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An Improved Synthesis of Procyanidin Dimers: Regio- and Stereocontrol of the Interflavan Bond

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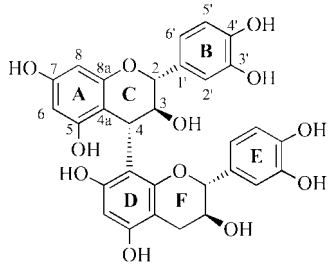
A direct and general synthesis of procyanidin dimers B1, B2, B3 and B4 (**10a–d**) is presented. The approach is based on the stoichiometric coupling of two protected monomeric units (the nucleophilic **2a–b** and electrophilic **4a–b** partners) and deals with the regio- and stereocontrol of the C4–C8 interflavan bond as well as the control of the degree of oligomerization. The synthesis involves a five-step pathway starting from the native catechin (**1a**) or epicatechin (**1b**) to the fully deprotected dimers **10a–d**. Furthermore, the process appears to be iterative as the coupling intermediates **9a–d** themselves can be readily used in further selective syntheses of trimers or higher oligomers.

Introduction

As a part of a wider research project aiming to study the tannin–tannin and tannin–protein aggregation phenomena,[1] we have been engaged in the selective synthesis of proanthocyanidin dimers and oligomers. These condensed tannins represent a major family of the polyphenolic compounds that are widespread in the vegetable kingdom.[2] In particular, they can be found in grape seeds[3] and skins[4] and, interestingly, may be present in red wines[5] at concentrations of up to 4 g L^{-1}. Tannin extractions from plants may give a common access to these different polyphenols. However, their identification, as well as their purification, remains tedious such that the small amounts available by such methods are not suitable for use in further studies. As the overall interest in tannins increased in the past decade[6] synthetic processes emerged to overcome the extraction limitations. For all the synthetic methods, the creation of the interflavan C4–C8 bond remains the key step (Scheme 1).

The proposed syntheses can be roughly divided into two different types of approaches involving either a nucleophilic addition or a nucleophilic substitution as the coupling reaction. The first method involves the nucleophilic addition of a C8-lithiated nucleophile onto a C4-protected ketoprocyanidin as substrate.[7] This reaction generally meets the regioselective and oligomerization control demands of the coupling reaction, but does not fulfil the stereochemical requirement of the newly formed C4 asymmetric carbon atom. In contrast, and in spite of recent advances made in the regio- and stereocontrol of the reaction,[8] the substitution method still suffers from a lack of selectivity in the control of the degree of oligomerization, thus requiring the nucleophilic partner to be used in large excess and restricting the actual synthetic methods to the preparation of procyanidin dimers. To the best of our knowledge, only two attempts to prepare procyanidin dimers under stoichiometric conditions have been reported in the literature. While total stereocontrol of the C4 benzylic carbon atom failed in the intermolecular approach,[9] the only approach that deals efficiently with the three elements to be controlled involves an eight-step synthesis that is based on an intramolecular coupling of monomeric units bound by a temporary diester link.[10] This method was successfully applied to the synthesis of the epicatechin–catechin (B1) and catechin–catechin dimers (B3). Nevertheless the method failed to be of general use as the stereochemistry of the C3 hydroxy moieties engaged in the connection prevented some coupling reactions,



Scheme 1. Usual ring and atom mapping of flavonoid dimer B3 (catechin-4α,8-catechin).

