Procyanidin oligomers. A new method for 4→8 interflavan bond formation using C8-boronic acids and iterative oligomer synthesis through a boron-protection strategy.

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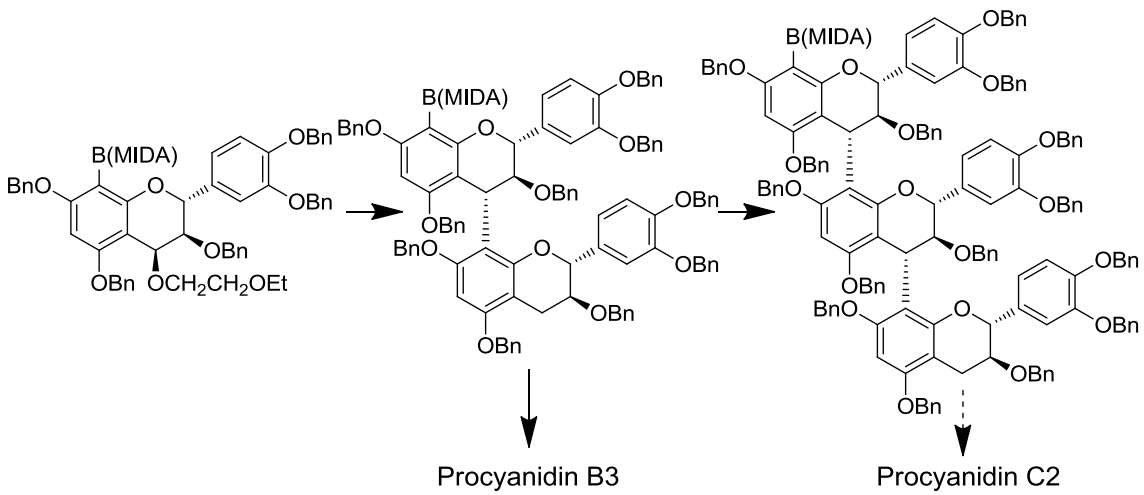
Graphical Abstract:



Abstract

Interest in the synthesis of procyanidin (catechin or epicatechin) oligomers that contain the 4→8 interflavan linkage remains high, principally due to research into their health effects. A novel coupling utilizing a C8-boronic acid as a directing group was developed in the synthesis of natural procyanidin B3 (i.e. 3,4-*trans*-(+)-catechin-4α→8-(+)-catechin dimer). The key interflavan bond was forged using a novel Lewis acid-promoted coupling of C4-ether **6** with C8-boronic acid **16** to provide the α–linked dimer with high diastereoselectivity. Through the use of a boron protecting group, the new coupling procedure was extended to the synthesis of a protected procyanidin trimer analogous to natural procyanidin C2.

Keywords: iterative synthesis, procyanidin oligomers, Lewis acid-promoted coupling, benzyl ether, procyanidin B3, boron protection.

1. Introduction.

1.1 Proanthocyanidins in nature and their significance.

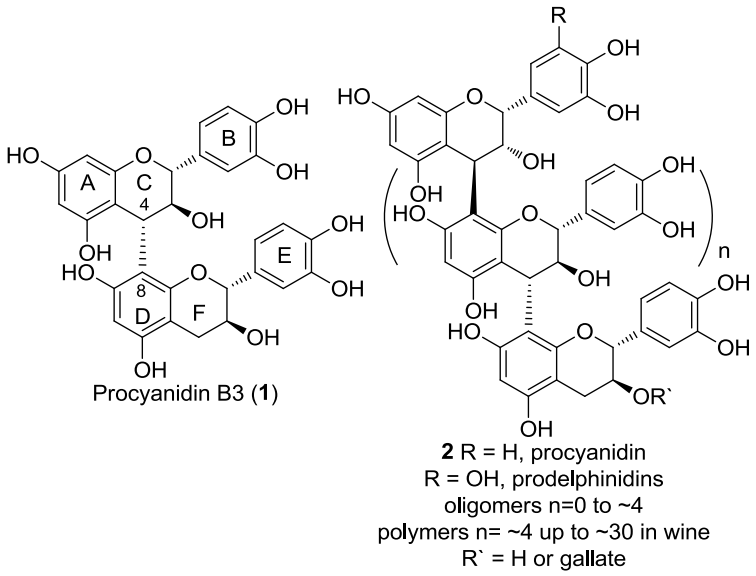
Proanthocyanidins, or condensed tannins, are a class of polyphenolic compounds that are found widely throughout nature, being obtained from many plant sources[1,2] including grapes[3] and wine.[4] The term proanthocyanidins covers closely related compounds (differing in B ring substitution) termed procyanidins (catechol ring) or prodelphinidins (pyrogallol ring) (**Figure 1**). The last two decades have seen an increasingly widespread interest in these compounds, principally due to their beneficial health effects.[2,5] 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] Proanthocyanidins also play important functions in some sensorial properties of red wine, particularly in astringency[9] and color stabilization.[10]

Given the diversity of the compounds encompassed under the banner of proanthocyanidins, there has been a desire to understand the structure-activity relationships which may exist for their biological and sensorial properties.[11] In order to study these relationships, pure, defined proanthocyanidin samples are required. As a consequence, synthesis from known starting materials has become an increasingly popular method used to obtain these compounds with known purities and defined structures.

1.2 Procyanidin oligomer synthesis.

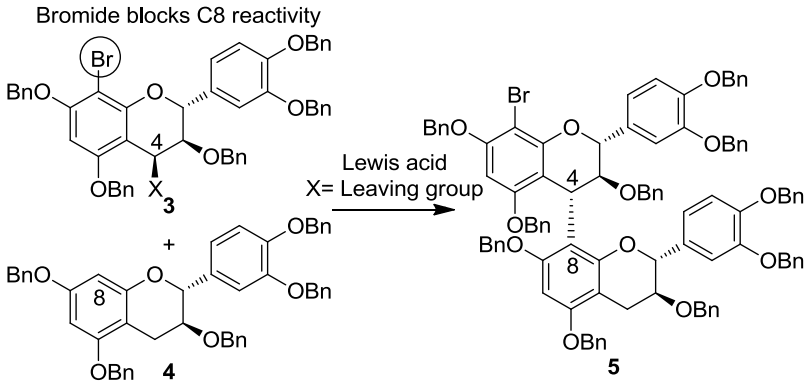
The synthesis of procyanidin ((epi)catechin) oligomers that contain the 4→8 interflavan linkage has been of particular interest (e.g. procyanidin B3, **Figure 1**). In efforts to produce pure, defined oligomers, the iterative synthesis of such compounds has been the focus of a number of studies.[12,13] However, efforts towards such iterative syntheses have been hampered due to the high chemical reactivity of these compounds,[12,14] which tend to react non-selectively to form polydisperse oligomeric mixtures. Controlling the degree of oligomerisation stands as the major challenge that needs to be addressed for successful iterative synthesis of procyanidin oligomers.

Figure 1: Procyanidin B3 (**1**) and representative 4→8 proanthocyanidin oligomers depicted by **2**.



Dimers, the simplest of all proanthocyanidin oligomers, have been primary targets of many selective oligomer syntheses.[15] Two notable selective syntheses of (epi)catechin dimers were reported by Ohmori *et al.*[12] and Tarascou *et al.*[13] Both used a C8-bromide (e.g. **3**) which played a critical role in blocking the formation of higher oligomers, leading to the selective formation of the desired protected dimer(s) (e.g. **5**, **Scheme 1**).

