] (entries 2 and 4 in conjunction with either catalyst. It was also found the bidentate catalyst Pd(DPEPhos)Cl_2 (entries 4 and 5) was more effective than its monodentate analogue $Pd(PPh_3)_2Cl_2$ (entries 2 and 3). These results mirrored those found in Chapter 2 (Section 2.2.6), where the bidentate catalyst gave superior results in Negishi cross-couplings. The cross-coupling using Pd(DPEPhos)Cl_2 in conjunction with NaOH provided the desired cross-coupled product **81b** in 95% yield (entry 5). This was the equal highest yield obtained for the coupling system.

While conducting these studies, a new *N*-heterocyclic carbene (NHC) ligand-based catalyst known as PEPPSI-IPr became commercially available (Figure 3).[91] This

catalyst was reported to be highly active in many organometallic cross-coupling reactions, including Suzuki couplings.

Figure 3: PEPPSI-IPr.



This catalyst was significantly cheaper than the phosphine-based catalysts used previously. Given this, and the interest in comparing results of NHC *vs*. phosphine ligand-based catalysts, PEPPSI-IPr was trialled for the Suzuki coupling under a variety of conditions (entries 6-10). By comparison of entries 4 and 5 with 8 and 9, this catalyst was as effective as Pd(DPEPhos)Cl_2 for the coupling when dioxane was employed as the solvent at 80 ^oC. The choice of temperature was critical, as the use of THF at 60 ^oC (entry 6) gave a reduced coupling yield compared to the use of dioxane at 80 ^oC (entry 8) when CsF was employed as the base. The effect of the base used was also examined for this catalyst. It was found that the strongest base NaOH (entry 9) afforded a greater coupling yield than the weaker bases CsF (entry 8) and K_2CO_3 (entry 7). This trend mirrored that observed with the phosphine based catalysts (entries 2-5). Using PEPPSI-IPr in conjunction with NaOH (entry 9) provided the cross-coupled product **81b** (8Ph-PBC) in 95%. This result rivalled the highest yield obtained using Pd(DPEPhos)Cl_2 as the catalyst (entry 5). Organ *et al* also reported Suzuki couplings using PEPPS-IPr were effective when used at room temperature.[91] Accordingly, the coupling was attempted at room temperature using CsF as the base in THF (entry 10). This failed to provide any coupling product, which showed that the coupling was not effective at room temperature.

Although the coupling of PBC-$B(OH)_2$ **104** to PhI could be achieved in good to excellent yields (60-95%), purification of the coupling product 8Ph-PBC **81b** proved difficult. The major byproduct of the reaction was deboronated PBC **52b**. Both the product **81b** and PBC **52b** showed very close R_f values in all solvent systems used for TLC analysis. Also, the product could not be purified by crystallisation due to the amorphous nature of the solid. The coupled product was purified by repeated

chromatography on silica gel. Generally, purification through two to three silica columns afforded the desired product **81b** in >95% purity by ^{1}H NMR as a white, foamy solid following concentration.

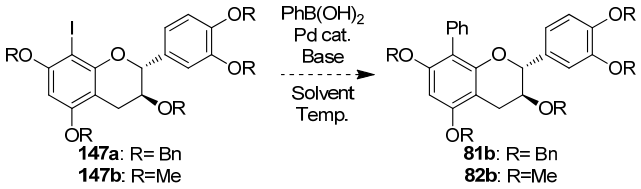
The structure of the biaryl coupling product **81b** (8Ph-PBC) was confirmed by the combination of NMR and HRMS analysis. Both the ^{1}H and ^{13}C NMR spectra for the product **81b** were recorded and compared to that of the starting PBC-B(OH)$_2$ **104**. In the ^{1}H NMR spectrum, the critical C6-H singlet shifted slightly from 6.27 ppm in PBC-B(OH)$_2$ to 6.35 ppm in the product. This C6-H singlet confirmed that the product was indeed substituted at C8. The ^{13}C NMR spectrum provided further evidence of the attachment of the phenyl group to C8. In comparison to the starting PBC-B(OH)$_2$ **104**, the aromatic signals in the 155-165 ppm range, which corresponded to quaternary carbons bound to oxygen in the A-ring (C5, C7 and C8a) had all shifted *ca*. 5-10 ppm upfield in the product spectrum to 152-156 ppm. This confirmed the product was no longer attached to any boron substituent. The C8 resonance of the product was observed at 113.4 ppm. This shift was consistent with C8 being attached to another aromatic carbon. Finally, the six carbon resonances for the attached phenyl ring were all present between 126 and 133 ppm. In particular, the *ipso* carbon was observed at 132.6 ppm, which was consistent for an aryl-substituted quaternary aromatic carbon. HRMS analysis confirmed the molecular formula of the product to be $C_{56}H_{48}O_6$, which was consistent with that of the assigned structure.

In summary, coupling of PBC-B(OH)$_2$ **104** to iodobenzene was achieved in good to excellent yields (60-95%) using a variety of catalysts, bases and solvents. The strength of the base and temperature of the reaction played critical roles in the yield of the coupling. Overall, the optimal conditions were obtained using Pd(DPEPhos)Cl$_2$ and NaOH in THF at 60 ^{o}C (Table 1, entry 5), or PEPPSI-IPr and NaOH in dioxane at 80 ^{o}C (Table 1, entry 9). Both conditions afforded the desired product **81b** (8Ph-PBC) in excellent 95% yield. Most importantly, this model cross-coupling demonstrated that C8-boronic acid **104** (PBC-B(OH)$_2$) participated in Suzuki cross couplings.

5.2.2.2 Model 2: Coupling of I-PBC 147a or I-PMC 147b with phenylboronic acid 148.

With the boronic acid portion of the 8-8 coupling (Scheme 7) shown to be active towards Suzuki couplings, attention then moved to the halide portion. As with boronic acid **104**, a model coupling reaction of C8-iodides **147a-b** was established to ascertain its activity towards a Pd-catalysed nucleophilic addition of a boronic acid at its C8-centre. To achieve this, phenyl boronic acid **148** ($Ph(BOH)_2$) was chosen as the model boronic acid (Scheme 10).

Scheme 10: Model coupling of I-PBC 147a and I-PMC 147b with phenylboronic acid (148, $PhB(OH)_2$).

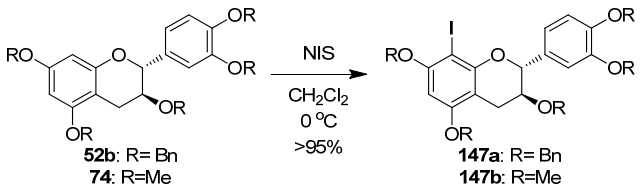


The use of $PhB(OH)_2$ as the nucleophile allowed examination of the susceptibility of C8-iodies **147a-b** towards oxidative addition of a Pd catalyst (Section 2.1.2.2). As stated earlier (Section 5.1.2), the electron donating groups present on the A-ring decreased the activity of that aromatic ring towards nucleophilic aromatic substitution. Oxidative addition of a Pd catalyst into the carbon-iodine bond was also hindered by these electronic effects. Through the use of $PhB(OH)_2$ **148**, the electronic factors of the 8-8 coupling could be studied without additional steric factors, as $PhB(OH)_2$ did not contain any large *ortho* groups that would have created additional steric congestion around the reactive centres.

Before any couplings were attempted, the appropriate C8-halides were required. Both C8-bromides **72** and **75** (Sections 3.2.2.1, 3.2.2.5) and C8-iodides **147a** and **147b** were already synthesised or available by literature methods. As already discussed (Section 2.1.2.2), aryl iodides are generally more reactive towards Pd-catalysed cross-couplings than the analogous bromides. This trend was also reported by Suzuki *et al* for Suzuki cross-couplings.[76] As a result, the C8-iodides **147a** and **147b** were selected as the preferred C8-halides for the cross-couplings with $PhB(OH)_2$ **148**.

The two C8-iodides **147a** and **147b** were readily synthesised in gram quantities from the starting materials PBC **52b** or PMC **72**. Selective C8 electrophilic aromatic iodination of PBC or PMC using one equivalent of *N*-iodosuccinimide (NIS) afforded the desired C8-iodides in near quantitative yields (Scheme 11).

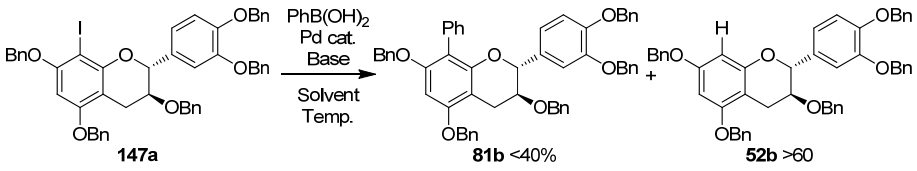
Scheme 11: Selective C8-iodination of PBC 52b and PMC 74 using NIS.



These reactions were generally carried out in anhydrous CH_2Cl_2 at 0 °C, but could also be performed in reagent grade acetone or anhydrous DMF [110] without any observed effect on the yield of reaction. Following aqueous workup, the products were purified by filtration over silica gel to provide almost quantitative yields of the iodides after concentration. I-PBC **147a** was isolated as a white amorphous solid, whereas I-PMC **147b** was isolated as a white, crystalline solid.

With the required C8-iodides **147a** and **147b** prepared, couplings to $PhB(OH)_2$ were then attempted. Couplings of $PhB(OH)_2$ to I-PBC **147a** were attempted first due to the fact that the benzyl protecting groups can be readily removed (Section 3.1.1), so the free phenolic C8-aryl catechins could be readily prepared if required. Initial coupling attempts using either Pd(DPEPhos)Cl_2 or PEPPSI-IPr as the catalyst in the presence of anhydrous NaOH or CsF in dioxane at 80 °C gave very poor results. At best, coupling yields of *ca*. 40% were obtained according to ^{1}H NMR analysis of crude reaction mixtures. The major by-product of the reaction was PBC **52b**, resulting from deiodination of the C8-iodide and subsequent protonolysis after aqueous quenching (Scheme 12). A small amount of the starting iodide **147a** was also seen in the ^{1}H NMR spectra of the crude products.

Scheme 12: Suzuki cross-coupling of I-PBC 147a with $PhB(OH)_2$ 148.



Given the poor conversion of I-PBC **147a** to the coupling product **81b** (8Ph-PBC) and the mixture of products, isolation of the desired product **81b** was never attempted. The presence of PBC **52b** was confirmed by the C6-H and C8-H doublets at 6.25 and 6.27 ppm observed in crude ^{1}H NMR spectra. This indicated that C8 had become protonated. The deiodination of aryl iodides has been shown to be a byproduct in Pd/Ni-catalysed cross-couplings.[133] Also, the presence of the large *ortho* groups, in particular the flexible C7 benzyloxy group, likely hindered the coupling to the extent that deiodination occurred at a comparable rate to the coupling reaction. With this result, I-PBC **147a** was not explored further in this model cross-coupling to $PhB(OH)_2$ and the I-PMC **147b** derivative became the focus for the coupling due to its reduced steric bulk at C7.

The coupling of I-PMC **147b** to $PhB(OH)_2$ **148** was carried using a variety of bases, catalysts, solvents and temperatures (Scheme 13) with varying levels of success (Table 2).

Scheme 13: Suzuki cross-couplings of I-PMC 147b to $PhB(OH)_2$ 148 under various conditions.

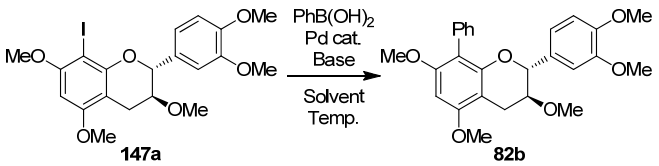


Table 2 demonstrated that the coupling was achieved using a variety of conditions in good to excellent yields (70-95%). It was quickly discovered that THF was not an appropriate solvent when using anhydrous basic conditions (entry 1). Upon heating of the reaction mixture, a white precipitate, assumed to be the "boronate" anion of $PhB(OH)_2$, formed rapidly and remained for the duration of the reaction. No coupling product was obtained as the boronic acid species was not available in solution to react. Switching the solvent to dioxane (entry 2) allowed the "boronate" anion to solubilise, and the coupled product **82b** (8Ph-PMC) was obtained in good yield. The use of the bidentate catalyst $Pd(DPEPhos)Cl_2$ (entry 3) afforded a greater coupling yield than its monodentate equivalent $Pd(PPh_3)_2Cl_2$ (entry 2) when used in conjunction with CsF. This trend mirrored that already noted from the earlier model coupling (Section 5.2.2.1) and results from Chapter 2 (Sections 2.2.4, 2.2.6). In

contrast to Sections 2.2.4 and 5.2.2.1, the coupling yield did not increase when NaOH (entry 4) was employed in the Pd(DPEPhos)Cl_2 catalysed coupling when compared to CsF (entry 3).

Table 2: Suzuki couplings of I-PMC 147b to PhB(OH)$_2$ 148.

Entry [a]	Catalyst	Base	Solvent	Temp. (^{o}C)	Yield (%) [b]
1	Pd(PPh_3)$_2Cl_2$	CsF	THF	60	0
2	Pd(PPh_3)$_2Cl_2$	CsF	Dioxane	80	70
3	Pd(DPEPhos)Cl_2	CsF	Dioxane	80	80
4	Pd(DPEPhos)Cl_2	NaOH	Dioxane	80	80
5	PEPPSI-IPr	CsF	Dioxane	80	80
6	PEPPSI- IPr	NaOH	Dioxane	80	85
7	PEPPSI- IPr	NaOH	Dioxane/H_2O	80	90
8	PEPPSI- IPr	CsF	Dioxane	rt	0
9	PEPPSI- IPr	NaOH	Acetonitrile	80	0
10	PEPPSI- IPr	NaOH	DMA	100	0
11	PEPPSI- IPr	NaOH	DMA/H_2O	100	95

[a]: General reaction conditions: I-PMC **147b**, (~100 mg); PhB(OH)$_2$, 2 equiv.; base, 4 equiv.; catalyst, 5mol%; solvent, 5 mL. All reactions were stirred at the specified temperature overnight.

[b]: Isolated yield following silica chromatography.

Couplings were also attempted using the NHC-ligand based catalyst PEPPSI-IPr. This catalyst provided, in most cases, either equivalent or superior coupling yields to that found using Pd(DPEPhos)Cl_2. For PEPPSI-IPr, the use of NaOH (entry 6) afforded a higher coupling yield compared to CsF (entry 5). Unlike the previous model cross coupling (section 5.2.2.1), the use of aqueous bases was beneficial to the coupling yield (entries 7 and 11). This was most likely due to the fact that unlike PBC-B(OH)$_2$ **104**, PhB(OH)$_2$ **104** did not have any electron donating *ortho* substituents, and so was far less prone to protolytic deboronation. Furthermore, the improved solubility of the "boronate" anion of PhB(OH)$_2$ in aqueous solvent (entry 7) compared to anhydrous solvents (entry 6) probably contributed to the higher coupling yields observed in the aqueous couplings. No coupling product was obtained when the coupling was carried out at room temperature (entry 8). This

showed that room temperature was not an appropriate temperature for the coupling reaction.

The coupling was also attempted using non-ethereal, polar solvents. When anhydrous base was employed, the use of either acetonitrile (entry 9) or DMA (entry 10) as the reaction solvent failed to provide any cross-coupled product. This was attributed to the poor solubility of the "boronate" anion of $PhB(OH)_2$ in these solvents. When aqueous DMA was employed at 100 ^oC, the coupled product **82b** was produced in excellent 95% yield (entry 11). This result was the highest yield obtained for this cross coupling. The "boronate" anion of $PhB(OH)_2$ was completely soluble in aqueous DMA. This solubility explained why the coupling failed using anhydrous DMA (entry 10), but proceeded efficiently in aqueous DMA (entry 11). The improved yield of the aqueous DMA system compared to other coupling conditions (entries 5-7) was attributed to the increased temperature used in the coupling and the improved solubility of the "boronate" anion of $PhB(OH)_2$ in the aqueous solvent. Most PEPPSI-IPr catalysed couplings were carried out at 80 ^oC in dioxane, whereas the use of DMA allowed for an increase in reaction temperature to 100 ^oC, which provided the coupled product in slightly higher yields compared to the dioxane couplings. This result further showed that the temperature of the reaction played an important role in the success of the coupling.

Purification of the cross-coupled product **82b** (8Ph-PMC) was achieved using silica chromatography. The major byproduct of the coupling reactions was PMC **74**, produced by deiodination of the starting C8-iodide **147b**. The extent of deiodination depended strongly upon the coupling conditions. This result was analogous to the I-PBC **147a** couplings (Scheme 11), but deiodination occurred at a much slower rate in the case of I-PMC **147b**. This strongly suggested that steric bulk of the C7 substituent played an important role in the coupling reaction. The reduced steric bulk of the C7 substituent of I-PMC **147b** compared to that of I-PBC **147a** dramatically increased the rate of coupling, so an increased ratio of coupled product to deiodinated product **74** was observed. More deiodination was observed when anhydrous bases were employed compared to aqueous bases. This also served to explain the increased coupling yields obtained when aqueous conditions were used.

The separation of the desired product **82b** from the byproduct PMC **74** was successful when a large (ca. 50-60 times) excess of silica was used for chromatography. Using this method, the desired coupling product **82b** (8Ph-PMC) was obtained as a white, amorphous solid after concentration in the yields reported in Table 2. Purity of the product was shown to be >95% by ^{1}H NMR analysis in the case of most of the coupling conditions.

Like its 8Ph-PBC **81b** analogue (Section 5.2.2.1), a combination of NMR and HRMS spectral analysis confirmed the structure of the cross-coupled product 8Ph-PMC **82b**. By comparison of ^{1}H NMR spectra of the starting I-PMC **147b** and the product **82b**, a downfield shift of the C6-H singlet from 6.1 ppm in starting material to 6.25 ppm in the product showed that the C8-iodide had been consumed to form the biaryl product **82b**. The five protons of the phenyl substituent were also seen as multiplet between 7.32 and 7.20 ppm. The ^{13}C NMR supported the assignments. The C8-carbon resonance of the starting material **147b** was observed at 66.1 ppm. This resonance shifted to 110.8 ppm in the product. This new peak was observed at the expected shift for the aryl-substituted C8. The six resonances due to the phenyl substituent were also present between 126 and 132 ppm. The *ipso* carbon was observed at 131.9 ppm, which was consistent with that expected for the phenyl-substituted quaternary carbon. HRMS confirmed the molecular formula of the product as $C_{26}H_{28}O_{6,}$ which was consistent with that of the assigned structure.

In summary, the coupling of I-PMC **147b** to $PhB(OH)_2$ **148** was achieved using a variety of bases, solvents and Pd catalysts. It was found that the coupling could be carried out using both anhydrous and aqueous basic conditions, with the latter providing higher coupling yields due to the reduced rates of deiodination of I-PMC **147b** and improved solubility of the "boronate" anion of $PhB(OH)_2$. The choice of solvent and reaction temperature also played a critical role in the outcome of the coupling. The optimal conditions for the coupling were obtained using PEPPSI-IPr as the catalyst in conjunction with NaOH in aqueous DMA at 100 ^{o}C. Under these conditions, 8Ph-PMC **82b** was prepared in 95% yield.

5.2.3 Couplings towards 8-8 dimer 146c.

The successful model cross-couplings (Sections 5.2.2.1 and Section 5.2.2.2) had shown that both PBC-$B(OH)_2$ **104** and I-PMC **147b** units were reactive under Suzuki

cross-coupling conditions using a variety of catalysts and bases in both anhydrous and aqueous solvents. Armed with a variety of potential coupling conditions, attention then turned to combining the two portions in order to construct 8-8 dimer **146c** (Scheme 14).

Scheme 14: Attempted synthesis of 8-8 dimer 146c through Suzuki cross-coupling of PBC-B(OH)$_2$ 104 to I-PMC 147c.

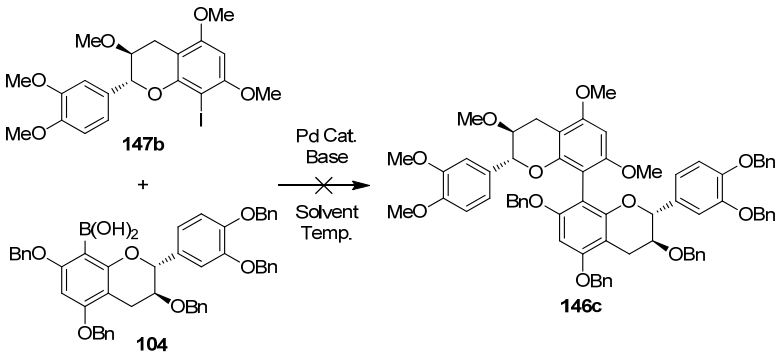


Table 3: Coupling conditions attempted to achieve 8-8 dimer 146c synthesis.

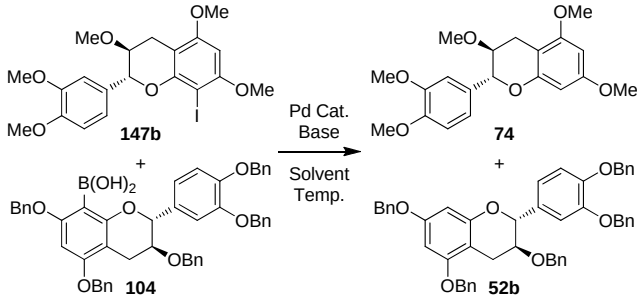
Entry [a]	Catalyst,	Loading (mol %)	Base	Solvent	Temperature (^{o}C)
1	PEPPSI-IPr,	10	NaOH	DMA/H_2O	100
2	PEPPSI-IPr	10	K_2CO_3	DMA/H_2O	100
3	PEPPSI-IPr	10	NaOH	Dioxane	80
4	PEPPSI-IPr	10	CsF	Dioxane	80
5	Pd(DPEPhos)Cl_2	5	NaOH	Dioxane	80
6	Pd(DPEPhos)Cl_2	5	CsF	Dioxane	80
7	Pd(DPEPhos)Cl_2	5	CsF	THF/H_2O	60
8	Pd(PPh_3)$_2Cl_2$	10	NaOH	Dioxane	80
9	Pd(PPh_3)$_2Cl_2$	10	NaOH	Dioxane/H_2O	80
10	Pd(PPh_3)$_2Cl_2$	10	K_2CO_3	Dioxane/H_2O	80
11	Pd(PPh_3)$_4$	10	NaOH	Dioxane/H_2O	80
12	Pd(PPh_3)$_4$	10	K_2CO_3	DMA	100
13	Pd(PPh_3)$_4$	10	K_2CO_3	DMA/H_2O	100

[a]: General reaction conditions: I-PMC **147b**, ~50 mg; PBC-B(OH)$_2$ **104**, 2 equiv.; base, 4 equiv.; catalyst, loading as above; solvent, 10mL. Reactions were stirred from 24 hours up to 4 days at the specified temperature.

Despite exhaustive efforts, this coupling proved an insurmountable challenge. A selection of the conditions attempted for the coupling is shown in Table 3.

None of these conditions afforded any cross-coupled product **146c** despite the long reaction times and high catalyst loadings. In all cases, PBC **52b** from deboronation of boronic acid **104** was obtained as the sole product from this species. The fate of I-PMC **147b** was dependent upon the length of reaction time. When shorter reaction times (*ca*. 24 hrs) were employed, the I-PMC **147b** was generally recovered with only small proportions of deiodinated PMC **74** observed by ^{1}H NMR analysis of crude reaction mixtures. The amount of deiodinated PMC **74** recovered increased with longer reaction times. Generally I-PMC **147b** had completely deiodinated within 48 to 72 hours depending upon the base and temperature employed (Scheme 15).

Scheme 15: Products of couplings of PBC-B(OH)$_2$ 104 with I-PMC 147b.



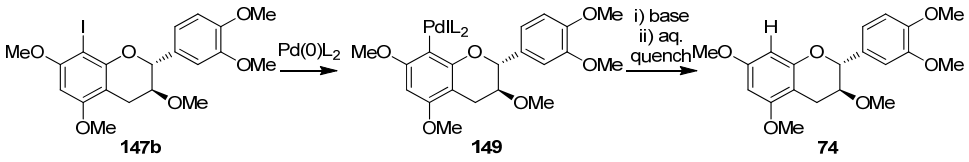
Analysis of ^{1}H and ^{13}C NMR of crude reaction mixtures was used to determine the reaction products. The overlapping distorted C6 and C8 doublets at *ca*. 6.25 ppm in the crude ^{1}H NMR were indicative of deboronated PBC **52b** and deiodinated PMC **74**, respectively. The presence of starting I-PMC **147b** was determined from the ^{13}C NMR. A peak at 66 ppm was indicative of the C8-iodide of I-PMC **147b**.

The results obtained in the earlier model coupling provided some insight towards explaining the lack of 8-8 dimer **146c** formed in these couplings. As shown earlier (Section 5.2.2.1), PBC-B(OH)$_2$ **104** rapidly deboronated to afford PBC **52b** in that model study, particularly when aqueous conditions were employed. So with the slower rate of oxidative addition of the Pd catalyst (Section 2.1.2.2) into I-PMC **147b** compared to iodobenzene, it was likely deboronation occurred at a faster rate than

oxidative addition. As a result, no boronic acid was available to participate in transmetallation to the Pd centre (Section 2.1.2.2) after oxidative addition.

With no boronic acid **104** available to continue the Pd catalytic cycle, I-PMC **147b** slowly deiodinated under the reaction conditions to form PMC **74**. The deiodination of I-PMC **147b** presumably occurred *via*. the oxidative addition of the Pd catalyst to afford intermediate **149**, which then underwent reductive breakdown to provide deiodinated PMC **74** [133] (Scheme 16). I-PMC **147b** did undergo deiodination when left in solution without any base or Pd catalyst, but deiodination took place over weeks rather than days. This suggested that the base and Pd centre played a role in the relative faster deiodination of I-PMC **147b** in the coupling reactions. This indicated that the oxidative addition of the catalyst into the C8-iodine bond was actually proceeding.

Scheme 16: Deiodination of I-PMC 147b *via*. oxidative addition of the Pd catalyst and reductive breakdown of complex 149.

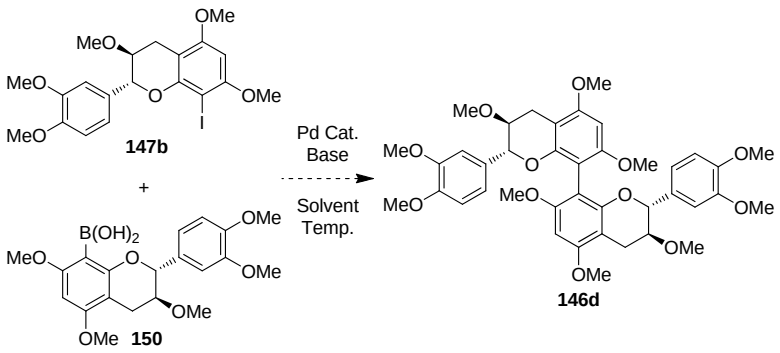


It was also possible that oxidative addition into I-PMC **147b** was occurring at a faster rate than deboronation of PBC-B(OH)$_2$ **104**. If this was the case, then it was probable that the steric bulk imparted by the large *ortho* groups on both the boronic acid and iodide coupling partners prevented the coupling from proceeding. This was consistent with results found in Chapter 2 (Section 2.2.6) regarding the difficulty in synthesising tetra-*ortho* biaryl species using Pd-catalysed cross-coupling technologies. It was not clear which mechanism was in operation, but the end result in either case was that no evidence of 8-8 dimer **146c** formation was ever obtained.

5.2.4 A new boronic acid: Attempts to synthesise PMC-B(OH)$_2$ 150.

In an attempt to reduce the steric bulk of the boronic acid portion in order to promote the 8-8 dimer **146d** formation, methyl protecting groups were considered as a replacement for the benzyl groups of PBC-B(OH)$_2$ **104** (Scheme 17).

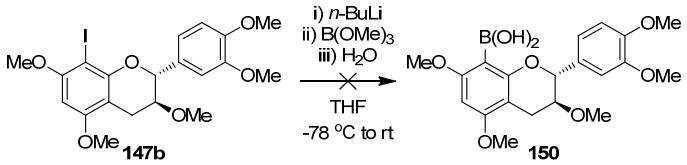
Scheme 17: Coupling of PMC-B(OH)$_2$ 150 and I-PMC 147b.



In the couplings of I-PMC **147b** or I-PBC **147a** to PhB(OH)$_2$ **148** (Section 5.2.2.2), the reduced steric bulk of methyl protecting groups compared to benzyl protecting groups was found to be beneficial. So it was envisaged that a similar reduction in steric bulk of the boronic acid partner could also be beneficial.

Before any of these cross-couplings could be attempted, synthesis of the desired boronic acid, PMC-B(OH)$_2$ **150**, was required. Formation of this derivative was attempted from I-PMC **147b** using the same low temperature lithium-halogen exchange with *n*-BuLi, transmetallation with B(OMe)$_3$ and aqueous hydrolysis sequence used to synthesise boronic acid **104** (Section 3.2.5, Scheme 18).

Scheme 18: Attempted synthesis of PMC-B(OH)$_2$ 150 from I-PMC 147b.



Frustratingly, this synthetic pathway proved unsuccessful. Despite numerous attempts, the boronic acid **150** could not be isolated in synthetically useful quantities. Analysis of crude reaction mixtures by ^{1}H NMR invariably showed PMC **74** as the major reaction product, with *ca*. 10-20% of another product assumed to be the desired boronic acid. ^{13}C NMR analysis confirmed this other compound was not starting material, but could not be used to identify the product as boronic acid **150**. The absence of the indicative C8 carbon at 66 ppm showed the starting iodide **147b** has been completely consumed. This other product was not readily isolated. The compound could not be crystallised and separation using silica chromatography provided only trace amounts of the product, suggesting the product was sensitive to

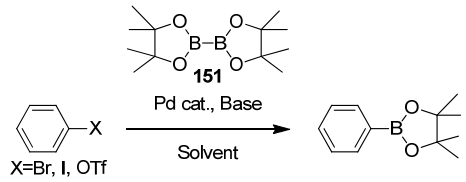
silica. ^{1}H NMR of the trace product isolated suggested that the product was boronic acid **150**, but could not be confirmed due to the small quantity available.

It was speculated that the poor solubility of the starting iodide **147b** and the resulting organolithium at low temperature was responsible for the low conversion obtained in this reaction. At *ca*. 100 mM, the reaction concentration used for the formation of PBC-B(OH)$_2$ **104**, I-PMC **147b** precipitated out of solution when cooled to -78 ^{o}C. To ensure complete solubility of the iodide and subsequent organolithium, a reaction concentration of 20 mM or less was required. This may have affected the efficacy of the reaction, resulting in the low conversions observed. The use of THF/Et$_2$O mixtures or PhCH$_3$ as the solvent did not have any beneficial effect on the reaction. So the formation of boronic acid **150** (PMC-B(OH)$_2$) was abandoned in favour of new methods for introducing the boron functionality at C8.

5.2.5 Towards new boron-containing compounds.

Given that boronic acid, PMC-B(OH)$_2$ **150** was not readily available in useful quantities from the lithiation, transmetallation and hydrolysis method used previously (Section 5.2.4), alternative methods were sought to gain access to C8-boronated compounds. One such method was Miyaura boronylation (Section 2.1.1.4).[68, 69] In such a reaction, an aryl halide or triflate was coupled with bis(pinacolato)diboron **151** in the presence of a base and a Pd catalyst to provide the corresponding arylpinacolboronate ester (Scheme 19).

Scheme 19: Formation of arylpinacolboronate esters by Miyaura boronylation.



It was considered such a reaction could be used to gain access to the desired C8-boronate ester of PMC **152** through the Pd-catalysed reaction of bis(pinacolato)diboron ((B-pin)$_2$) with I-PMC **147b** (Scheme 20).

Both Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ [69, 70] and PEPPSI-IPr [91] catalysts have been shown to be highly active in this boronylation reaction with a variety of aryl halide substrates. As a consequence, these catalysts were employed along with numerous bases and

solvents in an attempt to synthesise the boronate ester **152**. Unfortunately, these attempts proved unsuccessful. Some selected conditions are shown in Table 4.

Scheme 20: Pd-catalysed coupling of I-PMC 147b with (B-pin)$_2$ 151.

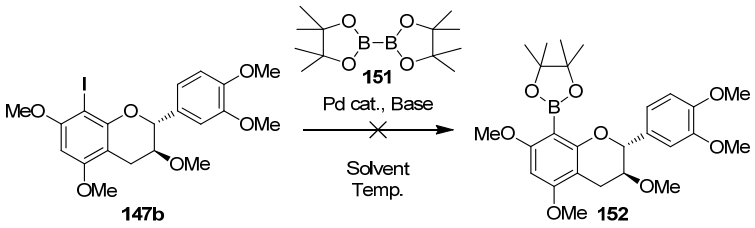


Table 4: Coupling conditions for boronylation of I-PMC 147b.

Entry [a]	Catalyst	Base	Solvent	Temp (^{o}C)
1	Pd(dppf)Cl_2.CH_2Cl_2	KOAc	DMF	80
2	Pd(dppf)Cl_2.CH_2Cl_2	KOAc	Dioxane	80
3	Pd(dppf)Cl_2.CH_2Cl_2	NaOH	Dioxane	80
4	Pd(dppf)Cl_2.CH_2Cl_2	Et_3N	Dioxane	80
5	PEPPSI-IPr	KOAc	DMF	80
6	PEPPSI-IPr	NaOH	Dioxane	80
7	PEPPSI-IPr	NaOH	DMF	120
8	PEPPSI-IPr	Et_3N	Dioxane	80
9	Pd(DPEPhos)Cl_2	KOAc	Dioxane	80
10	Pd(DPEPhos)Cl_2	NaOH	Dioxane	80

[a]: General reaction conditions: I-PMC **147b**, ~50 mg; bis(pinacolato)diboron **151**, 2 equiv.; base, 3 equiv; catalyst, 5 mol%; solvent, 5-10 mL. Reactions were stirred at specified temperature for 24-72 hours.

It was clear that neither Pd(dppf)Cl_2.CH_2Cl_2 (entries 1-4) or PEPPSI-IPr (entries 5-8) were active towards the coupling. As a result, Pd(DPEPhos)Cl_2 was also examined (entries 9, 10) due to earlier success achieved with this catalyst in coupling reactions (Sections 2.2.6, 2.2.7, 5.2.2.1, 5.2.2.2). This catalyst also failed to afford any coupled product **152**. When shorter reaction times were employed (*ca*. 24 hrs), the starting materials I-PMC **147b** and (B-pin)$_2$ **151** were recovered after aqueous quenching. With longer reaction times, PMC **74**, formed by the deiodination of I-PMC **147b**, along with starting (B-pin)$_2$ **151** were the dominant species recovered. This was consistent with earlier results obtained (Sections 5.2.2.2, 5.2.3), whereby I-PMC

147b slowly deiodinated in the presence of Pd when the appropriate cross-coupling reaction did not occur.

It was suspected that the steric bulk of the two coupling partners were principally responsible for the lack of coupling observed. The combination of the steric bulk imparted by the *ortho* groups flanking the C8-iodine bond of I-PMC **147b**, along with the overall size of $(B\text{-pin})_2$ **151** prevented reactivity of the two species. As a result, no coupling product **152** was ever obtained.

In summary, the studies towards the Suzuki cross-coupling pathway to 8-8 dimers **146b** or **146c**, showed that PBC-$B(OH)_2$ **104** was active towards iodobenzene (Section 5.2.2.1), but suffered from rapid deboronation due to the presence of the electron donating *ortho* substituents. As a result, coupling to the more sterically demanding electrophile I-PMC **147b** was severely hampered (Section 5.2.3). This combined with the fact that C8-boron-containing PMC analogues **150** and **152** could not be accessed (Sections 5.2.4 and 5.2.5), resulted in reassessment of possible coupling pathways towards the synthesis of 8-8 dimers **146**.

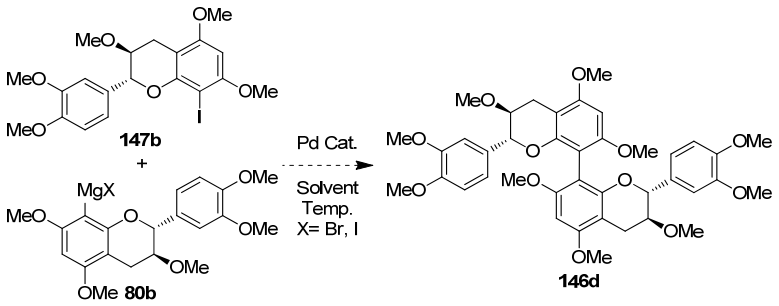
5.2.6 New methods towards the synthesis of 8-8 dimer 146.

With the failure of the Suzuki cross-coupling method for the synthesis of 8-8 dimers **146b** and **146c**, alternative pathways towards this target required consideration. While numerous pathways were identified, two were potentially viable. The first was to attempt a similar Pd-catalysed cross-coupling using another C8-metal (e.g. Magnesium) to replace the troublesome boronic acid. Alternatively, an Ullmann type homo-coupling of either I-PMC **147b** or PBC-$B(OH)_2$ **104** (Scheme 7) could be attempted. Since a cross-coupling pathway was still preferred over a homo-coupling method (Section 5.1.3), the use of a C8-Grignard was investigated first.

5.2.7 Grignard pathway towards 8-8 dimer 146d.

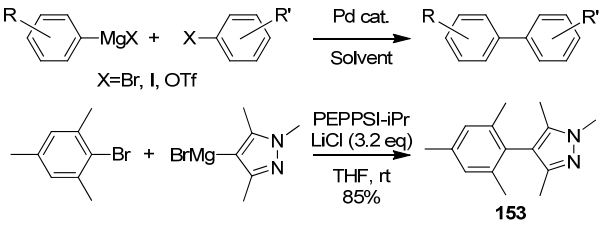
It was proposed that 8-8 dimer **146d** could be accessed through a Pd-catalysed cross-coupling of a C8-Grignard derivative with I-PMC **147b**. Such a reaction could be considered akin to the previously discussed Suzuki cross-coupling (section 5.2.3), with Grignard **80b** (PMC-MgX) replacing the boronic acid (Scheme 21). A Grignard was chosen as an alternative to the boronic acid as Grignard **80b** should be more robust and less prone to protonolysis in comparison to boronic acid **104**.

Scheme 21: Proposed coupling of PMC-MgX 80b to I-PMC 147b.



Pd-catalysed cross-couplings of Grignard species with halides are generally referred to in the literature as the Kumada, or fully the Kumada-Tamao-Corriu, cross-coupling reaction (Section 2.1.2.1).[88] Such couplings have been employed for the synthesis of biaryls using numerous Pd catalysts.[134, 135] In particular, Organ *et al* [136] successfully prepared the tetra-*ortho* functionalised biaryl species **153** using PEPPSI-IPr as a catalyst in the presence of LiCl (Scheme 22). With this literature base, it was deemed a Kumada cross-coupling approach towards the synthesis of 8-8 dimer **146d** was worthy of further exploration.

Scheme 22: The general Kumada cross-coupling and Organ *et al* formation of tetra-*ortho* biaryl species 153 using PEPPSI-IPr.



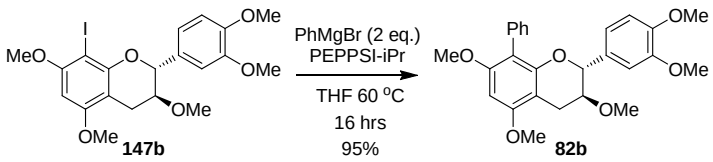
5.2.7.1 Model Grignard cross-coupling.

In order to successfully synthesise 8-8 dimer **146d** using the Kumada method, two issues needed to be addressed. Firstly, would I-PMC **147b** be active towards Pd catalysis in the presence of Grignard reagents? Secondly, could the C8-Grignard **80b** (PMC-MgX) be formed efficiently? Similarly to the Suzuki coupling models (Section 5.2.2), model systems were employed to assess these factors prior to attempting 8-8 dimer **146d** formation.

The activity of I-PMC **147b** towards Kumada cross-coupling conditions was determined by the use of phenylmagnesium bromide (PhMgBr) as a model aryl

Grignard reagent. Using PEPPSI-IPr as a catalyst in THF at 60 ^{o}C for 16 hours, the desired model biaryl **82b** (8Ph-PMC) was obtained in 95% yield after isolation using silica chromatography when two equivalents of the Grignard was employed (Scheme 23).

Scheme 23: Kumada coupling of I-PMC 147b with PhMgBr.

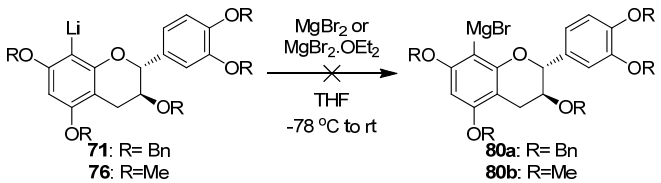


The use of 2 molar equivalents of PhMgBr was critical to the success of the coupling. The yield of the desired biaryl **82b** (8Ph-PMC) dropped to 81% and 53% respectively when 1.5 and 1.1 equivalents of PhMgBr were employed. With the high yield of model biaryl **82b** obtained using the PEPPSI-IPr catalyst, it was not necessary to carry out the coupling with alternative catalysts.

5.2.7.2 Towards the synthesis of a C8-Grignard.

With the model system coupling confirming that I-PMC **147b** was reactive towards PhMgBr under Kumada coupling conditions, attention turned towards the synthesis of the appropriate C8-Grignard derivative. This derivative was visited earlier in Chapter 3 (Section 3.2.2.5). Attempts to prepare the C8-Grignards **80a/80b** from organolithium derivatives **71** and **76** by transmetallation with $MgBr_2$ or $MgBr_2.OEt_2$ failed to provide a reactive C8-Grignard species (Scheme 24).

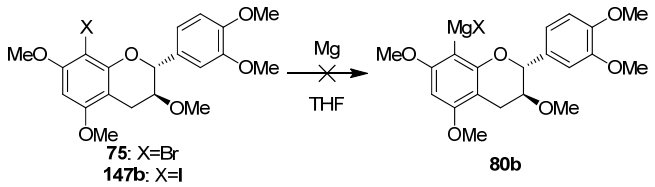
Scheme 24: Failed transmetallation of C8-organolithiums 71 and 76 with $MgBr_2$ or $MgBr_2.OEt_2$.



Considering the issues encountered with this transmetallation, revisiting these results was not merited. So another method to access the C8-Grignard **80b** was required. As the most direct route to the C8-Grignard **80b** was Mg insertion (Section 2.1.1.2) into

Br-PMC **75** or I-PMC **147b**, attention was focussed upon the development of such a method (Scheme 25).

Scheme 25: Attempted magnesium insertion into Br-PMC 75 or I-PMC 147b to provide C8-Grignard 80b.



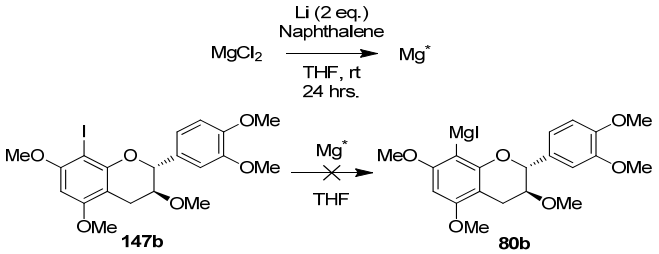
The direct magnesium insertion was initially attempted using both Br-PMC **75** and I-PMC **147b** as starting materials using convectional heating. These reactions were carried out by initially activating a slight excess of magnesium turnings by addition of 1,2-dibromoethane (*ca*. 10 mol%), which was briefly heated to 60 ^{o}C (Section 2.1.1.2). The halide **75** or **147b** was then added as a solution in THF, followed by a few iodine crystals and the resulting mixtures were refluxed for up to 24 hours. In the case of both halides, no consumption of any magnesium was observed, and the starting halides were recovered in almost quantitative yields.

Sonication was identified as a useful aid for magnesium insertion in the formation of 2,4,6-trimethoxyphenylmagnesium bromide (**39)** (Section 2.2.2). Accordingly, sonication promoted magnesium insertion into I-PMC **147b** was attempted. To achieve this insertion, a mixture of I-PMC **147b**, Mg turnings and a few crystals of iodine in THF were sonicated at 25-30 ^{o}C for 4 hours. After this time little magnesium had been consumed and the starting iodide **147b** was recovered following filtration and concentration. A small amount of deiodinated PMC **74** was also observed in the reaction mixture. The use of magnesium ribbon and powder were also investigated to improve the surface area-to-volume ratio of the magnesium compared to that of the turnings, but these variations proved futile. Reaction times of up to 12 hours were also attempted to no avail.

Since the magnesium insertions of I-PMC **147b** had failed using commercial magnesium ribbons, powder and turnings, the use of "Rieke" magnesium was considered. According to Rieke *et al*,[137] metallic magnesium prepared by the lithium metal induced reduction of $MgCl_2$ in THF using naphthalene as an electron carrier

was particularly reactive towards insertion into aryl halides. Accordingly, the preparation of C8-Grignard **80b** by insertion of "Rieke" magnesium (Mg^*) into I-PMC **147b** was attempted (Scheme 26).

Scheme 26: Preparation of "Rieke" magnesium and attempted insertion into 147b.



The reduction of $MgCl_2$ to the "Rieke" magnesium proved experimentally difficult, but was eventually achieved. The poor solubility of $MgCl_2$ in THF required that the reaction was vigorously stirred for 24 hours at room temperature. This was much longer than the 10 hours reported by Rieke.[137] This reduction afforded the "Rieke" magnesium as a black suspension. In Rieke's preparation, the Mg was allowed to settle and the supernatant was drawn off with a syringe to remove some of the naphthalene. As the Mg^* was to be used in the insertion into I-PMC **147b**, it was considered naphthalene would pose no issue, and the magnesium suspension was used as prepared.

An aliquot of the magnesium suspension was added to a solution of I-PMC **147b** in THF and vigorously stirred at room temperature for 24 hours. An aliquot of the reaction mixture was removed *via.* syringe and quenched. Crude ^1H NMR analysis of this quenched aliquot revealed only starting I-PMC **147b** and naphthalene were present, indicating that no insertion had occurred. The remaining reaction mixture was subjected to sonication for 6 hours at *ca*. 30 ^oC, after which a further aliquot was removed and quenched. ^1H NMR analysis of this aliquot confirmed no insertion had taken place. Finally, the solution was refluxed at 80 ^oC for 24 hours and then the whole mixture was quenched. The starting I-PMC **147b** was recovered almost quantitatively. The C8-iodide peak at 66 ppm in the ^{13}C NMR of the recovered mixture confirmed the presence of the starting iodide **147b**. The insertion was also attempted using *ca*. 5 equivalents of Mg^*, but no insertion into I-PMC **147b** was detected after 24 hours at 80 ^oC. With these results, the "Rieke" magnesium insertion

into I-PMC **147b** was not considered further in the formation of the C8-Grignard derivative **80b**.

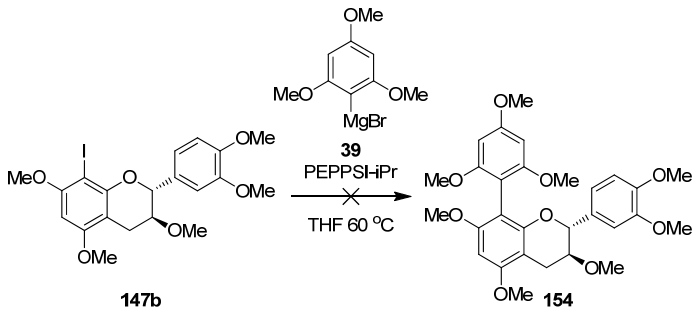
It was speculated that two main factors were involved in the lack of magnesium insertion using all the above methods. It was speculated that retention of residual solvents and moisture in both Br-PMC **75** and I-PMC **147b** starting materials may have retarded magnesium insertion. Residual solvent (CH_2Cl_2, hexanes/grease, EtOAc) and moisture peaks were observed in the ^1H NMR spectra of these C8-halides. Even after recrystallisation and prolonged exposure to high vacuum these impurities could not be completely removed. The second proposed factor was reaction scale. In comparison to the formation of 2,4,6-trimethoxyphenylmagensium bromide **39**, the insertions involving Br-PMC **75** and I-PMC **147b** were carried out on a far smaller scale due to the availability of the starting materials. Carrying out these heterogeneous insertions at a small scale was experimentally difficult due to the small quantities of magnesium used. With the use of these small quantities, trace impurities or residual moisture in the halides or magnesium may have been present in sufficient quantities to retard insertion. Neither of these speculations were confirmed, so the actual cause for the failed insertion reactions still remains unclear.

At this point it was recognised that if further studies towards the oxidative insertion of magnesium into Br-PMC **75** or I-PMC **147b** were to be carried out, much larger quantities of these compounds were required. The scaling up of the Br-PMC/I-PMC synthesis was considered to be too prohibitive in terms of time required to produce the halides and cost of the materials to achieve such scale-up. Accordingly, it was deemed more time and cost effective to investigate other methods for the formation of 8-8 dimer **146**. With this, the studies towards the formation of C8-Grignard **80b** ceased.