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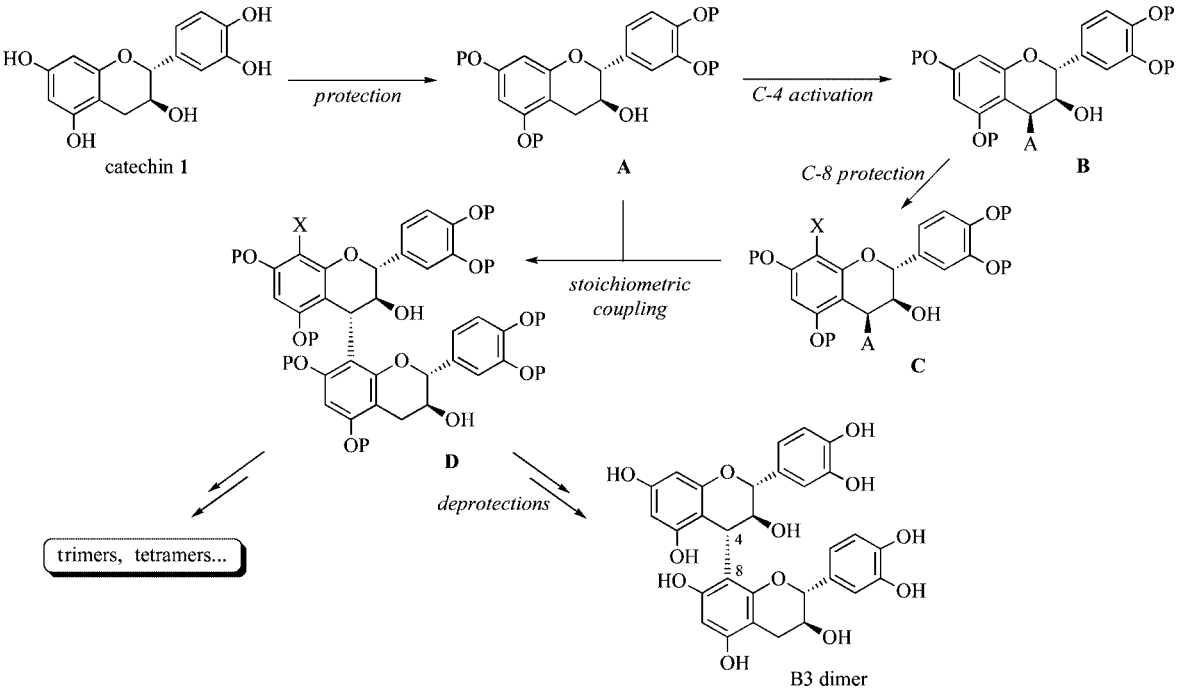


Scheme 2.

such as the synthesis of B2 and B4 dimers. In the course of our research we have developed a simple and efficient intermolecular synthesis of procyanidin dimers that deals with the required regio- and stereoselectivity as well as the oligomerization control of the reaction (Scheme 2). The key step involves a coupling reaction between equimolar amounts of a tetra-protected monomer **A** (the nucleophilic partner) and a C4-activated, C8-protected monomer **C** (the electrophilic partner). Furthermore, the process appears to be general and iterative considering that any coupling product of type **D** could be used as an intermediate for further sequential coupling reactions.