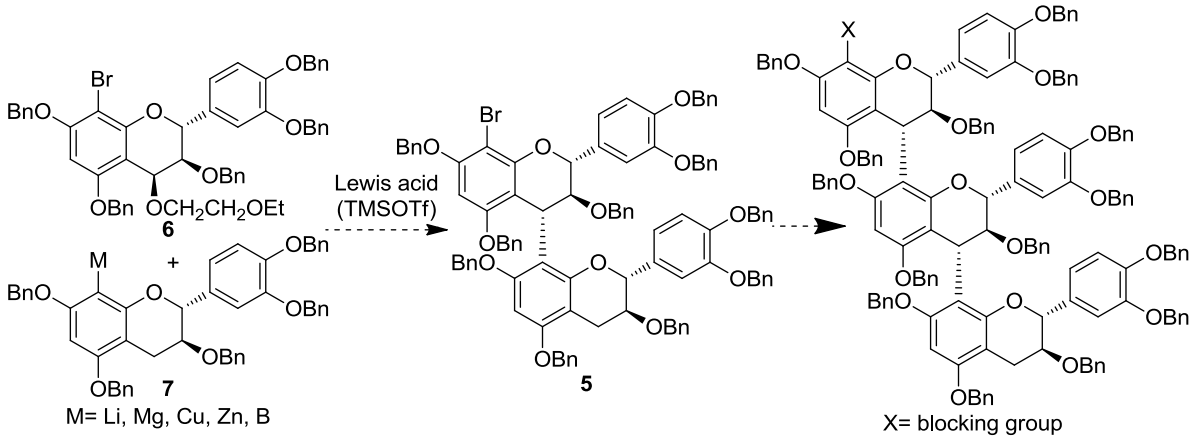
Scheme 1: Dimer formation using a C8 bromide blocking group to prevent uncontrolled oligomerisation.



Surprisingly, little attention has been focused on the use of C8-organometallic derivatives as directing groups for the selective synthesis of 4→8 oligomers. The only such report by Kozikowski *et al*. involved the addition of a C8-organolithium to a C4-ketone derivative.[16] This synthesis ultimately resulted in the formation of an unnatural 3,4-*cis*-epicatechin-

epicatechin dimer. In this context, the synthesis of the 3,4-*trans* catechin-catechin dimer (procyanidin B3, **1**) and iteration to analogous trimer were targeted using a C8-organometallic derivative to direct the formation of the 4→8 interflavan bond (e.g. **Scheme 2**). A C8-blocking group was viewed as an important component for controlled procyanidin synthesis.

Scheme 2: Interflavan bond formation through Lewis acid-promoted condensation of C4-ether **6** and a C8-organometallic **7**.



2. Results and discussion.

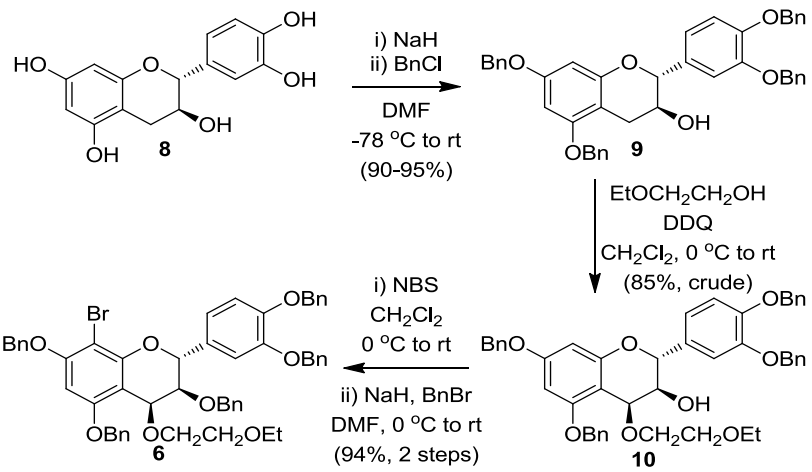
2.1 Synthetic approach.

Following a recent model study,[17] the synthesis of the key 3,4-*trans* 4→8 interflavan bond was approached using the Lewis acid-promoted coupling strategy depicted in Scheme 3. Related couplings by Saito *et al.*[18] have successfully employed this ethoxyethyl-C4-ether/Lewis acid combination for the selective, high yielding syntheses of 3,4-*trans* 4→8 linked (epi)catechin oligomers. In this case, the C8-bromide of C4-ether **6** was included to prevent formation of higher oligomers without requiring a large excess of nucleophile **7** (**Scheme 2**).

C4-Ether **6** was obtained in four steps from (+)-catechin (**8**) (**Scheme 3**). Benzyl protection of (+)-catechin (**8**) using NaH and BnCl in DMF employing a method adapted from Mustafa *et al.*[19] furnished tetrabenzyl ether **9** in excellent yields (90-95%) using 5-10 g of **8**. DDQ-mediated C4-oxidation of **9** using the method described by Saito *et al.*[18b] afforded the desired C4-*β*-ether **10** in 85% crude yield as a single stereoisomer (by ^{1}H NMR). Treatment of 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 yield in 4 steps) following purification by silica chromatography.

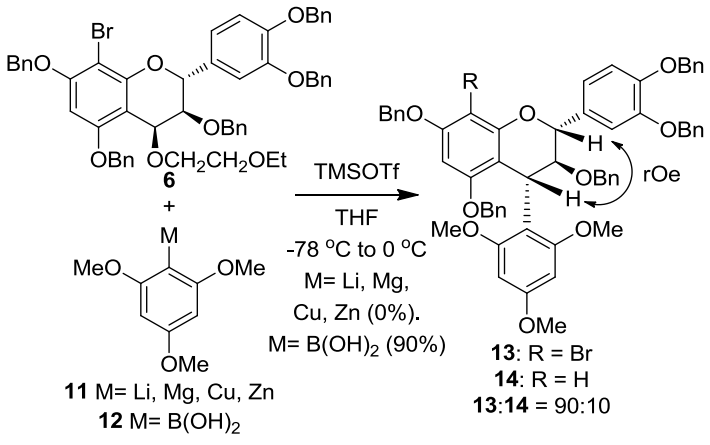
Scheme 3: Synthesis of C4-ether **6** from (+)-catechin (**8**).



2.2 Couplings of C4-ether 6 with model organometallic reagents.

Successful coupling of the C4-ether **6** required an appropriate organometallic **7** (**Scheme 2**) to use in the Lewis acid-promoted 4→8 coupling reaction. This was initially explored using the model system depicted in **Scheme 4**. 2,4,6-Trimethoxyphenylmetal derivatives **11** and **12** were chosen as suitable model species due to their identical phenyl ring oxygenation pattern to that of a C8-organometallic species such as **7** derived from (+)-catechin (**8**).

Scheme 4: Model system Lewis acid-promoted coupling of C4-ether **6** with 2,4,6-trimethoxyphenylmetal species **11** or **12**.