5.2.7.3 Coupling of MgBr-TMB 39 to I-PMC 147b.

As an aside to the Kumada couplings towards the synthesis of 8-8 dimer **146d**, the PEPPSI-IPr catalysed coupling of I-PMC **147b** to MgBr-TMB **39** was attempted in order to construct the tetra-*ortho* biaryl **154**. The attempted coupling was initially carried out addition of an aliquot of a preformed solution of **39** to a solution of I-PMC **147b** and PEPPSI-IPr in THF. The mixture was then stirred at 60 ^oC for 48 hours (Scheme 27).

Scheme 27: Attempted Kumada coupling of I-PMC 147b with MgBr-TMB 39.

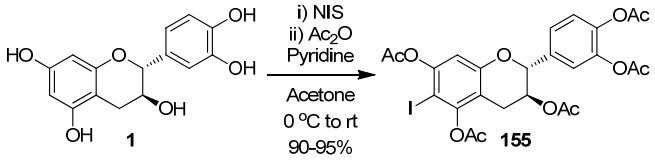


This initial coupling failed to provide any coupled product **154**, with hydrolysed TMB **33**, and a mixture of starting I-PMC **147b** and deiodinated PMC **74** observed by ^{1}H NMR analysis of the crude reaction mixture following quenching. The coupling was repeated using a 1:1 mixture of THF/NMP as the solvent, but provided no coupled product. The catalysts Pd(DPEPhos)Cl_2 and Pd(PPh_3)$_2Cl_2$ were used in place of PEPPSI-IPr without success. So the tetra-*ortho* biaryl **154** could not be constructed using a Kumada protocol. As a result, the Kumada cross-couplings towards 8-8 dimers **146** concluded. This last coupling did reinforce a fact that was already well known (Sections 2.2.7, 5.2.3); tetra-*ortho* biaryls are tough synthetic targets.

5.2.8 Coupling methods involving the use of 6-iodo-pentaacetyl-catechin 155.

During the 8-8 cross-coupling attempts discussed, the high electron density of the A-ring of the I-PBC **147a** or I-PMC **147b** was often noted to have a negative impact on the rate of oxidative addition of the Pd catalysts into the carbon-iodine bond (Sections 5.2.2.2, 5.2.3). As an aside, an iodide containing acetyl protecting groups was considered. It was reasoned that the electron withdrawing nature of the acetyl protecting groups would reduce the electron density of the A-ring sufficiently to allow more facile oxidative addition of a Pd catalyst. Kiehlmann *et al* [110] synthesised the compound 6-iodo-pentaacetyl-catechin **155** (6I-PAC) by selective C6-iodination of catechin using NIS in acetone, followed by acetylation using acetic anhydride (Ac_2O) in pyridine. Accordingly, this iodide was readily prepared by a one-pot iodination and acetylation of catechin **1** using the above conditions (Scheme 28).

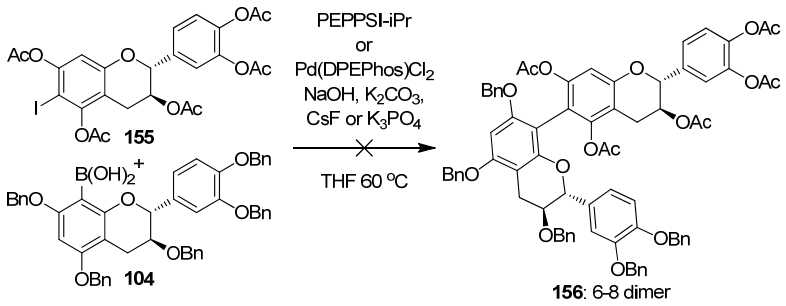
Scheme 28: Synthesis of 6I-PAC 155 from catechin 1 *via*. C6-iodination and acetylation.



Gram quantities of 6I-PAC **155** were repeatedly prepared in excellent yields (90-95%), following purification by silica chromatography.

The coupling of this C6-iodide **155** (6I-PAC) to PBC-B(OH)$_2$ **104** was attempted using a Suzuki coupling protocol in the presence of PEPPSI-IPr or Pd(DPEPhos)Cl$_2$ as a catalyst in order to construct 6-8 dimer **156** (Scheme 29).

Scheme 29: Attempted formation of 6-8 dimer 156 through Suzuki coupling of 6I-PAC 155 with PBC-B(OH)$_2$ 104.



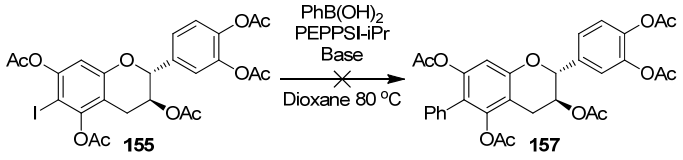
The couplings were initially attempted using KOH or K_2CO_3 as the base in THF. However, results of these couplings were inconclusive due to the large number of products formed. ^{1}H NMR analysis of crude reaction mixtures suggested that removal of some of the acetyl groups had occurred. These results, while disappointing, were conceivable given that both KOH and K_2CO_3 have been used in the deacetylation of acetyl-protected phenols.[138] Accordingly, the milder bases CsF and K_3PO_4 were also trialled for the coupling. These bases also furnished similarly inconclusive results; with ^{1}H NMR analysis of crude mixtures following quenching suggesting some deacetylation had occurred.

In analysis of the crude mixtures of these above reactions, no evidence of any cross-coupled product was observed. This was thought to be due to either steric strain imparted by the *ortho* groups of the coupling partners, or preferential reaction of the

base with the acetyl protecting groups. With the latter, this preferential reaction would have prevented activation of the boronic acid to the "boronate" anion (Section 2.1.2.4), which in turn prevented transmetallation of the boron centre to the Pd catalyst. This posed the question: was the lack of coupling a result of steric bulk or side reactivity of the base?

The synthesis of biaryl **157** through the Suzuki coupling of 6I-PAC **155** to $PhB(OH)_2$ **148** was attempted to potentially answer this question. $PhB(OH)_2$ was used to reduce steric bulk around the new biaryl bond compared to **156** so that the role of the base could be focussed upon (Scheme 30).

Scheme 30: Attempted Synthesis of biaryl 157 using a Suzuki coupling of 6I-PAC 150 with $PhB(OH)_2$.

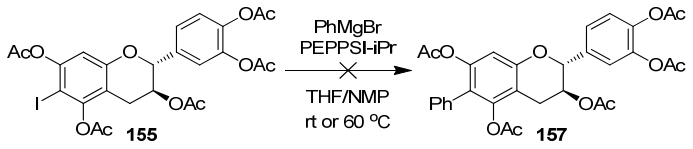


This coupling system was attempted using PEPPSI-IPr as the catalyst in conjunction with the following bases: K_2CO_3, KOH, CsF or K_3PO_4. In all cases, the results obtained suggested that deacetylation had occurred, with no evidence of the formation of any cross-coupled product **157**. This showed that the 6I-PAC **155** derivative was too sensitive towards basic conditions to be successfully used in a Suzuki cross coupling protocol.

Finally, the formation of biaryl **157** was attempted through the cross-coupling of 6I-PAC **155** to PhMgBr using a Kumada protocol. Despite the potential reactivity of the Grignard reagent towards esters, Organ *et al* had reported Kumada type couplings of substrates containing ester functionalities were achieved using the PEPPSI-IPr catalyst when THF/NMP solvent mixtures were employed.[136] Accordingly, the coupling was attempted using PEPPSI-IPr as the catalyst in THF/NMP (1:1) at both room temperature and 60 ^{o}C (Scheme 31).

These couplings also failed to provide any desired product **157**. Again deacetylation appeared to be the dominant side reaction according to ^{1}H NMR analysis of the crude reaction mixtures.

Scheme 31: Attempted formation of biaryl 157 by Kumada coupling of 6I-PAC 155 with PhMgBr.



With this result, investigations involving the use of 6I-PAC **155** as a coupling partner in Pd-catalysed cross-couplings ceased. It was clear the sensitivity of the acetyl group towards basic conditions made it an unsuitable protecting group for the catechin moiety. The potential use of other ester protecting groups that were more resistant to base, such as the pivaloyl or benzoyl groups, was considered. No investigations were carried out towards the use such groups as it was considered likely that the greater base tolerance of these groups compared to the acetyl group would be counter balanced by the increased steric bulk around the C6-iodide centre imparted by the protecting groups. With this, the likelihood of obtaining any 6-8 dimer **156** was doubtful, so did not warrant investigation. As a result, couplings towards 6-8 dimer **156** using ester protecting groups was not considered further and homo-coupling methods towards the synthesis of 8-8 dimers (Scheme 7) were investigated.

5.2.9 Homo-coupling methods towards 8-8 dimer synthesis.

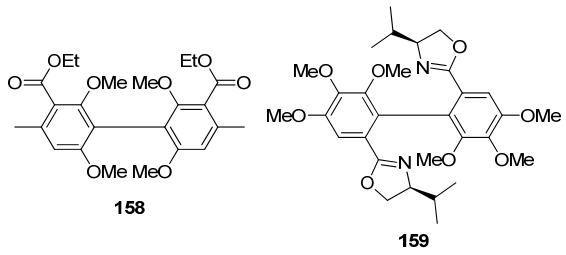
At this point it was decided that rather than stick to the cross-coupling method for the synthesis of 8-8 dimer **146** and potentially continue to trial metal after metal, it was considered more worthwhile to attempt some homo-coupling methods in order to synthesise the desired 8-8 dimer.

Kozikowski *et al* [114] reported the synthesis of 8-8 dimer **146a** in 22% yield by oxidative homo-coupling of C8-organolithium **71b** by addition of excess Iron(III) Chloride ($FeCl_3$) (Section 5.1.2). This example gave some encouragement that the use of a homo-coupling method towards the synthesis of 8-8 dimer **146** was feasible, and that an improvement of the biaryl yield obtained by Kozikowski *et al* was possible.

5.2.10 Ullmann couplings towards 8-8 dimer 146.

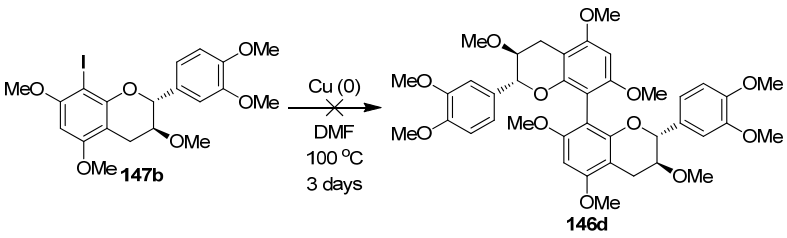
The copper-promoted homo-coupling of aryl halides, otherwise known as the Ullmann coupling,[139] has been applied to the synthesis of symmetrical biaryls for now on a century.[42] In particular, the method has been applied to the synthesis of numerous electron rich biaryls, including those containing four *ortho* substituents. Two examples of such biaryls formed by these methods are shown below (**158**, **159**, Figure 4).[140, 141]

Figure 4: Tetra-*ortho* biaryls formed using Ullmann homo-couplings technologies.



These examples provided a starting point for reaction conditions towards the homo-coupling of I-PMC **147b** to provide 8-8 dimer **146d**. Accordingly, the homo-coupling of I-PMC **147b** was attempted using a large excess of copper powder (*ca*. 10 equivalents) in DMF at 100 ^{o}C for 3 days (Scheme 32).

Scheme 32: Attempted copper-(0) promoted homo-coupling of I-PMC 147b.



These conditions failed to provide any 8-8 dimer **146d**. Deiodinated PMC **74** was the only product from the reaction mixture after filtration and concentration. It is generally accepted that couplings of this nature occur *via.* an initial oxidative insertion of the copper into the carbon-iodine bond to form an intermediate organocopper species.[61] This generated organocopper species then acts as a nucleophile to react with any remaining iodide to provide the homo-coupled product and copper (II) iodide. Assuming this mechanism to be true, then this strongly

suggested for the Ullmann couplings of I-PMC **147b** that oxidative addition of iodide to form the intermediate organocopper had occurred, but this species did not act as nucleophile. As a result, deiodinated PMC **74** was observed as the sole product. It was suspected that the steric bulk imparted by the four large *ortho* substituents retarded the nucleophilic addition of the generated organocopper species, which ultimately prevented the formation of 8-8 dimer **146d**. It was strongly suspected that the copper insertion occurred at a faster rate than nucleophilic addition of the generated organocopper species. As a result, eventually all the available I-PMC **147b** underwent oxidative addition to form the organocopper species, which was subsequently protonated upon aqueous quenching to form PMC **74**.

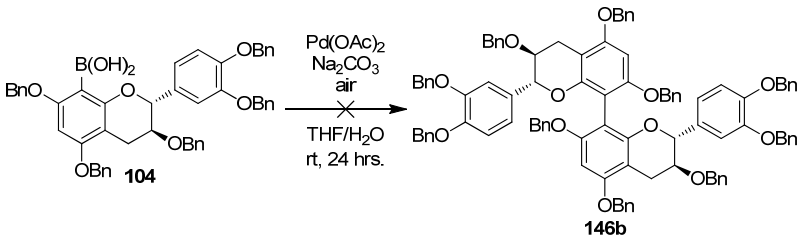
In order to promote the coupling, the reaction was attempted at 160 ^{o}C in DMF to determine the effect of temperature on the coupling. Again, only PMC **74** from the deiodination of the starting iodide **147b** was obtained under these conditions following filtration and quenching. The use of other polar solvents, such as NMP or acetonitrile also failed to provide any coupled product **146d**. Only PMC **74** was obtained. Finally, the use of sonication was explored for this reaction. However, this proved futile, with only PMC **74** observed in the reaction mixture following sonication in DMF at 60 ^{o}C for 24 hours. This result indicated that the sonication was increasing the rate of oxidative addition of the copper as complete deiodination occurred more quickly than compared to convectional heating. Nucleophilic attack, however, was still sufficiently retarded under these conditions to provide any coupled product. As a result, Ullmann couplings involving the use of copper powder were not studied further in the synthesis of 8-8 dimer **146d**.

5.2.11 Homo-couplings involving PBC-B(OH)$_2$ 104.

Since the Ullmann-type homo-coupling of I-PMC **147b** was not successful, a final effort towards the synthesis of 8-8 dimer **146b** was made by attempting the homo-coupling of boronic acid PBC-B(OH)$_2$ **104**. There have been numerous reports of Pd-catalysed homo-coupling of aryl boronic acid derivatives both with and without the use of a base.[142-145] Of the conditions used for such couplings, the most commonly used systems employed $PdCl_2$ or $Pd(OAc)_2$ as the catalyst and Na_2CO_3 as the base in ethereal and/or alcoholic solvents with the mixture open to atmospheric air. Accordingly, the homo-coupling of PBC-B(OH)$_2$ **104** was attempted using 10 mol%

$Pd(OAc)_2$ in THF/H_2O at 60 ^oC in the presence of 2 equivalents of Na_2CO_3 (Scheme 33).

Scheme 33: Attempted Pd-catalysed homo-coupling of PBC-B(OH)$_2$ 104.



The reaction was quenched by addition of sat. aq. NH_4Cl after 24 hours. ^1H NMR analysis of the crude mixture indicated that no 8-8 dimer **146b** was formed. PBC **52b**, formed by the deboronation of PBC-B(OH)$_2$ **104**, was observed as the sole product.

With this result, a number of homo-couplings were attempted using a variety of Pd reagents at catalytic (0.1 equiv), substoichiometric (0.5 equiv), and stoichiometric (1.1 equiv) ratios compared to the boronic acid. The use of base, solvent, additives and temperature were also explored. A selection of the conditions trialled is shown in Table 5.

Under all these conditions, no 8-8 dimer **146b** formation was observed. In all cases, only PBC **52b** was recovered. Once again the steric bulk of the large *ortho* groups of boronic acid **104** probably retarded the formation of the desired 8-8 dimer **146b**.

At this point, the efforts towards 8-8 dimer **146b** by both cross-coupling and homo-coupling techniques were ceased. Time and time again, the steric bulk of the large *ortho* substituents on the coupling partners, along with the electronic resistance towards nucleophilic substitution of C8-halides, proved an unassailable barrier towards the formation of 8-8 dimers **146b-d**. As a result, these couplings were abandoned in favour of efforts towards the synthesis of C8-alkyl substituted catechin derivatives.

Table 5: Homo-couplings of PBC-B(OH)$_2$ 104 using a Pd oxidant.

Entry [a]	Pd oxidant	Ratio (equiv)	Base	Solvent	Additive	Temp (^{o}C)
1	$Pd(OAc)_2$	0.1	Na_2CO_3	THF/H_2O	-	60
2	$Pd(OAc)_2$	0.1	-	THF/H_2O	-	60
3	$Pd(OAc)_2$	0.1	Na_2CO_3	THF/H_2O	PPh_3	60
4	$Pd(OAc)_2$	0.5	Na_2CO_3	THF/H_2O	-	60
5	$Pd(OAc)_2$	0.5	-	THF/H_2O	-	60
6	$Pd(OAc)_2$	1.1	Na_2CO_3	THF/H_2O	-	60
7	$Pd(OAc)_2$	0.1	-	THF/H_2O	CuCl	rt
8	$PdCl_2$	0.1	Na_2CO_3	THF/H_2O	-	rt
9	$PdCl_2$	1.1	Na_2CO_3	THF/H_2O	-	rt
10	PEPPSI-IPr	0.5	KOH	THF	-	60
11	PEPPSI-IPr	0.5	KOH	DMA/H_2O	-	100

[a]: General reaction conditions: PBC-B(OH)$_2$ **104**, ~100 mg; Pd oxidant, specified quantity; base, 2 equiv.; additive, 2 equiv.; solvent, 5-10 mL. Reactions were stirred at the specified temperature for 24 hours open to atmosphere before quenching with sat. aq. NH_4Cl.

5.2.12 Cross-couplings towards C8-substituted catechin derivatives.

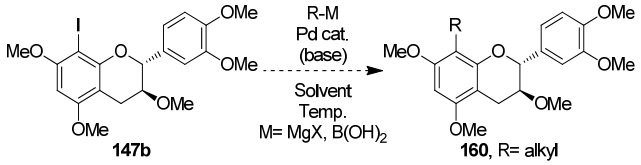
While the synthesis of the desired 8-8 dimer **146** was not achieved by any method attempted, the results obtained in model couplings (Sections 5.2.2, 5.2.7.1) did show that PBC-B(OH)$_2$ **104** and I-PMC **147b** could be coupled to phenyl derivatives using both Suzuki and Kumada protocols. Accordingly, focus shifted towards the use of such protocols in order to produce catechin analogues containing various C8-substiuents. Access to more of these C8-substituted catechin derivatives should allow a thorough examination of structure-function relationships of these molecules.

As C8-aryl and C8-vinyl catechins were already respectively synthesised using Suzuki protocols by Bernini *et al* [130] and Cruz *et al* [131] (Section 5.1.1.2), the development of a method towards C8-substituted catechins focussed upon the formation of C8-alkyl catechin derivatives.

5.2.12.1 Kumada cross-coupling strategy towards the synthesis of C8-alkyl catechins.

In order to access the desired C8-alkyl catechins **160**, both the Suzuki and Kumada cross-couplings of I-PMC **147b** to alkyl boronic acids or alkyl Grignards were considered (Scheme 34).

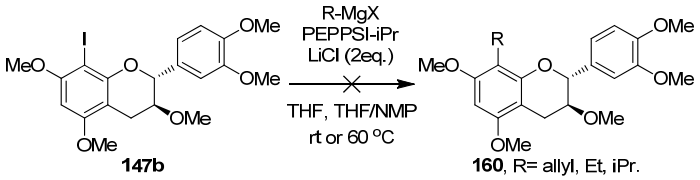
Scheme 34: Proposed formation of C8-alkyl catechins 160 through Pd-catalysed cross-couplings of I-PMC 147b with alkyl organometallics.



Both pathways had their merits. The commercial availability of a large number of alkyl boronic acids or alkyl Grignards meant either coupling approach could potentially provide access to a large and diverse range of C8-alkyl catechins with minimal effort and cost.

As the Suzuki method had already been employed in the earlier syntheses of aryl and vinyl substituted catechins (Section 5.1.1.2), it was considered a Kumada strategy towards alkyl substitution would provide a useful alternative to these Suzuki couplings. Also, numerous alkyl Grignard reagents were already at hand. Accordingly, the couplings of I-PMC **147b** with alkyl Grignards were attempted using PEPPSI-IPr as the catalyst (Scheme 35).

Scheme 35: Attempted PEPPSI-IPr catalysed Kumada coupling of I-PMC 147b with alkyl Grignards.



Three alkyl Grignard reagents, allylmagnesium bromide (allylMgBr), ethylmagnesium bromide (EtMgBr), and isopropylmagensium chloride (*i*-PrMgCl) were selected for initial screenings of the coupling reaction. In all cases, PEPPSI-IPr (5 mol%) was employed as the catalyst, THF as the solvent and reactions were

conducted at both room temperature and 60 ^{o}C for 24 hours. Only trace quantities of any coupling product (<5%) was observed for all of these reactions PMC **74** from deiodination of I-PMC **147b** being the dominant product in all cases. The use of THF/NMP (1:1) as the solvent and the addition of 2 equivalents of LiCl, as used by Organ *et al*,[136] failed to provide any coupled product **160** when used at either room temperature or 60 ^{o}C. Finally, the coupling of EtMgBr with I-PMC **147b** was attempted using either Pd(DPEPhos)Cl_2 or Pd(PPh_3)$_2Cl_2$ as the catalyst, both with and without LiCl as an additive. Under these catalytic conditions PMC **74** was the major product, with only trace amounts of coupled product being detected according to ^{1}H NMR analysis of the crude materials following quenching.

This lack of coupling was somewhat surprising on account of the fact the Grignard reagents used were not overly sterically encumbered. It has been reported that alkyl organometallic reagents (or more generally sp^3 hybridised organometallics) undergo transmetallation to Pd catalysts far more slowly than sp^2 hybridised organometallic centres, such as phenyl or vinyl organometallic reagents.[75, 76] In contrast to the alkyl Grignard couplings, the earlier coupling of the aryl Grignard PhMgBr to I-PMC **147b** using PEPPSI-IPr as a catalyst provided the biaryl **82b** (8Ph-PMC) in excellent 95% yield (Section 5.2.2.2). Taking these facts into account, it was assumed that the sluggishness of the transmetallation of the alkyl Grignard reagents was the primary factor in the failure of the alkyl Grignard couplings to I-PMC **147b**. It was believed oxidative addition of the Pd catalyst into I-PMC **147b** was occurring, but with the slow transmetallation of the alkyl Grignard, breakdown of the oxidative addition product dominated. This resulted in deiodination of I-PMC **147b** to provide PMC **74** as the major product.

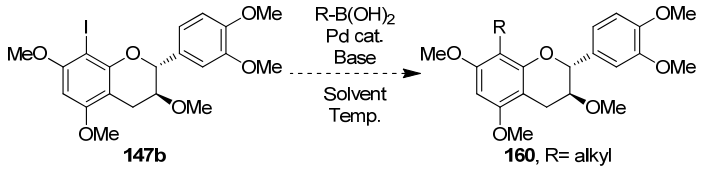
It was also noted that complete deiodination of I-PMC **147b** occurred in less than 24 hours under the Kumada coupling conditions. This was much faster than that noted for the Suzuki couplings trialled earlier (Sections 5.2.2.2, 5.2.3), where 48 to 72 hours was required for complete deiodination. This suggested that the organometallic reagent played a role in the deiodination reaction, and the nature of the organometallic was important in the rate of deiodination. As a result, deiodination occurred at a faster rate when the more aggressive Grignard reagents were employed compared to the boronic acid derivatives. The mechanism of deiodination of I-PMC **147b** in the presence of Grignard reagent was not clear. It was suspected, however,

that either a magnesium-iodine exchange reaction or a radical mechanism may have been involved.

5.2.12.2 Proposed Suzuki cross-coupling strategy towards the synthesis of C8-alkyl catechins.

At this point it was recognised that a Suzuki cross-coupling involving alkyl boronic acids or other boron containing compounds may be a more suitable pathway towards C8-alkyl catechin derivatives **147b**. It was thought the less aggressive nature of these nucleophiles compared to the Grignard reagents should reduce the rate of deiodination, and should promote cross coupling to a greater extent (Scheme 36).

Scheme 36: Proposed Suzuki cross-couplings of I-PMC 147b with alkyl boronic acids.



This pathway was never investigated. It was considered that enough time had been invested into the cross-coupling methods towards both the 8-8 dimer **146** and C8-substituted catechins **160** that it was not worthwhile purchasing the boronic acid derivatives required to investigate this coupling protocol as the project was coming to a close. At this point, the potential of this coupling procedure was duly noted for future investigation.

The failed Kumada cross-couplings towards C8-alkyl-substituted catechins signalled the end of investigations of Pd-catalysed cross-coupling towards the synthesis of both 8-8 dimers **146** and C8-substituted catechins **160**.

5.3 Conclusions.

Ultimately, the desired 8-8 dimers **146b-d** were not synthesised using any of the cross-coupling or homo-coupling methods attempted. The steric bulk of the large *ortho* substituents of the coupling components were generally touted as the primary barrier against efforts towards their synthesis. Electronic factors were also prominent, particularly the resistance of I-PMC **147b** towards oxidative addition of

palladium, copper or magnesium due to the high electron density of the A-ring of this C8-halide. The lability of the carbon-boron bond of boronic acid PBC-B(OH)$_2$ **104** was also a significant factor in the failure of Suzuki cross-coupling methods towards these targets. It was also found that changing from benzyl or methyl protecting groups of the halide coupling partner to acetyl groups in order to reduce electron density of the A-ring was not suitable due to the lability of this group under basic and/or nucleophilic conditions. The use of larger, more base-tolerant ester protecting groups, such as pivaloyl or benzoyl groups, was never investigated as it was likely the greater steric bulk of these protecting groups compared to the acetyl group would outweigh their robustness under coupling conditions.

Model system studies did show that C8-phenyl catechin derivatives, 8Ph-PBC **81b** and 8Ph-PMC **82b**, were synthesised using both Suzuki and Kumada coupling strategies. In the case of the Suzuki method, the synthesis of these C8-phenyl catechin derivatives was achieved from both PBC-B(OH)$_2$ **104** (Section 5.2.2.1) and I-PMC **147b** (Section 5.2.2.2). The coupling of PBC-B(OH)$_2$ **104** to iodobenzene provided 8Ph-PBC **81b** and the coupling of I-PMC **147b** to PhB(OH)$_2$ provided 8Ph-PMC **82b**. The optimal conditions for both couplings employed PEPPSI-IPr as the catalyst and NaOH as the base at 80-100 ^{o}C, with the former being carried out in dioxane and the latter in aqueous DMA. Extension of these Suzuki couplings to other aryl halides and aryl boronic acids opens up the potential for divergent synthetic methods towards C8-aryl substituted catechin derivatives.

A Kumada coupling protocol was also applied to the synthesis of 8Ph-PMC **82b** (section 5.2.7.1). This was achieved through a PEPPSI-IPr-catalysed coupling of I-PMC **147b** with PhMgBr. This coupling provided a useful alternative to the Suzuki protocol already mentioned (Section 5.2.2.2). Given the relative ease of preparation and cost of most Grignard reagents compared with their boron equivalents, such a protocol may be more applicable to the synthesis of C8-aryl-substituted catechins. This Kumada protocol could not be successfully applied to the coupling of 2,4,6-trimethoxyphenylmagnesium bromide (**39**) with I-PMC **147b**. The steric hindrance imparted by the *ortho* groups of the two coupling partners was again the most likely barrier to this coupling.

Attempts to extend the PEPPSI-IPr catalysed Kumada protocol to the coupling of I-PMC **147b** with alkyl Grignard reagents were not successful. In this case the slow transmetallation of the alkyl Grignards to the Pd centre was proposed as the probable obstacle in the coupling reaction. The use of alkyl boronic acids were considered as an alternative to the Grignard regents, but never investigated. The coupling of I-PMC **147b** and boronic acids will be further discussed in the final conclusions and future directions.

Chapter 6: General Conclusions and Future Directions.

6.1 General Conclusions.

First and foremost, the initial objective to develop a strategy for the synthesis of 4→8 catechin oligomers through the use of a C8-organometallic derivative was realised. Prior to the development of this coupling, several model coupling systems were implemented to determine the potential for use of C8-organometallics in cross-coupling reactions. The preliminary model system couplings of a variety of metallated 1,3,5-trimethozybenzene derivatives to benzyl bromide revealed that the optimal conditions for this coupling was the Pd(DPEPhos)Cl_2-catalysed Negishi cross-coupling using 2,4,6-trimethoxyphenylzinc chloride (**44)** as the organometallic partner (Section 2.2.6). These conditions provided the desired coupling product, Bn-TMB **35**, in very good yields (80-85%). The coupling of this derivative was also applied to a variety of benzyl and aryl halides in moderate to good yields to provide a suite of benzyl and aryl substituted 2,4,6-trimethoxybenzenes (Section 2.2.7).

Following the trimethoxybenzene model system studies, the extension of the coupling strategies to 4→8 catechin-catechin dimers was investigated. After several futile attempts to prepare and couple the C8-organozinc **67** or **77** and C8-organomagnesium **80a** and **80b** catechin derivatives, gram quantities of C8-boronic acid **104** (PBC-B$(OH)_2$) was consistently synthesised in good yield (60-65%, Section 3.2.5). Importantly, boronic acid **104** was isolatable by silica chromatography and readily identified using NMR and mass spectral techniques. In contrast, the Grignard or organozinc derivatives required *in situ* preparation, followed by immediate use. This did not allow for easy identification of the organometallic derivative and the lack of any coupled products meant that formation of the Grignard or organozinc was never determined beyond doubt. The certainty of boronic acid formation was a great advantage over the other organometallic derivatives studied.

The synthesised C8-boronic acid **104** was then used in the novel Lewis acid-promoted cross-coupling with the C4-ether **83** (8Br-4EE-PBC), which afforded gram quantities of catechin-catechin dimer **105** (8Br-PBC-PBC) in excellent yields (90-95%, Section 3.2.7). Two dimensional NMR experiments showed that the synthesised dimer possessed the desired 3,4-*trans* stereoselectivity. Removal of the bromide and benzyl protecting groups of dimer **105** provided the targeted natural

procyanidin B3 (**3**). This dimer was synthesised from (+)-catechin **1** in 6 linear steps in an overall yield of 54%, which was comparable or higher than other reported syntheses for procyanidin B3 (**3**).

Further studies of the Lewis acid-promoted cross-coupling reaction revealed a variety of Lewis acids in either stoichiometric or catalytic quantities promoted the coupling, affording comparable coupling yields and 3,4-*trans* stereoselectivity regardless of the conditions used (Section 3.2.4, Table 1). These observations led to the proposal of a mechanism for the coupling. This mechanism involved the activation of the boronic acid to the nucleophilic "boronate" anion species by co-ordination of the boron centre to the C4-oxygen of C4-ether **83**. The boronic acid was not sufficiently Lewis acidic to promote the reaction, and the addition of a catalytic quantity of a strong Lewis acid was required. Once initiated, the reaction proceeded according to the catalytic cycle proposed (Sections 3.2.4, 3.2.6).

The developed Lewis acid-promoted cross-coupling methodology was extended to the synthesis of the all catechin 4→8 trimer **129** (8B(MIDA)-PBC-PBC-PBC). This was achieved by the iterative coupling of the key boron-protected "chain extender" intermediate 8B(MIDA)-4EE-PBC **127** using sequential Lewis acid-promoted coupling and boron deprotection steps. The dimer intermediate **128** (8B(MIDA)-PBC-PBC) was formed by coupling of 8B(MIDA)-4EE-PBC **127** with C8-boronic acid **104** (PBC-B$(OH)_2$). Importantly, the coupling of the C4-ether was selective towards the free boronic acid. As a result, dimer **128** was formed selectively with no evidence of any higher oligomer formation (Section 4.2.4). The MIDA boron protecting group provided the basis for an iterative coupling strategy towards 4→8 catechin oligomers. Removal of the MIDA protecting group by treatment of dimer **128** with dilute aq. NaOH revealed the free C8-boronic acid dimer **111** (PBC-PBC-B$(OH)_2$). This was iteratively coupled to a further "chain extender" unit **127** (8B(MIDA)-4EE-PBC) using the developed Lewis acid-promoted coupling to provide trimer **129** (8B(MIDA)-PBC-PBC-PBC, Section 4.2.6). This coupling showed that the developed iterative strategy was applicable beyond dimer formation. Notably, the extension of the oligomer chain occurs at the C8-terminus of the growing oligomer as was originally designed. Synthesis of tetrameric species **131** by deprotection of trimer **129** and further coupling to **127 (**8B(MIDA)-4EE-PBC) was

attempted on a small scale, but results were inconclusive and a repeated attempt to synthesise this tetramer was not successful.

This extension method provided an advantage over the orthogonal activation strategy reported by Ohmori *et al* [38] (Section 4.1.1.2). The synthetic strategy reported in this thesis required only one chain extension species (**127**, 8B(MIDA)-4EE-PBC), whereas that reported by Ohmori *et al* required two (**24a** and **25b**).

The NMR and mass spectral data for compounds 8B(MIDA)-PBC-PBC **128** and 8B(MIDA)-PBC-PBC-PBC **129** was consistent with that expected for 4→8 linked catechin oligomers. However, purity of these protected oligomers was an issue and obtaining clean NMR spectra of these compounds was not achieved. Through the recovery and debenzylation of PBC-PBC **68**, derived from dimer **128** (8B(MIDA)-PBC-PBC), natural 3,4-*trans* procyanidin B3 (**3**) was obtained (Section 4.2.7). This confirmed the identities of compounds **128** (8B(MIDA)-PBC-PBC) and **111** ($8B(OH)_2$-PBC-PBC) as the assigned catechin-3,4-*trans*-4→8-catechin dimers. Insufficient quantities of trimer **129** (8B(MIDA-PBC-PBC-PBC) were obtained to allow deprotection of the trimer to reveal the free phenolic procyanidin. So at this point definitive assignment of trimer **129** as the 4→8 oligomer was not possible, but as the coupling method employed provided 3,4-*trans*-4→8 dimers, it was not unreasonable to extrapolate the coupling orientation to trimer **129**. The ^{13}C and ^{11}B NMR along with mass spectral data obtained for trimer **129** also strongly suggests that it is the assigned structure. An LC-MS was not accessible during the synthesis of these oligomers. The use of such an instrument would have been invaluable for the determination of structure and purity of the oligomers. It is strongly suggested that further studies in oligomer formation by these methods should be conducted with ready access to an LC-MS. The synthesis of tetramer **131** (8B(MIDA)-PBC-PBC-PBC-PBC) was also attempted, but was not conclusively prepared (Section 4.2.8). As a result, the synthesis of this oligomer on a larger scale would be valuable to further demonstrate the developed iterative coupling method. The stereochemistry of the interflavan bonds trimer **129** was assumed to be 3,4-*trans* . It was also reasonable to assume the couplings to form dimer **128** (8B(MIDA)-PBC-PBC) and trimer **129** (8B(MIDA)-PBC-PBC-PBC) should followed the same mechanism for the formation of dimer 8Br-PBC-PBC **105** (Section 3.2.7). Stereochemical confirmation of trimer

129 could be achieved through the use of two dimensional nOe NMR experiments in the future if the synthesis of these species is repeated.

The use of ^{11}B NMR was helpful in the structural identification of the boron-containing compounds synthesised. The co-ordination states of the boron atom of these compounds were determined using this technique. For free boronic acids, chemical shifts of approximately 30 ppm were observed, while the ^{11}B peak for the MIDA protected compounds were shifted upfield to 12-14 ppm. Notably, as the chain length of the oligomers, and hence the molecular weight increased, the observed ^{11}B peak became increasingly broad. This technique may therefore have some limitations for analysis of larger *n*-oligomers if this trend continues to the point where the ^{11}B peak cannot be distinguished from background noise in the NMR spectrum (Sections 3.2.6, 4.2.6). Conducting the ^{11}B NMR method in different solvents and increased temperatures may affect this broadening.

The importance of the "chain extender" unit 8B(MIDA)-4EE-PBC **127** in the success of this iterative coupling strategy cannot be understated. Addition of this species to the C8-terminus of a growing oligomer chain allowed for controlled, iterative synthesis of catechin oligomers as desired. If sufficient "chain extender" unit could be synthesised, then *n*-oligomers of any chain length could potentially be accessible. Also, the MIDA protecting group was readily removed under mild conditions to provide free C8- boronic acid derivatives of dimers and trimer oligomers. On top of these factors, the key bromide to boronic acid manipulation was achieved at the monomer stage, which avoided any requirements for completing this exchange on higher oligomers. This was most significant, as the conversion of the C8-bromide dimer **105** (8Br-PBC-PBC) to the corresponding dimeric boronic acid **111** was not successful (Section 4.2.1). The only significant drawbacks to 8B(MIDA)-4EE-PBC was that its preparation was not trivial. Synthesis of this species required 6 steps from (+)-catechin **1** in moderate overall yields of 30-35%. Also, rigorous purification of C8-bromide **83** (8Br-4EE-PBC) was essential, as the yield of conversion of this species to C8-boronic acid **126** (8B$(OH)_2$-4EE-PBC) was strongly dependent upon its purity. This drawback was more than adequately outweighed by its usefulness as a "chain extension" unit, however, and the starting materials for this species were readily available.

With the initial objective for an iterative synthetic strategy towards catechin oligomers achieved, further uses for C8-boronic acid **104** (PBC-B(OH)$_2$) were explored. Through the Suzuki cross-coupling with iodobenzene, boronic acid **104** was highly useful for the synthesis of the C8-phenyl-substituted catechin, 8Ph-PBC **81b** (Section 5.2.2.1). This coupling was achieved using a variety of Pd catalysts and bases, with the *N*-heterocyclic carbene ligand-based catalyst, PEPPSI-IPr, providing the best results.

The related 8Ph-PMC **82b** was also readily prepared *via*. a Suzuki cross-coupling of the C8-iodide **147b** (I-PMC) with phenylboronic acid (PhB(OH)$_2$) using a variety of Pd catalysts and bases. Again PEPPSI-IPr was the most effective catalyst for this coupling (Section 5.2.2.2). These two coupling methods provided useful convergent approaches to the synthesis of C8-aryl substituted catechins. The same biaryl (**82b**, 8Ph-PMC) was prepared by an alternative PEPPSI-IPr-catalysed Kumada cross-coupling of I-PMC **147b** with aryl Grignard phenylmagnesium bromide (PhMgBr). Under these conditions, 8Ph-PMC **82b** was prepared in excellent yield (95%, Section 5.2.7.1).

The extensions of these Suzuki cross-couplings (Sections 5.2.3) towards the formation of 8-8 dimers **146b-d** were not successful. Issues pertaining to both the boronic acid **104** (PBC-B(OH)$_2$) and C8-iodide **147b** (I-PMC) portions of the coupling were identified as potential inhibitors towards 8-8 dimer synthesis. In response to this, Kumada cross-coupling methods (Sections 5.2.7) and homo-coupling methods (Sections 5.2.10, 5.2.11) were designed in an attempt to complete the synthesis of 8-8 dimer **146b-d**. The Kumada pathway could not be explored as preparation of the required C8-Grignard analogue **80b** was never achieved. Neither the Ullmann homo-coupling of I-PMC **127b** in the presence of metallic copper or the Pd-promoted homo-coupling of PBC-B(OH)$_2$ **104** produced the requisite 8-8 dimers **146b-d** in any identifiable quantity. As a result, the synthesis of any 8-8 dimer by any of these methods was not achieved. The steric hindrance of the large *ortho* groups of the coupling partners was most commonly cited as the major barrier towards 8-8 dimer formation.

6.2 Future Directions.

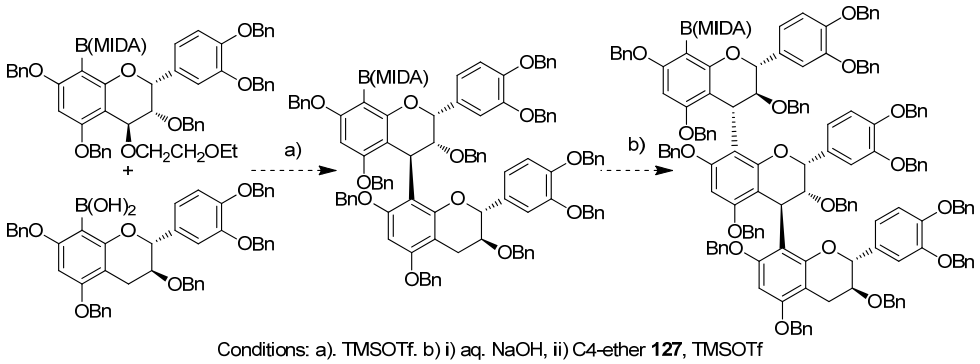
There are several directions to which the studies discussed in this thesis can be extended. These can be grouped into two general subclasses; extension of the 4→8 coupling methods and further uses of C8-organometallic derivatives in the synthesis of C8-substituted catechins and other "unusual" catechin dimers.

6.2.1 Extension of 4→8 coupling methods.

Before any further extension of the boron deprotection, Lewis acid coupling method towards 4→8 catechin oligomers is possible, larger scale synthesis of the trimer **129** and tetramer **131** oligomers is required to validate the method. Once validated, the method can potentially be applied to the synthesis of pentamer and higher *n*-oligomers.

Access to hetero-oligomers, or oligomers containing a mixture of flavan monomers such as epicatechin (**2**) or the gallocatechins (**1b, 2b**), has traditionally been difficult using most synthetic methods. [38] The synthesis of these compounds demands a strictly iterative method in order to control composition of the oligomer. As the oligomerisation method developed in Chapter 4 is strictly iterative, hetero-oligomers can potentially be synthesised by this method if the appropriate starting materials can be made (Scheme 1).

Scheme 1: Application of other flavan monomers in the boron deprotection, coupling strategy towards the synthesis of hetero-oligomers.

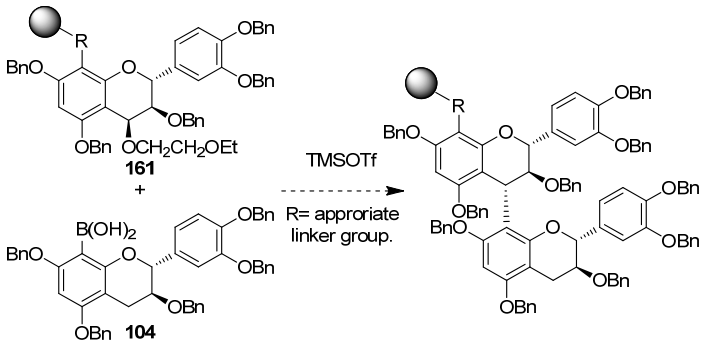


Conditions: a). TMSOTf. b) i) aq. NaOH, ii) C4-ether **127**, TMSOTf

If the appropriate boronic acids and "chain extender" species of various flavan-3-ol monomers can be made in reasonable quantities, then potentially any *n*-oligomer of any monomer composition can be produced using this coupling method.

The application of solid-phase technologies would be highly useful in the optimisation of the 4→8 coupling method. During the Lewis acid-promoted coupling reaction, the C8-boron group of 8B(MIDA)-4EE-PBC **127** essentially acted as a protecting group in the suppression of higher oligomer formation (Section 4.2.4). Linkage of C8 of a C4-ether compound to a solid phase resin could potentially replace the C8-boron group as a protecting group. Then the C4-ether **161** would be bound to the solid-phase resin and could undergo selective coupling with C8-boronic acid **104** to provide dimer **162** with no possibility for the formation of any higher oligomers (Scheme 2).

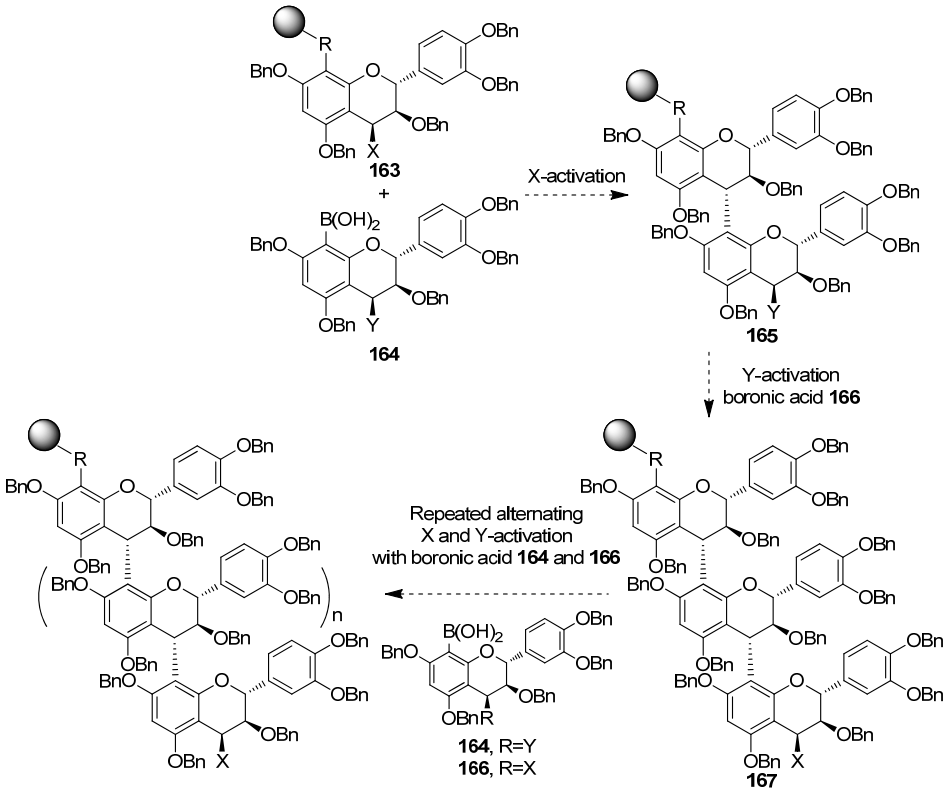
Scheme 2: Synthesis of catechin dimer 162 through solid-phase synthesis.



Synthesis of trimers and higher oligomers could also be produced by the solid-phase method through the application of an orthogonal activation method similar to that reported by Ohmori *et al* (Section 4.1.1.2).[38] If appropriate, orthogonally C4-functionalised-C8-boronic acids **164** and **166** could be synthesised, then an orthogonal activation strategy could be used to build *n*-oligomers by extension from the C4-terminus of the monomer attached to the solid phase resin (Scheme 3).

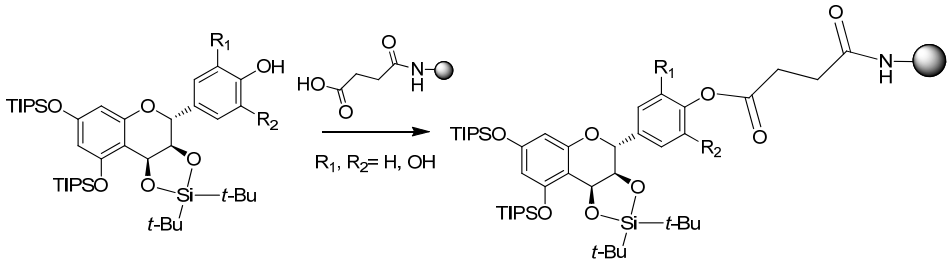
As an iterative synthetic method, this approach could also be highly useful for the synthesis of hetero-oligomers. Once the desired oligomer chain length is obtained, cleavage of the resin linker-C8 bond would provide the oligomer for further use.

Scheme 3: Solid phase synthesis of *n*-oligomers *via*. orthogonal activation strategy.



Very recently, Deffieux *et al* [146] reported the attachment of a catechin oligomer to a solid-phase resin through esterification of the C4′-OH (Scheme 4).

Scheme 4: Attachment of functionalised catechin to solid-phase resin through esterification of C4′-OH.



Accordingly, such a strategy may be applicable for the linkage of flavan monomers to a solid-phase resin for the solid-phase supported synthesis of *n*-oligomers.

An important consideration for the use of a solid-phase synthetic strategy is complete reactivity of the terminal C4-leaving group of the growing oligomer chain. If complete reaction cannot be guaranteed, then the composition of the resulting

oligomer would be uncertain. In other words, if the C4-leaving group in each coupling step failed to completely react to give an (*n*+1)-oligomer, then the oligomer chains would be a mixture of *n* and (*n*+1)-oligomers. This would lead to a polydisperse mixture of oligomer chains following completion of the coupling steps. As oligomer composition would be uncertain, this would limit the utility of the solid-phase method in the synthesis of defined catechin oligomers. Accordingly, any successful solid-phase method for the production of catechin oligomers would need to address this issue. If this is possible, a solid-phase strategy could be used to rapidly synthesise large quantities of catechin oligomers of any monomer composition and chain length.