Results and Discussion

Synthesis of the Precursors

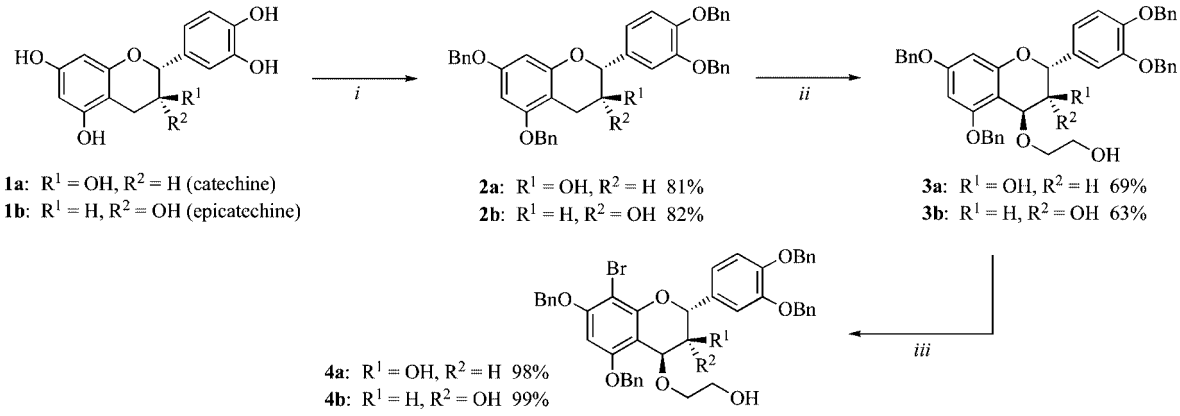
When the very first proanthocyanidin oligomers were synthesized using native catechin units[11] it quickly became apparent that protection of the phenolic functionalities was essential in order to achieve some regioselective control of the interflavan bond. Such protection is commonly achieved by using methyl,[12] acetyl[13] or benzyl[14] groups. Benzylic protection was chosen in order to benefit from the stability of benzyl ethers under basic or acidic conditions as well as to have the opportunity of deprotecting phenolic units simultaneously with a suitable C8 protecting group if necessary. The protection of the phenolic hydroxy moieties of catechin (**1a**) and epicatechin (**1b**) was then achieved in good yields, 81 and 82%, respectively, by using a modification of the literature method.[15] Note that control of the initial temperature remains crucial if undesired C6 and C8 alkylation side-products are to be avoided. As outlined above, the coupling reaction through nucleophilic substitution on the C4 carbon atom requires activation of the benzylic position with a potent leaving group. This was generally achieved by heteroatom functionalization with, for example, bromine,[16] sulfur[17] or oxygen.[8a–8b,18] In view of this we decided to make use of the potential of the carbon–oxygen bond which offers a good balance between the stability of the precursor and its reactivity in the presence of a Lewis acid. Thus, the C4 position of **2a** and **2b** was activated by DDQ oxidation of the C4 benzylic carbon atom in the presence of ethylene glycol. This reaction, initially developed by Roux and co-workers[18d] and exemplified by others,[8a,8b] can then be carried out with various nucleophiles including water and alcohols. As the nature of the alcohol presumably plays a significant role in the stereochemical control of the interflavan bond, we decided to use ethylene glycol as the nucleophile. Indeed, although ethylene glycol was not the most efficient alcohol for such activation, it has been shown that the subsequent coupling reaction of 4-hydroxyethoxyepicatechin **3b** could proceed with total stereocontrol of the interflavan bond.[8a] Activated catechin **3a** and epicatechin **3b** were obtained in 69 and 63% yields, respectively, and interestingly this reaction appeared to be totally diastereoselective. Owing to the conformational flexibility of the pyranyl ring **C**, the stereochemistry of the resulting asymmetric carbon atom could not be established directly from the H3,H4 coupling constants. For this reason, in the original paper dealing with the preparation of **3b** the uncertainty around the C4 stereochemistry was not eliminated.[8a] This was unambiguously resolved by NMR experiments coupled with molecular modelling[19] which showed that both catechin and epicatechin gave the same *S* diastereomers independently of the

stereochemistry of the contiguous C3 carbon atom (Scheme 3). These results are in agreement with the initial suggestion that the approach of DDQ could be controlled by the stereochemistry at the C2 atom and occurs on the lower face of the aromatic ring **A** in order to avoid interactions with the axial H2 atom.[18e] Finally, the last step of the precursor synthesis involves the regioselective aromatic halogenation of the C8 position to circumvent an uncontrolled oligomerization process during the coupling reaction. Regioselective halogenation reactions can be performed on catechins either at the C6 or C8 position,[20] depending mainly on the nature of the solvent used. Such functionalization was used in the nucleophilic addition approach[7] as well as in the intermolecular substitution coupling reaction.[9] This functionalization was achieved by using 1 equivalent of *N*-bromosuccinimide (NBS) in CH_2Cl_2[8a] to give the C4-activated, C8-protected catechin **4a** or epicatechin **4b** in quantitative yield.