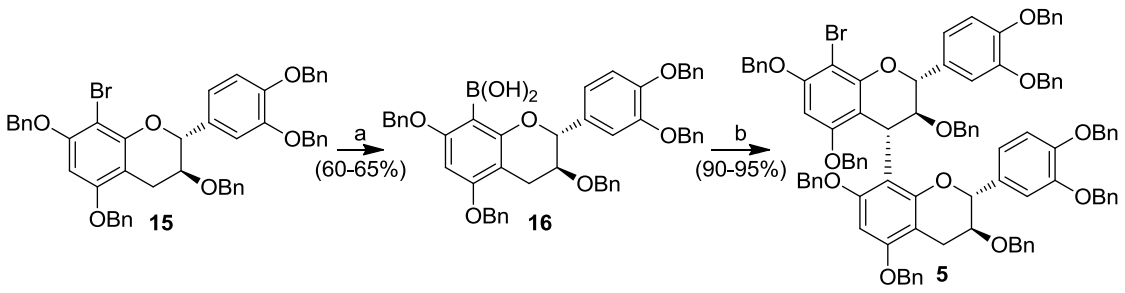
After trialling numerous organometallic species **11** (M = Li, Mg, Cu, Zn) without success, 4-arylflavan adduct **13** was successfully synthesised in 90% yield through the coupling of

2,4,6-trimethoxyphenylboronic acid [17,20] (**12**) (M = $B(OH)_2$) with C4-ether **6** (**Scheme 4**). The reaction product **13** contained 5-10% of an inseparable impurity. While the identity of the impurity was not confirmed, it was presumed to be the non-brominated 4-arylflavan moiety **14**. To the best of our knowledge the coupling of **6** and **12** represents the first such report of a Lewis acid-promoted coupling of an arylboronic acid with a benzyl ether. Notably, the desired 3,4-*trans* isomer of **13** was produced in >90% diastereomeric excess using this method. A ROESY NMR experiment confirmed this stereochemistry. An rOe interaction was observed between C2-H and C4-H, which showed that these two protons were on the same side of the heterocyclic C-ring. (**Scheme 4**) This rOe indicated that **13** possessed the desired 3,4-*trans* stereochemistry, with further confirmation provided by the large H_3-H_4 coupling constant (J = 8.2 Hz). Since the concept of using a C8-organometallic in a 4→8 style coupling was confirmed with model boronic acid **12**, compound **13** was used without further purification.

2.3 Synthesis of C8-boronic acid 16 and its application in 4→8 dimer synthesis.

After the successful application of boronic acid **12** in the synthesis of 4-arylflavan **13**, attention then turned towards using this method to produce the protected catechin-catechin dimer **5**. Prior to this, C8-boronic acid derivative **16** was synthesised from C8-bromide **15** [16] in good yields (**Scheme 5**). This was accomplished by low temperature lithium-halogen exchange of **15** with *n*-butyl lithium in THF, followed by transmetallation with excess $B(OMe)_3$. *In situ* aqueous hydrolysis provided boronic acid **16**. This series of transformations showed a marked scaling effect. No boronic acid **16** was formed using less than 0.5 mmol of the starting bromide **15**. Above this seemingly critical point, the isolated yield of boronic acid **16** increased as the amount of bromide **15** was increased. When conducted using 1 to 3 grams of **15**, boronic acid **16** was routinely isolated in 60-65% yield after silica chromatography. The ^{11}B NMR spectrum of **16** displayed a broad peak at 29.1 ppm, which was indicative of the presence of a boronic acid.[21] Additionally, no C8 resonance was observed in the ^{13}C NMR spectrum of **16**. This indicated the presence of a boron atom attached to C8, as resonances of carbon atoms attached to boron are not observed in ^{13}C NMR spectra due to quadrupolar relaxations through the carbon-boron bond.[21] These observations, combined with further NMR and HRMS data led to the assignment of **16** as the desired C8-boronic acid.

Scheme 5: Formation of C8-boronic acid **16** and subsequent coupling to C4-ether **6** to synthesise dimer **5**.



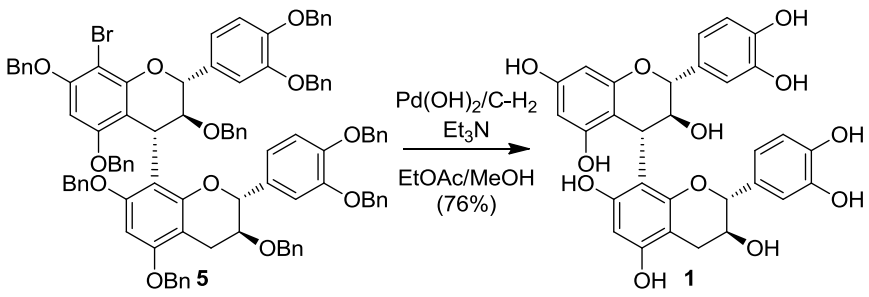
a) i) *n*-BuLi, -78 °C, THF, ii) $B(OMe)_3$ -78 °C to 0 °C, iii) H_2O, 0 °C to rt.
b) C4-ether **6**, TMSOTf, -78 °C, THF.

The key 4→8 bond of dimer **5** was constructed in excellent yields using the developed TMSOTf-mediated coupling of C4-ether **6** with C8-boronic acid **16** (**Scheme 5**). C4-Ether **6** was completely consumed in the reaction to form dimer **5** using only a slight excess (1.1 equivalent) of boronic acid **16**. Using these coupling conditions, dimer **5** was consistently synthesised in 90-95% yields regardless of the coupling scale, and gram quantities of **5** were successfully prepared. Additionally, the coupling temperature and reaction time were identical to that used in the synthesis of 4-arylflavan **13** (**Scheme 4**). 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. The coupling of **16** and **6** also exhibited excellent 3,4-*trans* stereoselectivity for dimer **5** (>90% by ^{1}H NMR). By analogy with the stereochemical studies of **13**, NMR ROESY experiments performed on **5** showed that 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* nature of the new 4→8 interflavan bond, as did the large H_3-H_4 coupling constant (J = 8.2 Hz).

2.4 Completion and confirmation of procyanidin B3 synthesis.

To complete the synthesis of procyanidin B3 (**1**), 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.*,[13] $Pd(OH)_2$-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 6**).

Scheme 6: Synthesis of procyanidin B3 (**1**) through one-pot deprotection of dimer **5.**

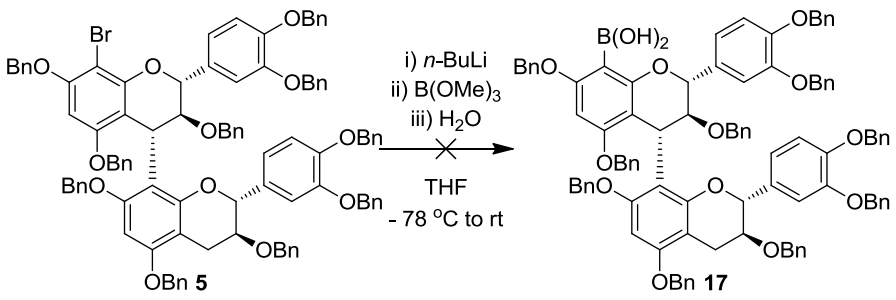


Comparison of the ^{1}H and ^{13}C NMR data and the optical rotation of the synthetic material to that reported for the same compound by Saito *et al.*[18] and the melting point data reported by Tarascou *et al.*[13] confirmed the identity of procyanidin B3 (**1**) as synthesised and that the natural 3,4-*trans* stereochemistry was obtained. On the whole, the novel application of boronic acid **16** and C4-ether **6** in a Lewis acid-mediated coupling provided a smooth transition to natural product **1** from catechin (**8**) in 54% overall yield in 6 linear steps.