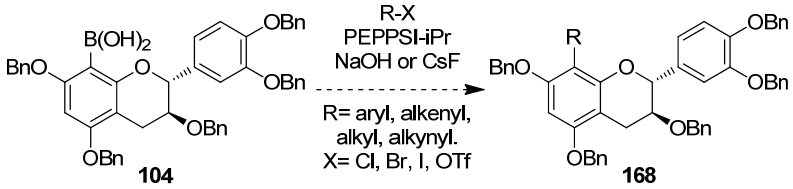
If sufficient quantities of pure *n*-oligomers of defined monomer composition can be produced by the boron deprotection, coupling strategy or a solid-phase method, then structure-function relation studies can be conducted. These could include sensory studies, model ferments and biological testing. Sensory studies into variations in astringency or bitterness of different oligomers would be of great use to the wine industry. If proanthocyanidins that impart desirable or undesirable sensory impacts can be identified, it may be possible to tailor viticultural and/or wine-making conditions in order to maximise production of "good" tannins and minimise the "bad" ones. Changes in tannin structure from grape tannins extracted into wine musts during wine making and ageing processes are not well understood. The use of model ferments involving spiking of synthetic proanthocyanidins may be useful in tracking the modification of tannin matter during the wine making processes. Finally, if *n*-oligomers of various monomer compositions are available, then the testing of biological properties, such as antioxidant or anticancer activities, can be conducted. If several oligomers of different composition are available, then structure-function relation studies can be conducted through comparison of the biological properties of different oligomers.

6.2.2 Further Uses of C8-organometallics in the synthesis of "unusual" interflavan linkages.

The successful application of C8-boronic acid **104** (PBC-B$(OH)_2$) in the synthesis of 8Ph-PBC **81b** (Section 5.2.2.1) through the use of a Suzuki cross-coupling method potentially opens the door for the synthesis of a variety of C8-substituted catechin

derivatives. Such derivatives could potentially be accessed by exchanging iodobenzene with a variety of other organic halides in the Suzuki cross-coupling reaction (Scheme 5).

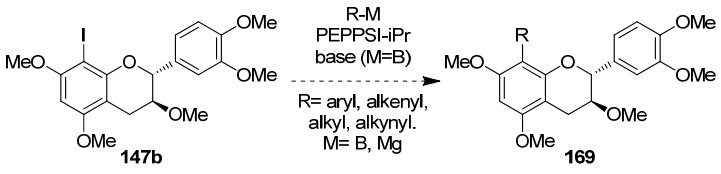
Scheme 5: Synthesis of C8-substituted catechins *via*. Suzuki cross-coupling of PBC-B(OH)$_2$.



If appropriate conditions can be found, this method could potentially be applied to synthesis of aryl, alkenyl, alkyl or alkynyl C8-substituted catechin derivatives. If a suite of these C8-substituted compounds could be produced, they would be highly useful in structure-function relation studies similar to those discussed above, as the different C8-substituents may show different astringencies or activities towards biological assays.

Access to these C8-substituted catechins may also be available *via*. the Pd-catalysed cross-coupling of C8-iodide **147b** (I-PMC) with appropriate C8-organometallics. As previously described, I-PMC **147b** is active towards the Pd-catalysed coupling of both phenylboronic acid (PhB(OH)$_2$) and phenylmagnesium bromide (PhMgBr, Sections 5.2.2.2, 5.2.7.1). These methods may be applicable to other boronic acids or Grignard reagents to produce a variety of C8-substiuted catechins (Scheme 6).

Scheme 6: Synthesis of C8-substituted catechins *via.* cross-couplings of I-PMC 147b.

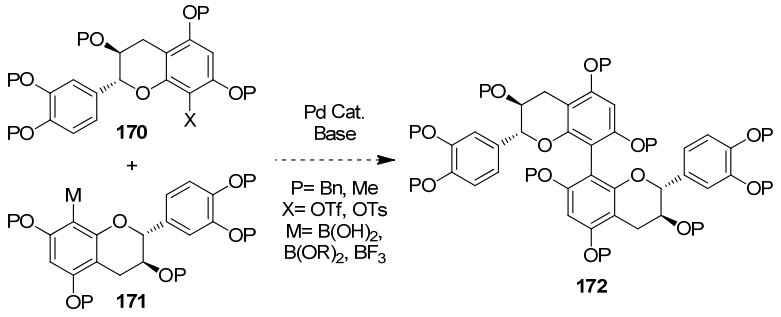


Notably, the synthesis of C8-alkyl catechins by coupling of I-PMC **147b** with alkyl Grignard reagents was not successful (Section 5.2.12). Accordingly, the use of milder boron nucleophiles may be more appropriate in this coupling strategy. Also, a plethora of boron-containing compounds, including alkyl, aryl, alkenyl and alkynyl

boronic acids, boronate esters and trifluoroboronate salts, are now commercially available at reasonable costs. These factors combined may allow rapid and easy access to a variety of C8-substituted catechin derivatives.

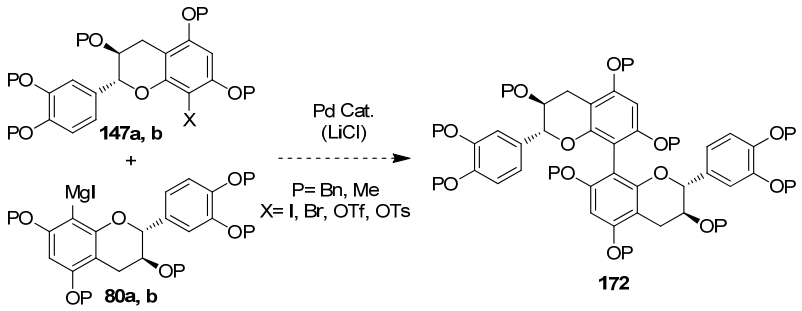
As discussed in Chapter 5, the syntheses of 8-8 dimers **146b-d** were never realised, principally attributed to the steric bulk of the large *ortho* groups of the coupling partners and electronic issues pertaining to the A-ring of the catechin moiety. Principal barriers towards the formation of this biaryl involved either the deboronation of PBC-B$(OH)_2$ **104** and/or deiodination of I-PBC **147a** or I-PMC **147b** under the coupling conditions attempted. Suzuki methods towards the synthesis of this compound are far from exhausted. Issues with deiodination may be addressed using alternate leaving groups such as a C8-triflate (OTf) or C8-tosylate (OTs, **170)**. Such leaving groups may be more resistant to degradation than the C8-iodide. Other C8-boron nucleophiles **171**, such as boronate esters or trifluoroboronate salts, may show more resistance towards deboronation than boronic acid **104**. The use of these alternative leaving groups and boron nucleophiles might be useful in the synthesis of the 8-8 catechin-catechin dimer **172** *via*. a Suzuki cross-coupling protocol (Scheme 7).

Scheme 7: 8-8 dimer 162 synthesis *via.* Suzuki coupling using alternate leaving groups and boron nucleophiles.



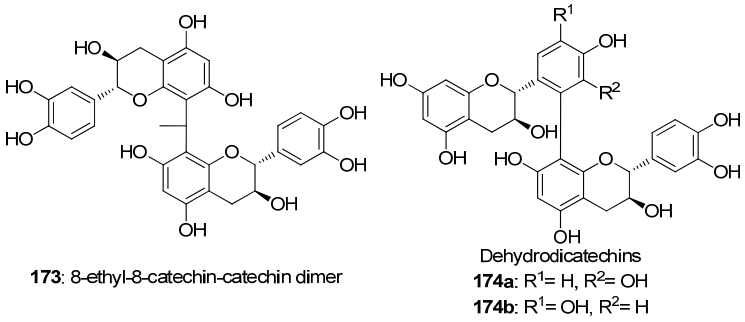
Also, in attempts to synthesis the 8-8 dimer, the synthesis of C8-Grignard **80b** was not successful using the direct insertion of magnesium into 8Br-PBC **75** or I-PMC **147b** (Section 5.2.7.2). This C8-Grignard may be another key alternative to C8-boronic acid **104** in the Pd-catalysed cross-coupling towards the 8-8 dimer. If this Grignard can be successfully prepared, then coupling with an appropriate C8-halide or pseudo halide may provide access to the 8-8 dimer **172** through the use of a Kumada cross-coupling strategy (Scheme 8).

Scheme 8: Kumada cross-coupling strategy towards the synthesis of 8-8 dimer 172.



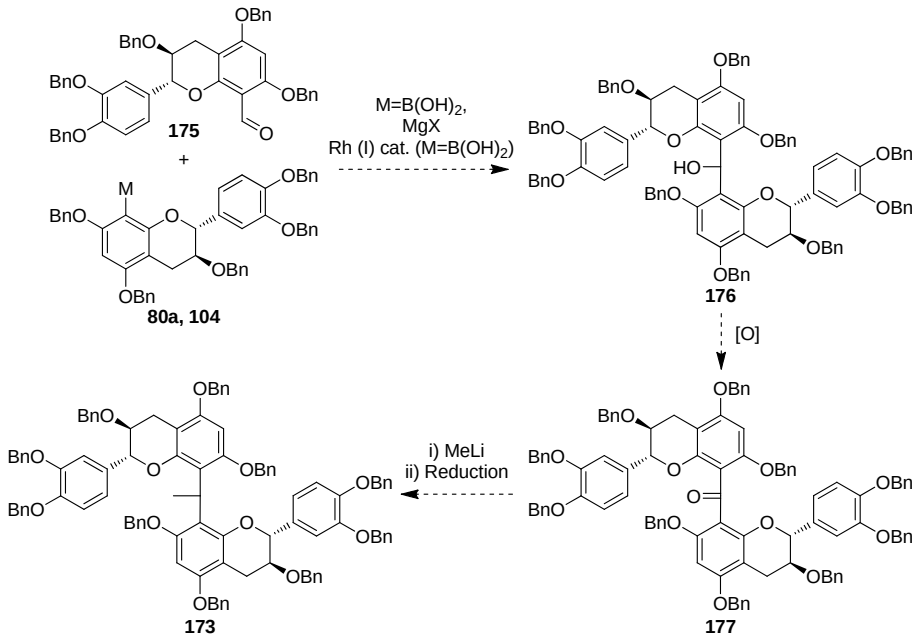
If C8-Grignards **80a** or **80b** can be produced, it may be useful in a powerful combination with C8-boronic acid **104** in the synthesis of other "unusual" catechin dimers. The synthesis of 8-ethyl-8-linked dimers **173** and the dehydrodicatechins **174a** and **174b**, dimers linked between C8 and either C2′ or C6′ (Figure 1), could be achieved using either of these C8-organometallic reagents. Both of these types of dimers have been shown to be formed in wine through oxidative processes.[3, 11, 147]

Figure 1: 8-ethyl-8 catechin-catechin dimer 173 and dehydrodicatechins 174a-b.



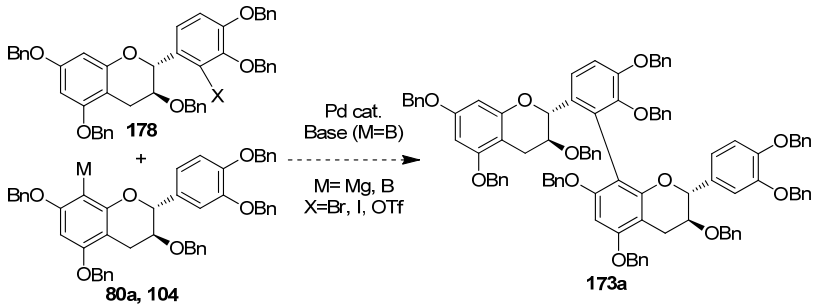
The 8-ethyl-8 linked dimer **173** could potentially be synthesised through the reaction of C8-formyl catechin derivative **175** with either C8-Grignard **80a** or C8-boronic acid **104**. Addition of C8-boronic acid **104** to aldehyde **175** requires the use of a Rhodium (I) catalyst.[148, 149] The C8-Grignard **80a** should undergo addition without the necessity of a catalyst (Scheme 9). The resulting alcohol **175** could then be oxidised to the ketone **177**. Addition of methyllithium and subsequent reduction of the produced alcohol could afford the desired 8-ethyl-8 dimer **173**.

Scheme 9: Addition of C8-Grignard 80a or C8-boronic acid 104 to C8-formyl-catechin 175 and subsequent formation of 8-ethyl-8 dimer 173.



Access to the dehydrodicatechins would be possible if an appropriate C2′ or C6′ halides **178** can be synthesised. These could then potentially be coupled to C8-boronic acid **104** or C8-Grignard **80a** using a suitable cross-coupling method (Scheme 10).

Scheme 10: Synthesis of dehydrodicatechin 173a *via*. Pd-catalysed coupling of C2′ halide 178 with C8-boronic acid 104 or C8-Grignard 80a.



Finally, these proposed methods towards the synthesis of C8-substituted catechins and "unusual" dimers could also be applied to other flavan units such as epicatechin (**2**). With these, a great number of oligomers containing various linkages and monomer compositions are potentially accessible. This would allow for great scope in studies towards structure-function relationships of proanthocyanidin oligomers.

Chapter 7: Experimental Methods for Chapters 2-5.

7.1 General Methods.

7.1.1 Materials.

Commercial reagents were purchased from Sigma-Aldrich and used without further purification unless noted. THF, toluene and Et_2O were distilled from sodium/benzophenone ketyl and CH_2Cl_2 and triethylamine from CaH_2 under an atmosphere of nitrogen prior to use. Ac_2O was distilled from P_2O_5 and stored over 4 Å molecular sieves under a nitrogen atmosphere for a period of one year. Pyridine was distilled from NaOH prior to use. Polar aprotic solvents, DMF, DMA, NMP, DME, 1,4-dioxane and acetonitrile were purchased as anhydrous reagents from Sigma-Aldrich and used as received. Catalysts $Pd(dba)_2$, $Pd(PPh_3)_4$, $PdCl_2$, $Pd(OAc)_2$, $Pd(dppf)Cl_2.CH_2Cl_2$, $Pd(PPh_3)_2Cl_2$ and PEPPSI-IPr were purchased from Sigma-Aldrich, used as received and stored under nitrogen between uses. *N*-Bromosuccinimide (NBS) was recrystallised from hot water prior to use. Catechin was purchased from Sigma-Aldrich as its dihydrate and was dried overnight in a 100 ^oC oven and cooled to room temperature in *vacuo* prior to use. Solution of *n*-BuLi and *t*-BuLi were purchased as solutions in hexanes and pentane, respectively, and titrated according to the method of Suffert [150] either prior to use or on a weekly basis when in regular use.

7.1.2 Experimental Procedures.

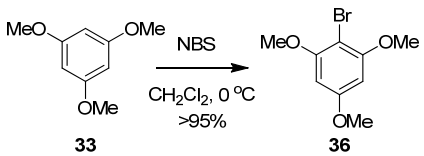
All reactions were conducted using anhydrous solvents under an argon atmosphere and performed in oven dried round bottom or vial flasks fitted with a rubber suba seal unless stated. Organic solutions were concentrated *via*. rotary evaporation under reduced pressure. Thin layer chromatography (TLC) was performed using the indicated solvent systems on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualised via exposure to a UV lamp (λ= 254nm) and developed by dipping in a $KMnO_4$ solution followed by brief heating using a heat gun. Silica and flash chromatography was conducted using EM Merck silica gel (230-400 mesh).

7.1.3 Spectral and structural analysis.

^{1}H NMR spectra were recorded on one of the following instruments: Bruker Avance III 600 or 400 MHz, Varian Gemini 300 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protonium in the NMR solvent ($CHCl_3$, δ = 7.26; CD_2HCN, δ = 1.93, centre line; CD_2HOD, δ = 3.31, centre line). Data is reported as the following: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), integration and coupling constant J (Hz). ^{13}C NMR spectra were recorded on one of the following instruments: Bruker Avance III 600 or 400 MHz, Varian Gemini 300 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane and referenced to the carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.0, centre line; CD_3CN, δ = 1.30, centre line; CD_3OD, δ = 49.1, centre line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). ^{11}B NMR were recorded on a Bruker Avance 400 at 60 ^{o}C and referenced to an external standard ($BF_3.OEt_2$). An acquisition time of 0.15s and recycle delay of 0.1s was used. High resolution mass spectra (HRMS) were performed by Sally Duck at the Monash University Mass Spectrometry Unit using one of the following instruments: Varian Saturn 4D GC/MS/MS fitted with a Zebron 30 m x 0.25 mm ID 5% phenyl polysiloxane column, (EI); Bruker BioApex II 47e FTMS fitted with an Analytica electrospray source (EI or ESI); Kratos 'Concept' high resolution double focussing mass spectrometer (EI or ESI); Micromass 'Quattro micro' (ESI). Optical rotations were measured with a PolAAR 21 polarimeter, referenced to the sodium D line (589 nm) at 25°C, using the spectroscopic grade solvents specified and at the concentrations (*c*, g/100mL) indicated. The measurements were carried out in a cell with a 1 dm path length. Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected.

7.2 Experimental procedures for chapter 2:

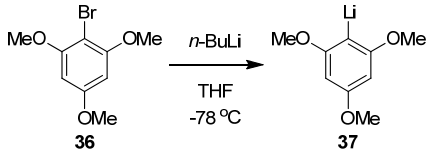
7.2.1 Scheme 16, 1-bromo-2,4,6-trimethoxybenzene (36, Br-TMB).



33 **36**

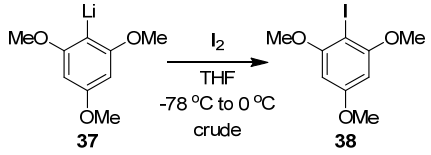
To a stirring solution of **33** (10.1 g, 59.8 mmol) in CH_2Cl_2 (200 mL) at 0°C, NBS (11.8 g, 66.5 mmol, 1.1 equiv.) was added as a solid. Stirring was continued at this temperature for 1 hr and then a solution of $Na_2S_2O_3.5H_2O$ (0.5 g) in water (100 mL) was added and vigorously stirred for 10 minutes. The phases were separated and the aqueous phase was then extracted with CH_2Cl_2 (2*50 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. The residue was then filtered over SiO_2 (CH_2Cl_2) to afford 14.7 g (99%) of a white, crystalline solid. ^1H and ^{13}C NMR corresponded to that reported by Mondal *et al* for the title compound.[97]

7.2.2 Scheme 16: Optimised method for the formation of 2,4,6-trimethoxyphenyllithium (37, Li-TMB).



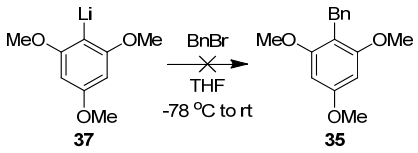
To a stirring solution of Br-TMB **36** (0.327 g, 1.32 mmol) in THF (4 mL) at -78 °C, *n*-BuLi (1.10 mL, 1.36 M in hexanes, 1.1 equiv.) was added dropwise at this temperature over two minutes. The mixture was then stirred for *ca*. 15 minutes at this temperature, during which a white precipitate formed. The Li-TMB **37** mixture was then used immediately as prepared.

7.2.3 Scheme 16: Formation of 1-iodo-2,4,6-trimethoxybenzene (38, I-TMB) from 37.



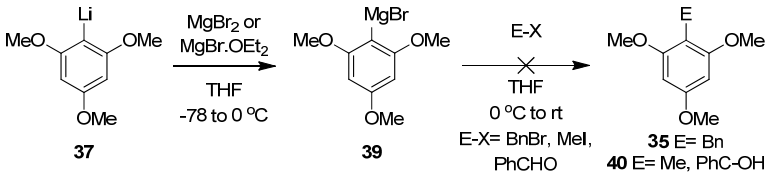
To a stirring solution of **37** in THF prepared by the optimised method (section 7.2.2) at -78 °C, solid I_2 (*ca.* 2 equiv.) was added and the resulting dark solution was allowed to warm to 0 °C over one hour. Excess $Na_2S_2O_3.5H_2O$ (0.5g) in water (100 mL) was added and the mixture stirred at room temperature for 10 minutes. The aqueous phase was then extracted with CH_2Cl_2 (3*10 ml). The combined organics were dried (Na_2SO_4), filtered and concentrated. The NMR data of the crude compound matched that reported by Higgs *et al* for the title compound.[98]

7.2.4 Scheme 17: Representative procedure for the attempted couplings of 37 to BnBr.



A solution of Li-TMB **37** in THF was prepared from Br-TMB **36** (*ca*. 300 mg, 1.2 mmol) and *n*-BuLi (1.1 equiv.) at -78 °C using the optimised procedure (Section 7.2.2). To this solution of **37**, BnBr (100 µL, 0.85 mmol) was added at this temperature. The mixture was stirred at this temperature for 4 hours and then warmed slowly warmed to room temperature overnight. The reaction was quenched by the addition of water (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (3*10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the crude residue showed no coupling product was obtained. Only TMB **33** and unreacted BnBr were observed.

7.2.5 Scheme 20: Formation of Grignard 39 from Li-TMB 37.



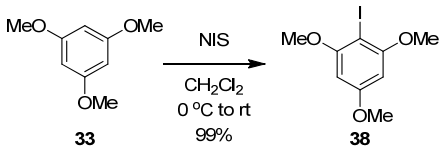
A solution of **37** in THF was prepared from Br-TMB **36** (ca. 1.2 mmol) and *n*-BuLi (1.1 equiv.) at -78 °C using the optimised procedure (Section 7.2.2). To this solution at -78 °C, $MgBr_2$ or $MgBr_2.OEt_2$ (1.1 equiv) was added as a solid. No dissolution of the salts was observed at this temperature. The mixture was then slowly warmed to 0 °C in an ice bath, during which the Mg salts dissolved to provide a clear, yellow solution, which was used immediately as prepared.

7.2.6 Scheme 20: Attempted coupling of Grignard 39 to electrophiles.

To three separate solutions of **39** prepared by the above procedure (Section 7.2.5), one of the following was added at 0 °C, BnBr (0.5 equiv.), MeI (1 equiv.), or benzaldehyde (1 equiv.). The resulting mixtures were stirred overnight at room temperature, and then quenched by the addition of sat. aq. NH_4Cl (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (3*10 mL). The combined organics

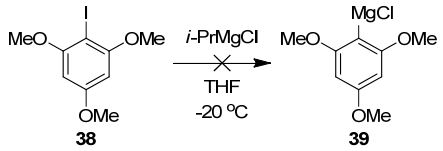
were dried (Na_2SO_4), filtered and concentrated to provide crude residues. In all cases, ^1H NMR analysis of the crude mixtures showed no coupling product was formed. In all cases TMB **33** was recovered. In the reactions performed with either BnBr or benzaldehyde, the electrophile was recovered unaltered.

7.2.7 Scheme 21: 1-iodo-2,4,6-trimethoxybenzene (38, I-TMB).



To a stirring solution of **33** (5.00 g, 29.7 mmol) in CH_2Cl_2 (100 mL), solid NIS (6.72 g, 29.9 mmol) was added at 0 ^oC. Stirring was continued at this temperature for 1 hr and then a solution of $Na_2S_2O_3.5H_2O$ (0.5 g) in water (100 mL) was added and vigorously stirred for 10 minutes. The phases were then separated and the aqueous phase was then extracted with CH_2Cl_2 (2*50 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. The residue was then filtered over SiO_2 (CH_2Cl_2) to provide 8.6 g (98%) of a white, crystalline solid. ^1H and ^{13}C NMR for the synthesised compound corresponded to that for the title compound produced in section 7.2.3.

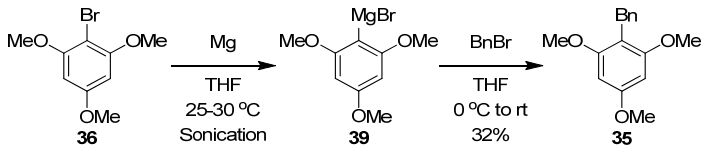
7.2.8 Scheme 21: Attempted formation of Grignard 39 from I-TMB 38 using *i*-PrMgCl.



To a stirring solution of I-TMB **38** (0.30 g, 1.02 mmol) in THF (5 mL) at -20 ^oC, *i*-PrMgCl (0.54 mL, 2M in THF, 1.07 mmol) was added dropwise over two minutes. The resulting solution was then stirred at this temperature for 30 minutes. TLC analysis (EtOAC/Hexanes 1:4) showed the reaction mixture contained only **38** with no evidence of any exchange occurring. The mixture was then left to stir for 6 hours with TLC analysis at 1, 2 and 6 hours. TLC analyses showed that I-TMB **38** was present unaltered. The reaction mixtures was warmed to room temperature following the final TLC analysis and quenched by the addition of water (10 mL). The resulting mixture was then extracted with CH_2Cl_2 (10mL) and the organic extract was dried

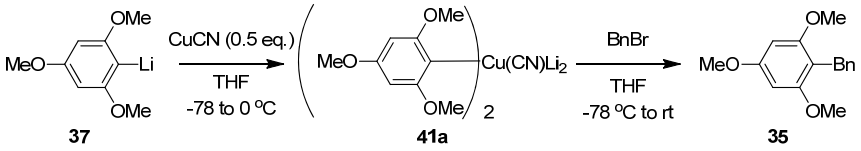
(Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis confirmed the presence of the starting iodide **38**.

7.2.9 Scheme 22: 1-benzyl-2,4,6-trimethoxybenzene (35, Bn-TMB) from Grignard 39 using sonication.



Mg turnings (110 mg, 4.52 mmol,) were oven dried at 100 °C for at least one week, and then cooled to room temperature *in vacuo*. A few drops of 1,2-dibromoethane were added and the mixture was heated to 70 °C for one minute and then cooled to room temperature. A solution of Br-TMB **36** (1.02 g, 4.13 mmol) in THF (5 mL) was then added to the Mg along with a few crystals of iodine. The resulting mixture was then sonicated for one hour while maintaining the sonicator water bath at 25-30 °C to provide a clear, colourless solution of **39**. This solution was then cooled to 0 °C and neat BnBr (0.5 mL, 4.15 mmol) was added dropwise and the resulting mixture was stirred for 24 hours at room temperature. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (2*20 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated. Silica gel chromatography of the residue (CH_2Cl_2/Hexanes 1:1) provided 340 mg (32%) of a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.07 (m, 5H), 6.15 (s, 2H), 3.93 (s, 2H), 3.80 (s, 3H), 3.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.59, 159.11, 142.50, 128.63,128.13, 125.42, 110.56, 90.92, 55.92, 55.53, 28.51. ^{1}H and ^{13}C NMR corresponded to that reported by Katritzky *et al* for the title compound.[151]

7.2.10 Scheme 23: 1-benzyl-2,4,6-trimethoxybenzene (35, Bn-TMB) from cuprate 41a.



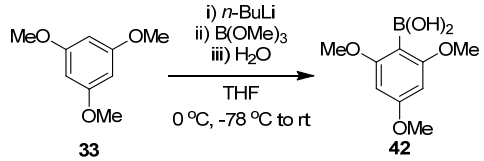
A solution of Li-TMB **37** in THF (4 mL) was prepared using the optimised procedure (Section 7.2.2) from Br-TMB **36** (0.30 g, 1,21 mmol) and *n*-BuLi (1.75 mL, 1.36M, 2.38 mmol). To the resulting solution, solid CuCN (55 mg, 0.61 mmol)

was added at -78 ^{o}C and the mixture stirred at this temperature for 15 minutes. No dissolution of CuCN was observed. The mixture was then warmed in an ice bath until the solids dissolved to afford a clear, yellow solution of **41a**. The solution was then immediately cooled to -78 ^{o}C. Neat BnBr (70 μL, 0.59 mmol) was added dropwise, resulting in the slow formation of a brown colour. The mixture was allowed to slowly warm in the cold bath to room temperature overnight and then quenched by the addition of sat. aq. NH_4Cl/25% aq. NH_4OH (9:1, 20 mL) and stirred for 30 minutes. The resulting mixture was filtered over celite and the filter cake was washed with CH_2Cl_2 (2*10mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3*10 mL). The combined organics were then washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated. Silica gel chromatography of the residue (CH_2Cl_2/Hexanes 1:1) provided 70 mg (46%) of a white solid that possessed the same ^{1}H and ^{13}C NMR spectral properties as the title compound prepared in Section 7.2.9.

7.2.11 Scheme 23: 1-benzyl-2,4,6-trimethoxybenzene (35, Bn-TMB) from cuprate 41b.

The above coupling (Section 7.2.10) was carried out using CuI over CuCN with the following reagents. Li-TMB **37** was prepared from Br-TMB **36** (0.29 g, 1.18 mmol), *n*-BuLi (1.72 ml, 1.36M, 2.34 mmol) in THF (4 mL). Solid CuI (112 mg, 0.58 mmol) was then added as the copper source and cuprate **41b** was prepared using the above method. BnBr (70 μL, 0.59 mmol) was added and the reaction was carried out as above. Isolation of the product by SiO_2 chromatography (CH_2Cl_2/Hexanes 1:1) provided 45 mg (30%) of a white solid that possessed identical ^{1}H and ^{13}C NMR spectral properties as obtained in Sections 7.2.9 and 7.2.10.

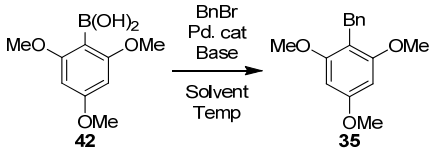
7.2.12 Scheme 25: 2,4,6-trimethoxyphenylboronic acid (42, TMB-B(OH)$_2$).



To a stirring solution of TMB **33** (11.3 g, 67.2 mmol) in THF (200 mL) at 0 ^{o}C, *n*-BuLi (45 mL, 1.6 M, 72 mmol) was added dropwise over 10 minutes. The resulting white suspension was stirred at this temperature for 2 hours and then cooled to -78

^{o}C. $B(OMe)_3$ (15 mL, 135 mmol) in THF (15 mL) was then added dropwise over one hour and the resulting mixture was stirred at -78 ^{o}C for one hour before being allowed to slowly warm in the cold bath to room temperature overnight. The resulting cloudy, white mixture was cooled to 0 ^{o}C and water (50 mL) was added dropwise with stirring over 30 minutes. The mixture then was poured into a mixture of water (100 mL) and CH_2Cl_2 (300 mL) and stirred vigorously for 15 minutes. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (4*50 mL), and the combined organics were dried (Na_2SO_4), filtered and concentrated to afford a white powdery solid. The mixture was then dissolved in minimal boiling $CHCl_3$ and a roughly equal portion of hot Et_2O was added. The mixture was cooled to room temperature and then placed in a -20 ^{o}C freezer overnight to allow crystallisation of the product. The resulting white crystals were isolated by suction, washed with cold Et_2O (10 mL) and dried *in vacuo* to yield 10.1 g (71%) of a white, crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.14 (s, 2H), 3.87 (s, 6H), 3.83 (s, 3H). NMR data for the synthesized compound corresponded to that reported for the title compound by Chaumeil e*t al*.[152]

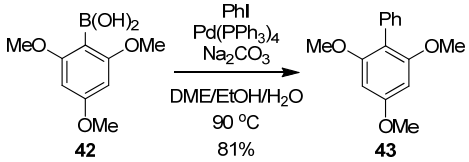
7.2.13 Table 1: General method for the coupling of TMB-B(OH)$_2$ 42 with BnBr.



A 25 mL round bottom flask was charged with **42** (~1.5 mmol) and the stated base (~3 mmol). The organic portion of the quoted solvent system (10 mL) was then added and the resulting mixture was degassed with an Argon sparge for 30 minutes. Neat BnBr (~1 mmol) was added followed immediately by the catalyst (5 mol%) and water (5 mL) if aqueous conditions were specified. The resulting mixtures were stirred overnight at the temperature specified by Table 1, then cooled to room temperatures and quenched by the addition of sat. aq. NH_4Cl (10 mL). The resulting mixtures were extracted with CH_2Cl_2 (2*20 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated. In all cases the crude residues were submitted to ^{1}H NMR analysis. In the residues of entries 1-6 only TMB **33** and BnBr were observed and were not treated any further. ^{1}H NMR analysis of the residues of entries 7-9 showed some product formation. The crude samples of these entries were

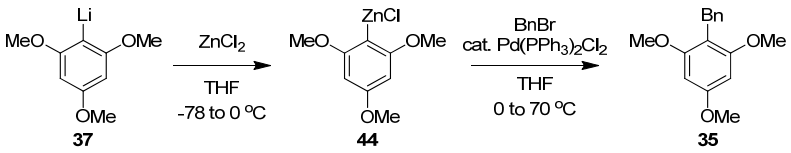
purified by silica gel chromatography (CH_2Cl_2/Hexanes 1:1) to provide Bn-TMB **35** in the yield specified in Table 1. The product of these couplings was confirmed to be the title compound through comparison of ^1H and ^{13}C NMR data of the obtained compounds with that of the same compound produced in Section 7.2.9.

7.2.14 Scheme 27: 2,4,6-trimethoxybiphenyl (43, Ph-TMB) from TMB-B(OH)$_2$ 42.



A solution of iodobenzene (67 µL, 0.60 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.02 mmol) in DME (10 mL) was stirred under N_2 at 50 ^oC for 10 minutes and then cooled to room temperature. A solution of **42** (0.17 g, 0.81 mmol) in DME/EtOH (6 mL/ 3 mL) was added *via*. cannular, followed immediately by an aqueous solution of Na_2CO_3 (0.85 g in 4 mL H_2O). The mixture was refluxed at 90 ^oC for 16 hours, cooled to room temperature, and then poured into sat. aq. NH_4Cl (20 mL). The resulting mixture was extracted with $CHCl_3$ (3*20 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. The residue was purified using silica gel chromatography (EtOAc/Hexanes 1:9) to provide 119 mg (81%) of a white, powdery solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 5H), 6.22 (s, 2H), 3.85 (s, 3H), 3.70 (s, 6H). Mpt. 152-154 ^oC (lit. 152 ^oC). ^1H NMR and Mpt. of the product corresponded to that reported by Becht *et al* for the title compound.[153]

7.2.15 Scheme 29: 1-benzyl-2,4,6-trimethoxybenzene (35, Bn-TMB) from TMB-ZnCl 44.



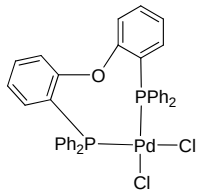
A solution of Li-TMB **37** in THF (4 mL) was prepared using the optimised procedure (Section 7.2.2) from Br-TMB **36** (0.32 g, 1,29 mmol) and *n*-BuLi (1 mL, 1.40 M, 1.4 mmol). To this, a solution of $ZnCl_2$ (1.4 mL, 1 M in THF, 1.4 mmol) was added dropwise *via*. syringe at -78 ^oC. At the addition of 1 equivalent of the $ZnCl_2$

solution, the white suspension from the production of **37** dissolved to give a clear, colourless solution. The solution was stirred at this temperature for 15 minutes, and then allowed to slowly warm to 0 ^{o}C in an ice bath over 30 minutes. Neat BnBr (100 μL, 0.84 mmol) was added at this temperature, followed immediately by solid $Pd(PPh_3)_2Cl_2$ (6 mg, 1 mol%). The mixture was then warmed to 70 ^{o}C and stirring was continued for 16 hours. The mixture was cooled to room temperature and dilute HCl (2 M, 5 mL) was then added, followed by CH_2Cl_2 (10 mL) and stirring was continued for a further 10 minutes. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (2*10 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. SiO_2 chromatography (CH_2Cl_2/Hexanes 1:1) of the residue provided 131 mg (60%) of a white powdery solid. The tile compound prepared by this method showed the same ^{1}H and ^{13}C NMR spectral properties for the same compound prepared in Section 7.2.9.

7.2.16 Table 2: 1-benzyl-2,4,6-trimethoxybenzene (35, Bn-TMB). General method for the Pd-catalysed coupling of TMB-ZnCl 44 with BnBr or BnCl.

The Pd-catalysed couplings described in Table 2 were carried out using the following method. TMB-ZnCl **44** (~1.5 mmol) was prepared by the above method (section 7.2.15). Neat BnBr or BnCl (100 μL, 0.84-0.87 mmol)), was added at 0 ^{o}C, followed immediately by the catalyst specified in Table 2. The reactions mixtures were then warmed to 70 ^{o}C (except entry 8) and stirred for the time specified in Table 2. The mixtures were then cooled to room temperature, then quenched, extracted and concentrated by the above procedure (section 6.2.15). Silica gel chromatography (CH_2Cl_2/Hexanes 1:1) of the residues provided the title compound Bn-TMB **35** in the yields specified in Table 2. The product of these couplings showed identical NMR spectral properties for the title compound prepared by the above method (Section 7.2.15).

7.2.17 [bis(*o*-diphenylphosphinophenyl)ether]palladium(II)chloride (46, Pd(DPEPhos)Cl_2).



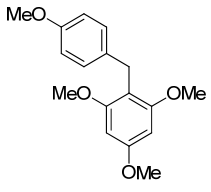
46

Pd(DPEPhos)Cl_2 was prepared using an adapted procedure as reported by Kranenburg *et al*.[154] A suspension of $Pd(PPh_3)_2Cl_2$ **47** (0.32 g, 0.46 mmol) and DPEPhos (0.30 g, 0.56 mmol) in THF (20 mL) was stirred for 24 hours. The solvent was then removed *in vacuo* and the remaining solids were collected, filtered by suction, and then washed with several portions of cold Et_2O. The residue solid was then collected and dried *in vacuo* to provide 0.32 g (96%) of the desired product as a dull yellow solid.

7.2.18 Table 3: General method for the Pd(DPEPhos)Cl_2-catalysed cross-coupling of TMB-ZnCl 44 with benzylic and aryl halides.

The cross-couplings reported in Table 3 were carried out using the above procedure (Section 6.2.15) for the cross-coupling of TMB-ZnCl **44** with BnBr using the following conditions: TMB-ZnCl was **44** prepared as above (Section 7.2.15) (~1.5 equiv.), then one of the aryl or benzyl halides **48a-48h** (1 mmol) and Pd(DPEPhos)Cl_2 (*ca*. 1 mol%) were added. All reactions except that described for entry 3 were stirred at 70 ^oC for the specified times. The reaction of entry 3 was stirred at 40 ^oC for the specified time. Isolation of the cross-coupled products was achieved by the use of SiO_2 chromatography as described below.

7.2.19: Table 3, entry 1: 2,4,6-trimethoxy-1-(4-methoxybenzyl)benzene (49a).

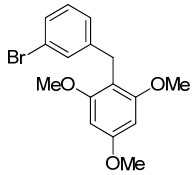


49a

Using the general procedure (Section 7.2.18), **49a** was obtained from the coupling of TMB-ZnCl **44** and **48a**. Purification using SiO_2 chromatography (CH_2Cl_2/Hexanes

1:1) provided the desired product in 68% yield as a white, powdery solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.8, 2H), 6.76 (d, *J* = 8.8, 2H), 6.15 (s, 2H), 3.88 (s, 2H), 3.80 (s, 3H), 3.79 (s, 6H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.78, 158.99, 157.59, 134.66, 129.48, 113.60, 110.97, 90.92, 55.89, 55.49, 55.37, 27.55. This NMR data corresponded to that reported by Hofmann *et al* for the title compound.[155]

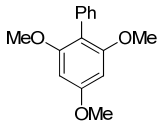
7.2.20: Table 3, entry 2: 2,4,6-trimethoxy-1-(3-bromobenzyl)benzene (49b).



49b

Using the general procedure (Section 7.2.18), **49b** was obtained from the coupling of TMB-ZnCl **44** with **48b**. Purification using SiO_2 chromatography (CH_2Cl_2/Hexanes 1:1) provided the desired product in 55% yield as a white, powdery solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.05 (m, 4H), 6.16 (s, 2H), 3.91 (s, 2H), 3.81 (s, 3H), 3.79 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.11, 158.99, 144.93, 131.67, 129.63, 128.52, 127.32, 122.23, 109.56, 90.85, 55.85, 55.48, 28.26. HRMS (ESI): calculated for $C_{16}H_{17}BrO_3$, $[M+H]^+$ 337.0434, found 337.0437. Mpt: 72-72 ^{o}C.

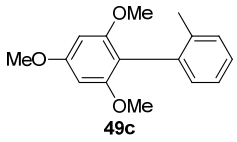
7.2.21: Table 3, entries 3 and 4: 2,4,6-trimethoxybiphenyl (43, Ph-TMB).



43

Using the general procedure (Section 7.2.18), Ph-TMB **43** was obtained from the coupling of TMB-ZnCl **44** with either iodobenzene **48c** or bromobenzene **48d**. Purification using SiO_2 chromatography (EtOAc/Hexanes 1:9) provided the desired product in 81% and 77% yields, respectively, as white, powdery solids. The product of both couplings displayed identical NMR spectral properties, which matched that reported for the title compound in Section 6.2.14.

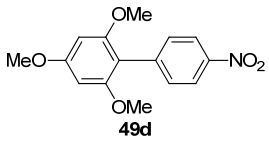
7.2.22: Table 3, entry 6: 2,4,6-trimethoxy-2′-methyl-biphenyl (49c).



49c

Using the general procedure (Section 7.2.18), **49c** was obtained from the coupling of TMB-ZnCl **44** with **48f**. Purification using SiO_2 chromatography (EtOAc/Hexanes 1:9) provided the desired product in 74% yield as white, powdery solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (br s, 1H), 7.28-7.07 (m, 4H), 6.27 (s 2H), 3.91 (s, 3H), 3.73 (s, 6H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.84, 158.54, 137.98, 134.36, 131.47, 129.68, 127.24, 125.35, 112.12, 91.00, 56.01, 55.54, 19.95. HRMS (ESI): calculated for $C_{16}H_{18}O_3$, $[M+H]^+$= 259.1329, found 259.1336. Mpt: 91-93 ^{o}C.

7.2.23 Table 3, entry 7: 2,4,6-trimethoxy-4′-nitro-biphenzyl (49d).

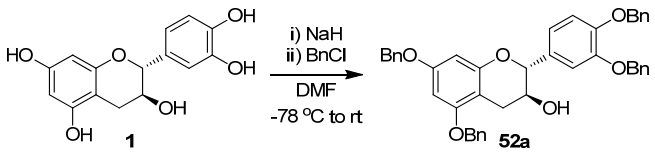


49d

Using the general procedure (Section 7.2.18), **49d** was obtained from the coupling of TMB-ZnCl **44** with **48g**. Purification using SiO_2 chromatography (EtOAc/Hexanes 1:9) provided the desired product in 80% yield as an orange, crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, 2H, J = 9.0,), 7.50 (d, 2H, J = 9.0), 6.23 (s, 2H), 3.86 (s, 3H), 3.72 (s, 6H). This ^{1}H NMR data corresponded to that reported by Abramovitch *et al* for the title compound.[156]

7.3 Experimental procedures for chapter 3.

7.3.1 Scheme 11: 5,7,3′,4′-tetra-O-benzyl-(+)-catechin (52a, TBC).

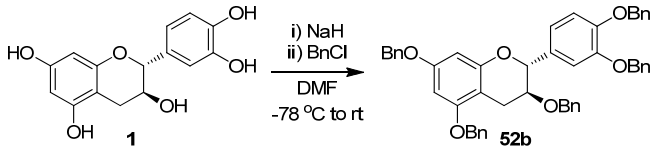


1 **52a**

To a stirring solution of (+)-catechin **1** (9.7 g, 33.4 mmol) in DMF (200 mL) at -78 ^{o}C, NaH (5.69 g, 60 % dispersion in mineral oil, 142 mmol, 4.25 equiv.) was added as a solid, followed immediately by neat BnCl (20 mL, 173 mmol, 5.2 equiv.) *via.*

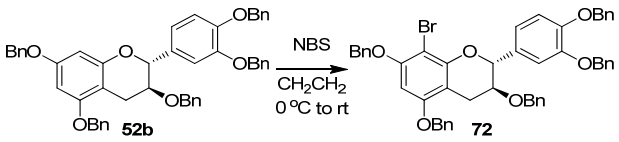
syringe. The resulting mixture was stirred vigorously at -78 ^{o}C for 15 minutes, then the cold bath was removed and stirring was continued at room temperature for 7 hours. The mixture was then poured into a mixture of EtOAc (400 mL) and water (600 mL) and stirred vigorously for 30 minutes. The phases were then separated and the organics were washed with brine (5*100 mL), then dried (Na_2SO_4), filtered and concentrated. The brown residue was then purified by filtration over SiO_2 (CH_2Cl_2/Hexane 1:1 eluted mineral oil and excess BnCl, then CH_2Cl_2 eluted product) to provide 20.5 g (94%) of a white, crystalline solid. ^{1}H and ^{13}C NMR of the product corresponded to that reported by Tarascou *et al* for the title compound.[39]

7.3.2 Scheme 11: 3,5,7,3′,4′-penta-O-benzyl-(+)-catechin (52b, PBC).



NaH (4.67 g, 117 mmol, 60% dispersion in mineral oil, 6 equiv.) and BnCl (15.6 mL, 135 mmol, 7 equiv.) were added to a solution of (+)-catechin **1** (5.61 g, 19.3 mmol) in DMF (120 mL) at -78 ^{o}C. The resulting mixture was stirred at this temperature for 15 minutes, then warmed to room temperature and stirred for a further 24 hours. The mixture was then quenched and extracted using the above procedure (Section 7.3.1). Filtration of the residue over SiO_2 (CH_2Cl_2/Hexane 1:1 eluted mineral oil and excess BnCl, then CH_2Cl_2 eluted product) afforded 13.0 g (91%) of a white foamy solid. ^{1}H and ^{13}C NMR of the product matched that reported by Kikuchi *et al* for the title compound.[108]

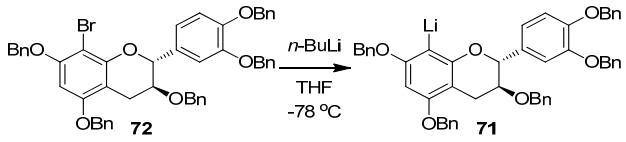
7.3.3 Scheme 14: 8-bromo-3,5,7,3′,4′-penta-O-benzyl-catechin (72, 8Br-PBC).



To a stirring solution of PBC **52b** (4.98 g, 6.7 mmol) in CH_2Cl_2 (100 mL) at 0 ^{o}C, NBS (1.32 g, 7.4 mmol) was added as a solid. The mixture was then allowed to slowly warm to room temperature in the ice bath with continuous stirring for 4 hours. The mixture was then quenched by the addition of aq. $Na_2S_2O_3.5H_2O$ (1 g in 30 mL water) and the resulting mixture was vigorously stirred at room temperature for 10

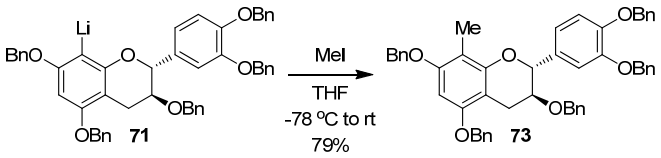
minutes. The phases were then separated and the aqueous phase was then extracted with CH_2Cl_2 (2*20 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. Filtration of the residue over SiO_2 (CH_2Cl_2) provided the desired product (5.27 g, 96%) as a white foamy solid. ^1H and ^{13}C NMR of the product matched that reported by Kozikowski *et al* for the title compound.[37]

7.3.4 Scheme 14: Representative procedure for 8-lithio-3,5,7,3′,4′-penta-O-benzyl-catechin (71, Li-PBC).



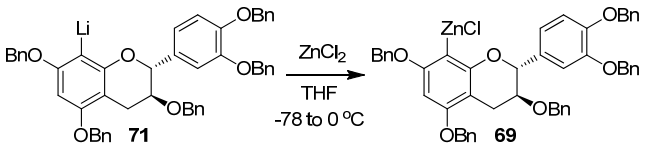
To a stirring solution of 8Br-PBC **72** (0.50 g, 0.61 mmol) in THF (6 mL) at -78 °C, *n*-BuLi (415 µL, 1.55 M in hexanes, 0.64 mmol, 1.05 equivalents) was added dropwise over 2 minutes, over which time the colourless 8Br-PBC **72** solution developed a deep yellow/orange colour. Stirring was continued at this temperature for 15 minutes. The generated organolithium was then used immediately as prepared.

7.3.5 Scheme 15: 8-methyl-3,5,7,3′,4′-penta-O-benzyl-catechin (73, Me-PBC).



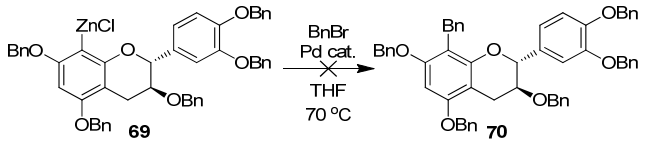
To a stirring solution of 8Li-PBC **71** (0.61 mmol) in THF (6 mL) prepared by the above procedure (Section 7.3.4), neat MeI (115 µL, 1.85 mmol, 3 equivalents) was added at -78 °C and the resulting mixture was stirred at this temperature for 1 hour, before being allowed to slowly warm in the cold bath to room temperature over 2 hours. Water (10 mL) and CH_2Cl_2 (10 mL) were added and the mixture was stirred vigorously for 10 minutes and the phases were separated. The aqueous phase was then extracted with CH_2Cl_2 (2*10 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated. Silica gel chromatography of the residue (CH_2Cl_2/Hexanes 3:1) afforded 0.37 g (79%) of the desired product as a white, foamy solid. ^1H and ^{13}C NMR of the obtained product matched that reported by Es-Safi *et al* for the title compound.[157]

7.3.6 Scheme 16: Representative procedure for formation of 3,5,7,3′,4′-penta-O-benzyl-catechin-8-zinc chloride (69, PBC-8ZnCl) from Li-PBC 71.