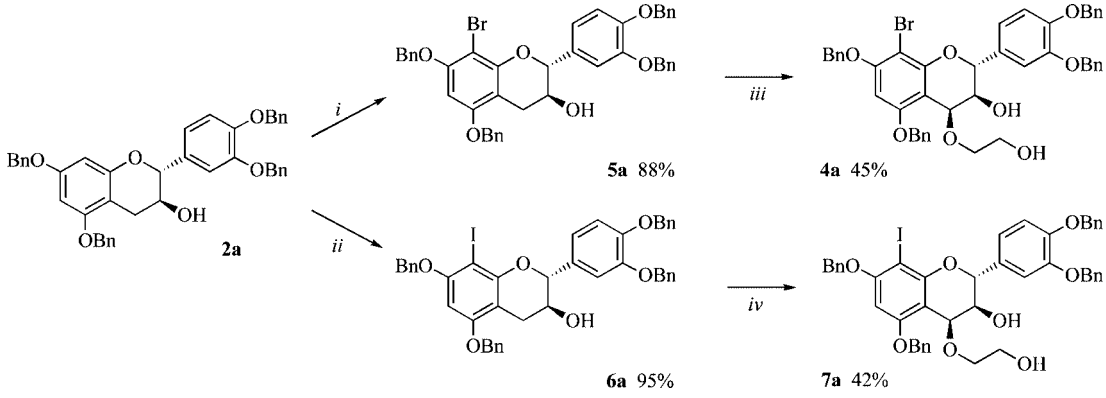
Alternatively, several attempts were made to activate tetra-*O*-benzylbromocatechin **5a** prepared from **2a** and *N*-bromosuccinimide (NBS) in CH_2Cl_2 or tetra-*O*-benzyliodocatechin **6a** prepared from **2a** and *N*-iodosuccinimide (NIS) in DMF.[20] The reaction led to the expected products **4a** and **7a**, but in significantly lower yields than those observed for the activation of non-halogenated substrates (Scheme 4). This may be explained by the lack of reactivity of the monoelectronic charge-transfer complex formed with DDQ when using halogenated catechins **5a** and **6a** as the substrates.

The Coupling Reaction

The coupling reaction of an activated unit with a protected monomer in the presence of a Lewis acid, first described by Kawamoto et al.,[14a] involved a C4-hydroxylated catechin as the electrophilic partner, giving a 3:2 mixture of the natural and nonnatural protected dimer. The stereoselective control was greatly improved by replacing the C4 hydroxy group with a methoxy[21] or other alkoxy group,[8,22] including the hydroxyethoxy functionality.[8a] Note that all of these methodologies required a large excess (5–10 equiv.) of the nucleophile in order to limit the reaction of the activated monomer with itself or with the dimeric product leading in both cases to oligomeric side-products. The first attempt at the coupling reaction was



Scheme 3. Reagents and conditions: i. K_2CO_3 (6 equiv.), BnBr (4.5 equiv.), DMF, 0 °C, 2 h, then room temp., 48 h; ii. ethylene glycol (6 equiv.), DDQ (2 equiv.), CH_2Cl_2, room temp., 3 h, then DMAP (2 equiv.), 10 min; iii. NBS (1 equiv.), CH_2Cl_2, –78 °C, 3 h, then room temp., 8 h.



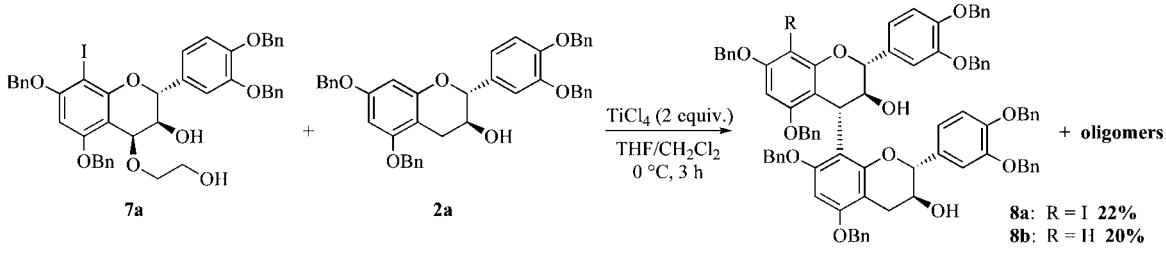
Scheme 4. Reagents and conditions: i. NBS (1 equiv.), CH_2Cl_2, –78 °C then room temp., 7 h; ii. NIS (1 equiv.), DMF, room temp., 24 h; iii. ethylene glycol (6 equiv.), DDQ (2 equiv.), CH_2Cl_2, room temp., 3.5 h; iv. ethylene glycol (6 equiv.), DDQ (2 equiv.), CH_2Cl_2, room temp., 2 h.