2.5 Attempted extension of method to higher oligomers.

The most obvious route for extending the new method to the synthesis of trimeric species was to convert dimeric bromide **5** to the corresponding dimeric boronic acid **17.** This boronic acid could then conceptually undergo a further Lewis acid-promoted coupling with C4-ether **6** to produce a trimer. The conversion of **5** to boronic acid **17** was attempted using the transmetallation conditions applied to the synthesis of boronic acid **16 (Scheme 7**). Using these conditions, **17** was never obtained and the debrominated analogue of dimer **5** was the only product isolated from this reaction, indicating that transmetallation to the boronate did not occur.

Scheme 7: Attempted formation of dimeric boronic acid **17** from bromide **5.**

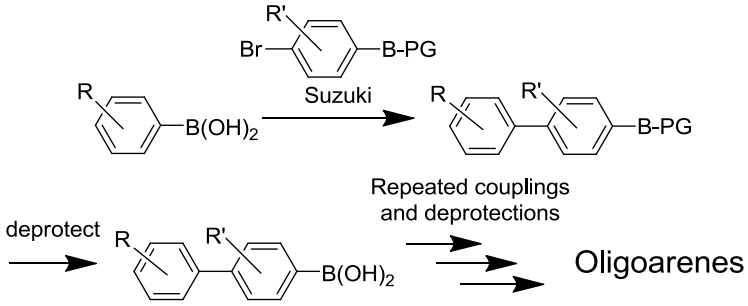


It was apparent there was an issue with attempting to manipulate functional groups at the dimer stage of the iterative synthesis. As a result, the method required amending so all the important functional group manipulations were undertaken on the monomeric species.

2.6 Boronic acid protection strategies.

Recently, methods for the iterative synthesis of oligoarene species have been developed by Gillis *et al.*[21] and Noguchi *et al.*[22]. These strategies involved the use of boron protecting groups to perform iterative Suzuki cross-couplings, as depicted in **Scheme 8**. Such a strategy seemed amenable to the iterative synthesis of catechin oligomers.

Scheme 8: Representation of boron protection strategy in iterative oligoarene synthesis.



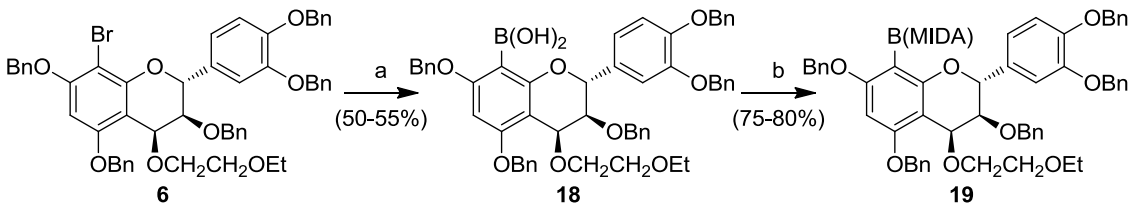
2.7 Application of boron protection strategy to catechin oligomers.

2.7.1 Synthesis of "chain extension" catechin unit.

Before any attempt to apply a boron protection strategy to the synthesis of catechin oligomers, an appropriate protecting group was required and a boron-protected C4-ether had to be synthesised. The *N*-methyliminodiacetic acid (MIDA) group as used by Gillis *et al.*[20] was chosen as this boronic acid protection employed mild conditions and the protecting group was predicted to be stable under the Lewis acid coupling conditions used earlier (Section 2.3).

Synthesis of the C8-boron-protected C4-ether **19** was achieved in two steps from the previously prepared C4-ether **6**. Initially, C 4-ether **6** was converted to C8-boronic acid **18** in 50-55% yields using the same method described for the preparation of C8-boronic acid **16**. Refluxing boronic acid **18** in toluene/DMSO in the presence of MIDA and CaH_2 afforded the boron-protected species **19** in 75-80% yields after purification (**Scheme 9**).

Scheme 9: Preparation of boron-protected C4-ether **19** from C4-ether **6**.



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

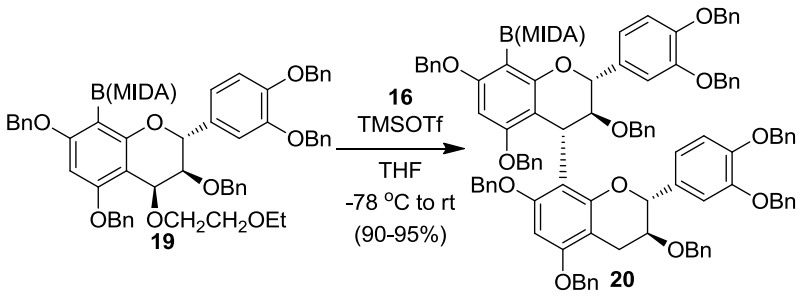
The ^{11}B and ^{13}C NMR spectra of **19** showed several diagnostic features. For the ^{11}B NMR spectra, the broad peak observed at 29.5 ppm for boronic acid **18** shifted to a narrower peak at 12.7 ppm for the MIDA protected equivalent **19**. This observed shift was consistent with that reported by Gillis *et al.* for tetrahedral, MIDA-protected boron species.[21] The shifts at 167.9 ppm and 46.9 ppm observed in the ^{13}C NMR spectrum of **19** were indicative of the carbonyl and *N*-methyl groups of the attached MIDA group, respectively. These key features, combined with the remaining shifts in the ^{1}H and ^{13}C NMR spectra and HRMS data, confirmed C4-ether **19** had the assigned structure.

This boron-protected species was dubbed the "chain extension" unit **19** as it was proposed this species could be serially coupled to the C8-terminus of a growing catechin oligomer by repeated coupling and deprotection steps (as indicated in **Scheme 8** for oligoarenes). Most significantly, the key bromide-to-boron conversion of **18** was achieved using a monomeric unit. This alleviated any necessity to perform functional group manipulations of higher oligomers, thereby overcoming the issue outlined in Section 2.5. As a result, it was anticipated that this route, using "chain extension" unit **19,** would be applicable to the iterative synthesis of catechin oligomers.

2.7.2 Use of "chain extension" unit 19 in dimer formation.

The utility of "chain extension" unit **19** in an iterative oligomer synthesis was validated through its coupling to C8-boronic acid **16** (**Scheme 10**). This coupling was completed using the same novel, Lewis acid-promoted coupling conditions described in Section 2.3.

Scheme 10: Lewis acid-promoted coupling of "chain extension" unit **19** to boronic acid **16**.