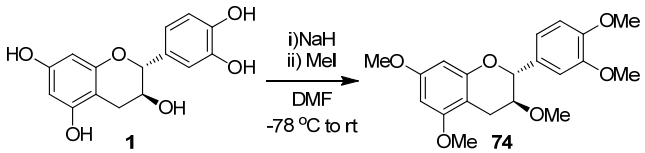
To a stirring solution of Li-PBC **71** (~0.61 mmol) in THF (6 mL) prepared by the above procedure (Section 7.3.4), a solution of $ZnCl_2$ (0.62 mL, 1 M in THF, 6.2 mmol) was added dropwise at -78 ^oC. Upon completion of the $ZnCl_2$ addition, the deep yellow/orange colour of the organolithium solution changed to a pale yellow colour. Stirring was continued at this temperature for 30 minutes before the solution was allowed to slowly warm to 0 ^oC over 1 hour. Following this, the assumed PBC-8ZnCl **69** solution was used immediately as prepared.

7.3.7 Scheme 17: Representative procedure for attempted cross-couplings of PBC-8ZnCl 69 to BnBr.



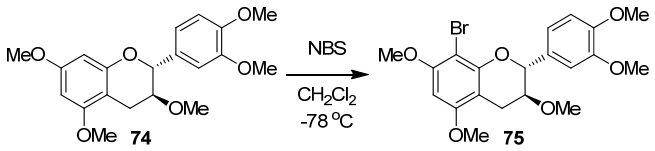
To a stirring solution of PBC-8ZnCl **69** (~0.61 mmol) in THF (6 mL) prepared by the above procedure (Section 7.3.6) at 0 ^oC, neat BnBr (70 μL, 0.59 mmol) was added *via*. syringe, followed immediately by Pd(DPEPhos)Cl_2 (22.2 mg, 5 mol%) as a solid. The resulting mixture was stirred at 70 ^oC for 20 hours before being cooled to room temperature. Dilute aq. HCl (2 M, 5 mL) was added and the mixture was stirred for 10 minutes. The aqueous phase was then extracted with CH_2Cl_2 (2*20 mL). The combined organics were washed with water (10 mL), then dried (Na_2SO_4), filtered and concentrated. ^1H NMR analysis of the crude residue showed only the presence of starting BnBr and PBC **52b** with no evidence of any coupled product.

7.3.8 Scheme 18: 3,5,7,3′,4′-penta-O-methyl-(+)-catechin (74, PMC).



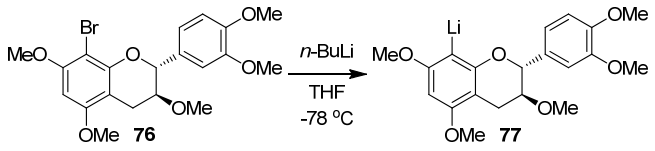
Using the same procedure for the synthesis of TBC **52a** (Section 7.3.1), NaH (3.18 g, 95 mmol, 60% dispersion in mineral oil, 5.6 equiv.) and MeI (10.7 mL, 172 mmol, 10 equiv.) were added to a solution of (+)-catechin **1** (4.96 g, 17.1 mmol) in DMF (120 mL) at -78 ^{o}C and the mixture was stirred at this temperature for 15 minutes, then warmed to room temperature and stirred for a further 24 hours. The mixture was then quenched and extracted using the procedure for TBC **52a** (Section 7.3.1.). Filtration of the residue over SiO_2 (CH_2Cl_2/Hexanes 2:1 eluted mineral oil, then CH_2Cl_2/Et_2O 9:1 eluted the product) provided 5.60 g (91%) of the desired product as a white, crystalline solid. The ^{1}H and ^{13}C NMR data of the obtained product matched that reported by Kiehlmann *et al* for the title compound.[110]

7.3.9 Scheme 18: 8-bromo-3,5,7,3′,4′-penta-O-methyl-catechin (75, 8Br-PMC).



Using the above procedure for 8Br-PBC **72** (Section 7.3.3), a mixture of PMC **74** (1.08 g, 2.98 mmol) and NBS (0.60 g, 3.34 mmol) in CH_2Cl_2 (45 mL) was stirred at -78 ^{o}C for 4 hours before being warmed to 0 ^{o}C. The mixture was then quenched and extracted using method set out in the aforementioned procedure. The residue was then filtered over SiO_2 (CH_2Cl_2 then CH_2Cl_2 /Et_2O 9:1) to provide the desired product (1.31 g, 99%) as a white solid. The ^{1}H and ^{13}C NMR data for the obtained product corresponded with that reported by Kiehlmann *et al* for the title compound.[110]

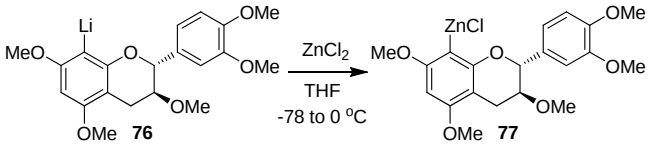
7.3.10: Scheme 18: Representative procedure for 8-lithio-3,5,7,3′,4′-penta-O-methyl-catechin 76 (Li-PMC).



To a stirring solution of 8Br-PMC **75** (0.25 g, 0.57 mmol) in THF (6 ml) at -78 ^{o}C, *n*-BuLi (435 μL, 1.44 M in hexanes, 0.64 mmol, 1.1 equivalents) was added dropwise over 2 minutes. No colour change was observed upon addition of *n*-BuLi. Stirring

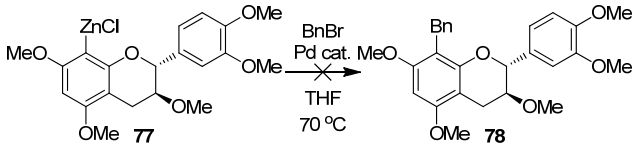
was continued at this temperature for 15 minutes. At this point the resulting organolithium solution was used immediately as prepared.

7.3.11 Scheme 19: General procedure for 3,5,7,3′,4′-penta-O-methyl-catechin-8-zinc chloride 77 (PMC-8ZnCl) formation from Li-PMC 76.



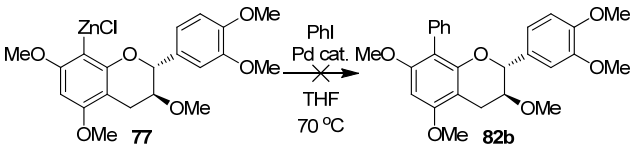
To a solution of Li-PMC **76** (~0.57 mmol) in THF (6 mL) prepared by the above method (Section 7.3.10), a solution of $ZnCl_2$ (625 μL, 1 M in THF 0.63 mmol) was added dropwise over 2 minutes at -78 °C. Stirring was continued at this temperature for 30 minutes before the solution was allowed to slowly warm to 0 °C over 1 hour. The assumed organozinc **77** was then used immediately at this temperature.

7.3.12 Scheme 19: Representative procedure for attempted cross-couplings of PMC-8ZnCl 77 to BnBr.



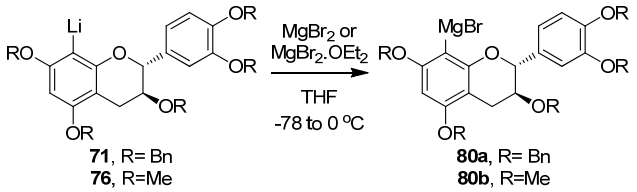
To a stirring solution of PMC-8ZnCl (~0.57 mmol) in THF (6 mL) prepared by the above procedure (Section 7.3.11) at 0 °C, neat BnBr (60 μL, 0.51 mmol) was added *via*. syringe, followed immediately by $Pd(DPEPhos)Cl_2$ (20 mg, 5 mol%) as a solid. The resulting mixture was stirred at 70 °C for 20 hours before being cooled to room temperature. Dilute aq. HCl (2 M, 5 mL) was added and the mixture stirred for 10 minutes. The aqueous phase was then extracted with CH_2Cl_2 (2*20 mL). The combined organics were washed with water (10 mL), then dried (Na_2SO_4), filtered and concentrated. ^1H NMR analysis of the crude residue showed only the presence of starting BnBr and PMC **74** with no evidence of any coupled product.

7.3.13 Scheme 20: Representative procedure for attempted cross-couplings of PBC-8ZnCl or PMC-8ZnCl to PhI.



Using the same coupling procedure as employed for the coupling of PBC-8ZnCl **69** to BnBr (Section 7.3.7), the coupling of PBC-8ZnCl (~0.61 mmol) to PhI (48 μL, 0.43 mmol) was attempted using Pd(DPEPhos)Cl_2 (22 mg, 5 mol%) as the catalyst at 70 ^oC. Following acid quenching and extraction, ^1H NMR analysis of the crude residue showed only starting PhI and PMC **74** were recovered with no evidence of any coupling product.

7.3.14 Scheme 21: Formation of 3,5,7,3′,4′-penta-O-benzyl-catechin-8-magnesium bromide 80a (PBC-8MgBr) from Li-PBC 71.



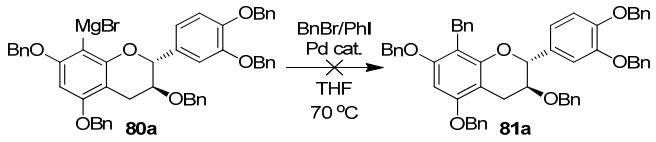
To a stirring solution of Li-PBC **71** (~0.61 mmol) in THF (6 mL) prepared by the general procedure (Section 7.3.6), solid $MgBr_2$ (0.124 g, 0.67 mmol) was added at -78 ^oC and the resulting suspension was stirred at this temperature for 15 minutes, then warmed to 0^oC in an ice bath. Upon warming, the $MgBr_2$ dissolved to provide a clear, pale yellow solution. This assumed Grignard reagent **80a** was then used immediately at this temperature.

7.3.15 Scheme 21: Formation of 3,5,7,3′,4′-penta-O-methyl-catechin-8-magnesium bromide 80b (PMC-8MgBr) from Li-PMC 76.

To a stirring solution of Li-PMC **76** (~0.57 mmol) in THF (6 mL) prepared by the general procedure (Section 7.3.10), solid $MgBr_2$ (0.115 g, 0.63 mmol) was added at -78 ^oC and the resulting suspension was stirred at this temperature for 15 minutes, then warmed to 0^oC in an ice bath. Upon warming, the $MgBr_2$ dissolved to provide a

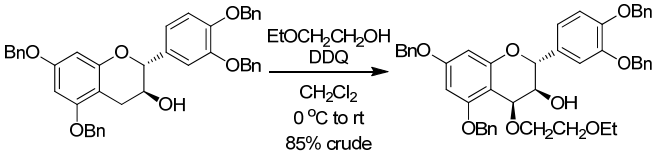
clear, colourless solution. This assumed Grignard reagent **80b** was then used immediately at this temperature.

7.3.16 Scheme 22: Representative procedure for attempted cross-couplings of PBC-8ZMgBr 80a or PMC-8MgBr 80b to BnBr or PhI.



A solution of PBC-8MgBr **80a** (~0.61 mmol) in THF was prepared from Li-PBC **71** (~0.61 mmol) following the above procedure (Section 7.3.14). To this stirring solution at 0 ^{o}C, neat BnBr (50 µl, 0.43 mmol) was added *via*. syringe, followed immediately by Pd(DPEPhos)Cl_2 (22 mg, 5 mol%) as a solid. The resulting solution was stirred at 70 ^{o}C for 24 hours before being cooled to room temperature. Sat. aq. NH_4Cl (10 mL) was then added with stirring and the aqueous mixture was extracted with CH_2Cl_2 (2*20 mL). The combined organics were sequentially washed with water (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the crude residue showed no evidence of any coupling product. Only starting BnBr and PBC **52b** were recovered.

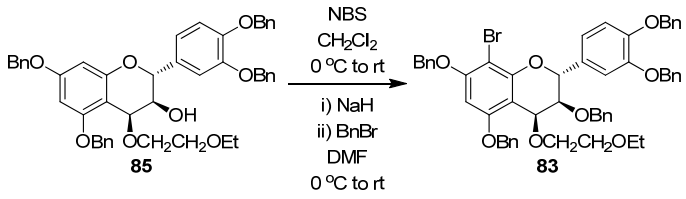
7.3.17 Scheme 24: 5,7,3′,4′-tetra-O-benzyl-catechin-4*β*-(2-ethoxyethyl)ether (85, 4EE-PBC).



To a stirring solution of TBC **52a** (2.02 g, 3.11 mmol) and 2-ethoxyethanol (5 mL) in CH_2Cl_2 (50 mL) at 0 ^{o}C, DDQ (1.42 g, 6.25 mmol) was added slowly and the resulting blue/purple mixture was stirred for 2 hours at room temperature. The reaction mixture was then poured into a mixture of sat. aq. $NaHCO_3$ (500 mL) CH_2Cl_2 (100 mL) and vigorously stirred for 30 minutes before the phases were separated. The organics were sequentially washed with sat. aq. $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), and then dried (Na_2SO_4), filtered and concentrated. The blue/green residue was then filtered over SiO_2 ($CHCl_3$) to provide an orange solid (1.95 g, 85%) of sufficient purity to be used in subsequent steps. The

^{1}H and ^{13}C NMR spectra of the product corresponded with that reported by Saito *et al* for the title compound.[31]

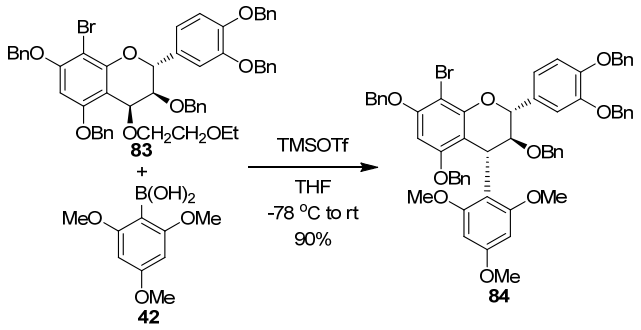
7.3.18 Scheme 24: 8-bromo-3,5,7,3′,4′-penta-O-benzyl-catechin-4*β*-(2ethoxyethyl)ether (83, 8Br-4EE-PBC).



To a stirring solution of 4EE-TBC **85** (2.36 g, 3.20 mmol) in CH_2Cl_2 (30 mL) at 0 ^{o}C, NBS (573 mg, 3.21 mmol) was added as a solid. The mixture was then allowed to slowly warm to room temperature with stirring over 4 hours. The mixture was then quenched by the addition of aq. $Na_2S_2O_3.5H_2O$ (1 g in 30 mL water) and the resulting mixture was vigorously stirred at room temperature for 10 minutes, then the phases were separated. The aqueous phase was then extracted with CH_2Cl_2 (2*50 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated to afford 2.59 g (99%) of a crude yellow/orange solid **86** (8Br-4EE-TBC). This crude product was immediately dissolved in anhydrous DMF (30 mL) and cooled to 0 ^{o}C with stirring. NaH (195 mg, 60% dispersion in oil, 4.88 mmol) was added as a solid, which resulted in the immediate formation of a cloudy, deep yellow suspension. The resulting mixture was stirred at this temperature for 30 minutes. Neat BnBr (570 µl, 4.80 mmol) was added *via*. syringe at this temperature. The cold bath was then removed and stirring was continued at room temperature for 3 hours. The mixture was then poured into a mixture of EtOAc (100 mL) and water (100 mL) and stirred vigorously for 30 minutes. The phases were then separated. The organic phase was then washed with brine (3*100 mL), then dried (Na_2SO_4), filtered and concentrated. The product was then isolated by gradient silica gel chromatography (EtOAc/Hexanes 1:9 to 1:4) to provide 2.73 g (95%) of a white foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.26 (m, 20H), 7.19-6.94 (m, 8H), 6.22 (s, 1H, **C6-H**), 5.36 (d, 1H, J= 10.2 Hz, **C2-H**), 5.19 (s, 2H), 5.08 (br s, 4H), 5.01 (d, 2H, J= 10.2 Hz), 4.85 (d, 1H, J=2.4 Hz, **C4-H**), 4.22 (d, 1H, J=12 Hz, C3- O-**C**$\mathbf{H_2}$-Ph), 4.06 (d, 1H, J=12 Hz, C3- O-**C**$\mathbf{H_2}$-Ph), 4.06-3.95 (m, 1H), 3.90-3.77 (m, 1H), 3.60-3.40 (m, 5H), 1.15 (t, 3H, J=7.2 Hz, C4-OCH_2CH_2-$OCH_2\mathbf{CH_3}$). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 156.90, 156.61, 152.26, 148.71, 148.87, 137.60, 137.27, 136.39, 137. 19, 136.30, 132.05, 128.5-126.8 (m), 120.85, 114.74, 114.12, 105.46, 92.56 (**C8**), 92.14 (**C6**), 78.56 (**C2**), 75.54 (**C3**), 71.79 (**C4**), 71.27, 70.99, 70.95, 70.64, 70.39, 69.75, 67.35, 66.26, 15.14. HRMS (ESI): calculated for $C_{54}H_{51}BrO_8$, [M+Na^+]= 929.2660. Found 929.2665.

7.3.20 Scheme 26: 8-bromo-4*α*-(2,4,6-trimethoxyphenyl)-3,5,7,3′,4′-penta-O-benzyl-catechin (84, 8Br-4TMB-PBC).



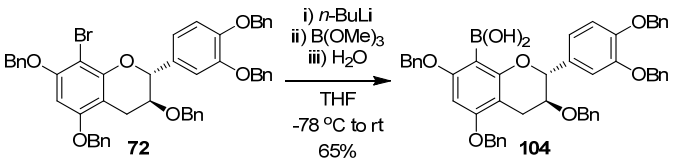
To a stirring solution of 8B-r4EE-PBC **83** (0.19 g, 0.21 mmol) and 2,4,6-trimethoxyphenyl boronic acid **42** (52 mg, 0.24 mmol) in THF (3 mL) at -78 °C, neat TMSOTf (45 μL, 0.25 mmol) was added dropwise. Stirring was continued for 1 hour at this temperature, and then the mixture was allowed to warm to room temperature in the cold bath over 3 hours. The mixture was then poured into sat. aq. $NaHCO_3$ (10 mL) and EtOAc (20 mL) and stirred vigorously for 10 minutes. The phases were then separated. The organic phase was sequentially washed with water (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by silica gel chromatography (EtOAc/Hexanes 1:4) to provide 190 mg (90%) of a white foamy solid. ^{1}H NMR (600 MHz, $CDCl_3$) 90:10 mixture of major and minor product. δ (major product only) 7.51-7.24 (m, 19H), 7.18-7.08 (m, 4H), 7.01 (d, 1H, J= 8.34 Hz), 6.97 (m, 2H), 6.70 (d, 2H, J= 6.96 Hz), 6.14 (s, 1H, **C6-H**), 6.04 (br s, 1H, TMB **C-H**), 5.98 (br s, 1H, TMB **C-H**), 5.25 (s, 2H, O-**CH_2**-Ph), 5.17 (q, 2H, J= 12 Hz, O-**CH_2**-Ph), 5.06 (dis d, 1H, J= 12 Hz, O-**CH_2**-Ph), 5.04 (dis d, 1H, J= 12 Hz, O-**CH_2**-Ph) 4.85 (d, 1H, J= 8.22 Hz, **C4-H**), 4.78 (d, 1H, J= 11.5 Hz, O-**CH_2**-Ph), 4.68 (d, 1H, J= 9.72 Hz, **C2-H**), 4.55 (d, 1H, J= 11.5 Hz, O-**CH_2**-Ph), 3.95 (dd, 1H, J= 9.72 and 8.22 Hz, **C3-H**), 3.82 (s, 3H, TMB-**OMe**), 3.72 (d, 1H, J= Hz, O-**CH_2**-Ph), 3.59 (d, 1H, J= Hz, O**CH_2**Ph), 3.47 (br s, 3H, TMB-**OMe**), 3.36 (br s, 3H, TMB-**OMe**). ^{13}C NMR (125 MHz, $CDCl_3$) δ (major isomer only) 159.32 (TMB-

Cq-OMe), 159.16 (TMB-**Cq**-OMe), 158.34 (TMB-**Cq**-OMe), 155.99, 153.88, 153.67, 148.56, 148.51, 137.83, 137.33, 137.24, 136.77, 137.61, 132.44, 126-129 (m, Bn **Ar-H**), 120.58, 114.72, 114.24, 113.48, 111.32, 94.47 (**C8)**, 92.69 (**C6**), 91.71 (TMB-**C**-H), 90.94 (TMB-**C**-H), 81.43 (O-**C**$\mathbf{H_2}$-Ph), 81.27 (**C2**), 73.87 (**C3**), 71.26 (O-**C**$\mathbf{H_2}$-Ph), 71.07 (O-**C**$\mathbf{H_2}$-Ph), 71.00 (O-**C**$\mathbf{H_2}$-Ph), 70.24 (O-**C**$\mathbf{H_2}$-Ph), 36.41 (**C4**). HRMS (ESI): calculated for $C_{59}H_{53}BrO_9$, $[M+Na^+]$= 1007.2765, found 1007.2767.

7.3.21 Table 1: General method for the Lewis acid-promoted cross-coupling of 8Br-4EE-PBC 83 with TMB-B(OH)$_2$ 42.

A stirring solution of 8B-r4EE-PBC **83** (*ca*. 50 mg, 55 μmol) and 2,4,6-trimethoxyphenyl boronic acid **42** (*ca*. 13 mg, 61 μmol) in the specified solvent (3 mL) at the specified temperature was prepared. The quantity of neat Lewis acid specified in Table 1 was then added dropwise and stirring was continued at the specified temperature, before being allowed to warm to room temperature. Stirring was then continued for the time period specified in Table 1. The mixture was then poured into a mixture of sat. aq. $NaHCO_3$ (10 mL) and EtOAc (20 mL) and stirred vigorously for 10 minutes. The phases were then separated. The organics were sequentially washed with water (20 ml) and brine (20 ml), then dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the crude residues was employed to determine the % conversion of the starting 8Br-4EE-PBC **83** stated in table 1. In the cases where an isolated yield was reported, silica gel chromatography (EtOAc/Hexanes 1:4) provided the compound in the yield stated in Table 1 as a white foamy solid. In all cases, the ^{1}H NMR matched the same compound reported in Section 7.3.20.

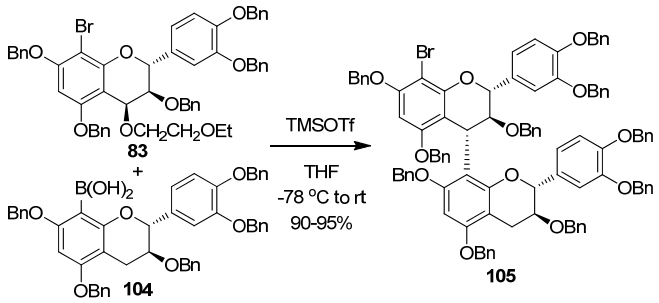
7.3.22 Scheme 36: 3,5,7,3′,4′-penta-O-benzyl-catechin-8-boronic acid (104, PBC-B(OH)$_2$).



To a stirring solution of 8Br-PBC **72** (2.09 g, 2.56 mmol) in THF (25 mL) at -78 ^{o}C, *n*-BuLi (2.1 mL, 1.35 M in hexanes, 2.84 mmol) was added dropwise over 2 minutes. The resulting deep yellow solution was stirred at this temperature for 15 minutes.

Neat $B(OMe)_3$ (600 μL, 5.38 mmol) was then added dropwise over 5 minutes at this temperature. The resulting mixture was allowed to stir at this temperature for 1 hour, before being slowly warmed to 0 ^oC in the cold bath over 4 hours. Water (5 mL) was then added dropwise over 10 minutes with stirring and the resulting mixture was poured into a mixture of EtOAc (100 mL) and ice (*ca*. 50 g) and allowed to warm to room temperature with stirring over 30 minutes. The phases were then separated and the organics were washed sequentially with water (25 mL) and brine (25 mL), then dried (Na_2SO_4), filtered and concentrated. Purification of the orange residue by gradient silica chromatography (EtOAc/Hexanes 1:4 to 1:2) provided 1.30 g (65%) of a white, foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.22 (m, 23H), 7.05-6.93 (m, 7H), 6.27 (s, 1H, **C6-H**), 5.19 (s, 2H), 5.11-5.07 (m, 6H), 4.85 (d, 1H, J=8.04 Hz, **C2-H**), 4.28 (d, 1H, J=12 Hz, C3-O-**CH_2**-Ph), 4.14 (d, 1H, J=12 Hz, C3-O-**CH_2**-Ph), 3.73 (m, 1H, **C3-H**), 3.03 (dd, 1H, J= 16.6 and 5.6 Hz, **C4-H**), 2.70 (dd, 1H, J= 16.6 and 8.7 Hz, **C4-H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ164.09, 160.42, 159.64, 149.14, 149.00, 137.70, 137.08, 136.98, 136.32, 135.51, 131.15, 130-125 (m), 120.18, 115.03, 113.44, 103.35, 91.27 (**C6**), 80.72 (**C2**), 73.83 (**C3**), 71.64, 71.27(x2), 71.18, 70.03, 26.12 (**C4**). ^{11}B NMR (126 MHz, CD_3CN) δ 29.1. HRMS (ESI) calculated for $C_{50}H_{45}BO_8$, $[M+NH_4^+]$= 802.3546, found 802.3553.

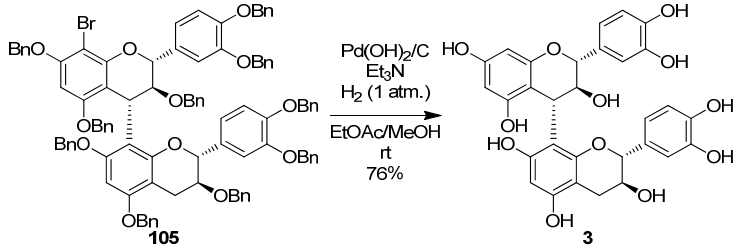
7.3.23 Scheme 37: 8-bromo-3,5,7,3′,4′-penta-O-benzyl-catechin-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (105, 8Br-PBC-PBC).



To a stirring solution of 8Br-4EE-PBC **83** (0.646 g, 0.71 mmol) and PBC-$B(OH)_2$ **104** (0.664 g, 0.89 mmol) in THF (7 mL) at -78 ^oC, neat TMSOTf (140 μL, 7.7 mmol) was added dropwise. Stirring was continued at this temperature for 1 hour, and then the reaction mixture was allowed to warm to room temperature in the cold bath over 3 hours. The mixture was then poured into sat. aq. $NaHCO_3$ (10 mL) and EtOAc (30 mL) and stirred vigorously for 10 minutes. The phases were then

separated. The organic phase was sequentially washed with water (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by silica gel chromatography to provide 1.05 g (95%) of a white foamy solid. ^{1}H NMR (600 MHz, $CDCl_3$, two rotamers: maj/min ~75:25) δ 7.61-6.86 (m, **Ar-H**, **B, E-ring-H**, maj and min) 6.79-6.74 (m, **B, E-ring-H,** maj and min), 6.65 (d, J= 7.2 Hz), 6.58 (d, J= 7.26 Hz) 6.43 (m, maj and min), 6.37 (s, **D6-H**, min), 6.31 (s, **D6-H**, maj), 6.22 (s, **A6-H,** maj), 6.15 (s, **A6-H**, min), 5.30-4.52 (m, O-**C**$\mathbf{H_2}$-Ph, maj and min), 4.89 (d, J= 8.2 Hz, **C4-H**, maj), 4.65 (d, J= 9.3 Hz, **C2-H**, maj and min), 4.26 (d, J= 12 Hz, O-**C**$\mathbf{H_2}$-Ph, maj), 4.18 d, J= 12 Hz, O-**C**$\mathbf{H_2}$-Ph, maj), 4.08 (dd, J= 9.3 and 8.2 Hz, **C3-H**, maj), 4.03-3.94 (m, **C3-H**, min and O-**C**$\mathbf{H_2}$-Ph, min), 3.83 (d, J= 11.52 Hz, C3-O-**C**$\mathbf{H_2}$-Ph, maj), 3.74 (d, J= 9.2 Hz, **F2-H**, maj), 3.59 (d, J= 11.52 Hz, C3-O-**C**$\mathbf{H_2}$-Ph, maj), 3.51-3.42 (m), 3.35 (d, J= 10.6 Hz), 3.26 (dd, J= 15.9 and 5.8 Hz, **F4-H**, maj), 3.21 (dd, J= 15.9 and 5.8 Hz, **F4-H**, min), 2.68 (dd, J= 16.4 and 10.1 Hz, **F4-H,** min), 2.54 (dd, J= 16.4 and 10.1 Hz, **F4-H**, min) ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer only) δ 157-153 (**C-A5, C-A7, CA-8a, C-D5, C-D7, C-D8a,** maj and min), 149-148 (**C-B3′, C-B4′, C-E3′, C-E4′,** maj and min), 138.5-1.36 (Bn **CqPh, maj and min**), 133.10, 132.60, 132.14, 131.56, 130-127 (Bn **Ar-H,** maj and min), 121.16, 120.53, 120.45, 119.58, 115.27, 114.81, 114.50, 114.33, 113.76, 113.11, 112.62, 112.01 (**C-D8**, min), 112.00 (**C-D8**, maj), 110.91, 110.77, 93.39 (**C-A8**, maj), 93.94 (**C-A8**, min), 93.28-93.27 (**C-A6,** maj and min), 93.10 (**C-D6**, min), 90.88 (**C-D6**, maj), 81.56 (**C-C2**, maj), 81.12 (**C-C2**, min), 80.80 (**C-F2**, maj)**,** 79.62 (**C-F2**, min), 79.21, 78.42, 75.52, 75.09, 74.41, 72.72, 72.42, 72-69 (Bn O-**C**$\mathbf{H_2}$-Ph), 36.52 (**C-C4**, min), 36.51 (**C-C4**, maj), 27.78 (**C-F4**, min**)**, 27.51 (**C-F4,** maj). HRMS (ESI): Calculated for $C_{100}H_{85}BrO_{12}$, $[M+NH_4^+]$= 1574.5563, found 1574.5579.

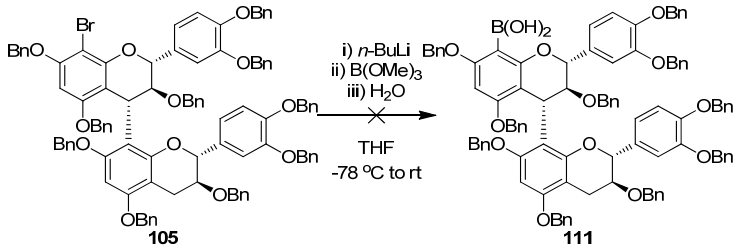
7.3.24 Scheme 38: (+)-catechin-4*α*-8-(+)-catechin 3 (3, Procyanidin B3).



Using the conditions specified by Tarascou *et al*,[39] 8Br-PBC-PBC **105** (0.199 g, 0.13 mmol), $Pd(OH)_2/C$ (200 mg), and Et_3N (180 μL, 1.3 mmol) in EtOAc/MeOH (3 mL, 3 mL) were stirred at room temperature under an atmosphere of H_2 for 20 hours. The solution was then filtered over celite and the filter cake washed with EtOAc (3*2 mL) and MeOH (3*2 mL). The resulting solution was then concentrated *in vacuo*. Filtration of the residue over silica gel (acetone/MeOH 95:5) and concentration afforded the native procyanidin as a yellow fluffy solid (56 mg, 76%). Melting pt. 216-221 ^oC (dec.), lit. 218-220 ^oC (dec.).[39] Optical rotation: $[\alpha]^{25}_D$= -218 (*c* 0.36, EtOH), lit. $[\alpha]^{24}_D$= -221 (*c* 0.38, EtOH).[31] ^1H and ^{13}C NMR data matched that reported by Saito *et al* [16, 31] for the title compound. The ^1H and ^{13}C NMR spectra of synthetic B3 (**3**) are displayed in Appendix 2-G.

6.4 Experimental procedures for chapter 4.

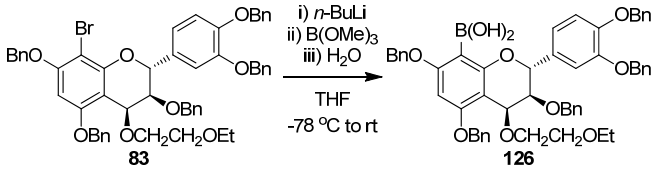
7.4.1 Scheme 4: Attempted formation of 3,5,7,3′,4′-penta-O-benzyl-catechin-8-boronic acid-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (111, 8B(OH)$_2$-PBC-PBC).



To a stirring solution of 8Br-PBC-PBC **105** (0.93 g, 0.6 mmol) in THF (25 mL) at -78 ^oC, *n*-BuLi (490 μL, 1.35 M in hexanes, 0.66 mmol, 1.1 equiv.) was added dropwise over 2 minutes and the resulting yellow solution was stirred at this temperature for 15 minutes. Neat $B(OMe)_3$ (135 μL, 1.2 mmol, 2 equiv.) was then added dropwise at this temperature over 5 minutes. The resulting mixture was then allowed to stir at this temperature for 1 hour, before being slowly warmed to 0 ^oC in the cold bath over 4 hours. Water (5 mL) was then added dropwise with stirring over 10 minutes before the mixture was poured into a stirring slurry of EtOAc (50 mL) and ice (*ca*. 50 g) and allowed to warm to room temperature over 30 minutes. The phases were then separated and the organics were washed sequentially with water (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated. TLC

analysis (EtOAc/Hexanes 1:2) of the residue showed only one product was obtained. ^{1}H NMR analysis of the crude residue suggested this product was PBC-PBC **68** and no evidence of any boronic acid formation was observed.

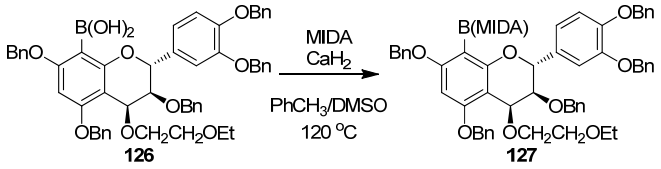
7.4.2 Scheme 9: 3,5,7,3′,4′-penta-O-benzyl-catechin-4*β*-(2-ethoxyethyl)ether-8-boronic acid (126, 8B(OH)$_2$-4EE-PBC).



To a stirring solution of 8Br-4EE-PBC **83** (2.23 g, 2.46 mmol) in THF (30 mL) at -78 ^{o}C, *n*-BuLi (1.8 mL, 1.50 M in hexanes, 2.7 mmol, 1.1 equiv.) was added dropwise over 2 minutes and the resulting yellow solution was stirred at this temperature for 15 minutes. Neat B(OMe)$_3$ (360 µL, 3.23 mmol, 1.3 equiv.) was then added dropwise at this temperature over 5 minutes. The resulting mixture was then allowed to stir at this temperature for 1 hour, before being slowly warmed to 0 ^{o}C in the cold bath over 4 hours. Water (5 mL) was then added dropwise with stirring over 10 minutes before the mixture was poured into a stirring slurry of EtOAc (100 mL) and ice (*ca*. 50 g) and allowed to warm to room temperature over 30 minutes. The phases were then separated and the organics were washed sequentially with water (30 mL) and brine (30 mL), then dried (Na_2SO_4), filtered and concentrated. Purification of the yellow residue by gradient silica chromatography (EtOAc/Hexanes 1:4 to 1:2) provided 1.11 g (52 %) of a white, foamy solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48-7.26 (m, 20H), 7.19-7.17 (m, 3H), 7.03-6.92 (m, 7H), 6.26 (s, 1H, **C6-H**), 5.34 (d, 1H, J= 10.2 Hz, **C2-H**), 5.22 (s, 2H, Ph- O-**CH$_2$**-Ph), 5.13-5.03 (m, 6H, 3 X Ph- O-**CH$_2$**-Ph), 4.85 (d, 1H, J= 3 Hz, C4-H), 4.21 (d, 1H, J= 12 Hz, C3-O-**CH$_2$**-Ph), 4.06 (d, 1H, J=12 Hz, C3-O-**CH$_2$**-Ph), 4.02 (m, 1H, C4-O-**CH$_2$CH$_2$**-OEt), 3.82 (m, 1H, C4-O-**CH$_2$CH$_2$**-OEt), 3.60 (dd, 1H, J= 10.2 Hz and 3 Hz, **C3-H**), 3.56 (m, 2H, C4-O-**CH$_2$CH$_2$**-OEt), 3.45 (q, 2H, J= 7.2 Hz, C4-OCH$_2$CH$_2$-O-**CH$_2$**CH$_3$), 1.16 (t, 3H, J= 7.2 Hz, C4-O-**C**H$_2$CH$_2$-O-CH$_2$**CH$_3$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.02, 160.75, 160.50, 149.15, 148.99, 137.44, 137.14, 137.03, 136.02, 135.28, 131.11, 130-126 (m, O-**CH$_2$**-Ph), 120.85, 114.95, 113.77, 104.99, 90.98 (**C6**), 78.08 (**C2**), 76.18 (**C3**), 71.83 (**C4**), 71.27, 71,22, 71.09, 70.80, 70.49, 69.83, 67.50, 66.34, 15.20 (C4-O-**C**H$_2$CH$_2$-O-CH$_2$**CH$_3$**). ^{11}B NMR (126 MHz,

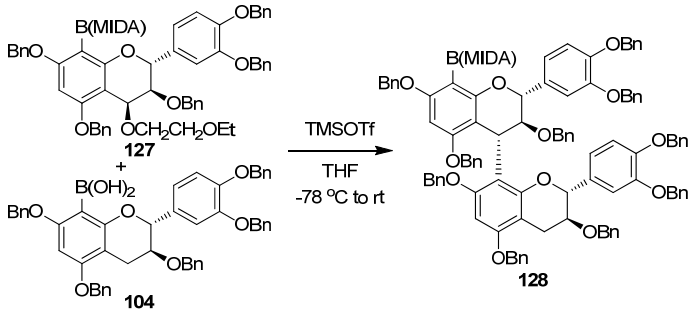
CD_3CN) δ 29.5. HRMS (ESI): Calculated for $C_{54}H_{53}BO_{10}$, [M+Na^+]= 895.3624, found 895.3627.

7.4.3 Scheme 9: 3,5,7,3′,4′-penta-O-benzyl-catechin-4*β*-(2-ethoxyethyl)ether-8-(*N*-methylimidodiacetyl)-boronate ester (127, 8B(MIDA)-4EE-PBC).



To a stirring solution of 8B(OH)$_2$-4EE-PBC **126** (1.11 g, 1.27 mmol) and *N*-methylimidodiacetic acid (0.38 g, 2.58 mmol, 2 equiv.) in toluene/DMSO (25 mL/2.5 mL) at room temperature, solid CaH_2 (0.53 g, 12.6 mmol, 10 equiv.) was added and the resulting mixture was stirred at this temperature for 5 minutes before being refluxed at 120 ^oC for 16 hours. The mixture was then cooled to room temperature and filtered over celite. The filter cake was washed with CH_2Cl_2 (3*10 mL) and the combined organics were washed with brine (4*50 mL), then dried (Na_2SO_4), filtered and concentrated. The residue was purified by SiO_2 chromatography (CH_2Cl_2, then CH_2Cl_2/Et_2O 90:10) to provide a white, amorphous solid (1.01 g, 80%)**.** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.26 (m, 20H), 7.20-7.19 (m, 4H), 7.00-6.93 (m, 4H), 6.17 (s, 1H, **C6-H**), 5.33 (d, 1H, J= J=10.8 Hz, **C2-H**), 5.19-4.98 (m ,8H, 4 X Ph-O-**CH_2**-Ph), 4.80 (br s, 1H, **C4-H**), 4.15 (dis m, 1H, C3-O-**CH_2**-Ph), 4.07 (dis m, 1H, C4-O-**CH_2CH_2**-OEt), 3.99 (dis m, 1H, C3-O-**CH_2**-Ph), 3.87 (dis m, 1H, C4-O-**CH_2CH_2**-OEt), 3.58 (dis m, 3H, **C3-H** and C4-O-**CH_2CH_2**-OEt), 3.5-3.30 (overlapping m, 6H, C4-O-**C**H_2CH_2-O-**CH_2**CH_3 and 2 X B(MIDA)-**CH_2**), 2.46 (s, 3H, B(MIDA)-N-**CH_3**), 1.17 (t, 3H, C4-O-**C**H_2CH_2-O-CH_2**CH_3**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.94 (B(MIDA)-**carbonyl**), 167.86 (B(MIDA)-**carbonyl**), 164.88, 159.74, 159.63, 148.67, 148.24, 137.59, 137.49, 137.22, 136.84, 136.47, 131.24, 130-126 (m, O-CH_2-**Ph**), 121.07, 114.43, 113.73, 104.53, 92.09 (**C6**), 75.42 (**C3**), 71.75 (**C2**), 71.09 (O-**CH_2**-Ph), 71.03 (2 X O-**CH_2**-Ph), 70.92 (**C4**), 70.26 (O-**CH_2**-Ph), 70.14 (O-**CH_2**-Ph), 69.85 (C4-O-**C**H_2CH_2-O-**CH_2**CH_3), 66.04 (2 X C4-O-**CH_2CH_2**-OEt), 62.98 (B(MIDA)-**CH_2**), 62.60 (B(MIDA)-**CH_2**). 46.91 (B(MIDA)-N-**CH_3**), 15.11 (C4-O**C**H_2CH_2-OCH_2**CH_3**). ^{11}B NMR (126 MHz, CD_3CN) δ 12.7. HRMS (ESI): Calculated for $C_{59}H_{58}BNO_{12}$, [M+Na^+]= 1006.3944, found 1006.3950.

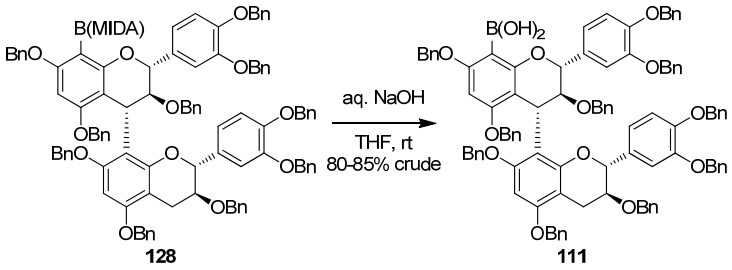
7.4.4 Scheme 11: 3,5,7,3′,4′-penta-O-benzyl-catechin-8-(*N*-methylimidodiacetyl)-boronate ester-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (128, 8B(MIDA)-PBC-PBC).



To a stirring solution of 8B(MIDA)-4EE-PBC **127** (0.61 g, 0.62 mmol) and PBC-$B(OH)_2$ **104** (0.55 g, 0.70 mmol) in THF (20 mL) at -78 ^oC, neat TMSOTf (130 µL, 0.72 mmol) was added dropwise at this temperature and stirring was continued at this temperature for 1 hour. The solution was then allowed to slowly warm in the cold bath to room temperature over 3 hours. Sat. aq. $NaHCO_3$ (5 mL) was added and the resulting mixture was stirred vigorously for 10 minutes and then extracted with EtOAc (2*20 mL). The combined organics were then sequentially washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated. Silica gel chromatography of the residue (CH_2Cl_2 then CH_2Cl_2/Et_2O 9:1) provided 0.95 g (94%) of a white, amorphous solid. ^1H NMR (600 MHz, $CDCl_3$, two rotamers: maj/min ~75:25) δ 7.53-7.12 (m, **Ar-H**, maj and min) 7.04-6.81 (m, **B, E-ring-H**, maj and min), 6.68 (s), 6.63 (d, J= 7.44 Hz, min) 6.59 (d, J= 7.44 maj), 6.22 (s, **D6-H**, min), 6.16 (s, **D6-H**, maj), 6.13 (s, **C6-H**, maj), 6.12 (s, **C6-H**, min), 5.36 (d, J= 12Hz, O-**CH_2**-Ph), 5.20-4.74 (m, O-**CH_2**-Ph overlapping with **C4-H**, maj and min), 4.65 (d, J= 11 Hz, O-**CH_2**-Ph, maj) 4.53 (d, J=11.0 Hz, O-**CH_2**-Ph), 4.40 (d, J= 9.3 Hz, **C2-H**, maj), 4.22 (d, J= 12.4 Hz, O-**CH_2**-Ph, maj and min), 4.14 (d, J= 12.4 Hz, O-**CH_2**-Ph, maj), 4.08 (overlapping dd, J= 9.2 Hz, **C3-H**, maj), 3.73 (d, J= 9.2 Hz, **F2-H**, maj), 3.47-3.19 (m, overlapping **F3-H, F-4H,** MIDA-**CH_2**, maj and min), 2.48 (dd, J= 15.9 and 9.9 Hz, **F4-H**, maj), 2.37 (s, MIDA-N-**CH_3**). ^{13}C NMR (125 MHz, $CDCl_3$, major isomer only) δ 167.9, 167.8 (2 X MIDA-**carbonyl**), 162.43, 160.94, 158.90, 155.16, 155.08, 153.88, 148.96, 148.75, 148.26, 147.96, 138.5-136 (Bn **CqPh**), 133.29, 131.65, 129-126 (Bn **Ar-H**), 120.70, 120.52, 114.47, 114.16, 112.59 (**C-A8**), 109.80, 104.09, 102.43, 93.88 (**C-A6**) , 91.73 (**C-D6**), 81.82 (**C-C2**), 80.73

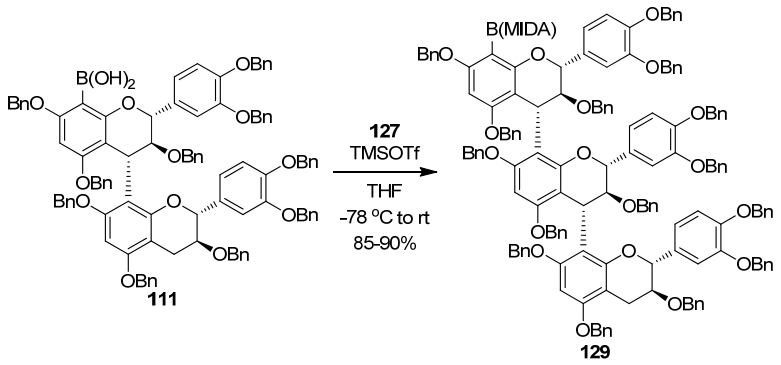
(**C-F2**), 79.23, 75,16, 74.13, 72.07, 71.3-69.8 (Bn O-**CH_2**-Ph), 63.15, 63.10 (2 X MIDA-**CH_2**), 46.86 (MIDA-N-**CH_3**), 36.66 (**C-C4**), 27.57 (**C-F4**). ^{11}B NMR (126 MHz, CD_3CN) δ 13.5. HRMS (ESI): calculated for $C_{105}H_{92}BNO_{16}$, $[M+Na^+]$= 1656.6401, found 1656.6409.

7.4.5 Scheme 12: 3,5,7,3′,4′-penta-O-benzyl-catechin-8-boronic acid-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (111, 8B(OH)$_2$-PBC-PBC).



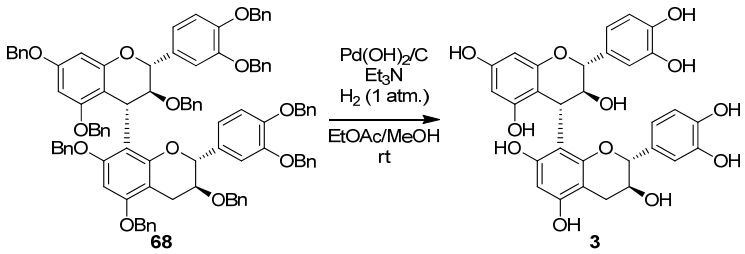
To a stirring solution of 8B(MIDA)-PBC-PBC **111** (0.389 g, 0.24 mmol) in THF (20 mL) at room temperature, dilute aq. NaOH (1 M, 4 mL) was added and the resulting mixture was vigorously stirred at this temperature under ambient atmospheric conditions for 2 hours. The reaction mixture was then poured into a mixture of pH=7 buffer (10 mL) and $CHCl_3$ (30 mL), stirred vigorously for 10 minutes and then the phases were separated. The aqueous phase was extracted with $CHCl_3$ (2*20 mL), then the combined organics were dried (Na_2SO_4), filtered and concentrated. Filtration of the residue over SiO_2 (EtOAc/Hexanes 1:2) provided 0.309 g (85%) of the crude free boronic acid as a yellow, foamy solid. HRMS: Calculated for $C_{100}H_{87}BO_{14}$, $[M+NH_4^+]$= 1540.6527, found 1540.6578.