conducted with equimolar amounts of the protected catechin **2a** and the iodinated substrate **7a**. In the presence of $TiCl_4$ as Lewis acid, the reaction led to the expected dimer **8** in 42% yield (Scheme 5). However this was accompanied by some trimeric (17%), tetrameric (6%) and pentameric (3%) oligomers.[23] The presence in nearly equimolar amounts of both iodinated **8a** and non-iodinated **8b** forms suggested that the carbon–iodine bond is far too fragile to resist under acidic conditions, thus leading in situ to C8-deprotected intermediates prone to subsequent oligomerization processes.

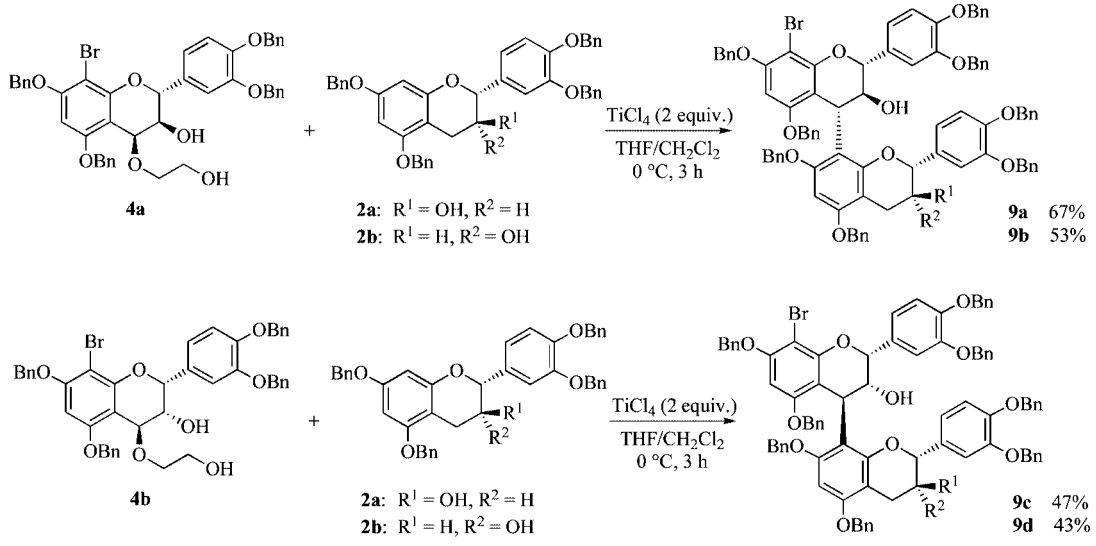
This encouraging result led us to replace the iodinated electrophile **7a** with its brominated congener **4a**, which was thought to be more resistant to acidic conditions. As expected, the reaction furnished the corresponding dimers **9a** (B3) and **9b** (B4) with no trace of either debrominated dimers or higher oligomers (Scheme 6). In marked contrast to other approaches involving acetate or thiophenyl as the activating group,[9] the reaction appears to be totally stereoselective leading to the natural configuration of the interflavan bond as a result of a clean inversion at the C4 asymmetric centre. The reaction was carried out under the same conditions with the bromide **4b** derived from epicatechin to give the dimers **9c** (B1) or **9d** (B2) as the sole products. In this case however the reaction occurs with total retention of the configuration at the attacked C4 carbon atom.