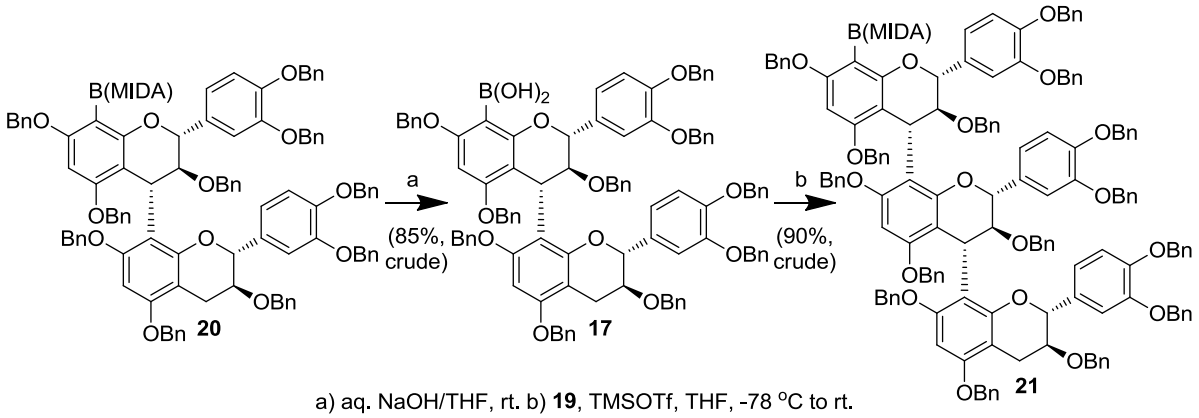


The boron-protected dimer **20** was consistently synthesised in excellent yields (90-95%) and the reaction was applicable to gram-scale synthesis of dimer **20**. The diagnostic C4 and C8 peaks at 36.7 ppm and 112.6 ppm in the ^{13}C NMR spectrum of dimer **20** indicated that the 4→8 bond was successfully forged. The ^{11}B NMR spectrum showed a peak at 13.5 ppm, which showed that the C8-boron atom of the top unit was still present as the MIDA-protected species. This observation confirmed the protective utility of the MIDA group during the Lewis acid-promoted coupling.

2.7.3 Deprotection of dimer 20 and synthesis of trimer.

Prior to testing the utility of the boron-protection and coupling strategy in the synthesis of higher oligomers, dimer **20** required deprotection to the free boronic acid **17**. Stirring dimer **20** in THF/aqueous NaOH at room temperature removed the MIDA group, while filtration of the reaction mixture over SiO_2 and concentration provided the free boronic acid dimer **17** in 85% crude yield (**Scheme 11**).

Scheme 11: Deprotection of dimer **20** and subsequent Lewis acid-promoted coupling to "chain extension" unit **19**.



The synthesis of trimer **21** was completed by the Lewis acid-promoted coupling of the free boronic acid dimer **17** with another equivalent of "chain extension" unit **19**. This coupling afforded a product tentatively assigned as trimer **21,** in 90% crude yield (**Scheme 11**).

Unfortunately, residual solvents, particularly aliphatic hydrocarbons from silica chromatography, could not be completely removed from trimer **21**. These residual solvents coincided with some peaks in the NMR spectra of **21**, particularly in the 1-3 ppm and 0-30 ppm regions of the ^{1}H and ^{13}C spectra respectively. However, several indicative features of the spectral data pointed towards the successful formation of trimer **21** as depicted in **Scheme 11**. Firstly, the HRMS data was consistent with that expected for the MIDA protected trimer **21**. Furthermore, the C4 and C8 resonances of the interflavan bonds at 36.7 and 36.9 ppm, and 112.6 and 112.8 ppm, respectively, in the ^{13}C NMR spectrum were consistent with that reported by Saito,[23] Kozikowski[8b] and Ohmori[12,24] for similar 4→8 linked (epi)catechin trimers and higher oligomers. The narrow peak at 13.7 ppm in the ^{11}B NMR spectrum and the carbonyl and *N*-methyl resonances at 168 and 47 ppm indicated that C8 of the uppermost unit was still attached to the B-MIDA group as expected. These data led to the tentative assignment of the product as trimer **21**. Attempts were made to remove the boron and benzyl groups to obtain the natural procyanidin C2, but due to the small quantity of trimer **21** synthesised, this was not achieved.

Nonetheless, the successful synthesis of a compound that is entirely consistent with trimer **21** shows two important things. Firstly, through the use of the boron protecting group, the novel Lewis acid-promoted coupling strategy is applicable to the synthesis of dimeric and trimeric catechin oligomers. Secondly, the "chain extension" unit **19** has been used successfully in two coupling events. It is not unreasonable, therefore, to envisage this unit could be sequentially used in Lewis acid-promoted couplings with other oligomeric C8-boronic acid species to produce oligomers beyond that of the trimer reported here.

3. Conclusions

A novel Lewis acid-promoted coupling of a benzylic ether to an aryl boronic acid was developed for its use in the synthesis of 4→8 catechin oligomers. Initially, this method was used in the synthesis of the dimer procyanidin B3 (**1**) from (+)-catechin (**8**) in good overall yield (54% over 6 steps). The key 4→8 interflavan bond was formed in excellent yields (90-95%) by the stereoselective Lewis acid-promoted coupling of C4-ether **6** with C8-boronic acid **16**. This represents the first synthesis and use of C8-boronic acid **16** in the formation of a

natural procyanidin dimer. Combining the Lewis acid-promoted coupling with a boron protection-coupling-deprotection strategy, the synthetic method was extended to the iterative synthesis of dimer and trimer species. This was achieved by sequential addition of "chain extension" unit **19** to a growing oligomer chain. Further studies are currently being undertaken towards the extension of these methods in the iterative synthesis of higher oligomers, along with examination of the mechanism for the novel Lewis acid-promoted coupling reaction.

4. Experimental.

4.1 General Procedures.

4.1.1 Materials: Commercial reagents were purchased from Sigma-Aldrich and used without further purification unless noted. THF was distilled from sodium/benzophenone ketyl and CH_2Cl_2 and triethylamine from CaH_2 under an atmosphere of nitrogen prior to use. DMF was purchased as Sureseal© anhydrous reagent from Sigma-Aldrich and used as received under an atmosphere of nitrogen or argon. *N*-Bromosuccinimide (NBS) was recrystallised from hot water prior to use. *n*-BuLi was used as received as a solution in hexanes and titrated according to the method of Suffert [25] either prior to use or on a weekly basis when in regular use. 2,4,6-Trimethoxyphenylboronic acid (**12**) was prepared according to the procedure described by Dennis *et al*.[17]

4.1.2 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 subaseal unless otherwise stated. Organic solutions were concentrated with 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 by exposure to UV light (λ = 254nm) and developed by dipping in a $KMnO_4$ solution followed by brief heating using a heat gun. Silica gel chromatography was conducted using E. Merck silica gel (230-400 mesh).

4.1.3 Spectral and structural analysis: ^{1}H NMR spectra were recorded on one of the following instruments: Bruker Avance III 600 or 400 MHz or Varian Gemini 300 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protons in the NMR solvent ($CHCl_3$, δ = 7.26; 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, dis = distorted), integration and coupling constant (*J*, Hz). ^{13}C NMR spectra were recorded on one of the following instruments: Bruker Avance III 600 (at 150MHz) or 400 MHz (at 100 MHz), Varian Gemini 300 MHz (at 75 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_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 128 MHz) at 60 ^oC and referenced to an external standard ($BF_3.OEt_2$) using CD_3CN as the solvent. An acquisition time of 0.15 s and recycle delay of 0.1 s were used. High resolution mass spectra (HRMS) were performed at the Monash University Mass Spectrometry Unit using a Micromass 'Quattro micro' instrument using electrospray ionisation (ESI) technique. Infrared spectra were recorded on a BIO-RAD FTS-40A Fourier Transform spectrophotometer with the absorptions recorded in wavenumbers (cm^{-1}). Samples were analysed as thin films on NaCl discs. Optical rotations were measured with a PolAAR 21 polarimeter, referenced to the sodium D line (589 nm) at 20 °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.