7.4.6 Scheme 13: 3,5,7,3′,4′-penta-O-benzyl-catechin-8-(*N*-methylimidodiacetyl)-boronate ester -4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (129, 8B(MIDA)-PBC-PBC-PBC).



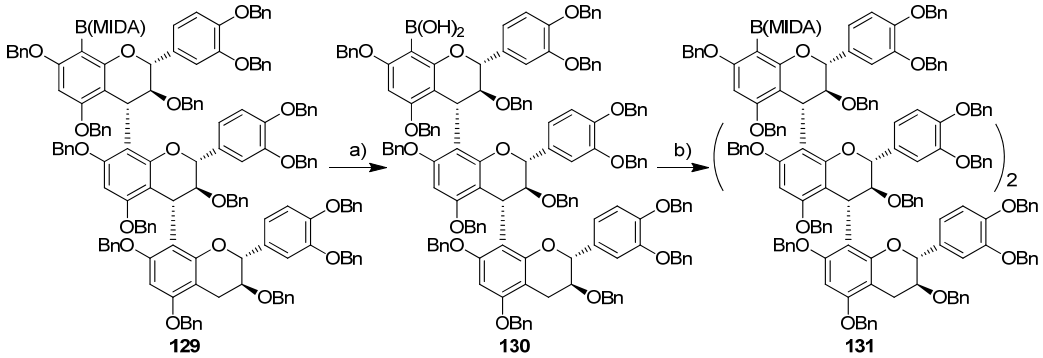
To the above crude boronic acid **111** (Section 6.3.5, 92 mg, 60 μmol), 8B(MIDA)-4EE-PBC **127** (52 mg, 53 μmol) was added and the mixture was dissolved with stirring in THF (3 mL), then cooled to -78 ^{o}C. Neat TMSOTf (11 μL, 61 μmol) was added dropwise and stirring was continued at this temperature for 1 hour. The solution was then allowed to slowly warm in the cold bath to room temperature over 3 hours. Sat. aq. $NaHCO_3$ (5 mL) was added and the resulting mixture was stirred vigorously for 10 minutes. The aqueous phase was extracted with EtOAc (2*20 mL). The combined organics were then sequentially washed with water (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated. Silica gel chromatography of the residue (CH_2Cl_2 then CH_2Cl_2/Et_2O 9:1) provided 113 mg (90%) of a white, amorphous solid. ^{1}H and ^{13}C NMR spectra shown in appendix 2-J1 and appendix J2-2. Selected ^{13}C resonances: 167.90, 167.88, (MIDA-**carbonyl**), 112.80, 112.56 (**C-A8** and **C-D8**), 63.29 (MIDA-**CH_2**), 46.99 (MIDA-N-**CH_3**), 36.70, 36.86 (**C-C4** and **C-F4**), unable to identify **C-I4** due to aliphatic impurities. ^{11}B NMR (126 MHz, CD_3CN) δ 13.7. HRMS: $C_{155}H_{134}BNO_{22}$, [M+NH_4^+]= 2389.9829, found, 2389.9872.

7.4.6 Scheme 14: Procyanidin B3 (3). Debenzylation of dimer 68 (PBC-PBC).



Debenzylation of dimer **68** (PBC-PBC, 64 mg, 43μmol) using the same conditions for the debenzylation of dimer **105** (Section 6.3.25) provided a pure sample of natural procyanidin B3 (**3**). ^{1}H and ^{13}C NMR data matched that for the same compound synthesised in Section 7.3.25.

7.4.8 Scheme 15: Attempted formation of 3,5,7,3′,4′-penta-O-benzyl-catechin-8-(*N*-methylimidodiacetyl)-boronate ester-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (131, 8B(MIDA)-PBC-PBC-PBC-PBC).



Conditions: a) aq. NaOH, THF, rt, 75-79% crude, b) **127**, TMSOTf, THF, -78 °C to rt.

Using the same procedure as described above (Section 7.4.5), MIDA deprotection of 8B(MIDA)-PBC-PBC-PBC **129** (113 mg, 41 μmol) using dilute aq. NaOH (1 M, 1 mL) afforded 74 mg (79 %) of the crude boronic acid 8B(OH)2-PBC-PBC-PBC **130** after filtration over silica gel (EtOAc/Hexane 1:2).

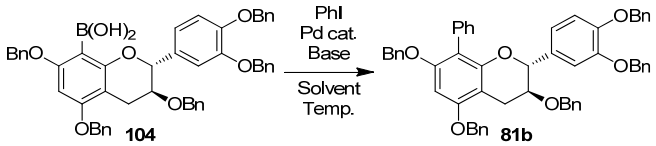
This crude boronic acid was coupled to 8B(MIDA)-4EE-PBC **127** (21 mg, 21 μmol) using TMSOTf (4.2 μl, 2.2 μmol) using the same procedure for the coupling described in section 6.4.6. Silica gel chromatography of the residue (CH_2Cl_2 then CH_2Cl_2/Et_2O 9:1) afforded 50 mg (75 %) of a white, amorphous solid assumed to be the tetramer by TLC analysis (EtOAc:Hexanes 1:2), R_f= 0.15. ^{1}H, ^{13}C and ^{11}B NMR

experiments were inconclusive for the identity of the isolated product and HRMS results were not sufficient accurate to identify the isolated product as the title compound.

The above procedure was repeated using 22 mg (22 μmol) of 8B(MIDA)-4EE-PBC **127** and 61 mg (27 μmol) of crude 8B$(OH)_2$-PBC-PBC-PBC **130**. In this case, no spot developed at R_f= 0.15 (EtOAc/Hexanes 1:2), which suggested no tetramer product had formed. The reaction was quenched and extracted according to the method of Section 7.4.6. ^{1}H NMR analysis of the crude reaction mixture suggested uncontrolled oligomerisation had taken place.

7.5 Experimental procedures for chapter 5.

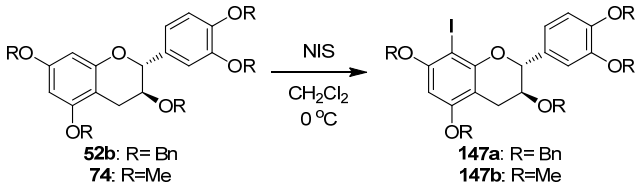
7.5.1 Scheme 9, Table 1: 8-phenyl-3,5,7,3′,4′-penta-O-benzyl-catechin (81b, 8Ph-PBC). General method for the cross-coupling of PBC-B$(OH)_2$ 104 to iodobenzene (PhI).



A stirring mixture of PBC-B$(OH)_2$ **104** (*ca*. 100 mg, 0.13 mmol), the specified catalyst (3 mol%), and the quoted base (4 equivalents) in the organic portion of the stated solvent (5 mL) was prepared at room temperature. Iodobenzene (11 μL, 0.1 mmol) was then added *via.* syringe, followed by water (2 mL) if stated in Table 1. The mixture was then stirred at the specified temperature for 20-24 hours, then cooled to room temperature and sat. aq. NH_4Cl (10 mL) was added. The aqueous phase was then extracted with CH_2Cl_2 (3*10 mL) and the combined organics were dried (Na_2CO_3), filtered and concentrated. The foamy residue was then submitted to repeated SiO_2 chromatography (EtOAc/Hexanes 1:9 to 1:4) until a foamy, white solid was obtained with >95% purity by ^{1}H NMR in the yields stated according to Table 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.20 (m, 30H), 7.00-6.80 (m, 3H), 6.35 (s, 1H, **C6-H**), 5.17 (s, 2H), 5.08 (s, 2H), 5.03 (s, 2H), 4.96 (s, 2H), 4.88 (d, 1H, J= 7.3 Hz, **C2-H**), 4.39 (d, 1H, J= 12Hz, C3- O-**CH_2**-Ph), 4.27 (d, 1H, J= 12Hz, C3- O-**CH_2**-Ph), 3.73 (m, 1H, **C3-H**), 3.06 (dd, 1H, J= 16.5 and 5.4 Hz, **C4-H**), 2.83 (dd, 1H, J= and 8 Hz, **C4-H**). ^{13}C NMR (100 MHz) δ 156.35, 155.44, 152.32, 148.73,

148.38, 138.10, 137.35, 137.35, 137.07, 133.98, 132.65, 131.34, 130-126 (m), 126.30, 119.89, 114.76, 113.35 (**C8**), 113.04, 103.18, 92.65 (**C6**), 79.06 (**C2**), 74.60 (**C3**), 71.46, 71.37, 71.26, 71.11, 70.09, 25.78 (**C4**). HRMS (ESI): Calculated for $C_{56}H_{48}O_6$, $[M+NH_4^+]$= 834.3789, found 834.3788.

7.5.2 Scheme 11: 8-iodo-3,5,7,3′,4′-penta-O-benzyl-catechin (147a, I-PBC).

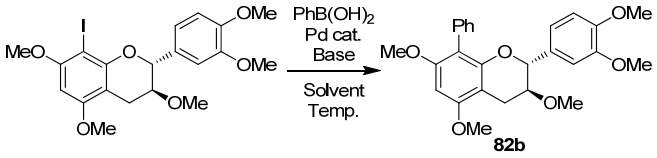


To a stirring solution of PBC **52b** (2.03 g, 2.74 mmol) in CH_2Cl_2 (35 mL) at 0 °C, NIS (0.68 g, 3.00 mmol) was added as a solid all at once. Stirring was continued at this temperature for 4 hours before a solution of $Na_2S_2O_3.5H_2O$ (0.5 g in 20 mL H_2O) was added and the resulting mixture was stirred vigorously at room temperature for 15 minutes. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (2*20 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. The white, foamy residue was then purified by filtration over silica gel (CH_2Cl_2) to give 2.29 g (96%) of a white, foamy solid. ^1H and ^{13}C NMR spectra corresponded with that reported by Tarascou *et al* for the title compound.[39]

7.5.3 Scheme 11: 8-iodo-3,5,7,3′,4′-penta-O-methyl-catechin (147b, I-PMC).

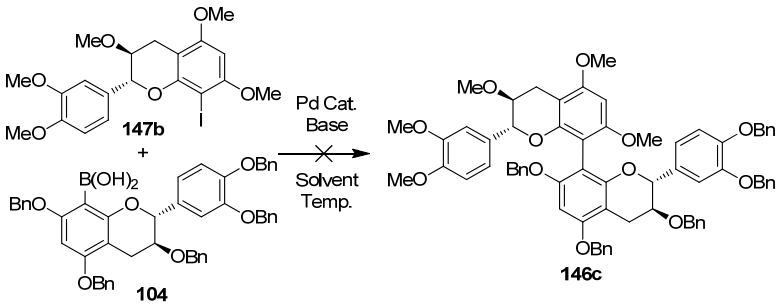
I-PMC **147b** was prepared from PMC **74** (5.02 g, 14.5 mmol) and NIS (3.56 g, 15.8 mmol) using the same procedure for the synthesis of I-PBC **147a** (Section 7.5.2). The product was purified by filtration over silica gel (CH_2Cl_2 then CH_2Cl_2/Et_2O 95:5), which provided 6.97 g (99%) of a white, crystalline solid. The ^1H and ^{13}C NMR spectra of the product corresponded with that reported by Kiehlmann *et al* for the title compound.[110]

7.5.4 Scheme 13, Table 2: 8-phenyl-3,5,7,3′,4′-penta-O-methyl-catechin (82b, 8Ph-PMC). General method for the coupling of I-PMC 147b to Ph-B(OH)$_2$ 148.



A 10 mL round bottom flask was charged with I-PMC **147b** (100 mg, 0.21 mmol), Ph-$B(OH)_2$ **148** (50 mg, 0.41 mmol, 2 equivalents) the specified catalyst (5 mol%), and if anhydrous base was employed, the specified base (4 equivalents). The flask was evacuated, and then filled with N_2. The organic portion of the specified solvent (5 mL) was added and the mixture stirred vigorously until all I-PMC **147b** dissolved. If aqueous base (4 equivalents) was employed, it was then added at this point as a solution in water (2 mL). The resulting mixtures were then stirred overnight at the specified temperature for 16-24 hours, and then cooled to room temperature. Sat. aq. NH_4Cl (5 mL) and EtOAc (20 mL) were then added and the mixture was vigorously stirred for 15 minutes, then the phases were separated. The organics were washed sequentially with sat. aq. K_2CO_3 (20 mL), water (20 mL) and brine (20 mL). The organics were then dried (Na_2SO_4), filtered and concentrated. The residues were purified by SiO_2 chromatography (CH_2Cl_2 then CH_2Cl_2/Et_2O 95:5) to provide a white, foamy solid in the yields specified in Table 2. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 6.87-6.78 (m, 3H), 6.25 (s, 1H, **C6-H**), 4.89 (d, 1H, J= 6.7 Hz, **C2-H**), 3.89 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.62 (m, 1H, **C3-H**), 3.29 (s, 3H), 2.97 (dd, 1H, J= 16.5 and 5.1 Hz, **C4-H**), 2.72 (dd, 1H, J= 16.5 and 7.3 Hz, **C4-H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.42, 156.51, 152.07, 148.63, 148.32, 134.05, 131.91, 131.23, 127.37, 126.25, 118.74, 111.59, 110.75 (**C8**), 109.60, 101.76, 88.56 (**C6**), 78.52 (**C2**), 76.69 (**C3**), 57.21, 56.11, 55.81, 55.75, 55.43, 24.32 (**C4**). HRMS (ESI): Calculated for $C_{26}H_{28}O_6$, $[M+H^+]$= 437.1959, found 437.1958.

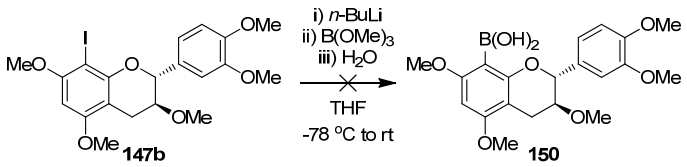
7.5.5 Scheme 14, Table 3: Attempted formations of 3,5,7,3′,4′-penta-O-methyl-catechin-8→8-3,5,7,3′,4′-penta-O-benzyl-catechin (8-8 dimer 146b). General method for the attempted coupling of PBC-$B(OH)_2$ 104 to I-PMC 147b.



A 25 mL round bottom flask was charged with I-PMC **147b** (50 mg, 0.10 mmol), PBC-$B(OH)_2$ **104** (150 mg, 0.20 mmol, 2 equivalents), the specified catalyst (5

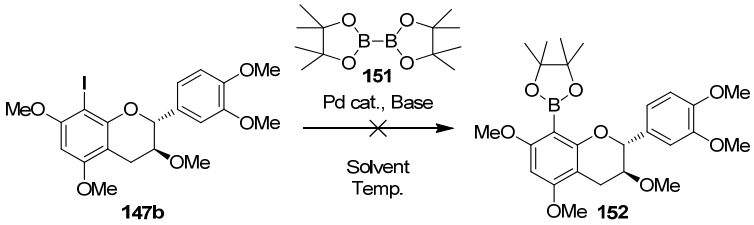
mol%), and if anhydrous base was employed, the stated base (4 equivalents). The flask was evacuated, and then filled with N_2. The organic portion of the specified solvent (10 mL) was then added and the mixture stirred vigorously until the I-PMC **147b** and PBC-B(OH)$_2$ **104** completely dissolved. If aqueous base (4 equivalents) was employed, it was added at this point as a solution in water (2 mL). The resultant mixture was then stirred at the specified temperature from 24 hours up to 4 days, and then cooled to room temperature. The reaction mixture was then poured into a stirring mixture of sat. aq. NH_4Cl (5 mL) and EtOAc (20 mL) and vigorously stirred for 15 minutes. The phases were then separated. The organics were washed sequentially with water (20 mL) and brine (20 mL), and then dried (Na_2SO_4), filtered and concentrated. ^{1}H and ^{13}C NMR analysis of the crude residues confirmed that only PBC **52b** and varying proportions of I-PMC **147b** and PMC **74** were present in all cases.

7.5.6 Scheme 18: Attempted formation of 3,5,7,3′,4′-penta-O-methyl-catechin-8-boronic acid (150, PMC-B(OH)$_2$).



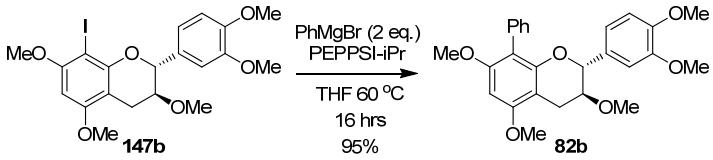
To a stirring solution of I-PMC **147b** (250 mg, 0.51 mmol) in THF (25 mL) at -78 ^{o}C, *n*-BuLi (370 µL, 1.52 M, 0.56 mmol) was added dropwise at this temperature and the resulting yellow solution was stirred at this temperature for 15 minutes. Neat B(OMe)$_3$ (115 µL, 1.03 mmol) was then added dropwise with stirring over 2 minutes and stirring was continued at -78 ^{o}C for 1 hour. The mixture was then allowed to warm in the cold bath to 0 ^{o}C over 3 hours. The resulting mixture was then poured into a slurry of EtOAc (50 mL) and ice/water (50 mL) and stirred vigorously for 30 minutes. The phases were then separated and the organics were sequentially washed with water (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue showed mostly PMC **74** and a small amount of another product tentatively assigned as the title compound. Silica gel chromatography (CH_2Cl_2 then CH_2Cl_2/Et_2O 90:10) provided mostly PMC **74**. Insufficient quantities of the other product were isolated to allow for characterisation of this species.

7.5.7 Scheme 20, Table 4: Attempted formation of 3,5,7,3′,4′-penta-O-methyl-catechin-8(pinacolato)boronate ester (152, PMC-B(OPin)$_2$). General method for the attempted couplings of I-PMC 147b to bis(pinacolato)diboron 151 ((B-pin)$_2$).



To a stirring solution of I-PMC **147b** (100 mg, 0.21 mmol) and bis(pinacolato)diboron **151** (105 mg, 0.41 mmol, 2 equivalents) in the specified solvent (5-10 mL), the specified base (3 equivalents) was added either as a solid or *via*. syringe when Et_3N was employed. The stated catalyst (5 mol%) was then added and the resulting mixtures were stirred at the specified temperature for 24-72 hours. After cooling to room temperature, the reaction mixtures were poured into a mixture of EtOAc (20 mL) and H_2O (20 mL) and stirred vigorously for 10 minutes. The phases were separated and the organics were sequentially washed with water (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated. The crude residues obtained were analysed by ^{1}H NMR. These spectra showed the crude mixtures contained only unreacted **151** ((B-pin)$_2$) and varying proportions of staring I-PMC **147b** and PMC **74** with no evidence of any formation of the title compound.

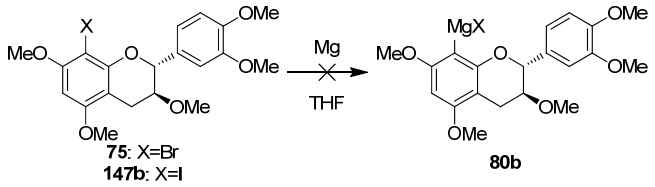
7.5.8 Scheme 23: 8-phenyl-3,5,7,3′,4′-penta-O-methyl-catechin (82b, 8Ph-PMC). Kumada coupling of I-PMC 147b with PhMgBr.



To a stirring solution of I-PMC **147b** (103 mg, 0.21 mmol) and PEPPSI-IPr (7 mg, 0.01 mmol, 5 mol%) in THF (5 mL) at room temperature, PhMgBr (210 μL, 0.42 mmol, 2 equivalents) was added dropwise. Upon addition of the Grignard reagent, the initial yellow solution turned a dark red. The resulting red solution was stirred at 60 ^{o}C for 16 hours. After cooling to room temperature, sat. aq. NH_4Cl (10 mL) was added and the mixture was vigorously stirred for 10 minutes. The aqueous phase was

then extracted with CH_2Cl_2 (3*10 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated. The residue was filtered over SiO_2 (CH_2Cl_2 then CH_2Cl_2/Et_2O 95:5) to provide 87 mg (95%) of a white, foamy solid that showed the same ^1H and ^{13}C NMR spectral properties as that reported for the title compound synthesised previously (Section 7.5.4).

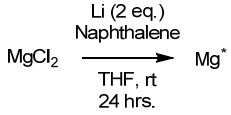
7.5.9 Scheme 25: 3,5,7,3′,4′-penta-O-methyl-catechin-8-magnesium halide (80b, PMC-8MgX). Representative procedures for the attempted Mg insertion of Br-PMC 75/I-PMC 147b.



Magnesium turnings (144 mg, 5.9 mmol), dried in at 100 ^oC for at least a week, were cooled to room temperature *in vacuo*. The turning were then activated by the addition of a few drops of 1,2-dibromoethane and the suspension was briefly heated to 60 ^oC for 5 minutes, then cooled to room temperature. To this suspension, a solution of Br-PMC **75** (2.43 g, 5.5 mmol) in THF (30mL) was added *via*. cannular and a few crystals of iodine were added. The mixture was heated without stirring to 60 ^oC for 30 minutes, over which time the red iodine colour remained, suggesting no Mg insertion had begun. The solution was then refluxed with stirring at 80 ^oC for 24 hours. After this time, no Mg had been consumed and ^1H NMR of an aliquot of solution showed only starting Br-PMC **75** was present.

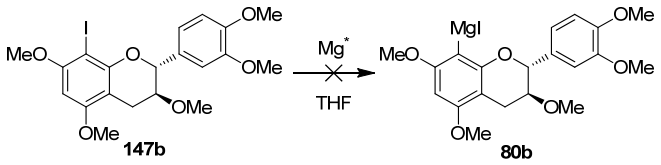
Magnesium turnings (29 mg, 1.19 mmol), were activated by the above procedure. To the Mg suspension, a solution of I-PMC **147b** (0.51g, 1.04 mmol) in THF (8 mL) was added *via*. cannular and a few crystals of iodine were added. The resulting suspension was then sonicated for 4 hours, with the sonicator water bath being maintained at 25-30 ^oC. After this time, little Mg had been consumed. The reaction mixture was then filtered to remove the Mg turnings and sat. aq. NH_4Cl (10 mL) was added to the filtrate. The resulting mixture was extracted with CH_2Cl_2 (2*10 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. ^1H NMR analysis of the crude reaction mixture showed the starting I-PMC **147b** was recovered as the major constituent, along with a trace amount of PMC **74**.

7.5.10 Scheme 26: "Rieke" magnesium from reduction of $MgCl_2$.



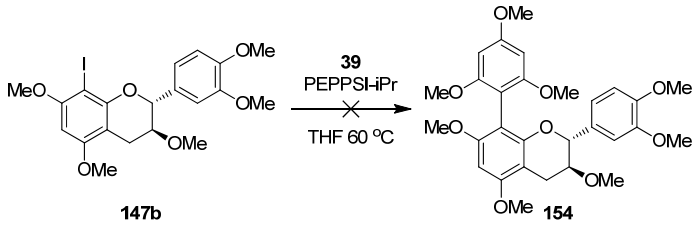
To a stirring suspension of anhydrous $MgCl_2$ (548 mg, 5.76 mmol) and naphthalene (160 mg, 1.25 mmol) in THF (20 mL), lithium metal (80 mg, 11.5 mmol) was added as small *ca*. 5 mg pieces. The resulting black slurry was then stirred vigorously for 24 hours to provide a black suspension of "Rieke" magnesium. This Mg suspension was then used with no further modifications.

7.5.11 Scheme 26: Attempted formation of 3,5,7,3′,4′-penta-O-methyl-catechin-8-magnesium iodide (80b, PMC-8MgI) using "Rieke" magnesium.



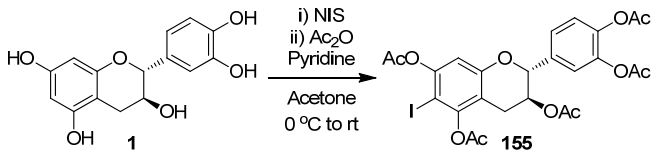
To a stirring solution of I-PMC **147b** (0.99 g, 2.1 mmol) in THF (15 mL), an aliquot of the "Rieke" magnesium suspension (18 mL, 4.1mmol, 2 equivalents) prepared as above (section 6.5.10) was added *via*. syringe. The resulting black slurry was stirred for 24 hours at room temperature. An aliquot (200 μL) was then removed and quenched by the addition of sat. aq. NH_4Cl (2 mL). The aqueous phase was then extracted with CH_2Cl_2 (10 mL) and the organics were dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of this aliquot showed only starting I-PMC **147b** and naphthalene were present. The remaining mixture was then sonicated at 30 ^oC for 6 hours and then a further aliquot (200 μL) was removed, then quenched and extracted as above. ^{1}H NMR analysis of this aliquot also showed only I-PMC **147b** and naphthalene. The remaining mixture was then refluxed at 80 ^oC for 24 hours, cooled to room temperature and then quenched and extracted as above. ^{1}H NMR analysis of the crude residue showed only starting I-PMC **147b** and naphthalene were present, confirming no Mg insertion had occurred.

7.5.12 Scheme 27: 8-2,4,6-trimethoxyphenyl-3,5,7,3′,4′-penta-O-methyl-catechin 154. Attempted Negishi cross-coupling of TMB-MgBr 39 to I-PMC 147b.



To a stirring solution of I-PMC **147b** (0.11 g, 0.23 mmol) and PEPPSI-IPr (16 mg, 0.02 mmol, 10 mol%) in THF (5 mL), an aliquot of a pre-prepared solution of **39** (550 µL, 0.83M in THF, 0.46 mmol, 2 equivalents, section 7.2.9) was added *via.* Syringe. The resulting solution was then stirred at 60 °C for 48 hours. The mixture was then cooled to room temperature and quenched by the addition of sat. aq. NH_4Cl (20 mL). The aqueous phase was then extracted with CH_2Cl_2 (2*20 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated. ^1H NMR of the crude residue showed no trace of any coupling product **154**. A combination of TMB **33**, starting I-PMC **147b** and PMC **74** were observed as the major constituents of the reaction mixture.

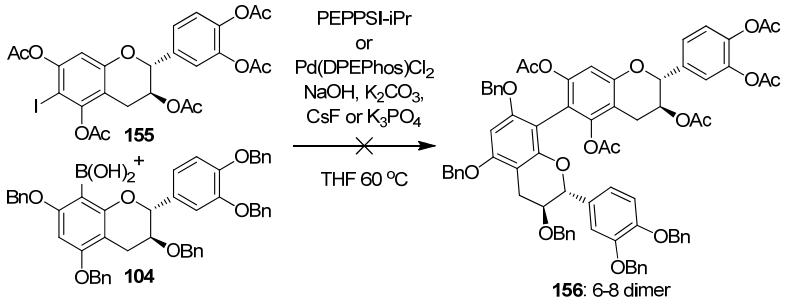
7.5.13 Scheme 28: 6-iodo-3,5,7,3′,4′-penta-O-acetyl-catechin (155, 6I-PAC).



To a stirring solution of (+)-catechin **1** (2.01 g, 6.92 mmol) in reagent grade acetone (30 mL) at 0 °C, NIS (1.60 g, 7.11 mmol) was added all at once and stirring was continued at this temperature for 1 hour. Neat anhydrous Ac_2O (2 mL) was added, followed immediately by neat pyridine (2 mL) *via*. syringe and the resulting mixture was stirred at 0 °C for 1 hour before being allowed to slowly warm to room temperature in the ice bath overnight. The resulting solution was then poured into a mixture of EtOAc (200 mL) and dilute HCl (1M, 200 mL) and then vigorously stirred for 15 minutes. The phases were then separated and the organic phase was sequentially washed with dilute HCl (1M, 100 mL), water (100 mL) and brine (100 mL), then dried (Na_2SO_4), filtered and concentrated. The orange/red residue was

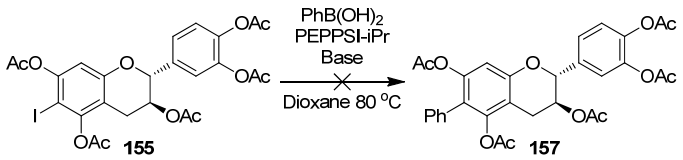
filtered over SiO_2 (CH_2Cl_2/Et_2O 9:1) to provide 4.12 g (95%) of a white, crunchy solid after concentration. ^1H and ^{13}C NMR of the product corresponded with that reported by Kiehlmann *et al* for the title compound.[110]

7.5.14 Scheme 29: 3,5,7,3′,4′-penta-O-acetyl-catechin-6→8-3,5,7,3′,4′-penta-O-benzyl-catechin (156). General method for the attempted coupling of 6I-PAC 155 to PBC-B(OH)$_2$ 104.



A 25 mL round bottom flask was charged with 6I-PAC **155** (100 mg, 0.16 mmol), PBC-B(OH)$_2$ **104** (250 mg, 0.32 mmol, 2 equiv.), base (4 equiv.) and catalyst (5 mol%) and then evacuated for 15 minutes at *ca*. 0.1 Torr. An N_2 atmosphere was introduced, and THF (10 mL) was added and the mixture was stirred until all the constituents other than the base dissolved. The mixture was then warmed to 60 ^oC and stirred 24 hours at this temperature before being cooled to room temperature. The reaction was then quenched by the addition of sat. aq. NH_4Cl (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (3*20 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated. In all cases, ^1H NMR analysis of the crude residues showed a complex mixture of products with no evidence of any coupling product.

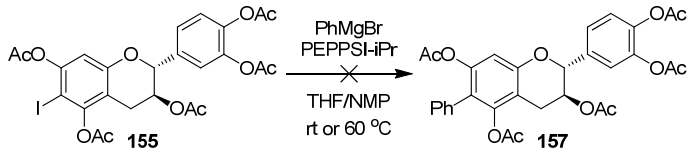
7.5.15 Scheme 30: 6-phenyl-3,5,7,3′,4′-penta-O-acetyl-catechin (157, 6Ph-PAC). General method for the attempted coupling of 6I-PAC 155 to Ph-B(OH)$_2$ 148.



A 25 mL round bottom flask was charged with 6I-PAC **155** (100 mg, 0.16 mmol), Ph-B(OH)$_2$ **148** (40 mg, 0.33 mmol, 2 equiv.), base (4 equiv.) and PEPPSI-IPr (5 mg,

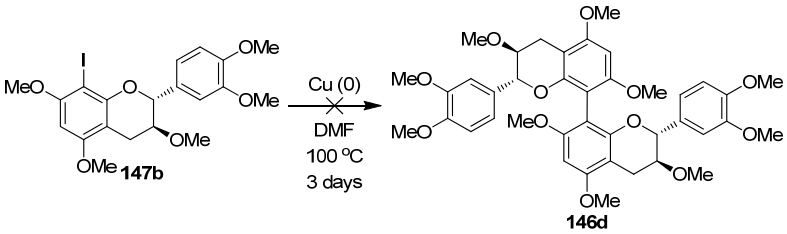
5 mol%) and then evacuated for 15 minutes at *ca*. 0.1 Torr. An N_2 atmosphere was introduced, and dioxane (10 mL) was added and the mixture was stirred until all the constituents other than the base dissolved. The mixture was then warmed to 80 ^oC and stirred at this temperature for 24 hours before being cooled to room temperature. The reaction was then quenched by the addition of sat. aq. NH_4Cl (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (3*20 mL) and the combined organics were then dried (Na_2SO_4), filtered and concentrated. In all cases, ^1H NMR analysis of the crude residues showed little or no evidence of any coupling product.

7.5.16 Scheme 31: 6-phenyl-3,5,7,3′,4′-penta-O-acetyl-catechin (157, 6Ph-PAC). General method for the attempted coupling of 6I-PAC 155 to PhMgBr.



To a stirring solution of 6I-PAC **155** (100 mg, 0.16 mmol) and PEPPSI-IPr (5 mg, 5 mol%) in THF/NMP (5 mL/ 5 mL) at room temperature, PhMgBr (320 µL, 1M in THF, 0.32 mmol, 2 equiv.) was added dropwise. The resulting red solution was stirred at 60 ^oC for 24 hours before being cooled to room temperature. Sat. aq. NH_4Cl (10 mL) was then added with stirring. The resulting mixture was extracted with CH_2Cl_2 (3*20 mL) and the combined organics were then dried (Na_2SO_4), filtered and concentrated. ^1H NMR analysis of the crude residue showed no evidence of any cross-coupled product.

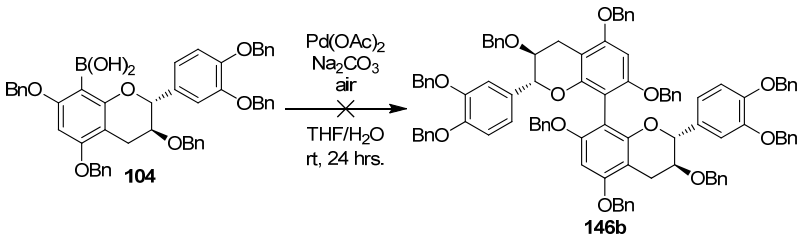
7.5.17 Scheme 32: 3,5,7,3′,4′-penta-O-methyl-catechin-8→8-3,5,7,3′,4′-penta-O-methyl-catechin 146d. Attempted Copper (0) promoted homo-coupling of I-PMC 147b.



A 10 mL flask was charged with I-PMC **147b** (100 mg, 0.21 mmol) and copper powder (140 mg, 2.2 mmol, 10 equiv.) and then evacuated for 15 minutes at *ca*. 0.1

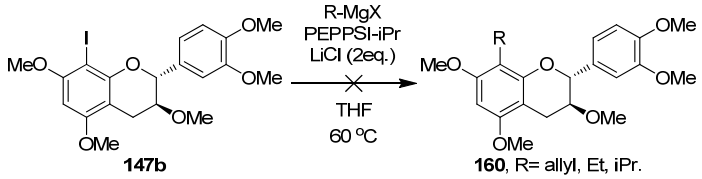
Torr. An N_2 atmosphere was then introduced, and anhydrous DMF (5 mL) was added and the mixture stirred at 100 ^oC for 3 days. The mixture was then cooled to room temperature and filtered over celite. The filter cake was washed with CH_2Cl_2 (2*10 mL) and the combined organics were washed with brine (5*20 mL), then dried (Na_2SO_4), filtered and concentrated. ^1H and ^{13}C NMR analysis of the crude residue showed no evidence of any coupling product. Only PMC **74** from deiodination of the starting I-PMC **147b** was recovered.

7.5.18 Scheme 33, Table 5: 3,5,7,3′,4′-penta-O-benzyl-catechin-8→8-3,5,7,3′,4′-penta-O-benzyl-catechin 146b. General method for the attempted homo-couplings of 104.



A 25 mL round bottom flask was charged with PBC-$B(OH)_2$ **104** (100 mg, 0.13 mmol), the specified quantity of Pd. oxidant and, if stated, PPh_3 or CuCl (2 equiv.). The flask was evacuated for 10 minutes, and then Ar was introduced. The organic solvent (10 mL) was then added and the mixture was vigorously stirred until all the solid materials dissolved. If required, the specified base (2 equiv.) was added at this point; either as a solid or as a solution in water (5 mL). The resulting mixtures were stirred at the specified temperatures for 24 hours, and then cooled to room temperature if required. Sat. aq. NH_4Cl (10 mL) was added and the resulting mixtures were vigorously stirred for 10 minutes, then extracted with CH_2Cl_2 (3*10 mL). The combined organics were then dried (Na_2SO_4), filtered and concentrated. ^1H NMR analysis of the crude residues in all cases showed PBC **52b** as the sole product.

7.5.18 Scheme 35: 8-ethyl-3,5,7,3′,4′-penta-O-methyl-catechin (160, 8Et-PMC). Representative procedure for the attempted cross-couplings of I-PMC 147b with alkyl Grignard reagents.



To a stirring solution of I-PMC **147b** (100 mg, 0.21 mmol) and PEPPSI-IPr (7 mg, 5 mol%) and LiCl (18 mg, 0.43 mmol) in THF (5 mL), EtMgBr (420 μL, 1M in THF, 0.42 mmol) was added dropwise over 2 minutes. The resulting red solution was then stirred at 60 ^{o}C for 24 hours, before being cooled to room temperature. The mixture was then poured in to sat. aq. NH_4Cl (10mL) and EtOAc (20 mL) and stirred vigorously for 10 minutes. The phases were then separated. The organic phase was washed with brine (2*10 mL), then dried (Na_2SO_4), filtered and concentrated. ^{1}H and ^{13}C NMR analysis of the crude residue showed PMC **74** as the principal constituent.

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Appendices.

Appendix 1: Manuscripts in preparation for publication.

Appendix 2: ^{1}H, ^{13}C and ^{11}B NMR for new compounds.

Biaryls and diarylmethanes: Phloroglucinol adducts via Pd(DPEPhos)Cl_2-catalyzed Negishi cross-couplings.

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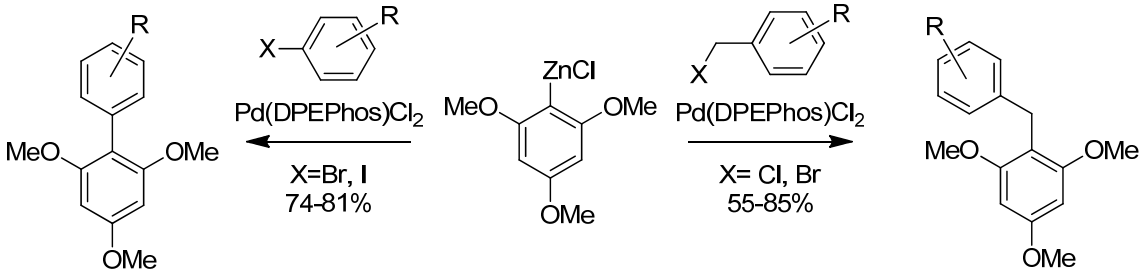
Expected journals of submission: Organic Letters or Tetrahedron

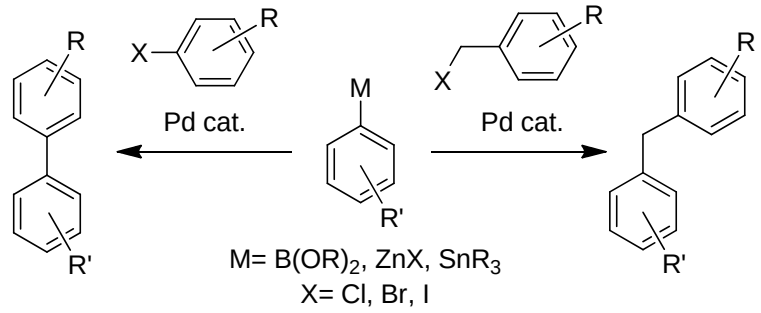
Abstract:

Several functionalized biaryls and diarylmethanes containing the phloroglucinol subunit were synthesized in 55-85% yields using Negishi cross-couplings of 2,4,6-trimethoxyphenylzinc chloride with aryl and benzyl halides in the presence of catalytic quantities of Pd(DPEPhos)Cl_2. These simple to prepare couplings were generally complete in 1-24 hours depending on the halide, and are applicable to aryl and benzyl halides containing both electron-donating and electron-withdrawing groups.



Biaryls and diarylmethanes continue to be seen as fundamental motifs in organic synthesis,[1] industrial processes [2] and medicinal chemistry.[3] Given their significance, the synthesis of such compounds has received great attention.[1,4] The palladium-catalyzed cross-coupling of aryl or benzyl halides with arylmetallic species has become an increasingly important and popular method for the synthesis of these structural motifs (Scheme 1). The Suzuki method,[5] involving the use of arylboronic acids and/or boronate esters, is perhaps the most popular method and has been widely used for both biaryl [6] and diarylmethane [7] syntheses. Stille [8] and Negishi [9] protocols have also been applied to the separate formation of both substructures. However, the use of a single method for the preparation of both types of derivatives was considered for further development.

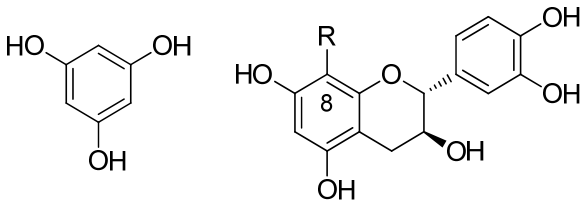
Scheme 1: Palladium-catalyzed cross-couplings of arylorganometallic derivatives with aryl and benzyl halides.



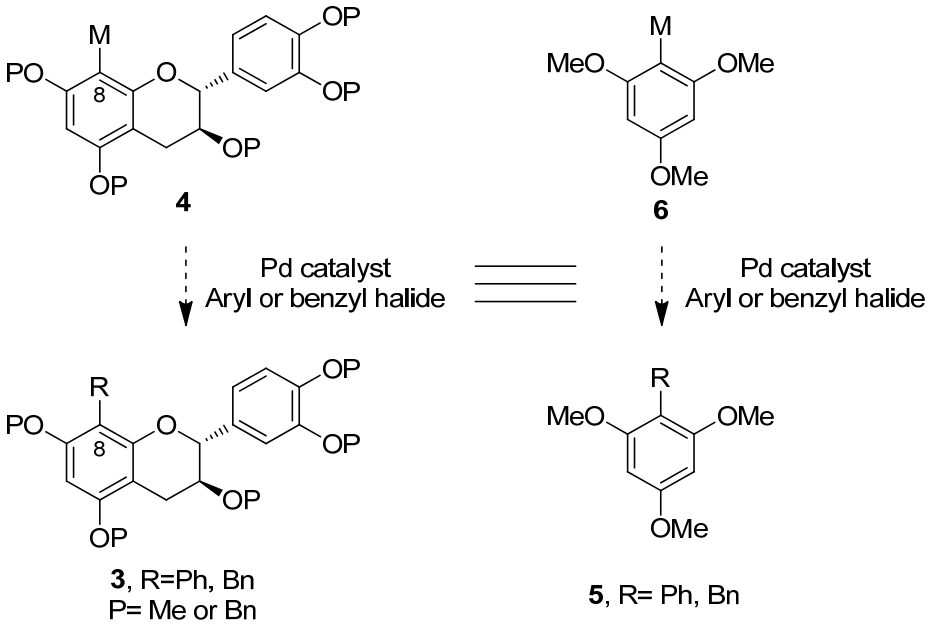
Of particular interest was the synthesis of biaryl and diarylmethane derivatives containing the 1,3,5-trimethoxyphenyl (TMP) subunit. This subunit is a useful protected precursor to phloroglucinol **1** (Figure 1), a commonly occurring unit in many natural products,[10] including tannins or proanthocyanidins.[11] One subgroup of such proanthocyanidins are the C8-substituted catechin derivatives **2** (Figure 1). Access to substituted catechins has received increased attention over the last decade in order to gain some insight into structure-activity relationships of these compounds.[12] In particular, the biological properties of these molecules, which include antioxidant [13] and anticancer [14] activities, have been of great interest in this field of study.

Access to a variety of protected C8-phenyl- and C8-benzyl-substituted catechin derivatives **3** using a C8-metallated moiety **4** in Pd-catalyzed cross-coupling procedures presented an interesting pathway towards the synthesis of these compounds. Given the complexity of the catechin derivative, cross-couplings of the 1,3,5-trimethoxyphenyl subunit were screened as a model system to establish the potential of such a pathway (Scheme 2). Accordingly, the synthesis of phenyl- and benzyl-substituted trimethoxybenzenes **5** were targeted through the development of suitable cross-couplings of metallated2,4,6-trimethoxyphenyl derivatives **6** with aryl and benzyl halides.

Figure 1: Phloroglucinol 1 and C8-substituted (+)-catechin 2.

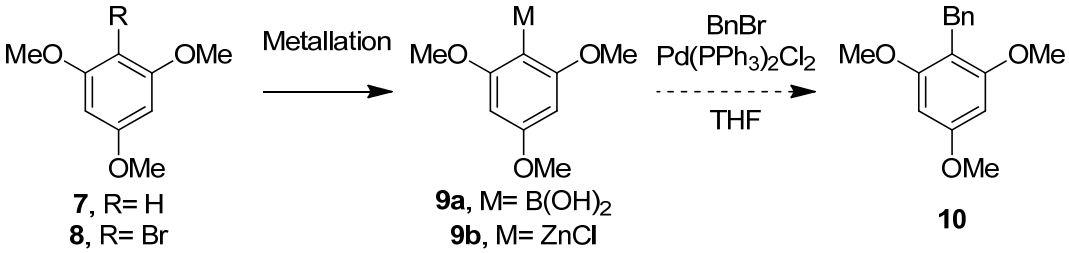


Scheme 2: Pd-catalyzed cross-coupling pathway to C8-susbtituted catechins 3 *via* C8-metallated catechins 4 and the model coupling system of organometallic 6 to afford trimethoxyphenyl adduct 5.



To test the initial scope of the designed synthetic pathway, 1,3,5-trimethoxybenzene (**7**) or its mono-brominated analogue **8** [15] was converted to either boronic acid **9a** (M=$B(OH)_2$) or organozinc **9b** (M=ZnCl). The formation of diarylmethane **10** was then attempted through the $Pd(PPh_3)Cl_2$-catalyzed coupling of these organometallics with benzyl bromide (BnBr, Scheme 3).

Scheme 3: Proposed method for the synthesis of diarylmethane 10 from organometallic derivatives 9a or 9b.



7, R= H
8, R= Br

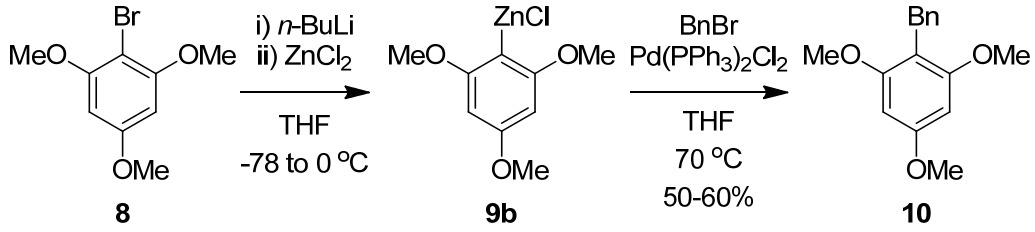
9a, M= $B(OH)_2$
9b, M= ZnCl

10

Attempts to couple boronic acid **9a** [16] with BnBr were met with little success. This coupling was attempted using either anhydrous or aqueous NaOH, or K_2CO_3, as the base in conjunction with $Pd(PPh_3)_2Cl_2$ as the catalyst. Under aqueous basic conditions the coupled product **10** was produced only in very poor yields (10-20%) following purification by silica chromatography. Using anhydrous basic conditions, no coupling product was ever obtained. In these cases, only the starting BnBr and 1,3,5-trimethoxybenzene (**7**), formed through protonolysis of **9a**, were recovered after aqueous quenching.

Given the poor coupling results obtained using boronic acid **9a**, the organozinc derivative was investigated as the organometallic coupling partner. Formation of organozinc **9b** was achieved using a low temperature lithium-halogen exchange of bromide **8** [17] using *n*-butyllithium in THF, followed by addition of anhydrous $ZnCl_2$ as a solution in THF.[18] The organozinc species presumed to form was then immediately coupled to BnBr in the presence of catalytic $Pd(PPh)_2Cl_2$ (Scheme 4).[19]

Scheme 4: Formation of organozinc 9b and its $Pd(PPh)_3Cl_2$-catalyzed coupling to BnBr.



8 **9b** **10**

Using these catalytic conditions, the desired diarylmethane **10** was consistently isolated in 50-60% yield when organozinc **9b** was employed in slight excess (1.5 equivalents) with stirring for 16-20 hours at 70 ^{o}C in the presence of 1 mol% of the catalyst.

In an effort to improve the isolated yield of diarylmethane **10**, numerous Pd(0) and Pd(II) catalysts were employed at various loadings and temperatures using either benzyl bromide or benzyl chloride (BnCl) as the electrophilic partners in the aforementioned cross-coupling (Table 1). Reactions were carried out in THF, monitored by TLC for the consumption of the halide and were stopped after a maximum of 48 hours.

Table 1: Catalyst screening in the Negishi cross-coupling of 9b with BnBr or BnCl.