Importantly, each dimer **9a**–**d** was obtained as a mixture of two rotamers (compact and extended forms) that result from slow rotational exchange around the C4(**C**)–C8(**D**) interflavan bond. Furthermore, the ratio observed for each pair of rotamers depends on the nature of the solvent.[24] Finally, as pointed out above, the flexibility of the heterocycles **C** and **F** allows a rapid equilibrium between the pseudoaxial or pseudoequatorial forms resulting in average values for the $^3J_{H,H}$ coupling constants. Considering all of this, the unambiguous assignment of the three-dimensional structures of the native procyanidin dimers B1, B2, B3 and B4 derived from **9a**–**d** was not a trivial task and was achieved by a combination of two-dimensional NMR experiments (TOCSY, ROESY, HMQC, HMBC) and NOE experiments correlated with MM3 calculations.[25]

Looking at the reversal of the reactivity that occurred simply by replacing **4a** with its epimer **4b**, it would seem obvious that the stereochemistry at the C3 atom governs the stereoinduction of the newly formed C4 asymmetric carbon atom. However, this is not the only factor to take into account as previous work by Kawamoto[14] and Vercauteren and their co-workers,[21] carried out under similar conditions and with the same Lewis acid, led only to partial stereocontrol depending on the nature of the substitution at the C4 position (3:2 with a hydroxy leaving group and 2:1 with methoxy as the leaving groups). Considering that $TiCl_4$

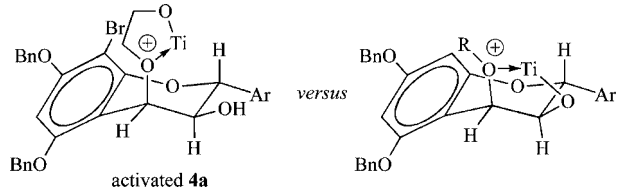


Scheme 5. Coupling reaction with iodide **7a**.



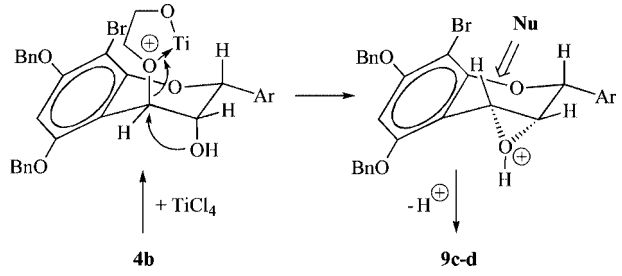
Scheme 6. $TiCl_4$-mediated coupling procedure with bromide **4a**.

preferentially adopts a bis-chelated state when possible and that the hydroxyethoxy substituent is a particularly good bidentate ligand, the origin of the total stereoinduction can be found in the mode of complexation of $TiCl_4$ and its consequences on the rigidification of the **C** cycle conformation which modifies the facial stereodifferentiation of the incoming nucleophile (Scheme 7).



Scheme 7. Comparison of mono- and bidentate activating groups.

A similar activated intermediate would explain the reversal of the stereoselectivity observed when using **4b**. Indeed, because the C3 hydroxy group is not engaged in the coordination sphere of the titanium, it is available to provide anchimeric assistance as a result of the axial–axial position of the neighbouring groups. This would lead to a transient protonated epoxide, which could be regiospecifically opened by attack by the nucleophilic at the benzylic carbon to provide **9c** and **9d** with an overall retention of configuration at the C4 position (Scheme 8).



Scheme 8. Nucleophilic substitution mechanism with **4b**.