4.2 Synthetic procedures.

4.2.1 5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin (**9**).

The title compound was prepared by an adaption of the procedure for the same compound reported by Mustafa *et al*.[19]

To a stirring solution of (+)-catechin **8** (9.70 g, 33.4 mmol) in DMF (200 mL) at −78 ^oC, NaH (5.7 g, 60 % dispersion in mineral oil, 142 mmol, 4.25 equiv.) was added as a solid, followed immediately by neat BnCl (20.0 mL, 173 mmol, 5.2 equiv.). The resulting mixture was stirred vigorously at −78 ^oC for 15 minutes, then the cold bath was removed and stirring was continued at room temperature for 7 hours. The mixture was poured into EtOAc (400 mL)/water (600 mL) and stirred vigorously for 30 minutes. The phases were then separated and the organic layer was washed with brine (5 × 100 mL), then dried (Na_2SO_4), filtered and concentrated. The brown residue was 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 the tetrabenzyl

product (20.5 g, 94%) as a white, crystalline solid after removal of the solvent. The ^{1}H and ^{13}C NMR spectra of the product corresponded to that reported by Mustafa *et al.* for the title compound **9**.[19]

4.2.2 (2*R*,3*S*,4*S*)-5,7,3′,4′-tetrabenzyloxy-4-(2″-ethoxy-ethoxy)-flavan (**10**).

The title compound was prepared by an adaption of the procedure for the same compound reported by Saito *et al*.[18b]

To a stirring solution of **9** (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 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 organic layer was sequentially washed with sat. aq. $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), then dried (Na_2SO_4), filtered and concentrated. The blue/green residue was then filtered over SiO_2 ($CHCl_3$) to provide ether **10** as an orange solid (1.95 g, 85%) after solvent removal. The compound was 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 **10**.[18b]

4.2.3 (2*R*,3*S*,4*S*)-8-bromo-3,5,7,3′,4′-pentabenzyloxy-4-(2″-ethoxy-ethoxy)-flavan (**6**).

To a stirring solution of **10** (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 allowed to slowly warm to room temperature with stirring over 4 hours. The mixture was 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 and the phases were separated. The aqueous phase was then extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated to afford 2.59 g (99%) of a crude yellow/orange solid. 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 0 ^{o}C for 30 minutes and neat BnBr (570 μL, 4.80 mmol) was added. The cold bath was then removed and stirring was continued at room temperature for 3 hours. The mixture was then poured into EtOAc (100 mL)/water (100 mL) and stirred vigorously for 30 minutes. The phases were separated and the organic phase was 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 title compound **6** (2.73 g, 95%) as a white foamy solid after solvent removal. ^{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-**CH$_2$**-Ph), 4.06 (d, 1H, *J* = 12 Hz, C3- O-**CH$_2$**-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**CH$_3$**). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 156.6, 152.3, 148.9, 148.7, 137.6, 137.3, 137.2, 136.4, 136.3, 132.1, 128.5-126.8 (Benzyl **Ar-H**), 120.9, 114.7, 114.1, 105.5, 92.6 (**C8**), 92.1 (**C6**), 78.6 (**C2**), 75.5 (**C3**), 71.8 (**C4**), 71.3, 70.99, 70.95, 70.6, 70.4, 69.8, 67.4, 66.3, 15.1. HRMS (ESI) calculated for $C_{54}H_{51}{}^{79}BrO_8$ [M+Na^+], 929.2660; found, 929.2665.

4.2.4 (2*R*,3*S*,4*R*)-8-bromo-3,5,7,3′,4′-pentabenzyloxy-4-(2″,4″,6″-trimethoxyphenyl)-flavan (**13**).

To a stirring solution of **6** (0.19 g, 0.21 mmol) and 2,4,6-trimethoxyphenyl boronic acid (**12**) (52 mg, 0.24 mmol) in THF (3 mL) at −78 ^{o}C, neat TMSOTf (45.0 μL, 0.25 mmol) was added dropwise. Stirring was continued for 1 hour at −78 ^{o}C, and then the mixture was allowed to warm to room temperature in the cold bath over 3 hours. The mixture was poured into sat. aq. $NaHCO_3$ (10 mL)/EtOAc (20 mL) and stirred vigorously for 10 minutes. The phases were separated and 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 title compound **13** (190 mg, 90%) as a white foamy solid after solvent removal. ^{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* = 8.3 Hz), 6.97 (m, 2H), 6.70 (d, 2H, *J* = 7 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 (d, 1H, *J* = 12 Hz, O-**CH$_2$**-Ph), 5.04 (d, 1H, *J* = 12 Hz, O-**CH$_2$**-Ph) 4.85 (d, 1H, *J* = 8.2 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* = 9.7 and 8.2 Hz, **C3-H**), 3.82 (s, 3H, TMB-**OMe**), 3.72 (d, 1H, *J* = 6 Hz, O-**CH$_2$**-Ph), 3.59 (d, 1H, *J* = 6 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) 159.3 (TMB-**Cq**-OMe), 159.2 (TMB-**Cq**-OMe), 158.3 (TMB-**Cq**-OMe), 156.0, 153.9, 153.7, 148.56, 148.51, 137.8, 137.33, 137.24, 136.8, 136.6, 132.4,

129-126 (Benzyl **Ar-H**), 120.6, 114.7, 114.2, 113.5, 111.3, 94.5 (**C8)**, 92.7 (**C6**), 91.7 (TMB-**C**-H), 90.9 (TMB-**C**-H), 81.4 (O-**CH$_2$**-Ph), 81.3 (**C2**), 73.9 (**C3**), 71.3 (O-**CH$_2$**-Ph), 71.07 (O-**CH$_2$**-Ph), 71.00 (O-**CH$_2$**-Ph), 70.3 (O-**CH$_2$**-Ph), 36.4 (**C4**). HRMS (ESI) calculated for $C_{59}H_{53}{}^{79}BrO_9$ [M+Na$^+$], 1007.2765; found 1007.2767. FTIR (thin film): 3062, 3031, 2935, 2876, 2836, 1599, 1513, 1496, 1454, 1415, 1338, 1203, 1120, 1027, 811, 736, 698.

4.2.5 3,5,7,3′,4′-penta-*O*-benzyl-(+)-catechin (**4**).

The title compound was prepared by an adaption of the procedure described above for 5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin (**9**).

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 **8** (5.61 g, 19.3 mmol) in DMF (120 mL) at −78 ^{o}C. The resulting mixture was stirred at −78 ^{o}C for 15 minutes, then warmed to room temperature and stirred for a further 24 hours. The mixture was then quenched and extracted using the same procedure as for that of **9**. 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 pentabenzylcatechin **4** (13.0 g, 91%) as a white foamy solid after solvent removal. ^{1}H and ^{13}C NMR spectra of the product matched that reported by Kikuchi *et al.* for the title compound **4**.[26]

4.2.6 8-bromo-3,5,7,3′,4′-penta-*O*-benzyl-catechin (**15**).

The title compound was prepared by an adaption of the procedure for the same compound reported by Kozikowski *et al*.[16]

To a stirring solution of **4** (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 reaction was 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 separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were 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 after solvent removal. ^{1}H and ^{13}C NMR spectra of the product matched that reported by Kozikowski *et al*. for the title compound **15**.[16]

4.2.7 3,5,7,3′,4′-penta-*O*-benzyl-catechin-8-boronic acid (**16**).