Entry	Catalyst	Loading (mol %)	Electrophile	Temp (^oC)	Time (hours)	Yield [a] (%)
1	$Pd(PPh_3)_2Cl_2$	1	BnBr	70	20	60
2	$Pd(PPh_3)_2Cl_2$	1	BnCl	70	20	61
3	$Pd(PPh_3)_4$	4	BnBr	70	24	55
4	$Pd(DPEPhos)Cl_2$ [b]	1	BnBr	70	1.5	84
5	$Pd(DPEPhos)Cl_2$	1	BnCl	70	1.5	85
6	$Pd(DPEPhos)Cl_2$	5	BnCl	20	48	19
7	$Pd(dba)_2$/ DPEPhos [c]	5	BnBr	70	2.5	64
8	$Pd(dppf)Cl_2.CH_2.Cl_2$ [d]	3	BnBr	70	48	52

[a] Isolated yield after silica gel purification

[b] DPEPhos= bis(*o*-diphenylphosphinophenyl) ether

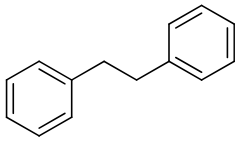
[c] dba= dibenzylideneacetone

[d] dppf= 1,1′-bis(diphenylphosphino)ferrocene

It was found that the bidentate ligand catalyst $Pd(DPEPhos)Cl_2$ [20] was by far the most effective catalyst employed in the transformation, showing higher yields (84-85%), faster coupling rates and requiring only low catalyst loading (*ca*. 1 mol%) at 70 ^oC (entries 4 and 5) in comparison with the other catalytic systems attempted. The effect of temperature for this catalyst was also examined. When the coupling was carried out at 20 ^oC (entry 6) diarylmethane **10** was produced in only very poor yield (19%) despite the use of higher catalyst loading (5 mol%) and a longer reaction time. This low coupling yield was attributed to the poor catalyst solubility at 20 ^oC, apparent because the catalyst remained as a yellow suspension upon addition to the reaction mixture; heating to approximately 30 ^oC was required to ensure complete dissolution of the catalyst. Interestingly, no distinguishable differences between the reactivity of benzyl chloride and benzyl bromide were observed. Both halides showed similar coupling yields and reaction times using either $Pd(PPh_3)_2Cl_2$ or $Pd(DPEPhos)Cl_2$ as the catalyst (compare entries 1 with 2, and 4 with 5). Comparison of the results of entry 1 with entry 3, and entry 5 with entry 6, clearly shows Pd(II) catalysts were more effective than Pd(0) catalysts for this coupling procedure.

The greater effectiveness of $Pd(DPEPhos)Cl_2$ compared to $Pd(PPh_3)_2Cl_2$ was due the formation of bibenzyl **11** (Figure 2) as a byproduct in *ca.* 10% yields (with respect to the halide) when $Pd(PPh_3)_2Cl_2$ was employed as the catalyst. In the $Pd(DPEPhos)Cl_2$-catalyzed couplings, this byproduct was not produced. As a result, all the added halide was available to participate in the cross-coupling with organozinc **9b**, which in turn provided diarylmethane **10** in greatly improved yields.

Figure 2: Bibenzyl 11, obtained as a byproduct in the $Pd(PPh_3)_2Cl_2$-catalyzed cross-couplings.

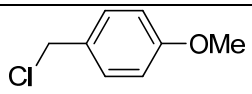
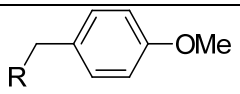
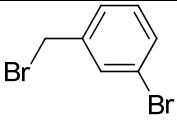
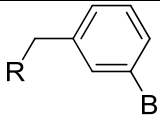


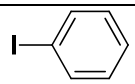
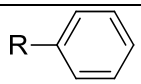
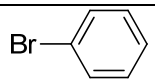
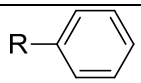
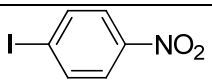
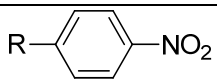
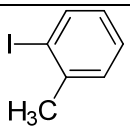
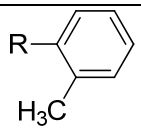
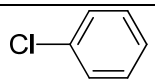
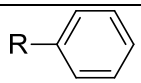
11

The coupling was also attempted using another bidentate ligand catalyst, $Pd(dppf)Cl_2.CH_2Cl_2$ (entry 8) at 70 ^oC. The coupling using this catalyst was very sluggish, with TLC analysis showing BnBr was still present even after 48 hours, and 52% was the highest coupling yield obtained using this catalyst. It was noted that this catalyst did not appear to dissolve completely in the reaction mixture. This provided some explanation for the sluggish reaction rate as the actual catalyst loading present in solution was likely much lower than that added to the reaction mixture (3 mol%).

In order to further investigate the scope of this methodology, the optimized $Pd(DPEPhos)Cl_2$-catalyzed coupling procedure was expanded to the coupling of organozinc **9b** with numerous benzyl and aryl halides containing a variety of functional groups to furnish substituted diarylmethanes and biaryls containing the 1,3,5-trimethoxyphenyl subunit (Table 2).

Table 2: $Pd(DPEPhos)Cl_2$-mediated cross-couplings of 2,4,6-trimethoxyphenylzinc chloride 9b with benzyl and aryl halides.

Entry	Halide	Rxn Time (hrs) [a]	Product [b]	Yield (%) [c]
1	 **12a**	4	 **13a**	68
2		3 [d]		55

	12b		**13b**	
3	 **12c**	5	 **13c**	81
4	 **12d**	24	 **13c**	77
5	 **12e**	4	 **13d**	80
6	 **12f**	6	 **13e**	74
7	 **12g**	48	 **13c**	0

[a] Reaction conditions: Halide (1 equiv), **9b** (1.5 equiv.), THF, $Pd(DPEPhos)Cl_2$ (~1 mol%), 70 ^{o}C. Reactions were monitored by TLC for consumption of halide.

[b] R= 2,4,6-trimethoxyphenyl.

[c] Isolated yields following silica chromatography.

[d] Conducted at 40 ^{o}C.

A variety of cross-coupling products were constructed in acceptable to very good yields using low catalyst loading (*ca*. 1 mol%) in reasonable reaction times. Entries 1 and 2 show benzyl bromides and chlorides containing either electron donating or electron withdrawing substituents can be coupled to organozinc **9b** using the developed catalytic system. In order to establish the selectivity of cross-couplings of benzyl bromides in comparison with aryl bromides, the reactivity of bromide **12b** in the coupling system was explored (entry 2). Reduction of the reaction temperature to 40 ^{o}C resulted in the selective coupling of the

benzylic bromide (at 70 ^{o}C, mixtures of aryl and benzyl coupled products were obtained). This strongly suggested under these reaction conditions, oxidative addition of the catalyst into the benzyl carbon-bromine bond was much faster in comparison to the aryl bromide. The reduced reaction temperature resulted in a decreased coupling yield compared to that obtained for the couplings of other benzyl halides. The 55% isolated yield of diarylmethane **13b**, however, was acceptable when the difficult nature of the coupling was taken into consideration. Furthermore, this selective coupling provides opportunities for iterative syntheses of larger and more elaborate motifs, as the remaining aryl bromide could be coupled to other organometallic reagents in a subsequent step.

Aryl halides **12c-f** (entries 3-6) also readily coupled to organozinc **9b** under the conditions developed to provide the corresponding biaryls **13c-d**. Notably, biaryl **13c** was obtained in comparable yields using either iodobenzene **12c** (entry 3) or bromobenzene **12d** (entry 4) as the coupling electrophile. A much longer reaction time was required, however, to achieve complete coupling of **12d**. Additionally, chlorobenzene **12g** could not be coupled under the developed conditions (entry 7). This suggested that the nature of the aryl halide (Cl, Br or I) played an important role in the rate of the coupling reaction, which contrasted to the earlier results observed for the coupling rates of benzyl halides. The coupling system was also extended to incorporate aryl iodides containing either electron withdrawing (entry 5) or electron donating (entry 6) substituents. Comparison of the coupling yields and times of these aryl iodides suggested that the yield was not greatly effected by the substituent, but the coupling rate increased slightly in the presence of the strongly electron withdrawing nitro group.

In summary, various biaryls and diarylmethanes containing the highly electron rich 2,4,6-trimethoxyphenyl subunit were synthesized in moderate to very good yields utilizing a single Pd(DPEPhos)Cl_2-catalyzed Negishi coupling protocol. Importantly, this method was applicable to the coupling of both benzyl and aryl halides containing electron withdrawing and electron donating substituents. Extension of these methods to other aromatic and aliphatic electrophiles is currently underway in order to access additional products containing the phloroglucinol subunit. The application of similar Pd-catalyzed coupling procedures towards the synthesis of C8-subsituted catechin derivatives is also under investigation.

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17: Directed lithiation of 1,3,5-trimethoxybenzene (**7**) with *n*-BuLi could be used. However, at *ca*. 1 mmol scale more consistent results were obtained *via* transmetallation from the bromide **8**.

18: Numerous zinc chloride sources were screened. The most consistent results were achieved using anhydrous powder purchased from Aldrich (product no. 429430). The powder was dissolved in dry THF to make a 1M solution which was stored under nitrogen and could be used for up to a month after preparation.

19: For examples of the use of this catalyst in Negishi couplings see: (a) de Lang, R-J.; van Hooijdonk M.J.C.M.; Brandsma, L.; Kramer, H.; Seinen, W. *Tetrahedron*, **1998**, *54*, 2953-2966. (b) Goldfinger, M.B.; Crawford, K.B.; Swager, T.M. *J. Am. Chem. Soc.*, **1997**, *119*, 4578-4593. (c) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.*, **1997**, *62*, 3158-3175.

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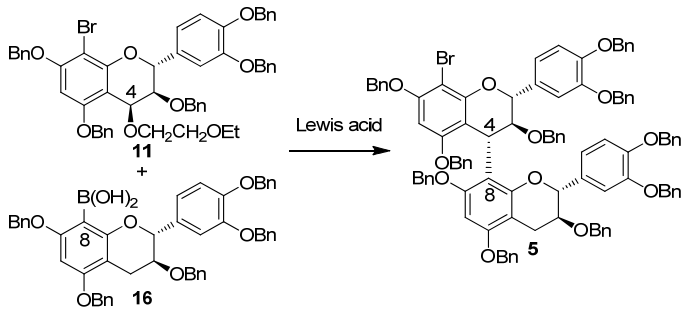
Procyanidin dimer B3. A new synthetic method towards the synthesis of the 4→8 interflavan bond using a C8-boronic acid.

Expected journal of submission: Organic Letters.

Abstract:

The 3,4-*trans*-(+)-catechin-4α→8-(+)-catechin dimer, or natural procyanidin dimer B3 (**1**), was synthesised from (+)-catechin in 54% overall yield in linear 6 steps. Synthesis of the key interflavan 4→8 bond was achieved using the novel Lewis acid-promoted coupling of C4-ether **11** with C8-boronic acid **16** reported herein.



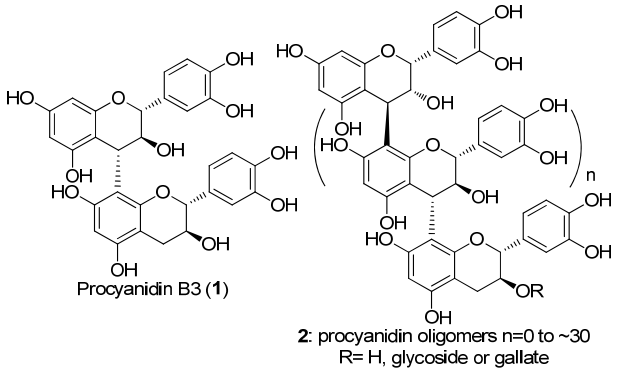
Paper:

Procyanidins, or condensed tannins, are a class of naturally occurring polyphenols that occur throughout nature,[1,2] including grapes [3] and wine.[4] The last two decades have seen an increasingly widespread interest in these compounds, principally due to their beneficial health effects.[2,5] In particular, such compounds have been reported to show powerful free-radical scavenging [6] and antioxidant [7] activities, along with anti-tumor promoting and DNA polymerase inhibitory effects.[8] Given the diversity of the compounds encompassed under the banner of procyanidins, there has been a greater emphasis in recent history for obtaining these materials as pure, defined compounds in an effort to further understand if any structure-activity relationships [9] exist in these processes. As a consequence, synthesis of these compounds from known starting materials has become an increasingly popular method used to obtain these compounds with known purities and defined structures.

Of particular interest is the synthesis of procyanidin ((epi)catechin) oligomers that contain the 4→8 interflavan linkage (Figure 1). In efforts to produce pure, defined oligomers, the iterative synthesis of such compounds have been the focus of a

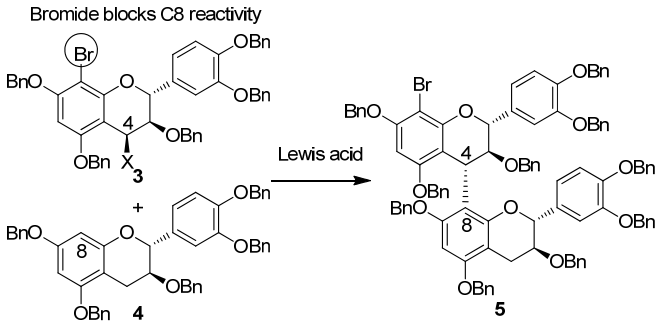
number of studies.[10,11] However, efforts towards such iterative syntheses have been hampered due to the inherent chemical reactivity of these compounds,[10,12] which tend to react unselectively to form polydisperse oligomeric mixtures. As a result, control of the degree of oliogmerisation stands as the major challenge that needs to be addressed for successful iterative syntheses of procyanidin oligomers.

Figure 1: Procyanidin B3 (1) and representative 4→8 procyanidin oligomers 2.



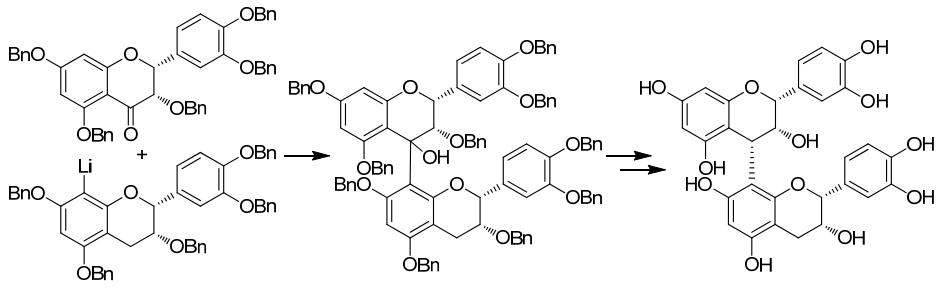
As the most simple of all procyanidin oligomers (other than the commercially available monomers), dimers have been primary targets of many selective oligomer syntheses. Two notable selective syntheses of (epi)catechin dimers were reported by Ohmori *et al*,[10] and Tarascou *et al.* [11] Both used a C8-bromide (eg **3**) as a protecting group, which played a critical role in blocking the formation of higher oligomers, leading to the selective formation of the desired dimer(s) (eg **5**, Scheme 1).

Scheme 1: Dimer formation by use of C8 bromide blocking group.



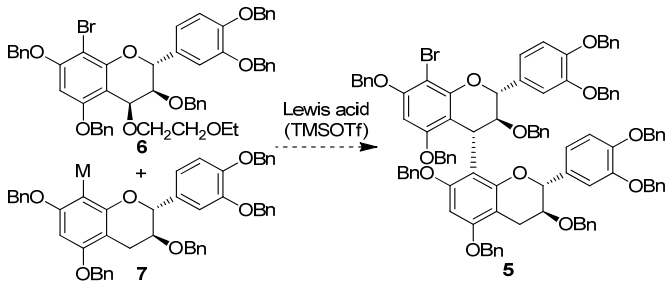
Notably little attention has been focussed on the use of C8-organometallic derivatives as directing groups for the selective synthesis of 4→8 oligomers. The only such report involved the addition of a C8-organolithium to a C4 ketone derivative.[13] This synthesis resulted in the ultimate formation of an unnatural 3,4-*cis*-epicatechin-epicatechin dimer (Scheme 2).

Scheme 2: Kozikowski *et al* addition of C8-organolithium to C4-ketone.



Given the lack of examples of C8-organometallics and some encouraging results from a recent model system study,[14] the synthesis of procyanidin B3 (**1**) was targeted using an appropriate C8-organometallic derivative. Notably, such a synthesis requires that the 4→8 bond exhibit 3,4-*trans* stereochemistry, as seen in the natural dimer **1**. As a result, the synthesis of the key 3,4-*trans*, 4→8 interflavan bond was targeted through a Lewis acid-promoted condensation of C4-ether **6** with an appropriate C8 organometallic species **7** (Scheme 3).

Scheme 3: Lewis acid-promoted condensation of C4-ether 6 and a C8-organometallic 7.

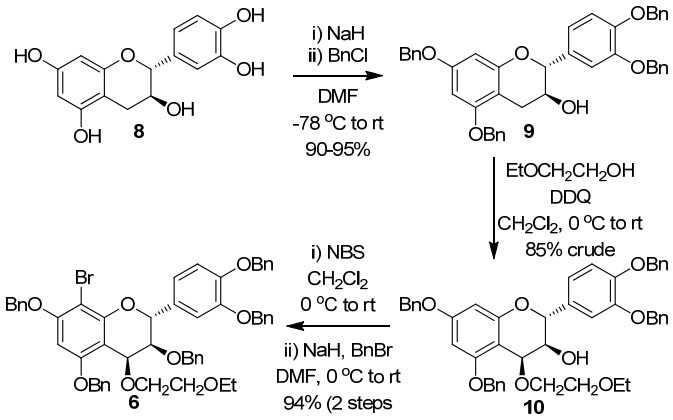


After a literature survey, C4-ether **6** and TMSOTf were chosen as the preferred C4-ether/Lewis acid combination for the coupling. Related couplings by Saito *et al* [14] using this combination have furnished 4→8 linked (epi)catechin dimers in excellent yields and 3,4-*trans* stereoselectivities. Installation of the aforementioned C8 bromide on the C4-ether moiety was also employed in order to suppress the formation of higher oligomers in the coupling reaction.

C4-ether **6** was obtained in four steps from (+)-catechin (**8**, Scheme 4). Benzyl protection of the (+)-catechin (**8**) phenols using NaH and BnCl in DMF furnished tetra benzyl ether **9** in excellent 90-95% yields using 5-10 g of **8**. DDQ mediated C4-oxidation of **9** using the method described by Saito *et al* [15] afforded the desired C4-*β*-ether **10** in 85% crude yield as a single stereoisomer. Treatment of the crude C4-ether

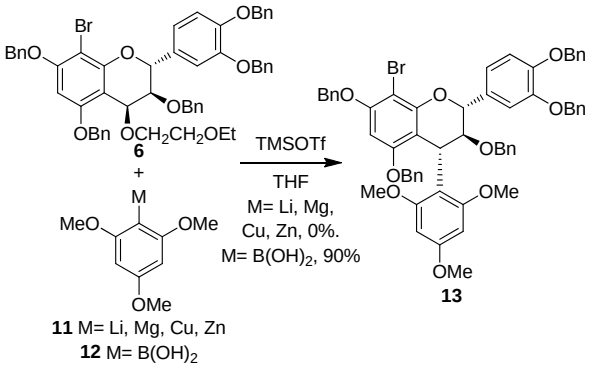
10 with one equivalent of NBS, followed by benzylation of the C3-OH provided the desired C4-ether **6** in 94% yield (76% overall in 4 steps) following rigorous purification by silica chromatography.

Scheme 4: Synthesis of C4-ether 6 from (+)-catechin (8).



With the successful synthesis of C4-ether **6**, the next task was to establish an appropriate metal to use in the Lewis acid-promoted 4→8 coupling reaction. This was achieved using the model system depicted in Scheme 5. The 2,4,6-trimethoxybenzene derivative was chosen as a suitable model species due to its similar 2,4,6-oxygenated substitution to that of the C8-organometallic species.

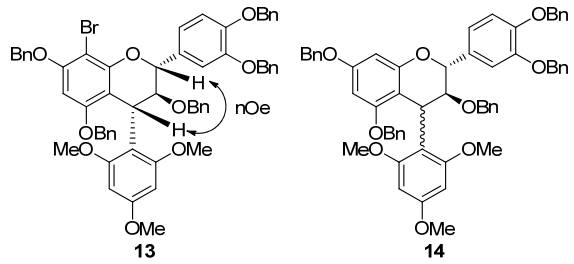
Scheme 5: Model system Lewis acid-promoted coupling of C4-ether 6 with metallated 2,4,6-trimethoxybenzene derivatives.



After trialling numerous organometallic species **11** (M= Li, Mg, Cu, Zn), successful formation of pseudo dimer **13** was achieved in 90% yield using 2,4,6-trimethoxyphenylboronic acid (**12**, M= $B(OH)_2$).[15] Notably, the desired 3,4-*trans* isomer was produced in at least 90% diasteriomeric excess using this method. Confirmation of this stereochemistry was obtained using a ROESY NMR

experiment. An nOe resonance was observed between C2-H and C4-H, which confirmed that these two protons were on the same side of the heterocyclic C-ring, which was indicative that **13** exhibited the desired 3,4-*trans* stereochemistry (Figure 2a).

Figure 2: (a) Confirmation of 3,4-trans of 13 stereochemistry due to nOe resonance of C2-H and C4-H and (b) the debrominated byproduct, 14.

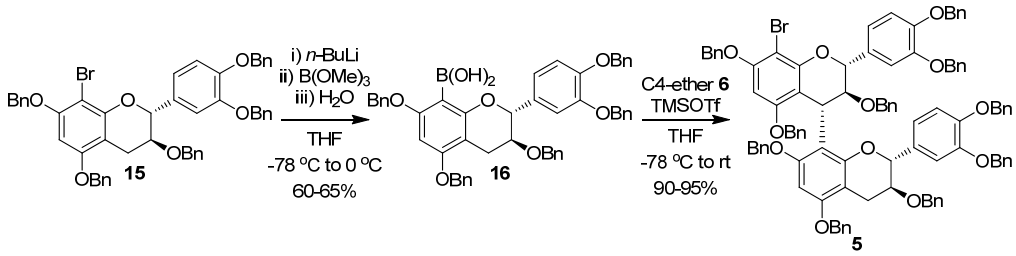


In this reaction, dimer **14** (Figure 2b) was produced in *ca.* 10% yields. Initially this product was assumed to form by debromination of pseudo dimer **13** under the Lewis acidic conditions (Figure 2 b). It was later confirmed that this product was due to incomplete bromination of **6** during its synthesis, and the non-brominated material was carried through the synthesis. Separation of byproduct **14** from the desired product **13** was never successful. An indicative C6-H, C8-H doublet of doublets either side of the C6-H singlet in the ^{1}H NMR spectra of **6** that integrated for *ca.* 10% confirmed the presence of the non-brominated by-product in the C4-ether starting material **6**. So **14** was not formed from debromination of **13**. The stereochemistry of **14** was not confirmed. Although it would not be unreasonable to consider it likely that **14** should also be dominantly 3,4-*trans*, this could not be confirmed as **14** could not be isolated. As a result, the stereoselectivity of the reaction could not be stated at greater than 90%.

After the successful application of the boronic acid in the synthesis of pseudo dimer **13**, attention then turned towards the extension of this method for the formation of the catechin-catechin dimer **5**. Before this coupling was attempted, the C8-boronic acid derivative **16** was synthesised from the known C8-bromide **15** [13] in good yields by initial low temperature lithium-halogen exchange with *n*-butyl Lithium in THF, followed by transmetallation with excess $B(OMe)_3$ and subsequent aqueous hydrolysis. This metallation showed a marked scaling effect. No boronic acid product was formed using less than 0.5 mmol of the starting bromide **15**. Above this

critical scale, the isolated yield of boronic acid **16** increased as the amount of bromide **15** increased. When conducted using 1 to 3 grams of **15**, the desired boronic acid **16** was routinely isolated by silica chromatography in 60-65% yield. The key 4→8 bond of dimer **5** was then constructed in excellent yields through the TMSOTf-mediated coupling of C4-ether **6** with the newly synthesised C8-boronic acid **16** (Scheme 6).

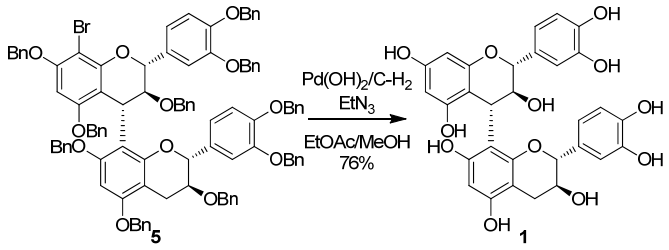
Scheme 6: Formation C8-boronic acid 16 and subsequent coupling to C4-ether 6.



Dimer **5** was consistently synthesised in consistent 90-95% yields regardless of coupling scale. Using the coupling conditions, gram quantities of **5** were successfully prepared. Importantly, the coupling conditions used for this dimer synthesis were the same as that used the model system (Scheme 5). This suggested that the greater steric encumbrance of boronic acid **16** compared to that of the model boronic acid **12** appeared to have no detrimental effect on the coupling reaction. This coupling showed also exhibited excellent 3,4-*trans* stereoselectivity. Similarly to the model system stereochemical studies, NMR ROESY experiments of **5** showed that the C2-H and C4-H of the upper, or C8-terminus, catechin unit were on the same side of the heterocyclic C-ring. This confirmed the desired 3,4-*trans* of the newly forged 4→8 interflavan bond was obtained in the coupling.

Finally, in an unoptimised procedure, the bromide and benzyl protecting groups of dimer **5** were removed in a one pot hydrogenolysis process. Using the conditions reported by Tarascou *et al*,[11] $Pd(OH)_2$ mediated hydrogenolysis of dimer **5** in the presence of excess triethylamine afforded the desired (+)-catechin-4α→8-(+)-catechin dimer, or procyanidin B3 (**1**) in 76% yield (Scheme 7).

Scheme 7: Synthesis of procyanidin B3 (1) through one-pot deprotection of dimer 5.



Comparison of the ^{1}H and ^{13}C NMR data and the optical rotation of the synthesised B3 to that reported for the same product by Saito *et al* [15] and the melting point data reported by Tarascou *et al* [11] confirmed that the desired procyanidin B3 (**1**) was synthesised and that the natural 3,4-*trans* stereochemistry was obtained.

In conclusion, procyanidin B3 (**1**) was synthesised from (+)-catechin (**8**) in a good overall yield (54% over 6 steps). The key 4→8 interflavan bond was formed in excellent 90-95% yield by the novel, stereoselective Lewis acid-promoted coupling of C4-ether **6** with C8-boronic acid **16**. To the best of our knowledge, this represents the first synthesis and use of C8-boronic acid **16**. Further studies are currently being undertaken towards the extension of these methods in the iterative synthesis of trimers and higher oligomers, along with studies into the mechanism of the novel Lewis acid-promoted coupling reaction.

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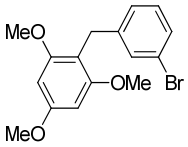
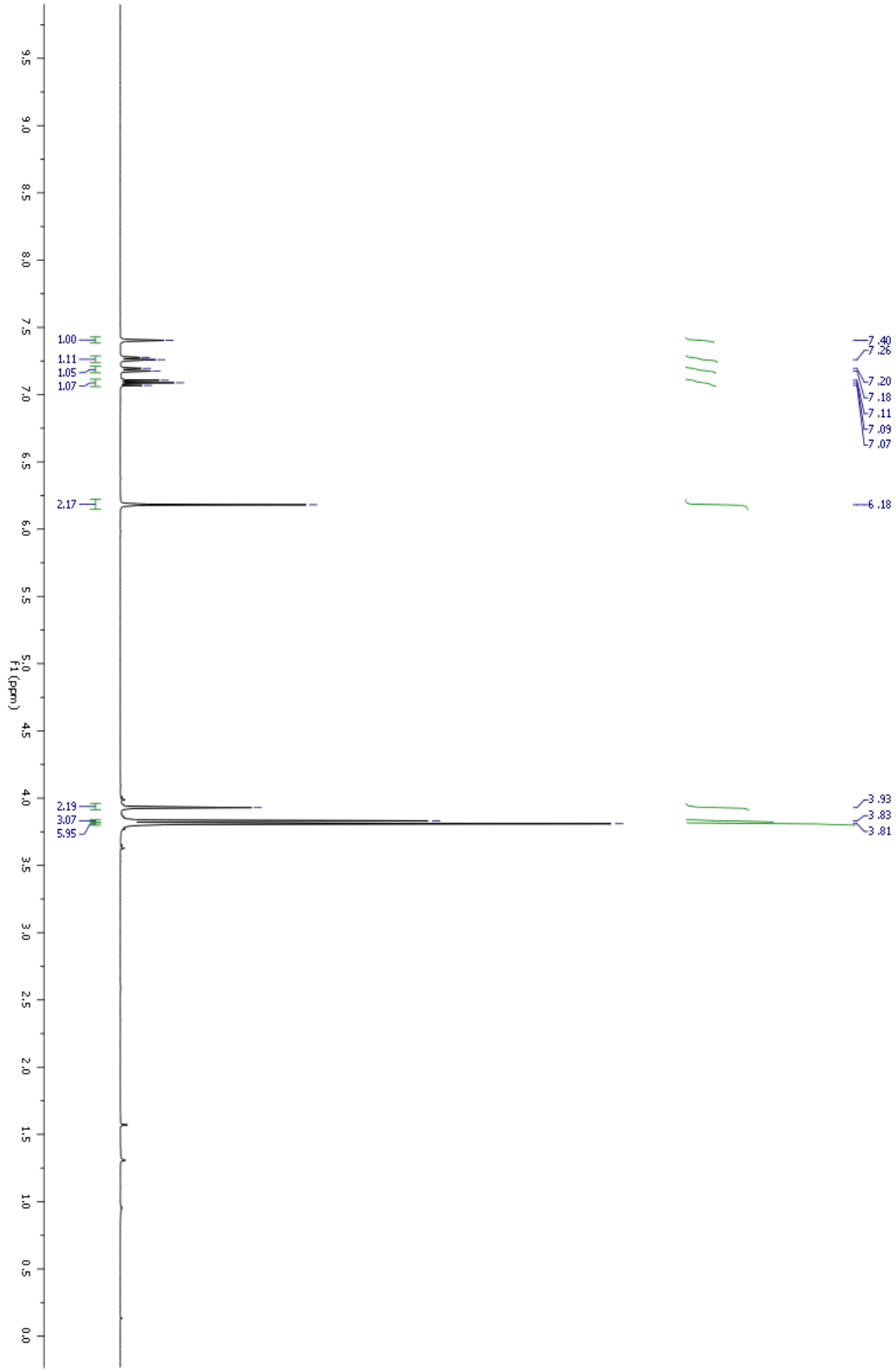
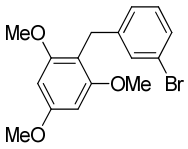
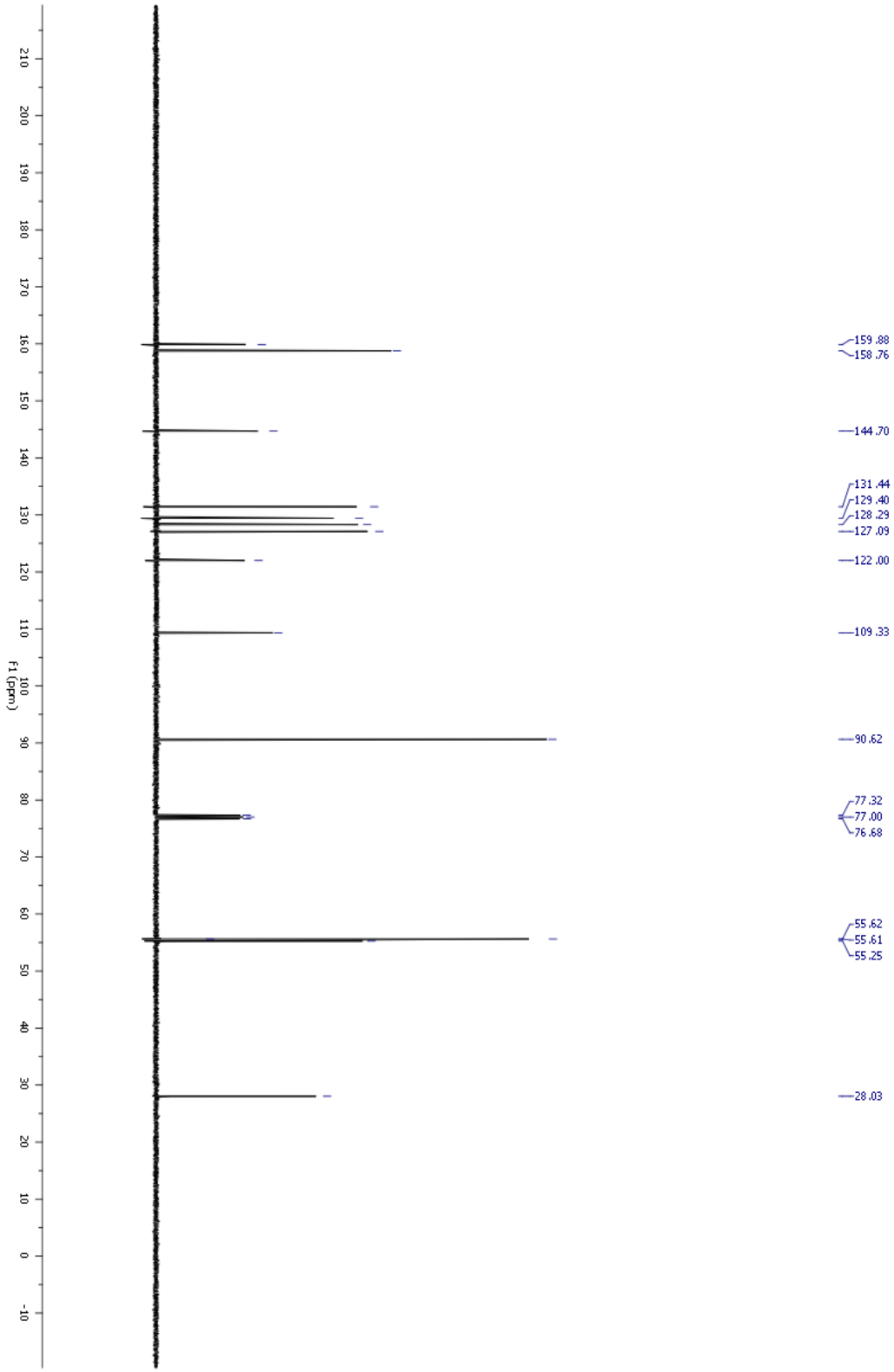
Appendix 2-A1. ^{1}H NMR for compound 49b.


MeO
OMe
Br
MeO

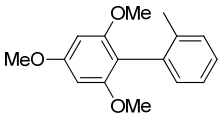

f1 (ppm)
1.00
1.11
1.05
1.07
2.17
2.19
3.07
5.95
7.40
7.26
7.20
7.18
7.11
7.09
7.07
6.18
3.93
3.83
3.81

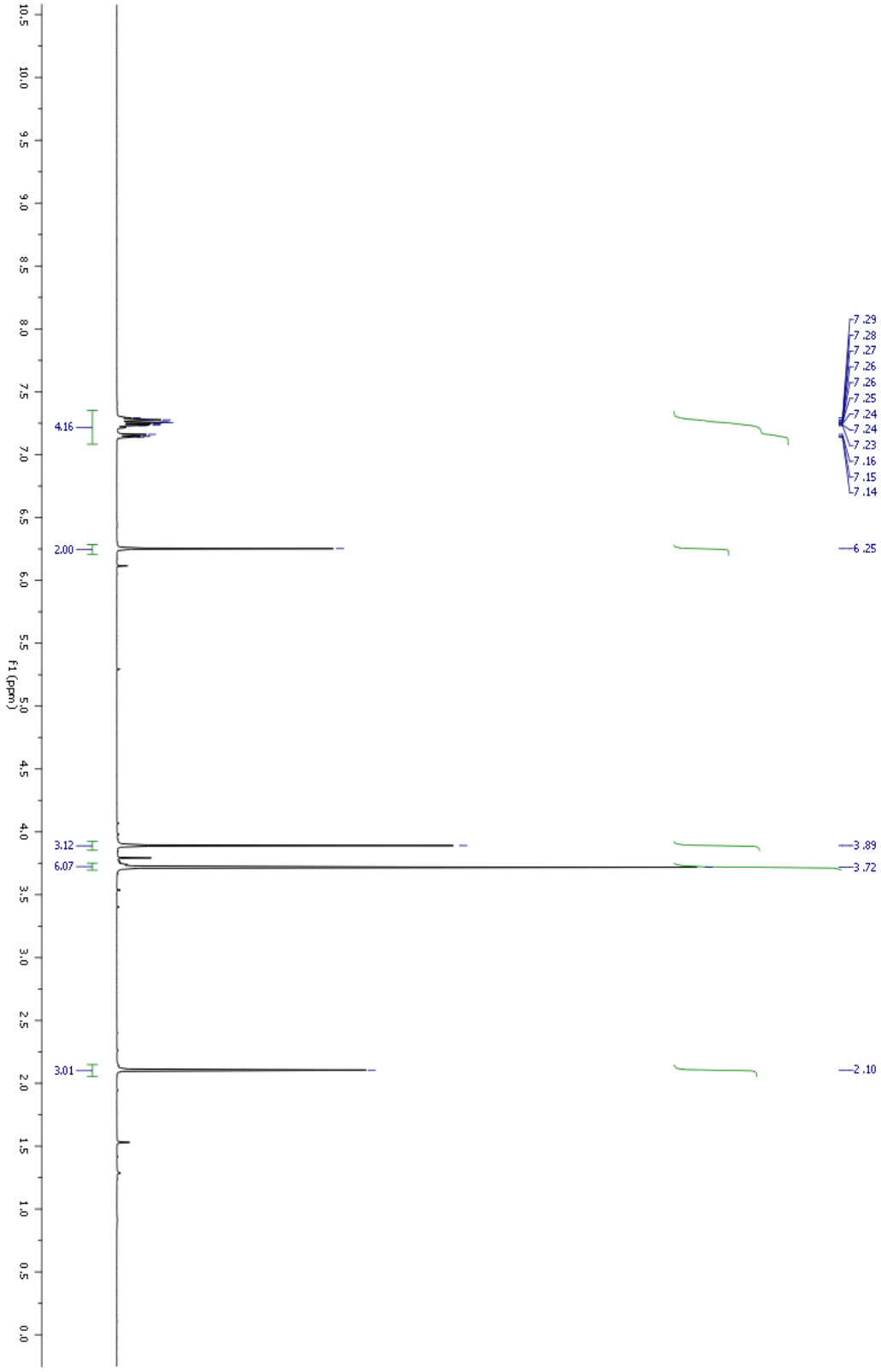
Appendix 2-A2. ^{13}C NMR for compound 49b.



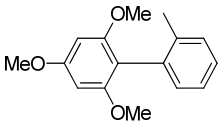


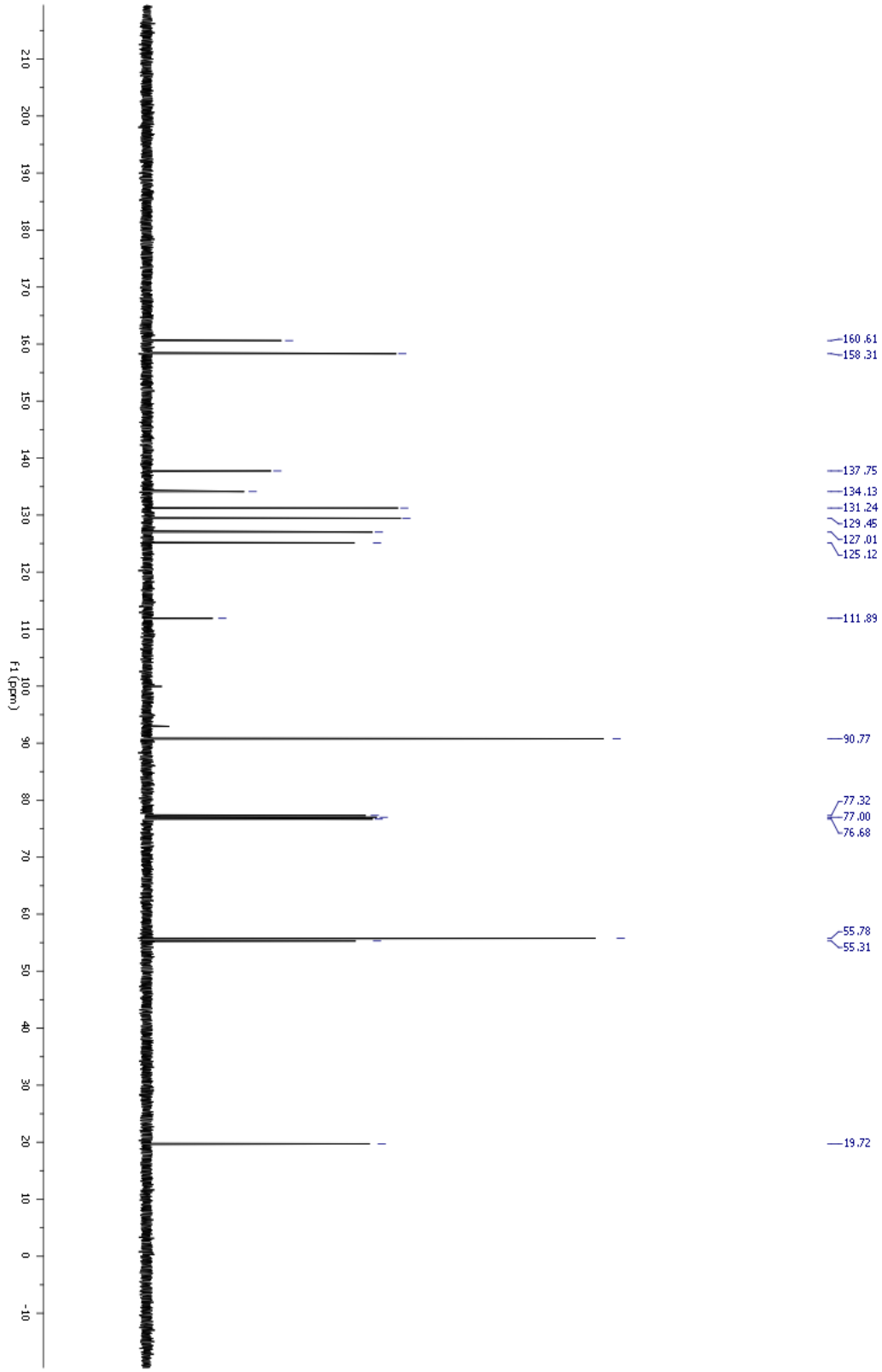
Appendix 2-B1. ^{1}H NMR for compound 49c.



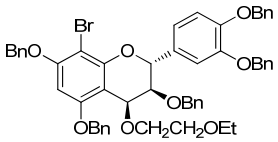


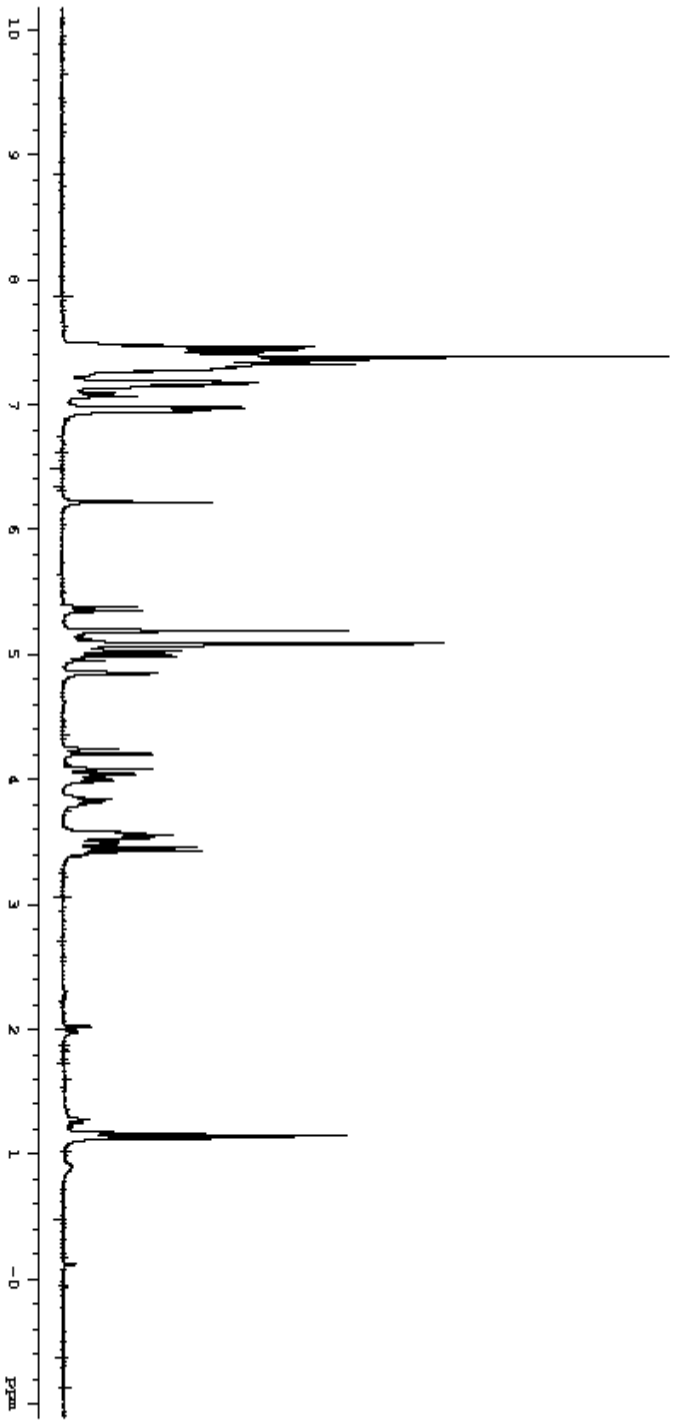
Appendix 2-B2. ^{13}C NMR for compound 49c.



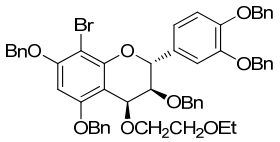


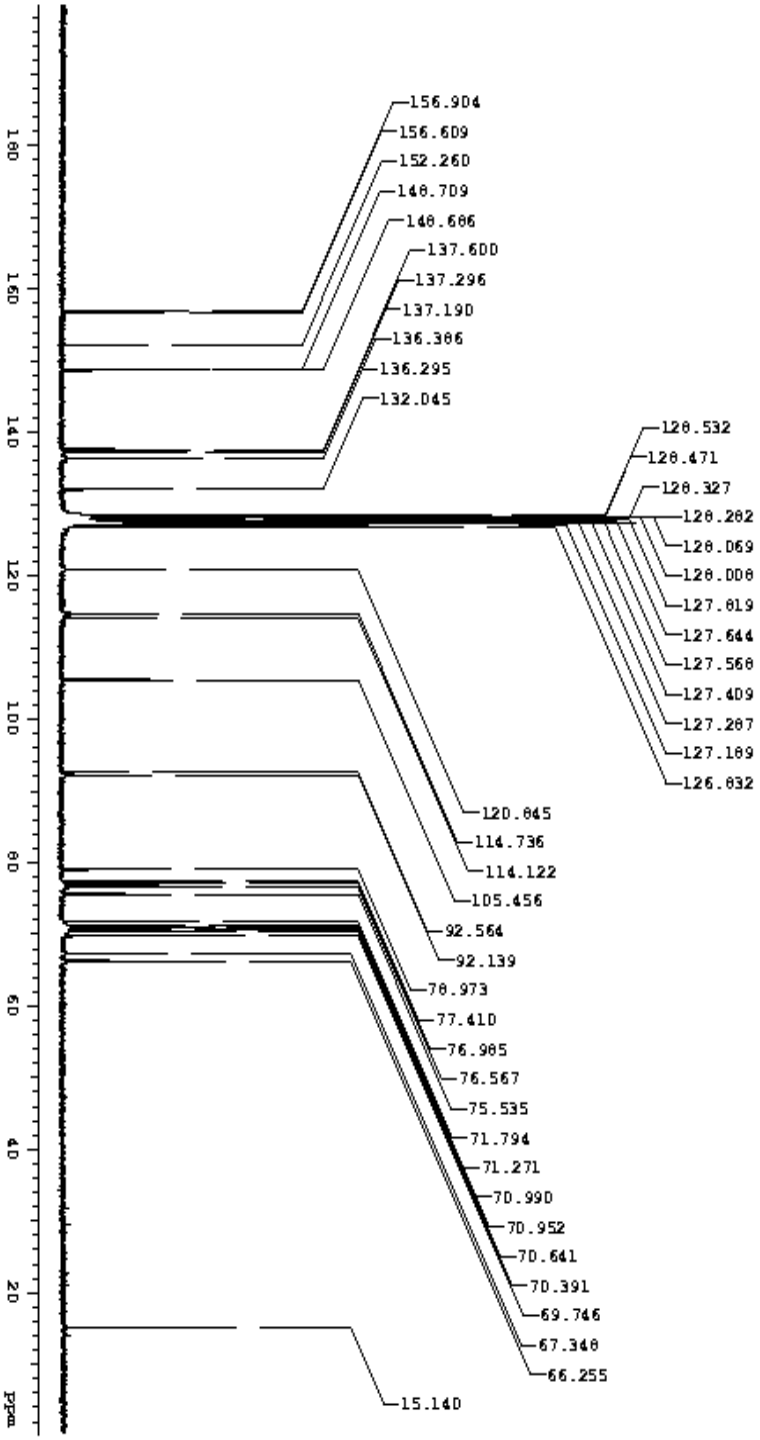
Appendix 2-C1. ^{1}H NMR for 8Br-4EE-PBC 83.