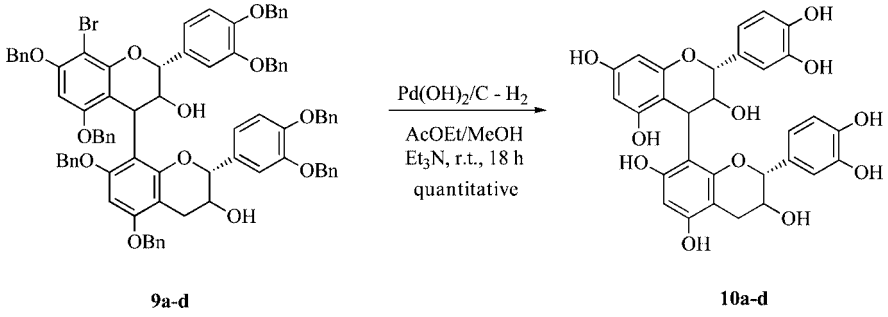
The last step of the synthesis involves the debenzylation of the phenolic units and the debromination of the C8 position. Usually, dehalogenation of procyanidins can be achieved with BuLi, leading to the corresponding lithiated derivatives,[26] or with reducing agents such as LAH.[9] However, we anticipated that the bromine–carbon bond could be sufficiently reactive for a one-pot procedure to be successful. The first attempts using Pd/C and H_2[13b,14] or cyclohexadiene[27] were deceiving, leading only to partial debenzylation. Thus we changed to Pearlman's catalyst, which was found to be far more efficient. Various solvents were tried, including alcohols, ethyl acetate and THF, and a 1:1 mixture of methanol/ethyl acetate was found to offer a good balance between dissolution of the starting bromides **9a**–**d** and all the partially deprotected intermediates. Promisingly, the first attempt led to a mixture of partially debrominated procyanidin dimers. We were then able to optimize the reaction by using triethylamine as additive, which has been reported to activate the palladium-mediated hydrodechlorination of aromatic compounds.[28] In this case the amine first activates the catalyst by reducing it in situ to Pd^0, but also traps the generated hydrobromic acid, thus avoiding premature degradation of the native procyanidin dimers **10a**–**d** (Scheme 9). After careful optimization of the amine/palladium/substrate ratio, the native procyanidin dimers B1, B2, B3 and B4 were isolated in quantitative yields.

Conclusions

In conclusion, we have developed an efficient synthesis of procyanidin dimers based on the intermolecular nucleophilic substitution of activated monomers **4** with equimolar amounts of protected monomers **2** acting as nucleophiles. This reaction fulfils the three conditions required for selective preparation of procyanidin dimers: i) control of the regioselectivity of the interflavan C4–C8 bond, ii) control of the created C4 stereocentre, giving exclusive access to the natural isomer and iii) total control of the degree of oligomerization. Furthermore, the synthesis involves only five steps from the native monomers **1** to the totally deprotected dimers **10**, and although the reactions have not been fully optimized yet, the overall yields are in the range of 22% for **10d** to 37% for **10a**. Finally, the coupling intermediates **9** can be used in further syntheses, either by activating the C4 position of the lower unit or by deprotecting the C8 position of the upper unit. This last point, which highlights the iterative aspect of the process, is currently under investigation.

Experimental Section

All reactions were performed under argon with magnetic stirring and with anhydrous solvents. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride, ethyl acetate,



Scheme 9. One-pot deprotection procedure to give native procyanidin dimers.

methanol and triethylamine were distilled from calcium hydride and DMF, from magnesium sulfate. (+)-Catechin and (–)-epicatechin were purchased from Fluka. Pearlman's catalyst [20% Pd-$(OH)_2$/C] was obtained from Aldrich and contained up to 50% H_2O. The reactions were monitored by thin-layer chromatography carried out on SDS silica gel plates (silica 60 F254) using UV light and phosphomolybdic acid solution in 2-propanol for detection. Column chromatography was performed using silica gel 60 (0.063–0.200 mm, Merck) or silica gel 40 (0.040–0.060 mm, Merck) for flash chromatography. Melting points (m.p.) were determined with a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin–Elmer FTIR Paragon 1000 spectrometer (KBr disc) and values are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with either a Bruker Avance DPX 300 or a Bruker Avance NB 400 spectrometer at room temperature (22 °C). The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ for protected compounds and H_2O/D_2O (90:10) or D_2O/[D_6]ethanol (88:12) for deprotected compounds with TMS as an internal standard. Chemical shifts δ and coupling constants J are given in ppm and Hz, respectively. Mass spectra were obtained on a Micromass Autospec-Q mass spectrophotometer [electron-impact ionization (70 eV) or LSIMS].