To a stirring solution of **16** (2.09 g, 2.56 mmol) in THF (25 mL) at –78 °C, *n*-BuLi (2.10 mL, 1.35 M in hexanes, 2.84 mmol) was added dropwise over 2 minutes. The resulting deep yellow solution was stirred at –78 °C for 15 minutes, then neat $B(OMe)_3$ (600 μL, 5.38 mmol) was added dropwise over 5 minutes. The resulting mixture was allowed to stir at –78 °C for 1 hour, before being slowly warmed to 0 °C 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 EtOAc (100 mL)/ice (*ca*. 50 g) and allowed to warm to room temperature with stirring over 30 minutes. The phases were separated and the organic layer was 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 boronic acid **17** (1.30 g, 65%) as a white, foamy solid after solvent removal. ^{1}H 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-**C**$\mathbf{H_2}$-Ph), 4.14 (d, 1H, *J* = 12 Hz, C3-O-**C**$\mathbf{H_2}$-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, $CDCl_3$) δ164.1, 160.4, 159.6, 149.1, 149.0, 137.7, 137.1, 137.0, 136.3, 135.5, 131.2, 130-125 (Benzyl **Ar-H**), 120.2, 115.0, 113.4, 103.4, 91.3 (**C6**), 80.7 (**C2**), 73.8 (**C3**), 71.6, 71.3 (x2), 71.2, 70.0, 26.1 (**C4**). ^{11}B NMR (126 MHz, CD_3CN) δ 29.1. HRMS (ESI) calculated for $C_{50}H_{45}{}^{11}BO_8$ [M+NH_4^+], 802.3546; found, 802.3553. FTIR (thin film): 3519, 3063, 3032, 2928, 2871, 1600, 1580, 1515, 1497, 1454, 1426, 1302, 1265, 1174, 1098, 1027, 763, 697.

4.2.8 8-bromo-3,5,7,3′,4′-penta-*O*-benzyl-catechin-4*α*→8-3,5,7,3′,4′-penta-*O*-benzyl-catechin (**5**).

To a stirring solution of **6** (0.65 g, 0.71 mmol) and **17** (0.66 g, 0.89 mmol) in THF (7 mL) at –78 °C, neat TMSOTf (140 μL, 7.7 mmol) was added dropwise and stirring was continued at –78 °C for 1 hour. The reaction was then allowed to warm to room temperature in the cold bath over 3 hours. The mixture was poured into sat. aq. $NaHCO_3$ (10 mL)/EtOAc (30 mL) and stirred vigorously for 10 minutes. The phases were separated and 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 dimer **5** (1.05 g, 95%) as a white foamy solid after solvent removal. ^{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* = 7.2 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-**CH$_2$**-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-**CH$_2$**-Ph, maj), 4.18 d, *J* = 12 Hz, O-**CH$_2$**-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-**CH$_2$**-Ph, min), 3.83 (d, *J* = 11.52 Hz, C3-O-**CH$_2$**-Ph, maj), 3.74 (d, *J* = 9.2 Hz, **F2-H**, maj), 3.59 (d, *J* = 11.52 Hz, C3-O-**CH$_2$**-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, 149-148 (**C-B3′, C-B4′, C-E3′, C-E4′,** maj and min), 138.5-133.6 (Bn **CqPh, maj and min**), 133.1, 132.6, 132.1, 131.6, 130-127 (Benzyl **Ar-H,** maj and min), 121.2, 120.53, 120.45, 119.6, 115.3, 114.8, 114.5, 114.3, 113.8, 113.1, 112.6, 112.0 (**C-D8**, min), 112.0 (**C-D8**, maj), 110.9, 110.8, 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), 81.6 (**C-C2**, maj), 81.1 (**C-C2**, min), 80.8 (**C-F2**, maj)**,** 79.6 (**C-F2**, min), 79.2, 78.4, 75.5, 75.1, 74.4, 72.7, 72.4, 72-69 (Bn O-**CH$_2$**-Ph), 36.52 (**C-C4**, min), 36.51 (**C-C4**, maj), 27.8 (**C-F4**, min**)**, 27.5 (**C-F4,** maj). HRMS (ESI) calculated for $C_{100}H_{85}{}^{79}BrO_{12}$ [M+NH_4^+], 1574.5563; found, 1574.5579. FTIR (thin film): 3062, 3030, 2930, 2870, 1601, 1514, 1498, 1454, 1418, 1380, 1213, 1171, 1117, 1027, 735, 697.

4.2.9 (+)-catechin-4*α*→8-(+)-catechin (**1**).

Using the conditions specified by Tarascou *et al.*,[13] compound **5** (0.20 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 filtered over celite and the filter cake washed with EtOAc (3 × 2 mL) and MeOH (3 × 2 mL) and the resulting solution was concentrated *in vacuo*. Filtration of the residue over silica gel (acetone/MeOH 95:5) and concentration afforded the native procyanidin **1** as a yellow fluffy solid (56 mg, 76%), mp 216-221 ^{o}C (dec.), lit. 218-220 ^{o}C (dec.).[13] Optical rotation: $[\alpha]^{25}_{D}$= -218 (*c* 0.36, EtOH), lit. $[\alpha]^{24}_{D}$= -221 (*c* 0.38, EtOH).[18b] The mp title compound **1** matched that reported by Tarascou *et al.*[13] and the ^{1}H and ^{13}C NMR and optical rotation $[\alpha]^D$ data matched that reported by Saito *et al.*[18a,, 18b] for the same compound.

4.2.10 3,5,7,3′,4′-penta-O-benzyl-catechin-4*β*-(2-ethoxyethyl)ether-8-boronic acid (**18**).

To a stirring solution of **6** (2.23 g, 2.46 mmol) in THF (30 mL) at –78 ^{o}C, *n*-BuLi (1.8 mL, 1.50 M in hexanes, 2.70 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 –78 ^{o}C 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 × 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_2CH_2**-OEt), 3.82 (m, 1H, C4-O-**CH_2CH_2**-OEt), 3.60 (dd, 1H, *J* = 10.2 Hz and 3 Hz, **C3-H**), 3.56 (m, 2H, C4-O-**CH_2CH_2**-OEt), 3.45 (q, 2H, *J* = 7.2 Hz, C4-O**C**H_2CH_2-O-**CH_2**CH_3), 1.16 (t, 3H, *J* = 7.2 Hz, C4-O-**C**H_2CH_2-O-CH_2**CH_3**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 160.8, 160.5, 149.2, 149.0, 137.4, 137.1, 137.0, 136.0, 135.3, 131.1, 130-126 (Benzyl **Ar-H**), 120.9, 115.0, 113.8, 105.0, 91.0 (**C6**), 78.1 (**C2**), 76.2 (**C3**), 71.8 (**C4**), 71.3, 71.2, 71.1, 70.8, 70.5, 69.8, 67.5, 66.3, 15.2 (C4-O-**C**H_2CH_2-O-CH_2**CH_3**). ^{11}B NMR (126 MHz, CD_3CN) δ 29.5. HRMS (ESI): Calculated for $C_{54}H_{53}{}^{11}BO_{10}$, [M+$Na^+$], 895.3624, found 895.3627. FTIR (thin film): 3527, 3063, 3032, 2925, 2870, 1601, 1514, 1454, 1430, 1380, 1218, 1176, 1112, 1027, 736, 697.