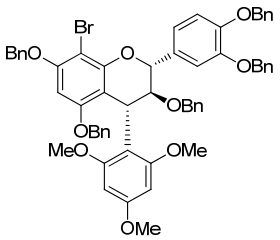


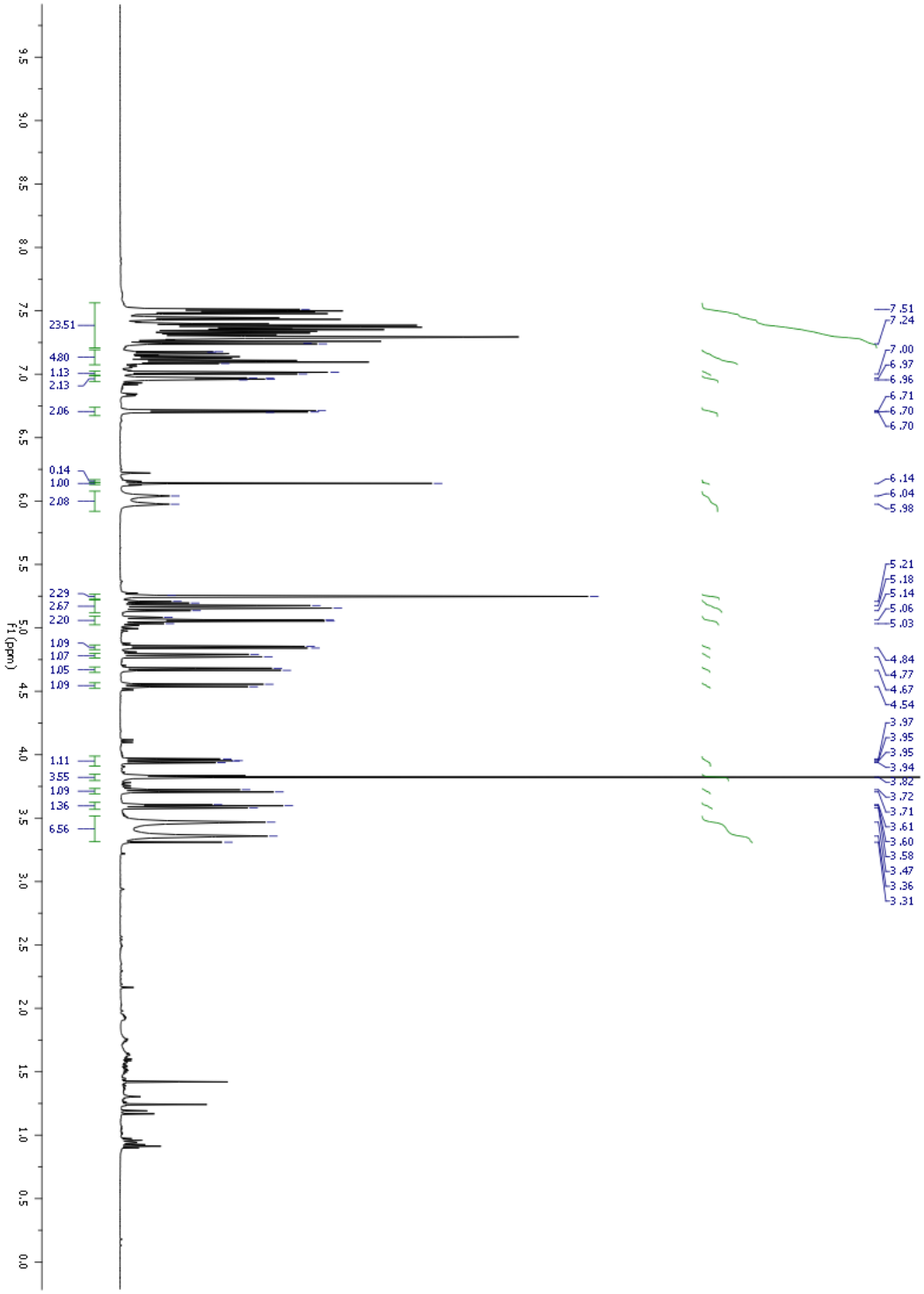
Appendix 2-C2. ^{13}C NMR for 8Br-4EE-PBC 83.



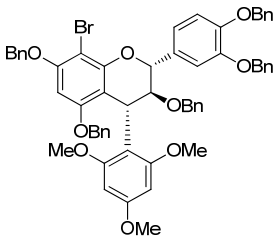


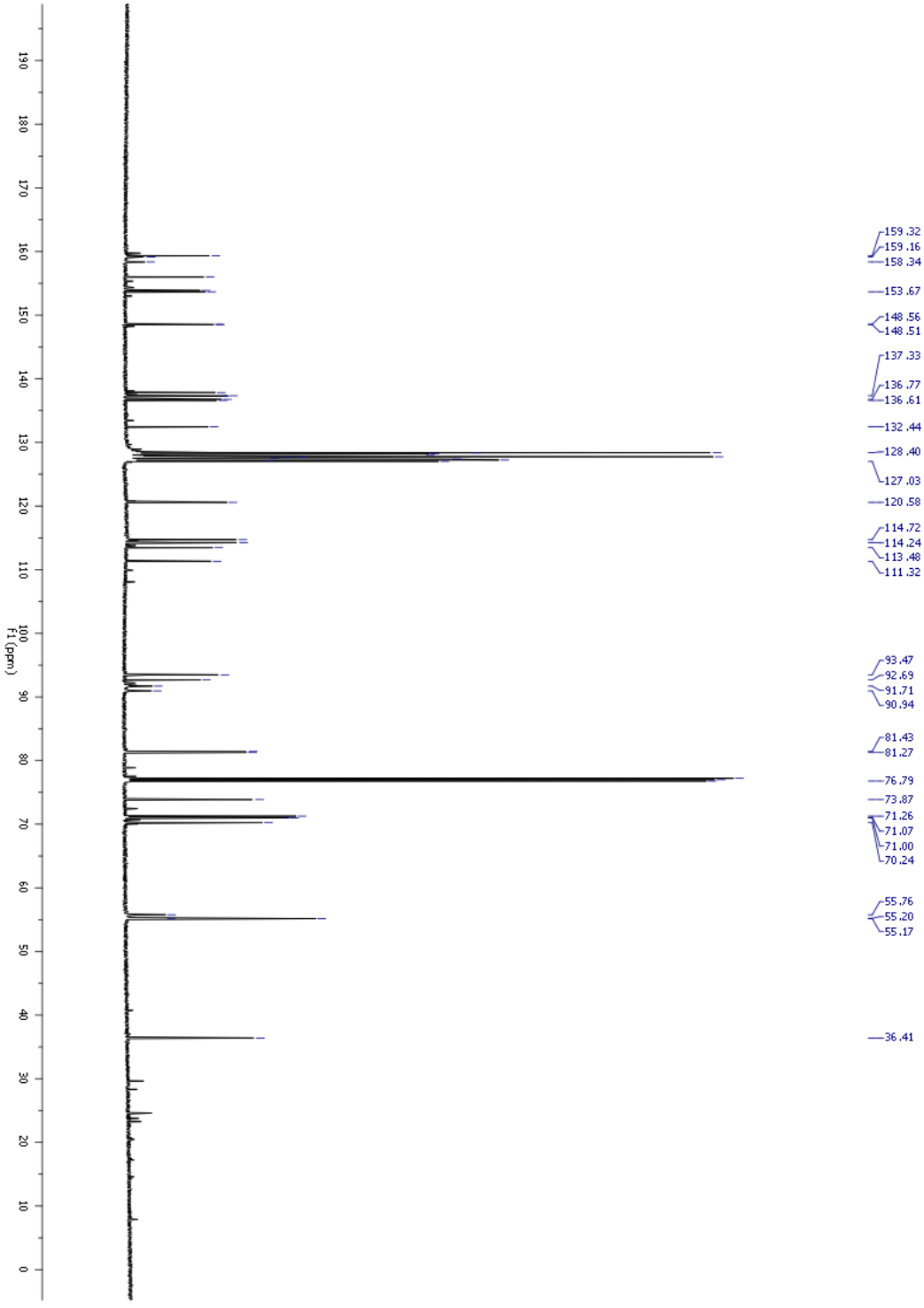
Appendix 2-D1. ^{1}H NMR for 8Br-4TMB-PBC 84.



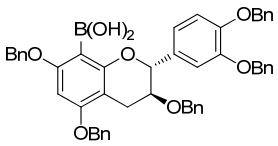


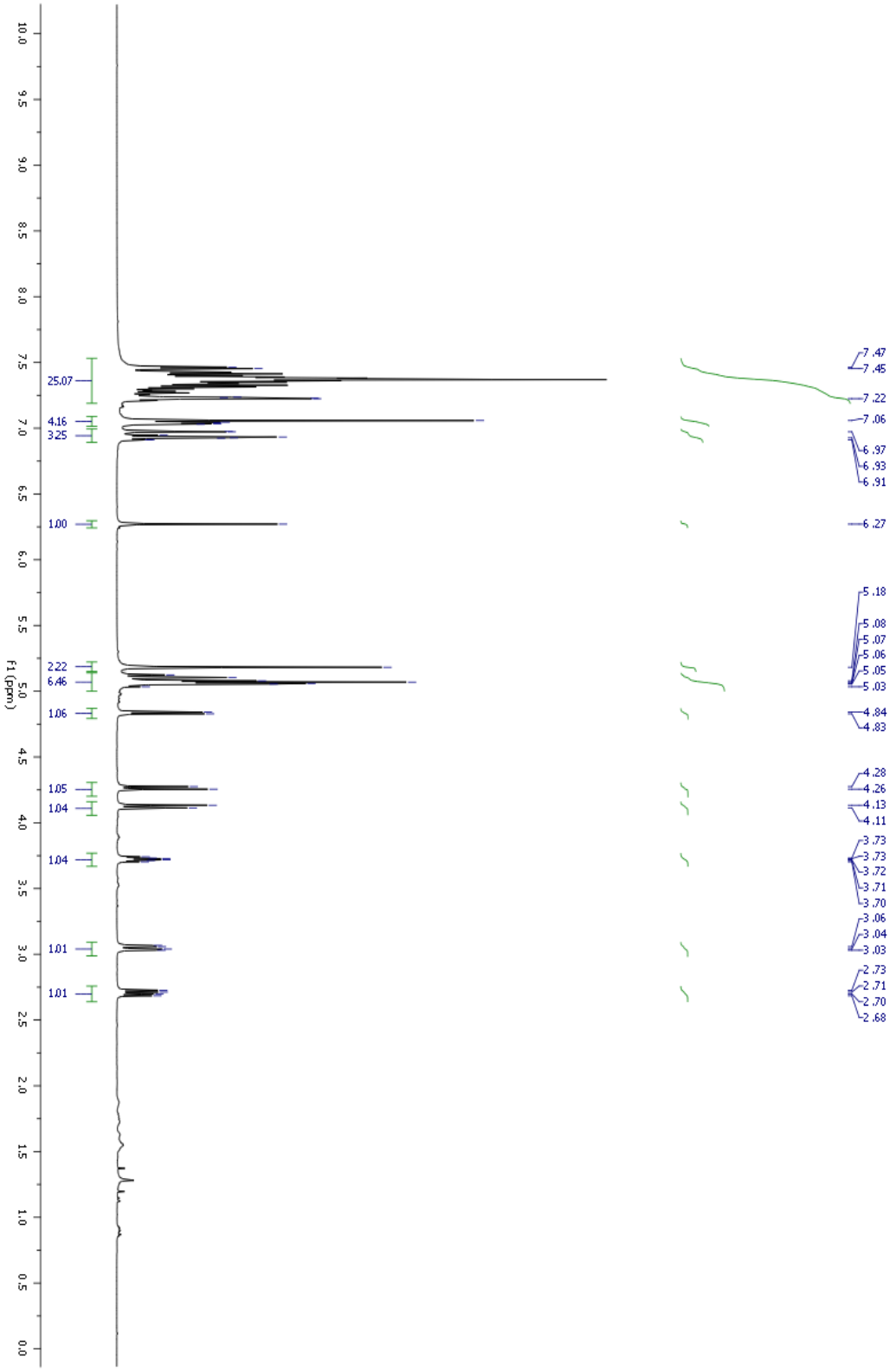
Appendix 2-D2. ^{13}C NMR for 8Br-4TMB-PBC 84.





Appendix 2-E1. ^{1}H NMR for PBC-B(OH)$_2$ 104.





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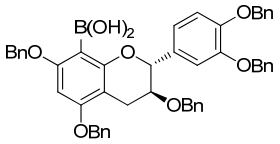

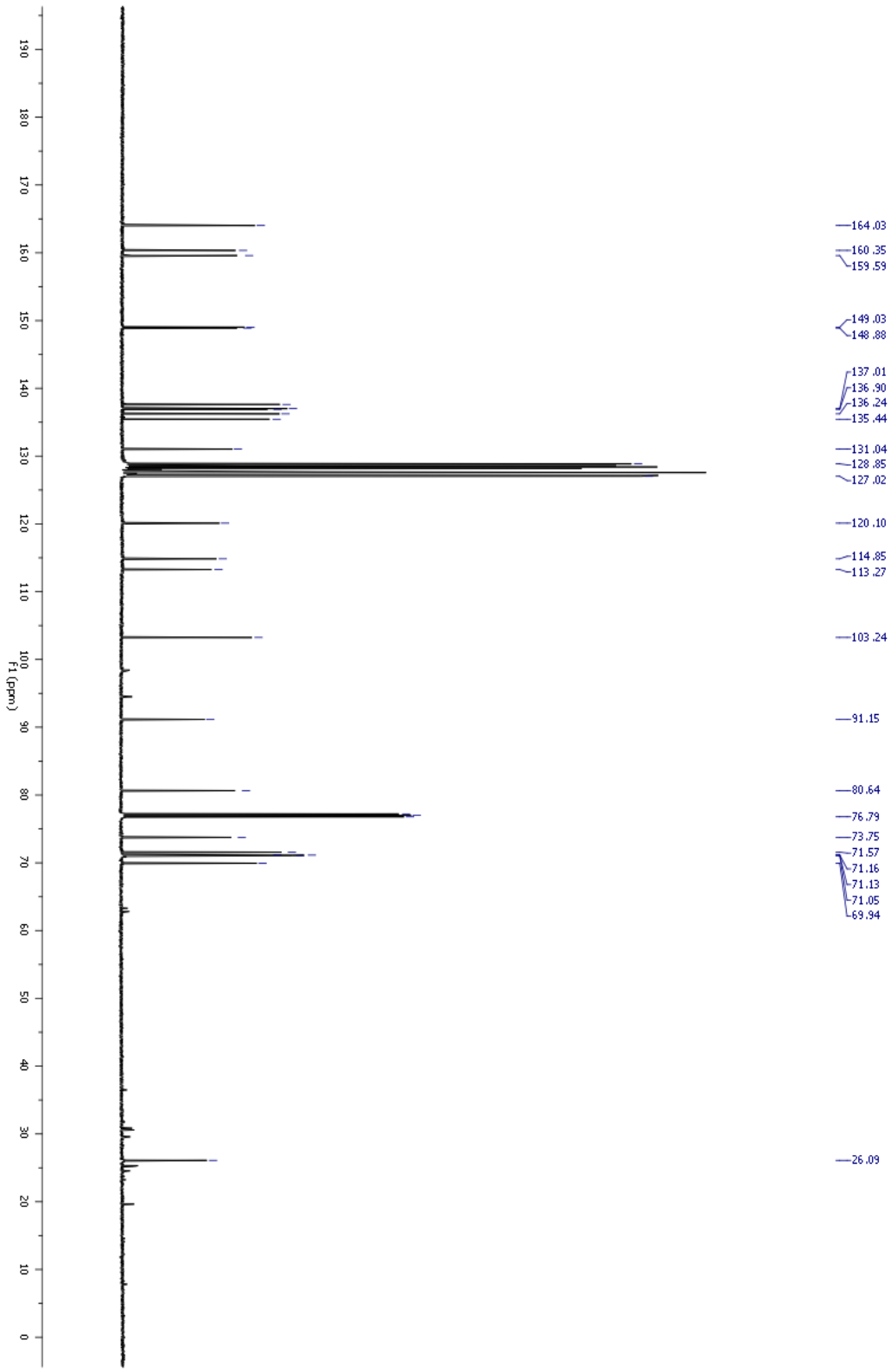

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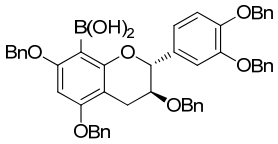
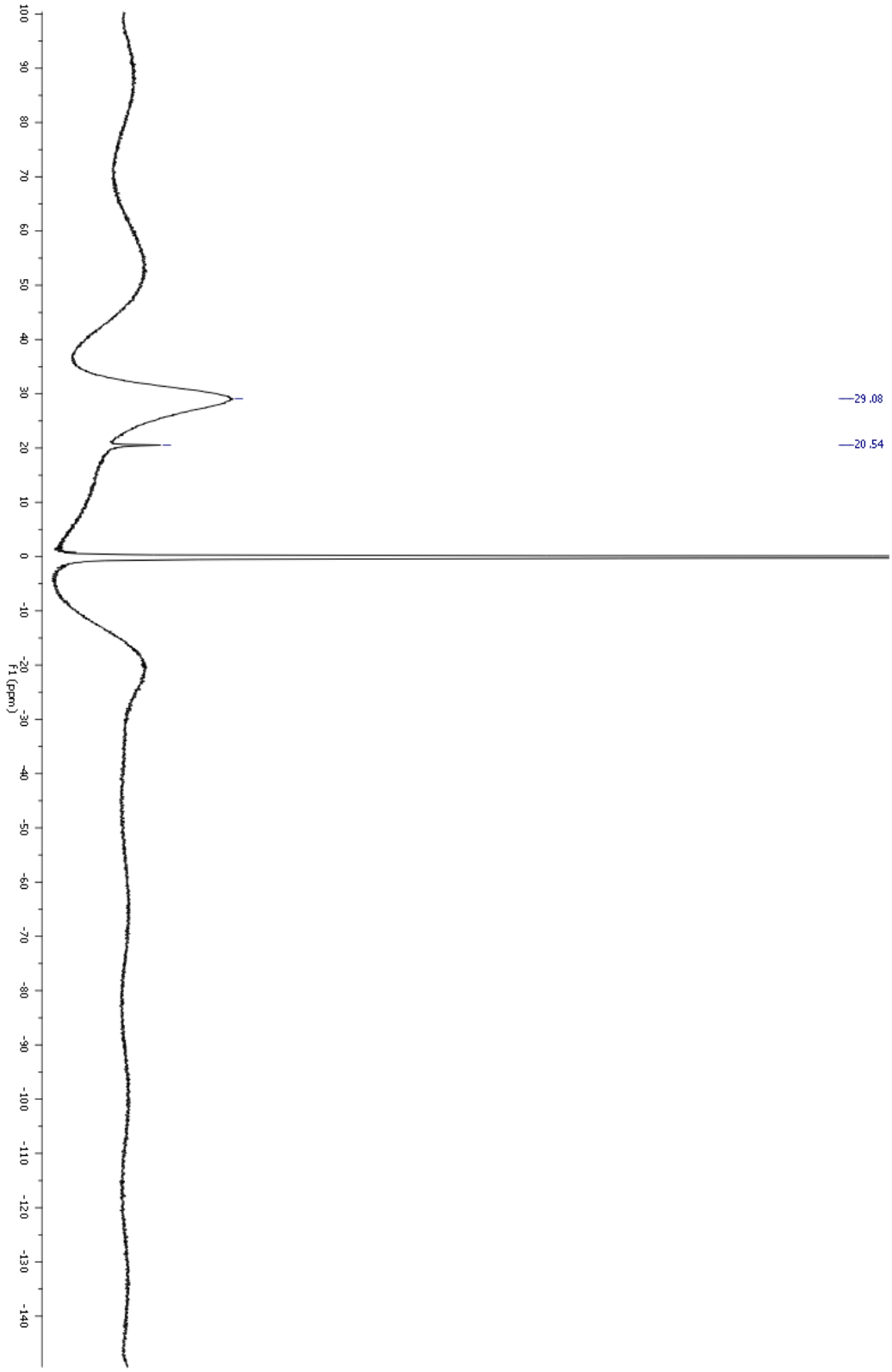
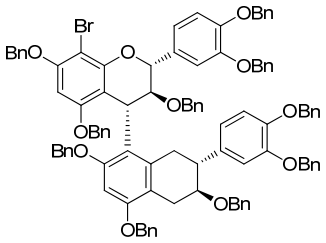
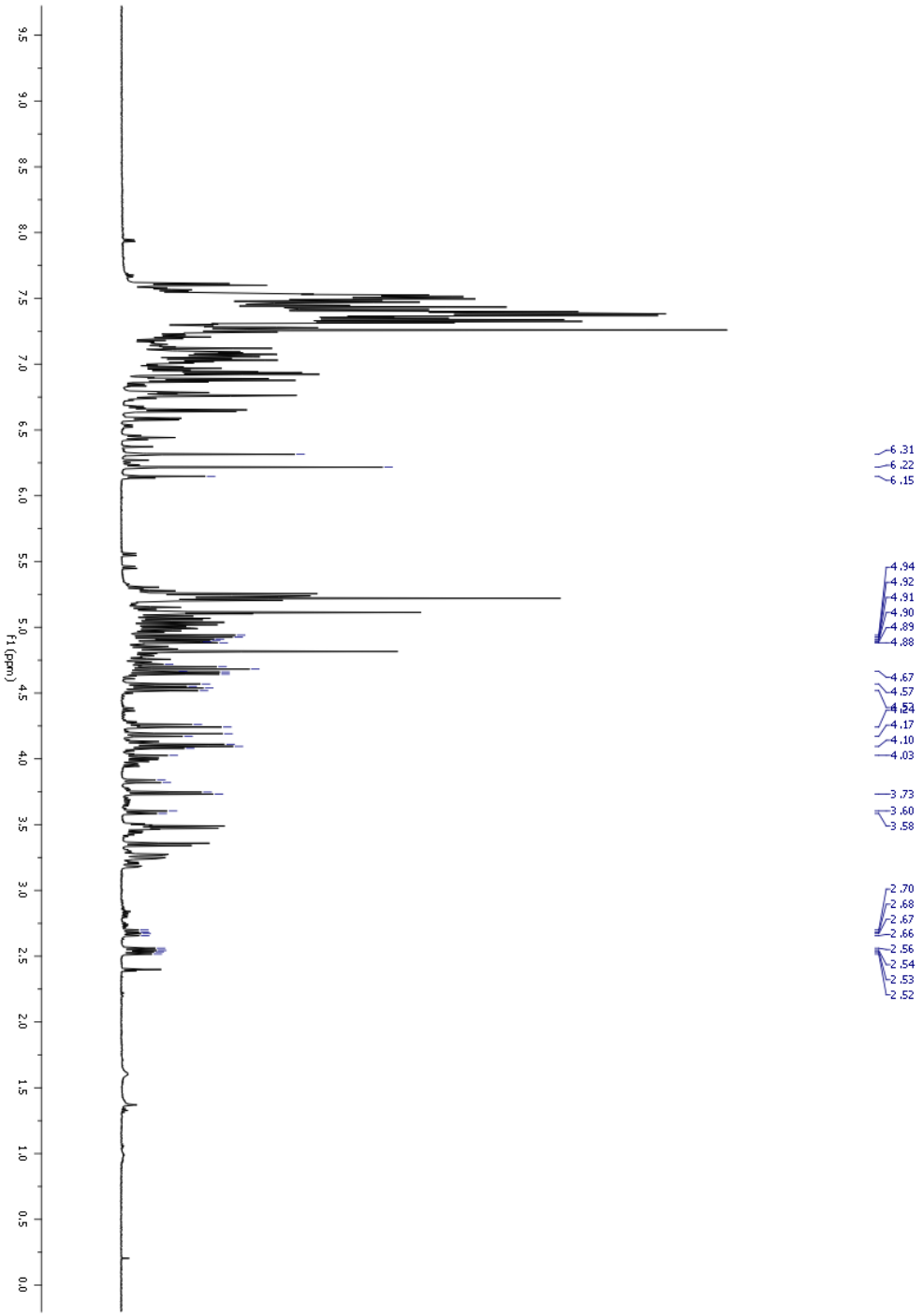


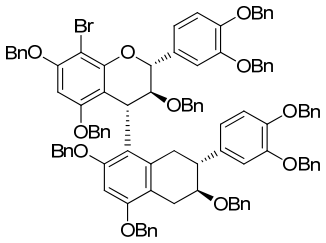


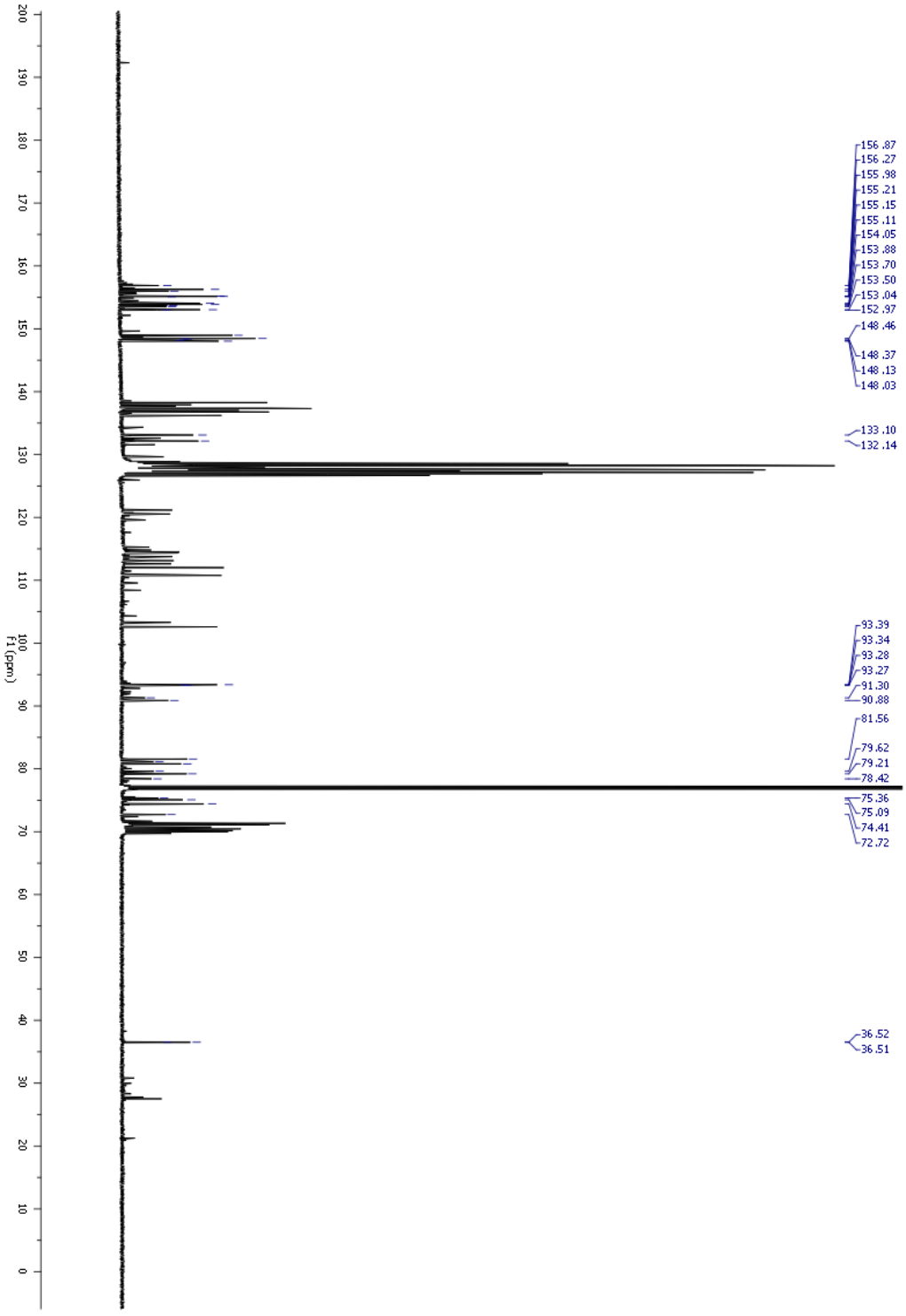
Appendix 2-F1. ^{1}H NMR for 8Br-PBC-PBC 105.



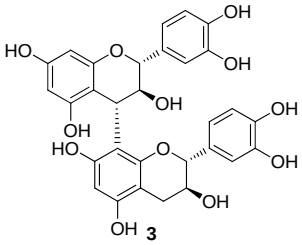


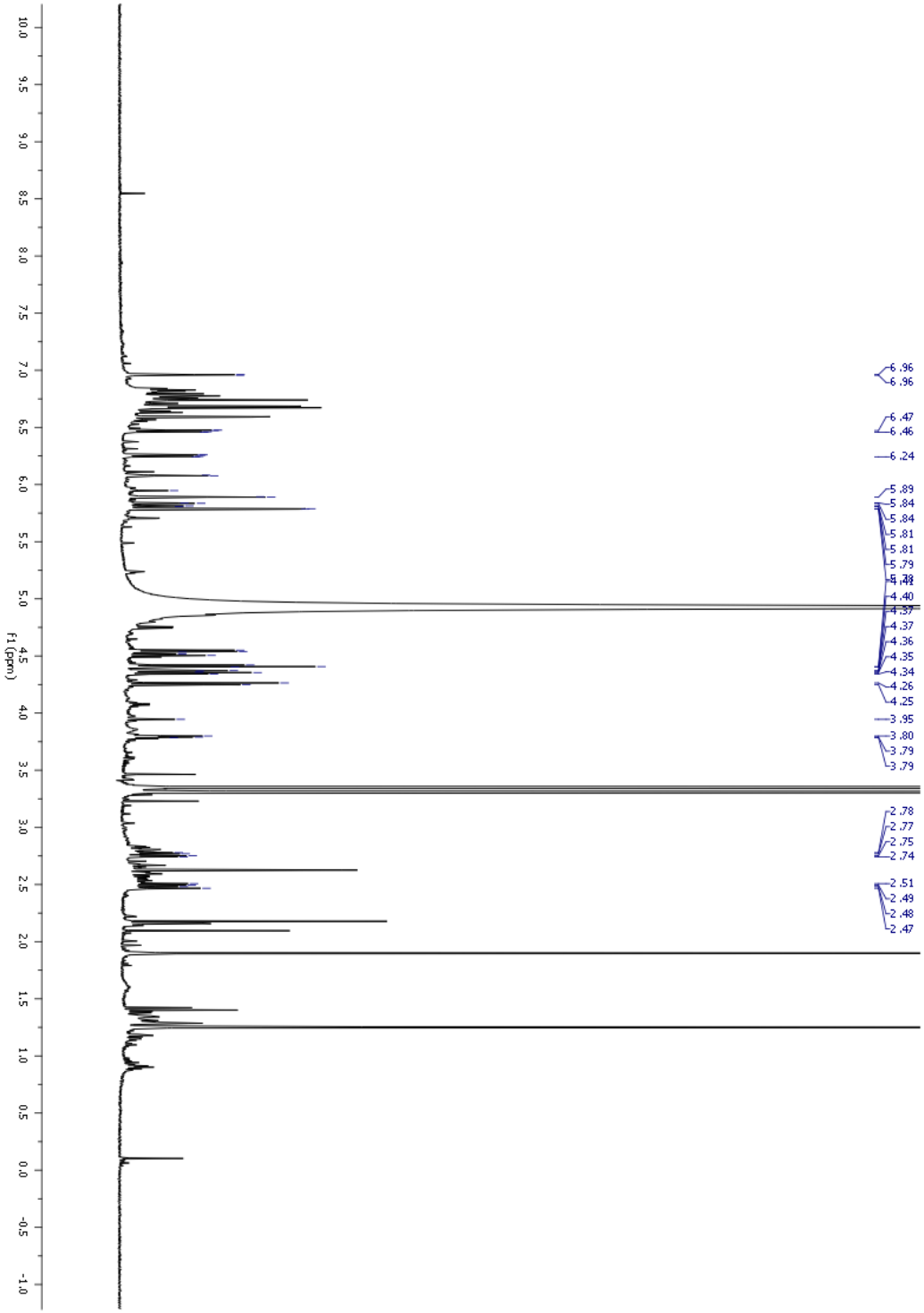
Appendix 2-F2. ^{13}C NMR for 8Br-PBC-PBC 105.



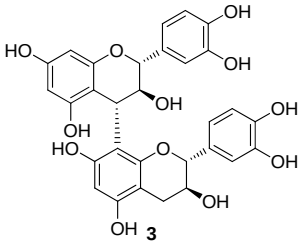


Appendix 2-G1. ^{1}H NMR for Procyanidin B3 (3).





Appendix 2-G2. ^{13}C NMR for Procyanidin B3 (3).



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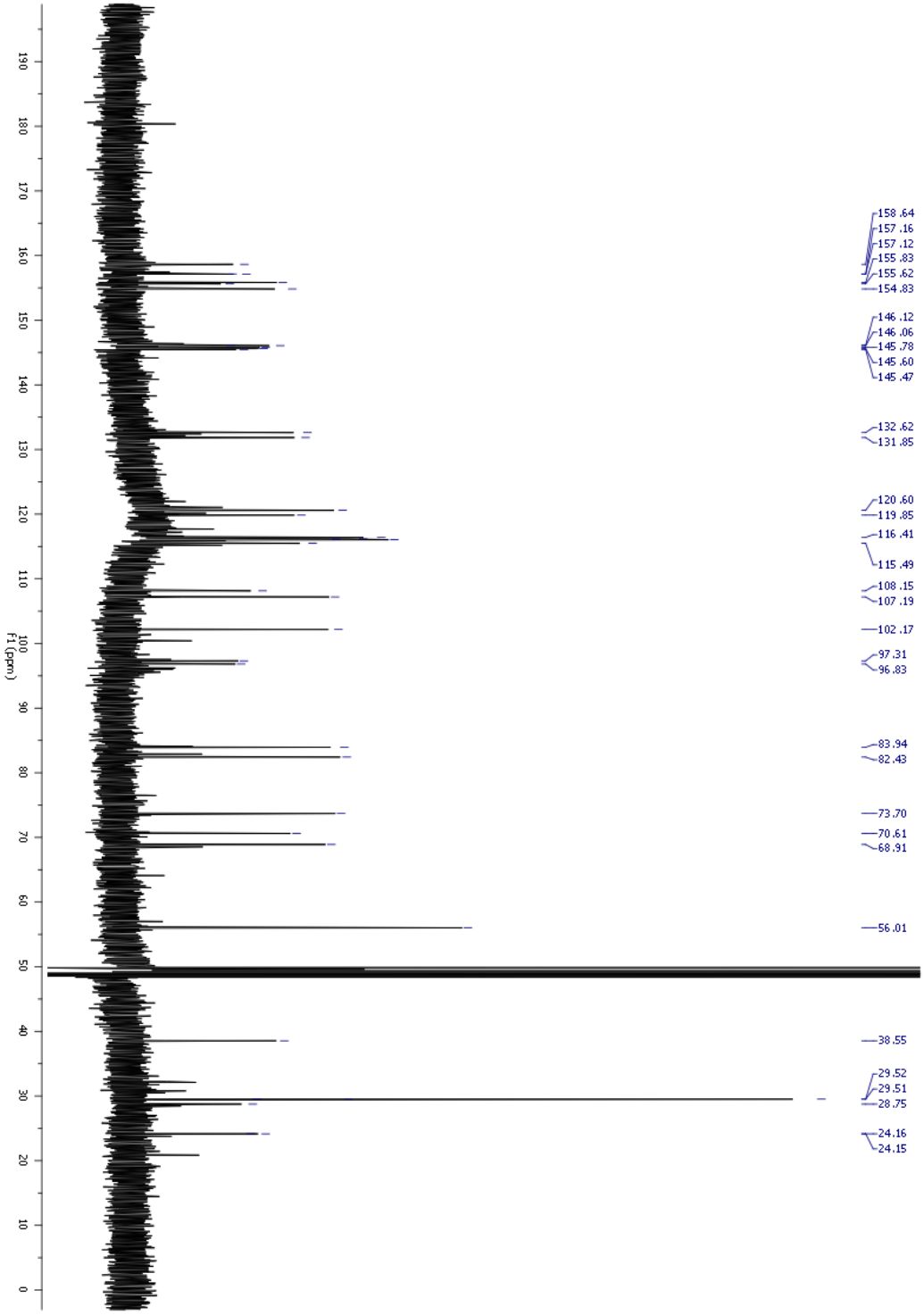
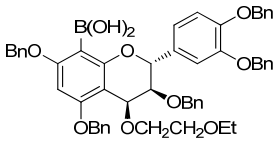
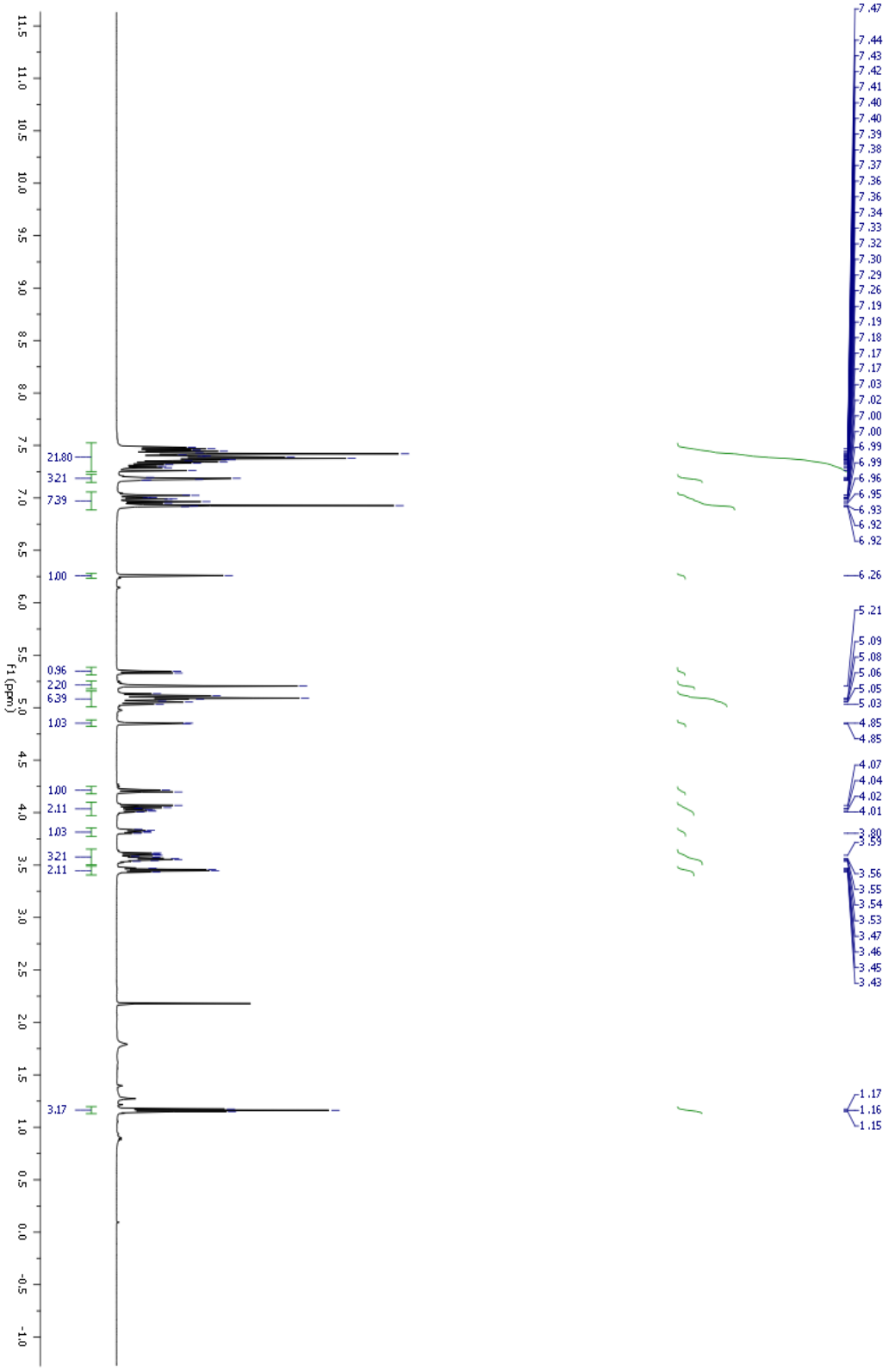


Appendix 2-H1. ^{1}H NMR for 8B(OH)$_2$-4EE-PBC 126.





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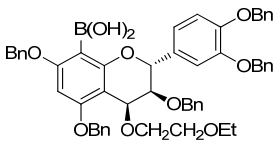
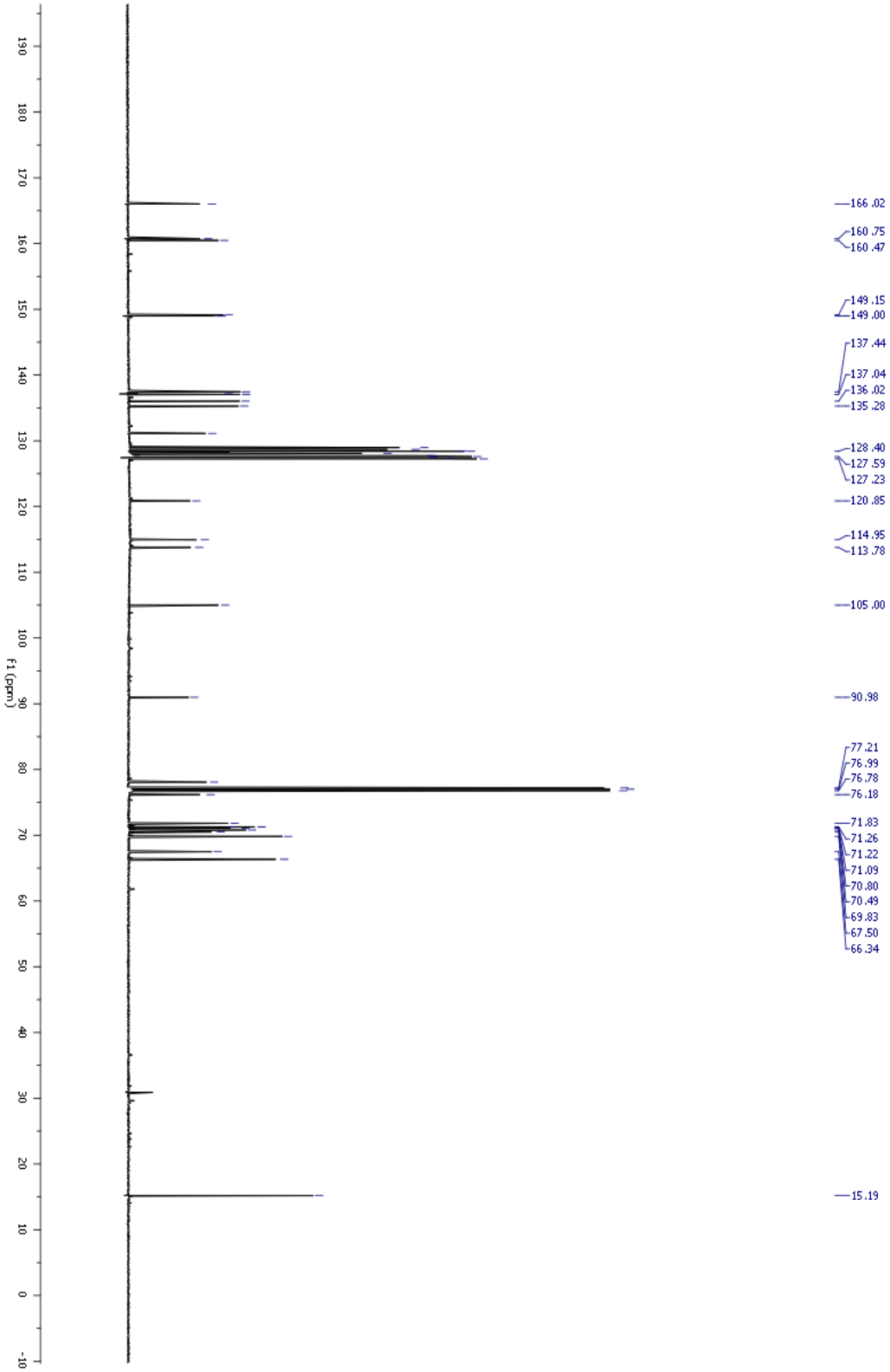
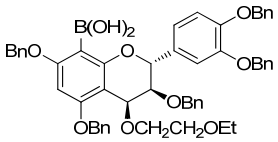
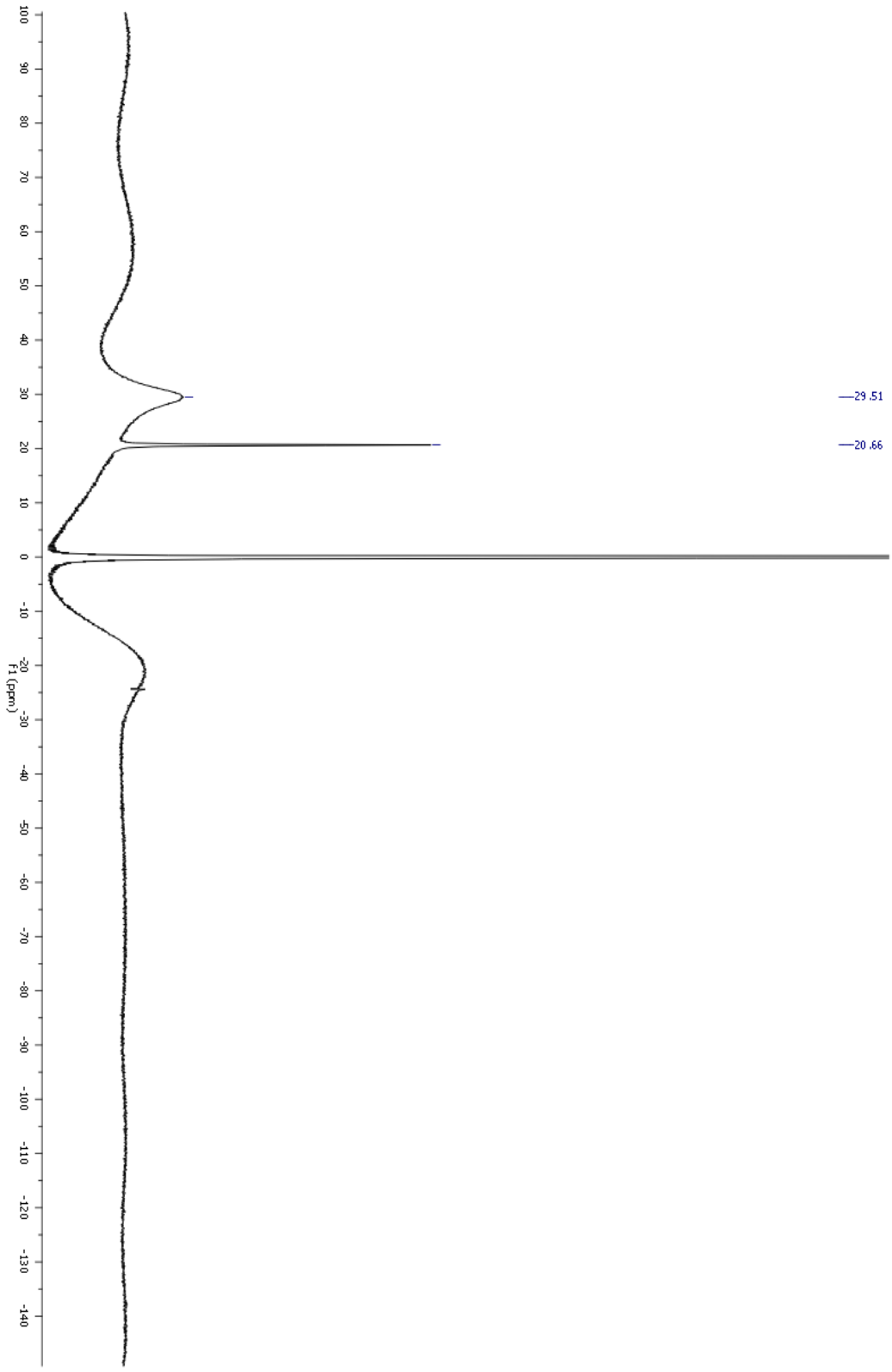


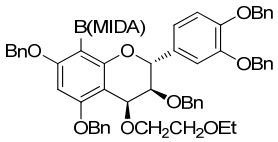


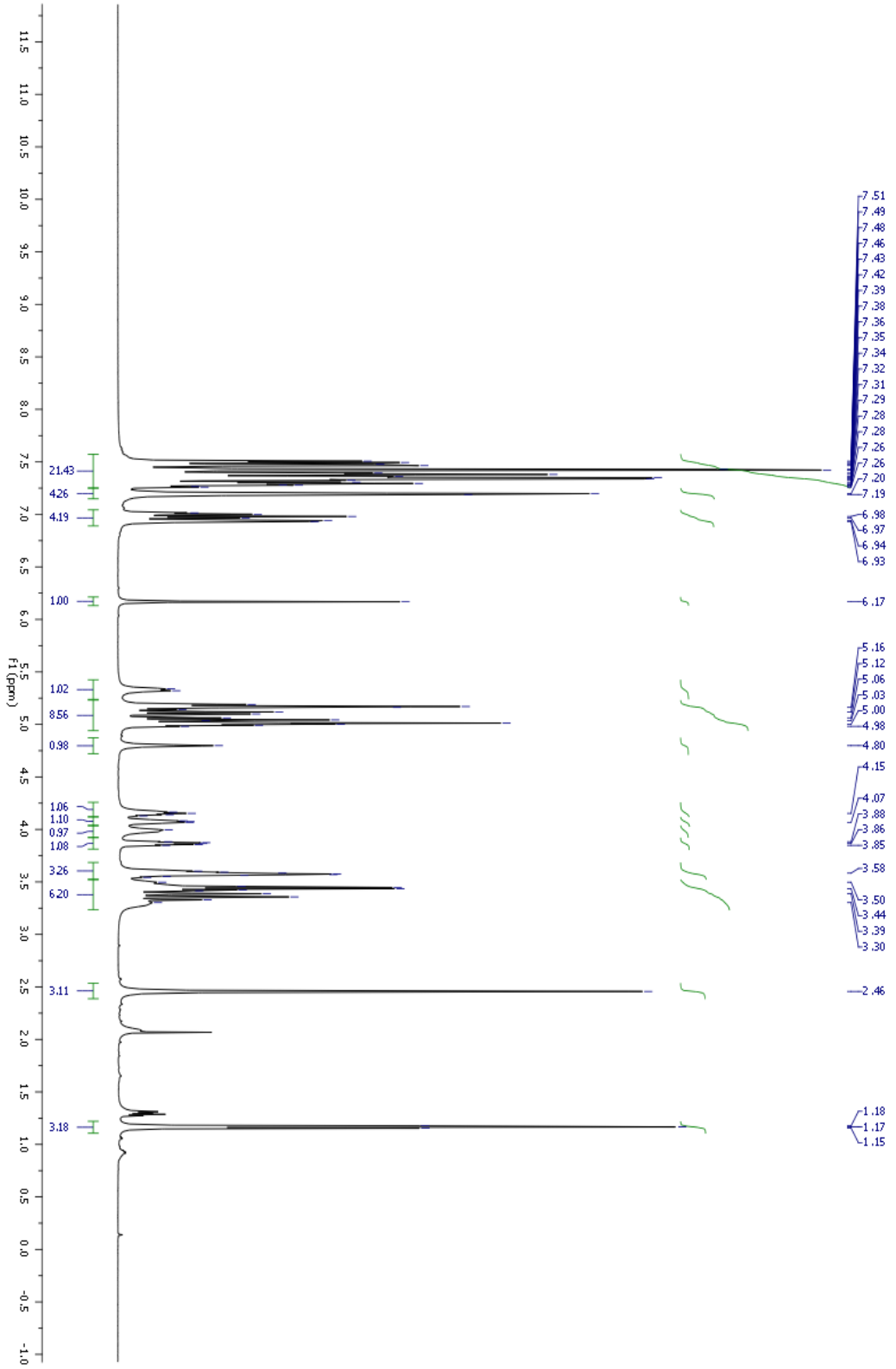
Appendix 2-H3. ^{11}B NMR for 8B(OH)$_2$-4EE-PBC 126.



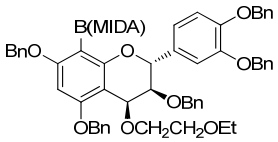


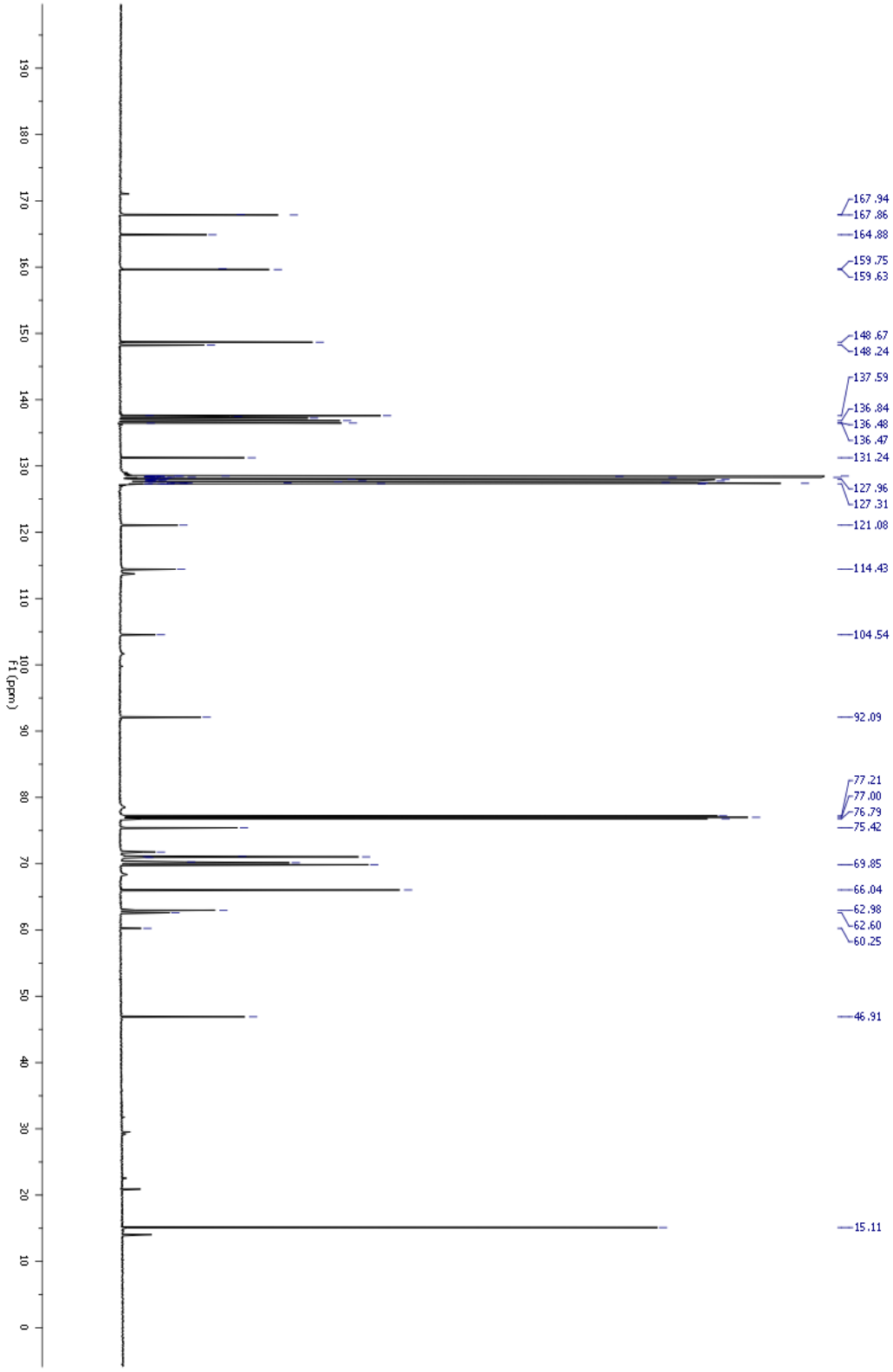
Appendix 2-I1. ^{1}H NMR for 8B(MIDA)-4EE-PBC 127.



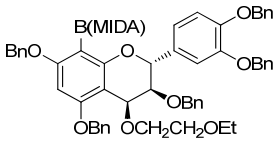


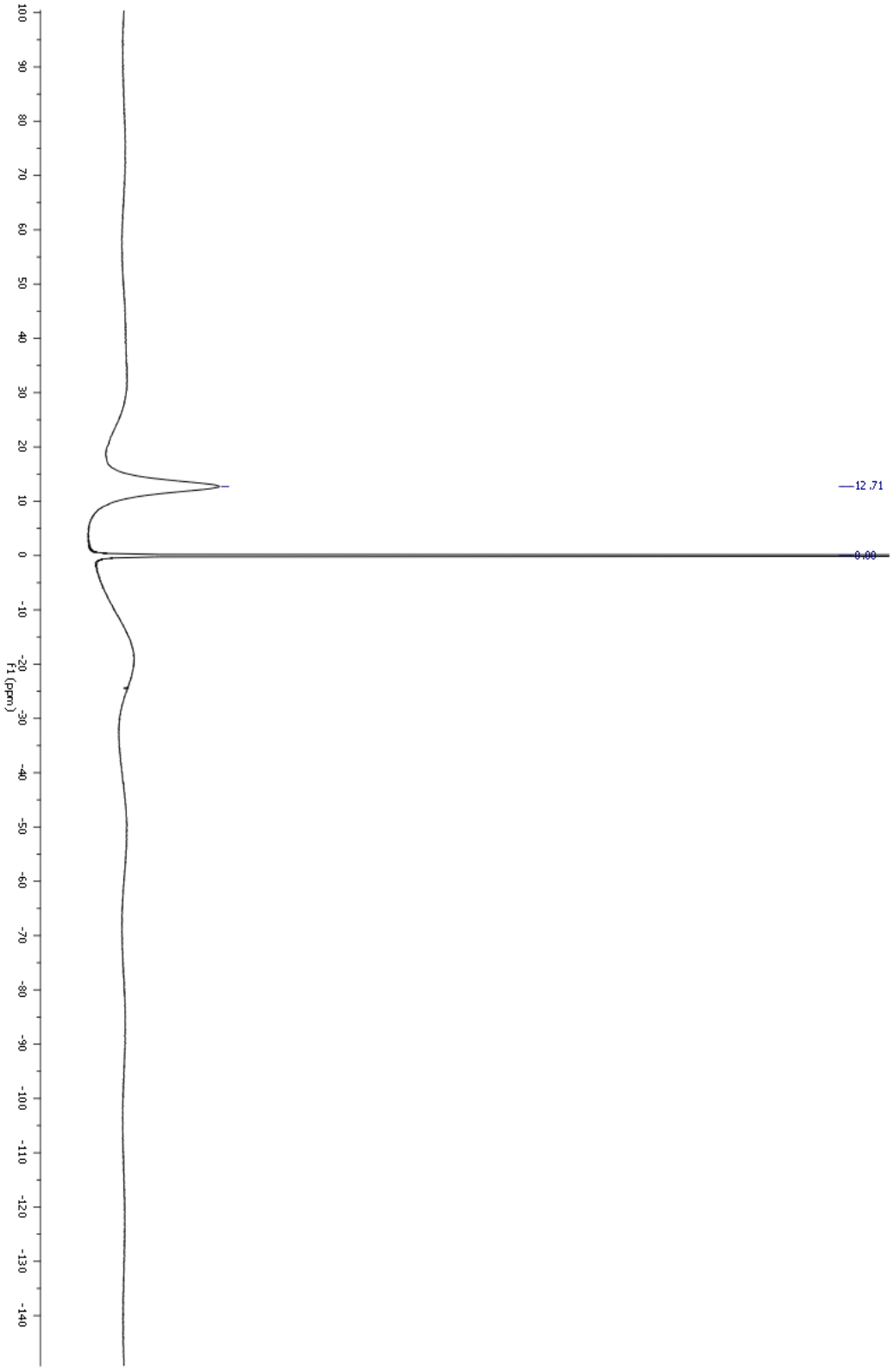
Appendix 2-I2. ^{13}C NMR for 8B(MIDA)-4EE-PBC 127.



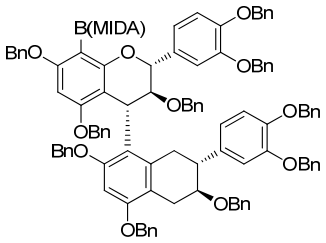


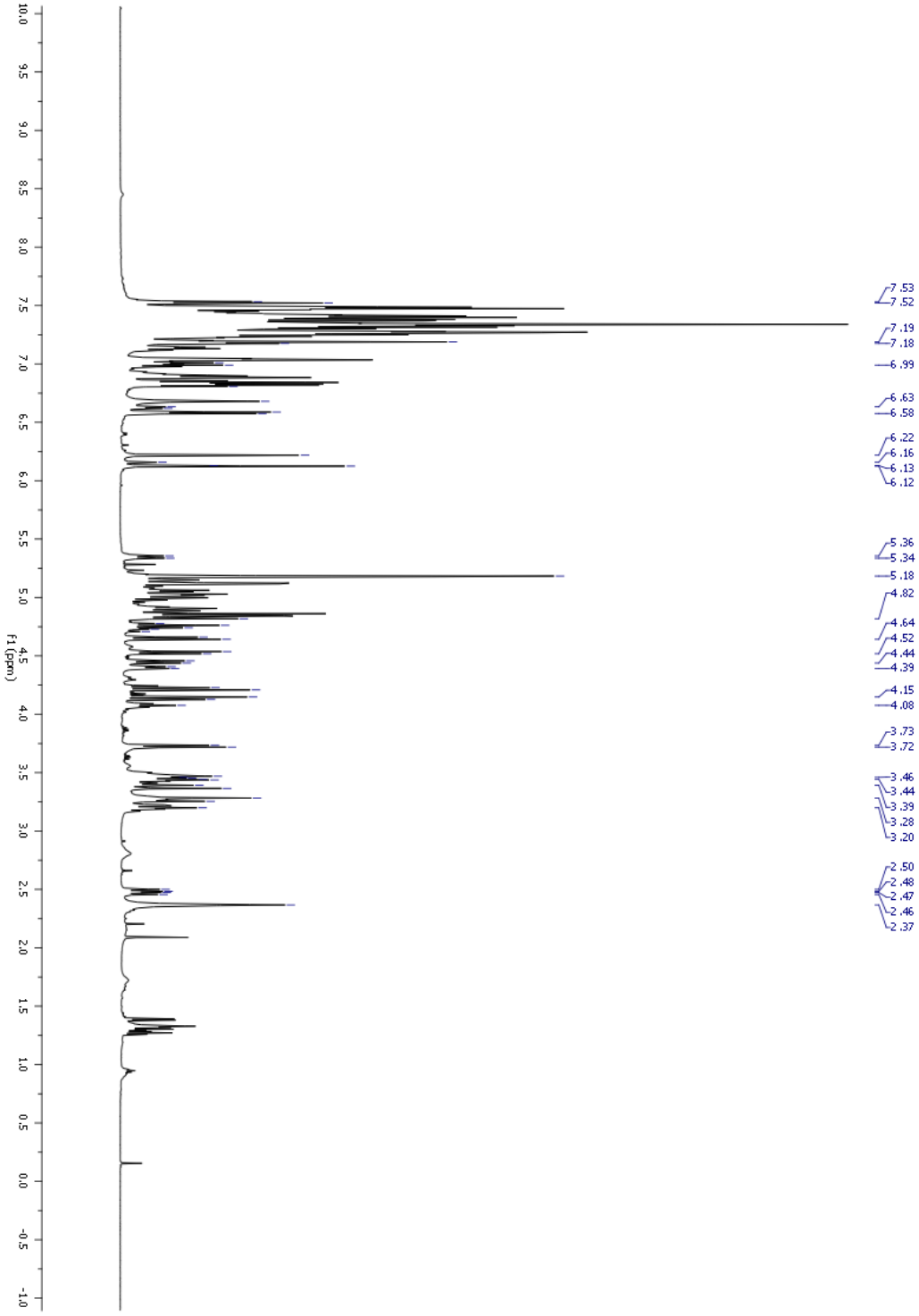
Appendix 2-I3. ^{11}B NMR for 8B(MIDA)-4EE-PBC 127.



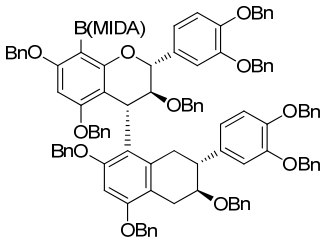


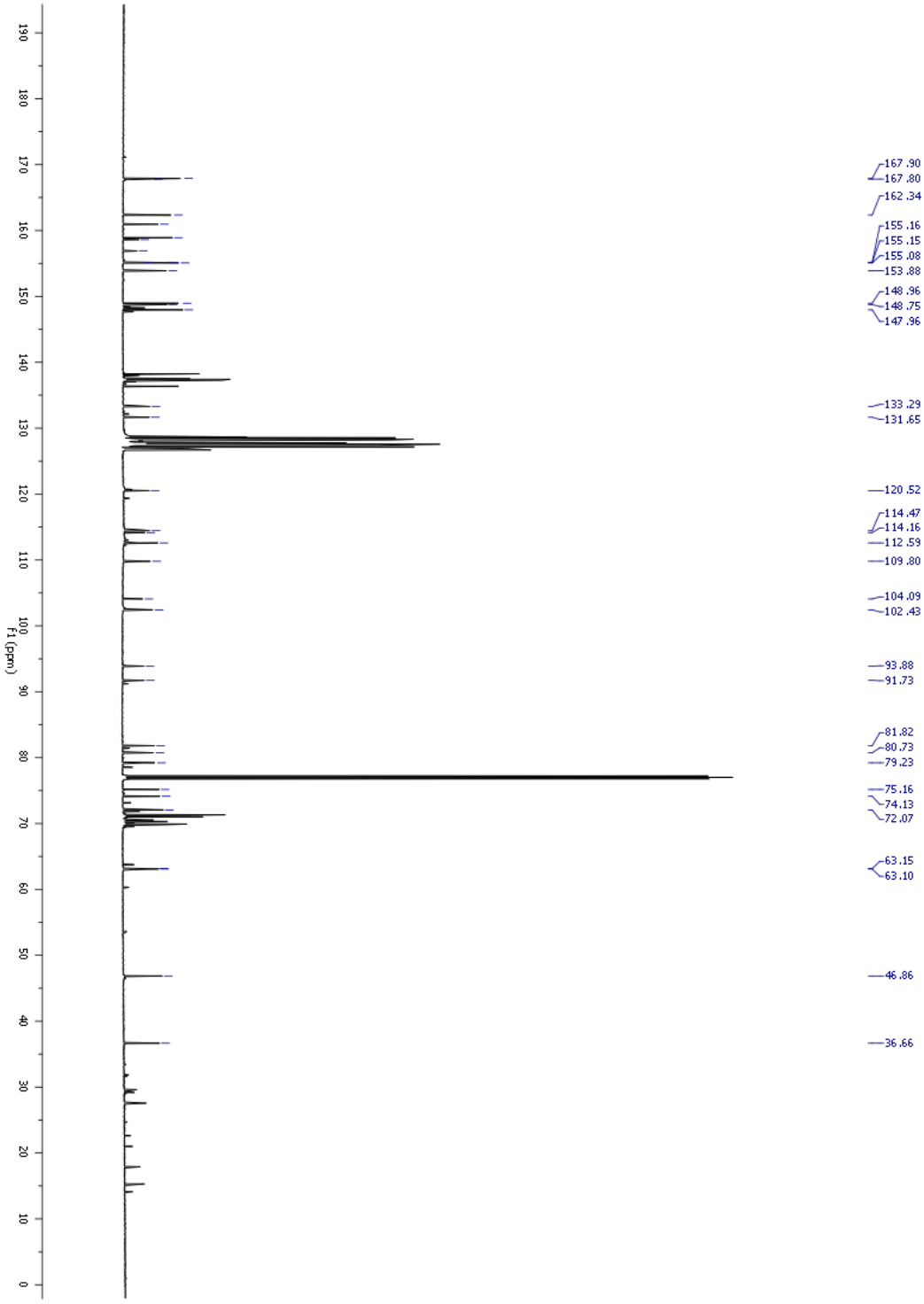
Appendix 2-J1. ^{1}H NMR for 8B(MIDA)-PBC-PBC 128.



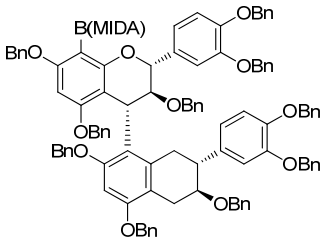


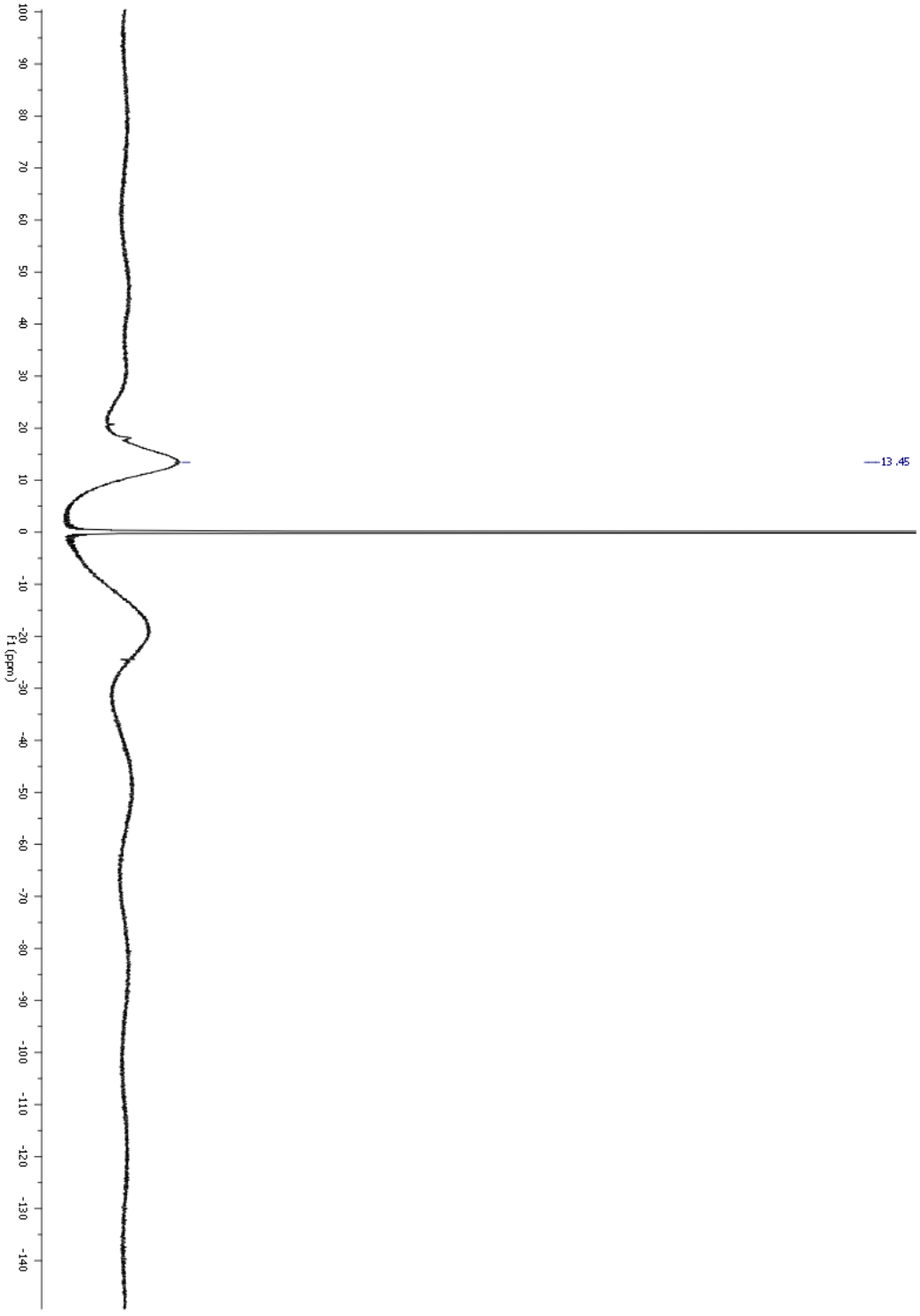
Appendix 2-J2. ^{13}C NMR for 8B(MIDA)-PBC-PBC 128.



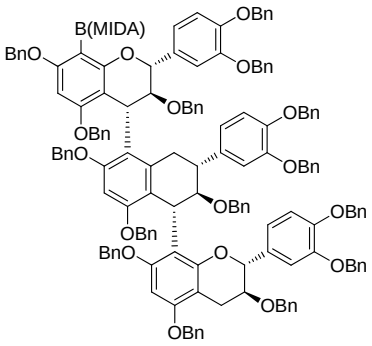


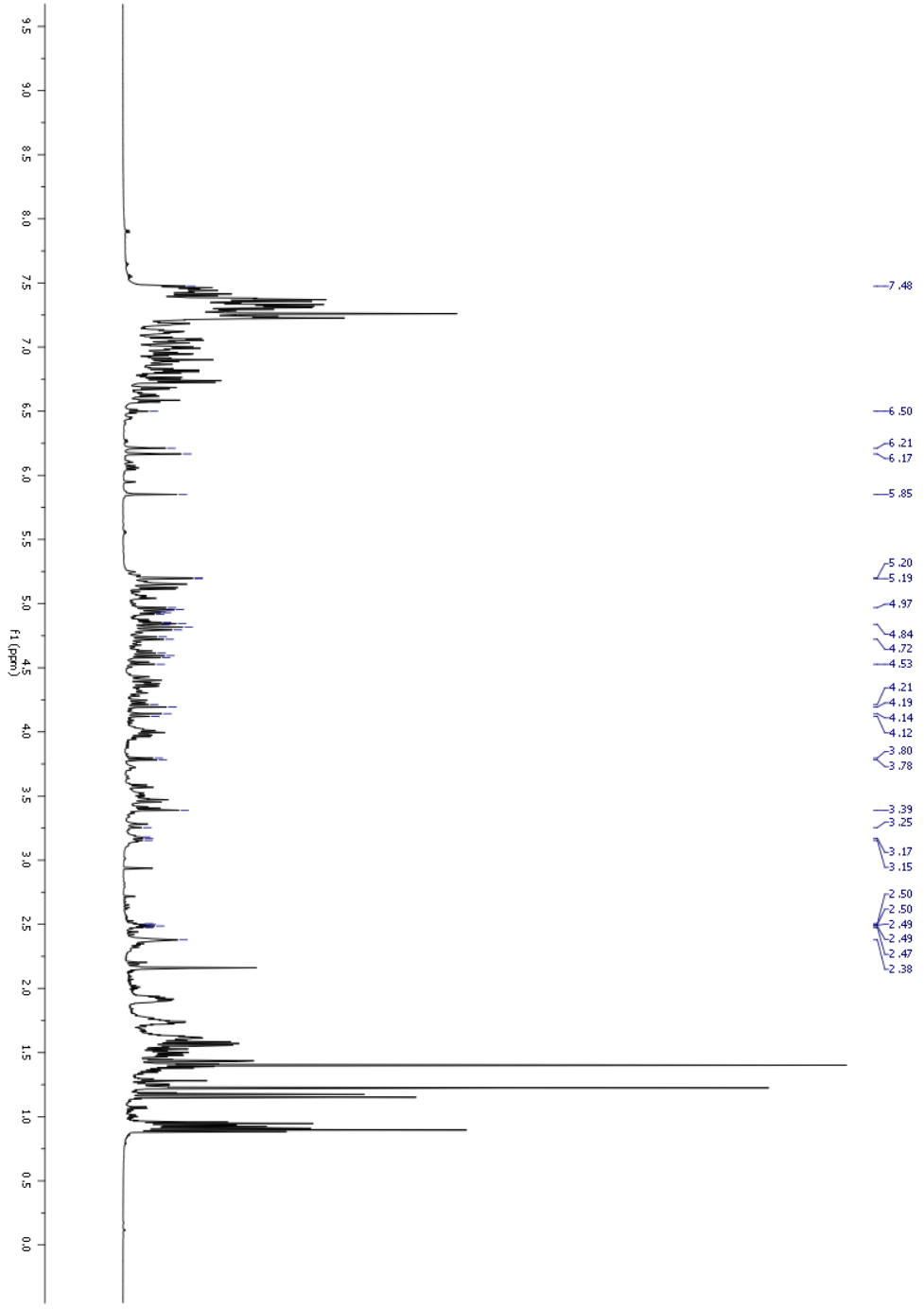
Appendix 2-J3. ^{11}B NMR for 8B(MIDA)-PBC-PBC 128.



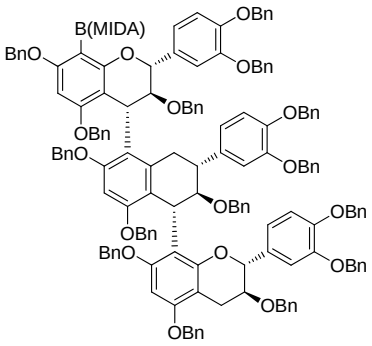


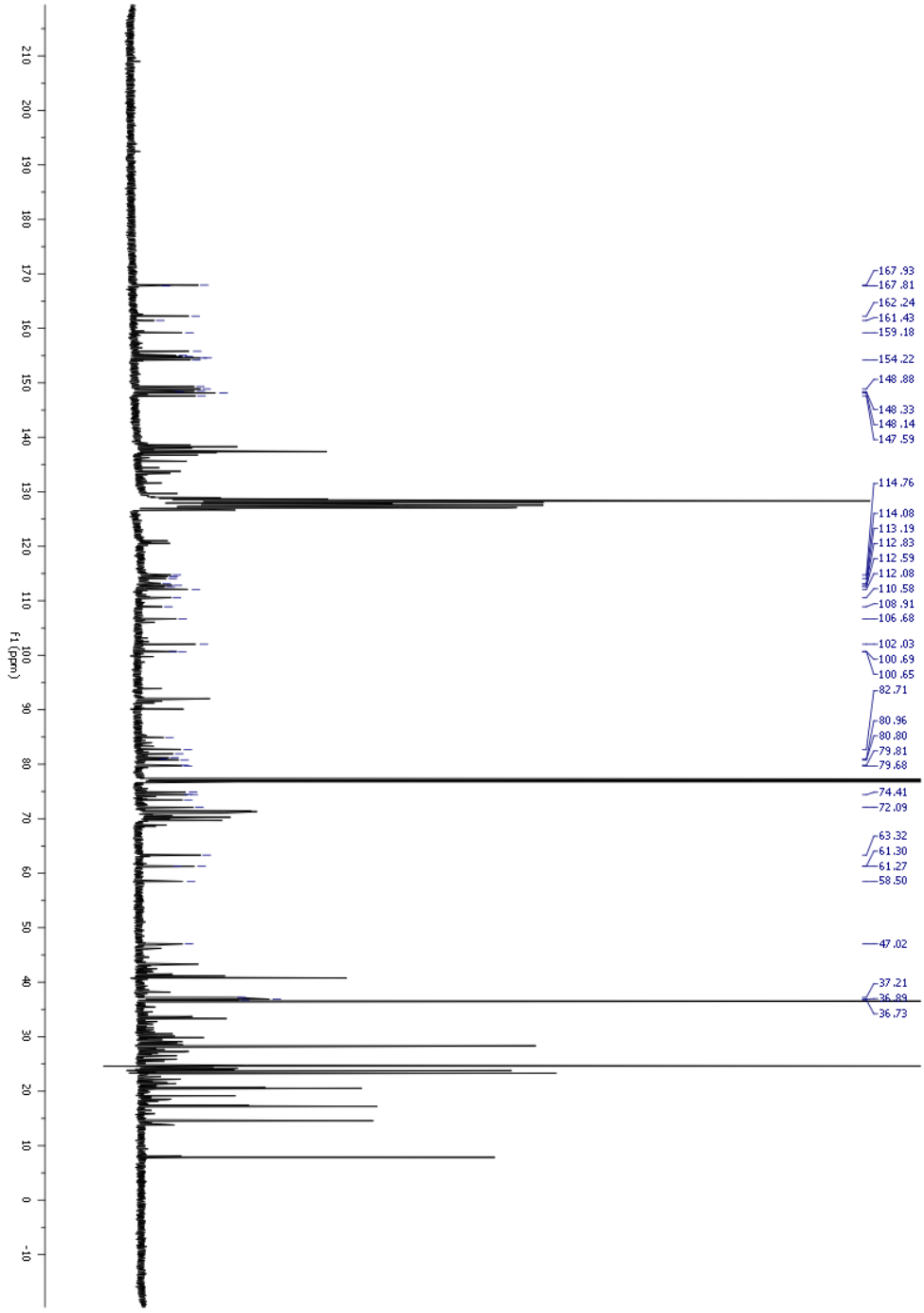
Appendix 2-K1. ^{1}H NMR for 8B(MIDA)-PBC-PBC-PBC 129.



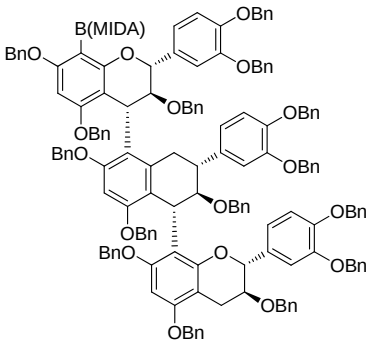


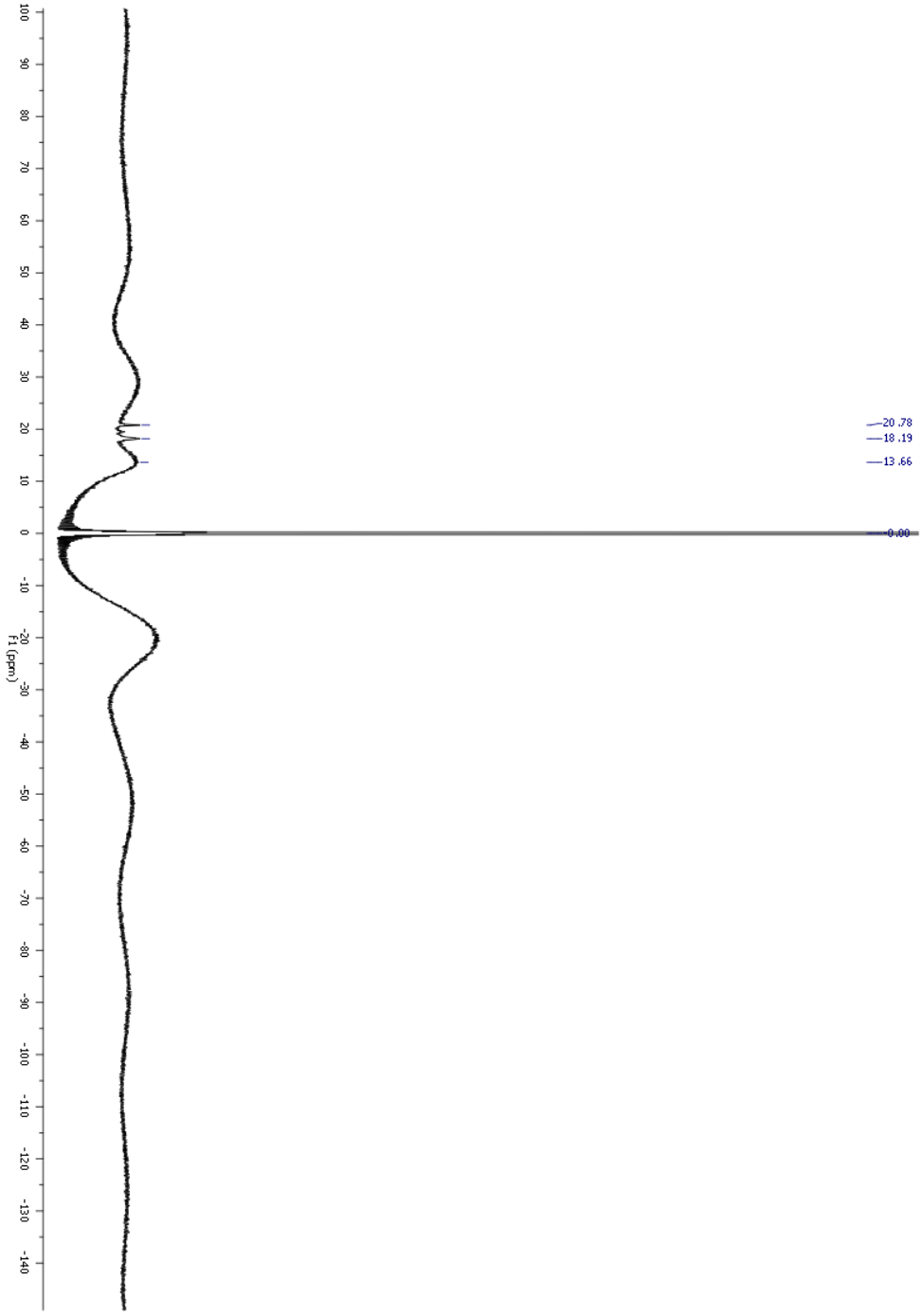
Appendix 2-K2. ^{13}C NMR for 8B(MIDA)-PBC-PBC-PBC 129.



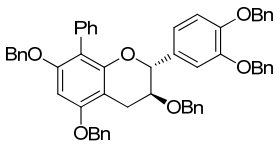


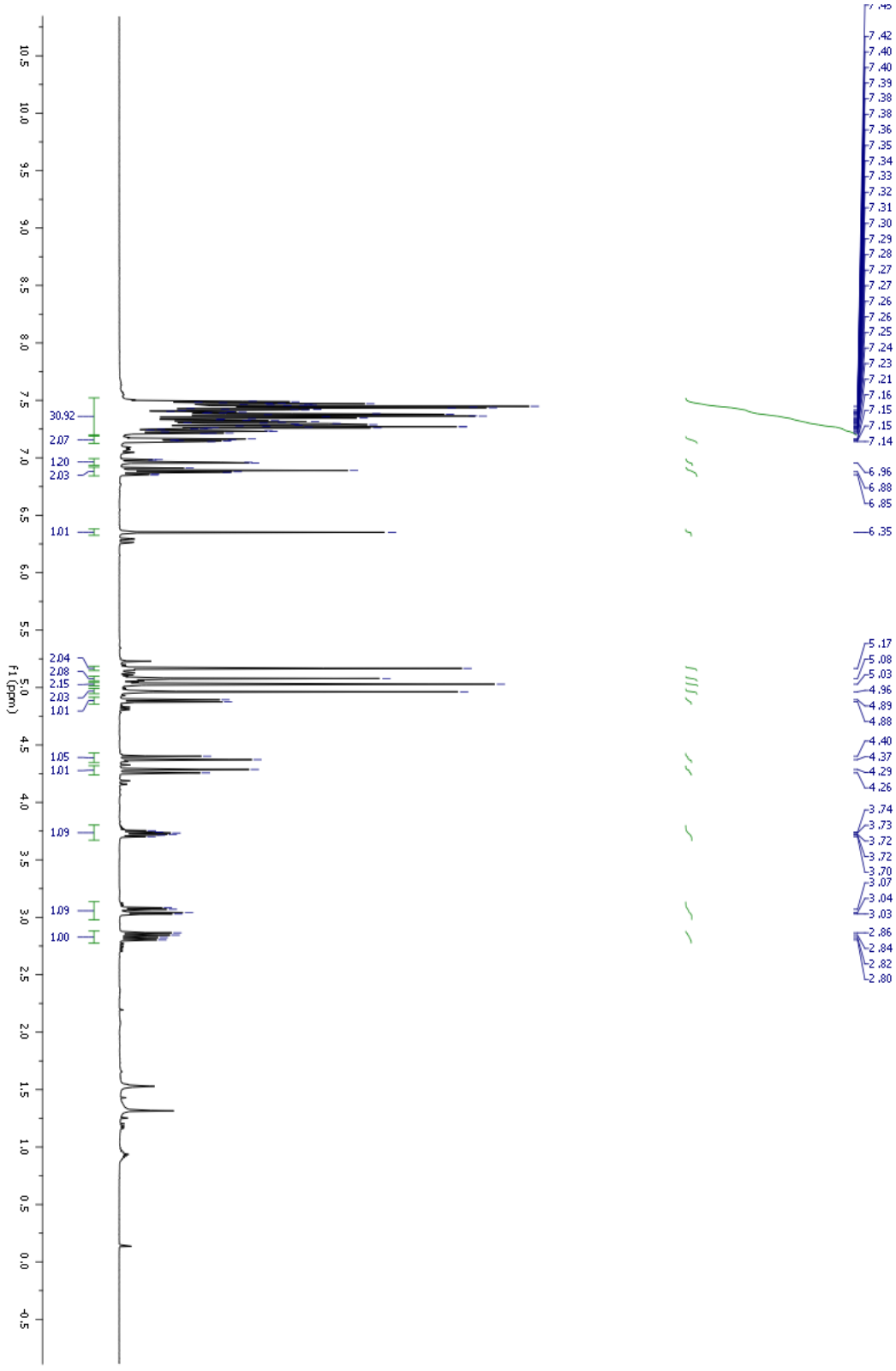
Appendix 2-K3. ^{11}B NMR for 8B(MIDA)-PBC-PBC-PBC 129.



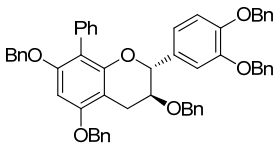


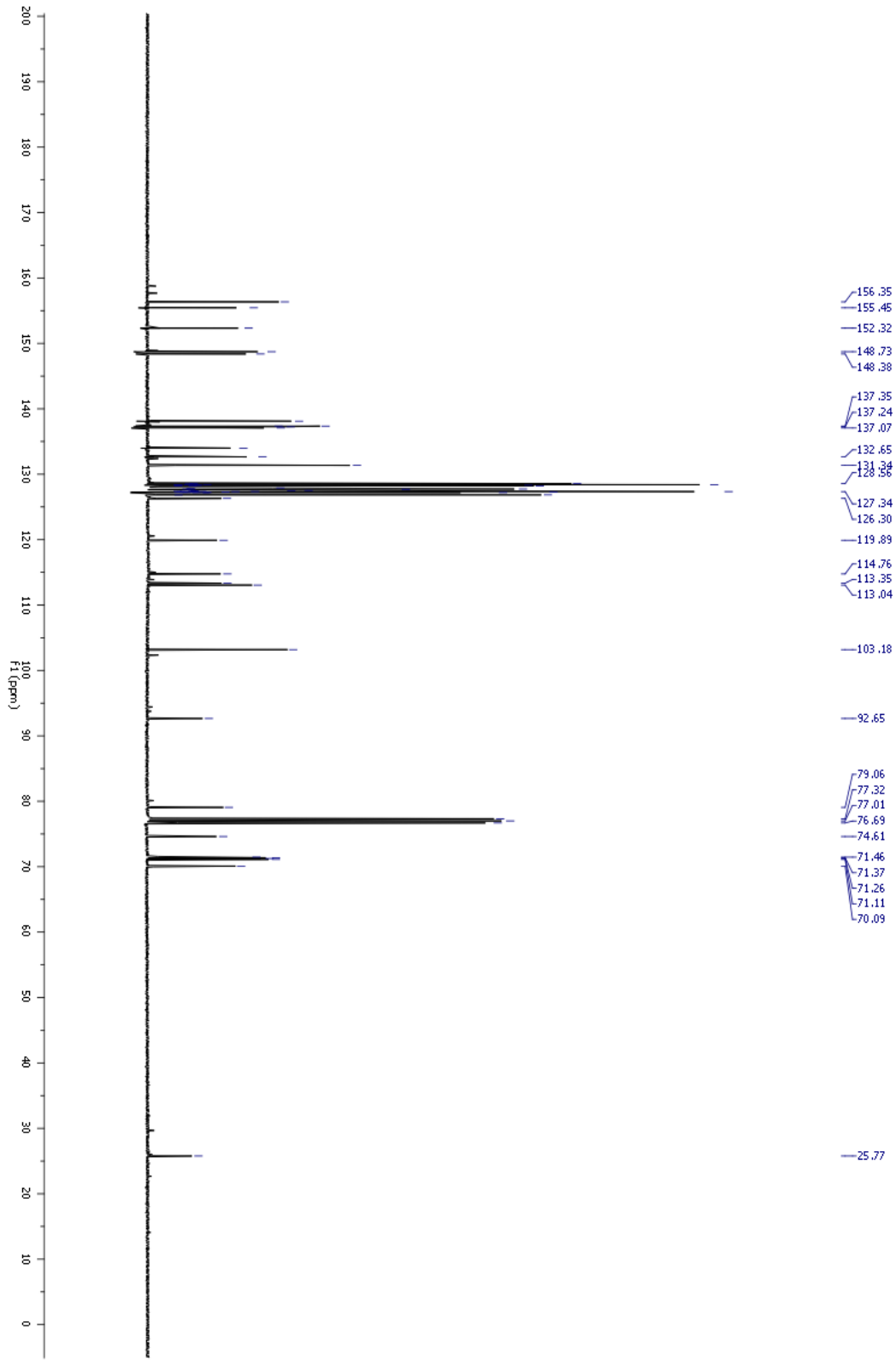
Appendix 2-L1. ^{1}H NMR for 8Ph-PBC 81b.



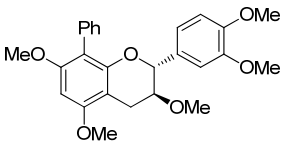


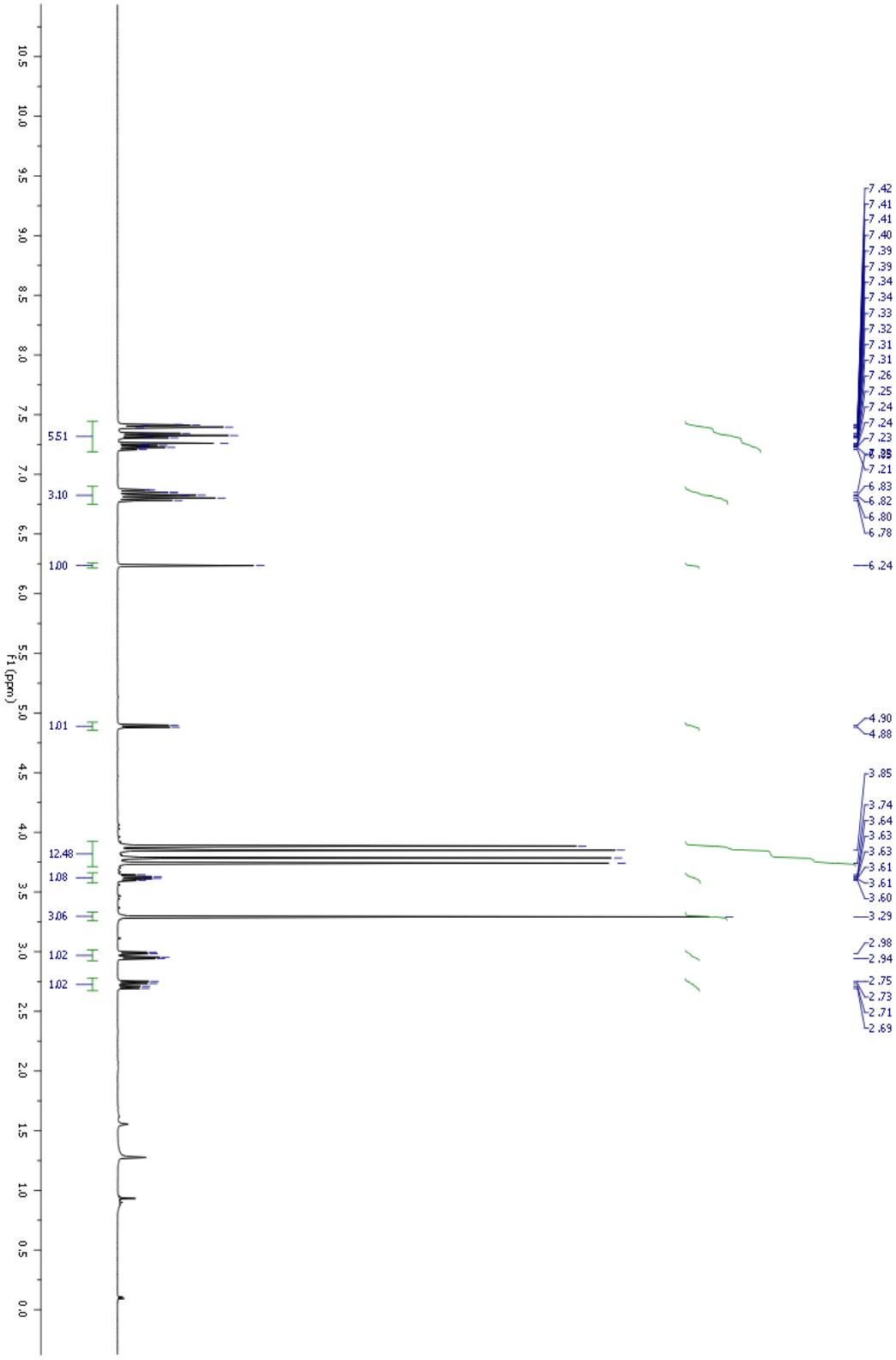
Appendix 2-L2. ^{13}C NMR for 8Ph-PBC 81b.





Appendix 2-M1. ^{1}H NMR for 8Ph-PMC 82b.





Appendix 2-M2. ^{13}C NMR for 8Ph-PMC 82b.