4.2.11 3,5,7,3′,4′-penta-O-benzyl-catechin-4*β*-(2-ethoxyethyl)ether-8-(*N*-methyliminodiacetyl)-boronate ester (**19**).

To a stirring solution of **18** (1.11 g, 1.27 mmol) and *N*-methyliminodiacetic 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 room temperature for 5 minutes before being refluxed at 120 ^{o}C for 16 hours. The mixture was 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* = 10.8 Hz, **C2-H**), 5.19-4.98 (m, 8H, 4 × 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 × 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**), 164.9, 159.7, 159.6, 148.7, 148.2, 137.6, 137.5, 137.2, 136.8, 136.5, 131.2, 130-126 (Benzyl **Ar-H**), 121.1, 114.4, 113.7, 104.5, 92.1 (**C6**), 75.4 (**C3**), 71.8 (**C2**), 71.1 (O-**CH_2**-Ph), 71.0 (2 × O-**CH_2**-Ph), 70.9 (**C4**), 70.3 (O-**CH_2**-Ph), 70.1 (O-**CH_2**-Ph), 69.9 (C4-O-**C**H_2CH_2-O-**CH_2**CH_3), 66.0 (2 × C4-O-**CH_2CH_2**-OEt), 63.0 (B(MIDA)-**CH_2**), 62.6 (B(MIDA)-**CH_2**). 46.9 (B(MIDA)-N-**CH_3**), 15.1 (C4-O**C**H_2CH_2-OCH_2**CH_3**). ^{11}B NMR (126 MHz, CD_3CN) δ 12.7. HRMS (ESI): Calculated for $C_{59}H_{58}{}^{11}BNO_{12}$, [M+$Na^+$], 1006.3944, found 1006.3950. FTIR (thin film): 3062, 3031, 2926, 2869, 1766, 1595, 1496, 1451, 1429, 1301, 1265, 1209, 1126, 1090, 1028, 838, 737, 698.

4.2.12 3,5,7,3′,4′-penta-O-benzyl-catechin-8-(*N*-methyliminodiacetyl)-boronate ester-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (**20**).

To a stirring solution of **19** (0.61 g, 0.62 mmol) and **16** (0.55 g, 0.70 mmol) in THF (20 mL) at −78 °C, neat TMSOTf (130 μL, 0.72 mmol) was added dropwise at this temperature and stirring was continued at −78 °C for 1 hour. The mixture was 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. ^{1}H 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* = 7.4 Hz, min) 6.59 (d, *J* = 7.4 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 × MIDA-**carbonyl**), 162.4, 160.9, 158.9, 155.2, 155.1, 153.9, 148.9, 148.8, 148.3, 148.0, 138.5-136 (Bn **CqPh**), 133.3, 131.7, 129-126 (Benzyl **Ar-H**), 120.7, 120.5, 114.5, 114.2, 112.6 (**C-A8**), 109.8, 104.1, 102.4, 93.9 (**C-A6**) , 91.7 (**C-D6**), 81.8 (**C-C2**), 80.7 (**C-F2**), 79.2, 75.2, 74.1, 72.1, 71.3-69.8 (Benzyl O-**CH$_2$**-Ph), 63.2, 63.1 (2 × MIDA-**CH$_2$**), 46.9 (MIDA-N-**CH$_3$**), 36.7 (**C-C4**), 27.6 (**C-F4**). ^{11}B NMR (126 MHz, CD_3CN) δ 13.5. HRMS (ESI): calculated for $C_{105}H_{92}{}^{11}BNO_{16}$, [M+$Na^+$], 1656.6401, found 1656.6409.

4.2.13 3,5,7,3′,4′-penta-O-benzyl-catechin-8-boronic acid-4*α*→8-3,5,7,3′,4′-penta-O-benzyl-catechin (**17**).

To a stirring solution of **20** (0.39 g, 0.24 mmol) in THF (20 mL) at room temperature, dilute aq. NaOH (1 M, 4 mL) was added. The resulting mixture was vigorously stirred at room 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 the phases were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 20 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated. Filtration of the residue over SiO_2 (EtOAc/Hexanes 1:2) provided 0.31 g (85%) of the crude free boronic acid as a yellow, foamy solid. HRMS: Calculated for $C_{100}H_{87}{}^{11}BO_{14}$, [M+$NH_4^+$], 1540.6527, found 1540.6578.

4.2.14 3,5,7,3′,4′-penta-O-benzyl-catechin-8-(*N*-methyliminodiacetyl)-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 (**21**).

To the crude boronic acid **17** (92 mg, 60 μmol), **19** (52 mg, 53 μmol) was added and the mixture was dissolved with stirring in THF (3 mL), and then cooled to –78 ^{o}C. Neat TMSOTf (11 μL, 61 μmol) was added dropwise at –78 ^{o}C and stirring was continued at this temperature for 1 hour. The solution was 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 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. ^1H NMR (600 MHz, $CDCl_3$, multiple rotamers) δ 7.5-7.24 (m, Benzyl **Ar-H**), 7.24-6.5 (m, Benzyl **Ar-H**, **B**, **E**, **H** ring protons, maj and min), 6.21 (s, **D-6** maj), 6.17 (s, **G-6** maj), 6.16-6.04 (m, **A-6**, **D-6**, **G-6**, minor isomers) 5.85 (s, **A-6** maj), 5.5-4.5 (m, Benzyl **CH_2, C-2**, **F-2**, **I-2**, maj and min), 4.5-4.0 (m, Benzyl **CH_2, C-3**, **F-3**, **C-4**, maj and min), 3.6-3.1 (m, **I-3**, **F-4**, MIDA **CH_2**), unable to definitively identify **H-4** protons and MIDA N-**CH_3** due to impurity interferences. ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) 167.9 (MIDA-**carbonyl**), 167.8, (MIDA-**carbonyl**), 162.2, 131.4, 159.2, 155-154 (**B**, **E**, **H** ring quaternaries), 148.9-147.6 (**D**, **G** ring quaternaries), 139-131 (Benzyl quaternaries,), 130-126 (Benzyl **Ar-H**), 121.1, 120.9, 114.8, 114.1, 113.2, 112.8 (**D8**), 112.6 (**G8**), 110.6, 108.9, 108.8, 106.7, 106.2 102.0, 100.69, 100.65, 100.3, 93.9 (**C6**), 92-90 (**D6, D8, G6, G8**), 82.7-79.7 (**C2**, **F2**, **I2**, **C3**, maj and min), 74-68 (Benzyl **CH_2**, **F3**, **I3**, maj and min), 63.3 (MIDA-**CH_2**), 61.3 (MIDA-**CH_2**), 58.5, 47.0 (MIDA-N-**CH_3**), 37.2 (**C4 or F4**), 36.9 (**C4 or F4**), unable to definitively identify **C-I4** due to impurity interferences. ^{11}B NMR (126 MHz, CD_3CN) δ 13.7. HRMS: $C_{155}H_{134}{}^{11}BNO_{22}$, [M+$NH_4^+$], 2389.9829, found, 2389.9872.

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Supplementary Data

Characterisation data, ^{1}H, ^{13}C and ^{11}B NMR spectra for new compounds are available.

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