3′,4′,5,7-Tetra-*O*-benzyl-(+)-catechin (2a):[14b] Benzyl bromide (3.7 mL, 4.5 equiv.) and K_2CO_3 (5.71 g, 6 equiv.) were added to a solution of (+)-catechin (**1a**) (2.00 g, 6.89 mmol) in DMF (35 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then at room temperature for 48 h. The mixture was then diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried with $MgSO_4$. Removal of the solvents gave a viscous brown residue; the title compound **2a** was purified by silica gel chromatography (CH_2Cl_2) to give a white solid (3.64 g, 5.59 mmol, 81% yield). M.p. 124–126 °C. IR (KBr): $\tilde{\nu}$ = 3465, 3417, 1618, 1592, 1513, 1498, 1454, 1378, 1143, 1217, 1116, 1026, 753, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 7.48–7.28 (m, 20 H, Ar-H), 7.05 (s, 1 H, 2′-H), 6.98 (s, 2 H, 5′-H, 6′-H), 6.29 and 6.23 (AM, $^4J_{6,8}$ = 2.3 Hz, 2 H, 6-H, 8-H), 5.20 (s, 2 H, CH_2Ph), 5.19 (s, 2 H, CH_2Ph), 5.05 (s, 2 H, CH_2Ph), 5.01 (s, 2 H, CH_2Ph), 4.65 (d, $^3J_{2,3}$ = 8.3 Hz, 1 H, 2-H), 4.03 (m, 1 H, 3-H), 3.13 and 2.67 (ABX, $^2J_{4\alpha,4\beta}$ = 16.4 Hz, $^3J_{4\alpha,3}$ = 5.6 Hz, $^3J_{4\beta,3}$ = 8.9 Hz, 2 H, 4α-H and 4β-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 158.82 (C-7), 157.79 (C-5), 155.29 (C-8a), 149.37 and 149.10 (C-4′,C-3′), 137.15 (CqPh), 137.00 (CqPh), 136.93 (CqPh), 136.88 (CqPh), 130.92 (C-1′), 128.59 (2 CHPh), 128.52 (4 CHPh), 128.48 (2 CHPh), 127.99 (CHPh), 127.89 (CHPh), 127.85 (2 CHPh), 127.52 (2 CHPh), 127.49 (2 CHPh), 127.24 (2 CHPh), 127.12 (2 CHPh), 120.60 (C-6′), 115.04 (C-5′), 113.93 (C-2′), 102.30 (C-4a), 94.41 (C-8), 93.85 (C-6), 81.58 (C-2), 71.32 (CH_2Bn), 71.25 (CH_2Bn), 70.13 (CH_2Bn), 69.92 (CH_2Bn), 68.20 (C-3), 27.62 (C-4) ppm. MS (LSIMS): *m*/*z* (%) = 651 (40) $[M]^+$, 409 (14), 332 (13), 319 (100), 307 (38), 229 (19). HRMS: calcd. for $C_{43}H_{39}O_6$ 651.2747; found 651.2748.

3′,4′,5,7-Tetra-*O*-benzyl-(–)-epicatechin (2b):[8a] This title compound was prepared following the same procedure as that described for 3′,4′,5,7-tetra-*O*-benzyl-(+)-catechin (**2a**) except that (–)-epicatechin (**1b**) (1.00 g, 3.45 mmol) was used in place of (+)-catechin **1a**. Compound **2b** was purified by silica gel chromatography (CH_2Cl_2) to give a white solid (1.84 g, 2.82 mmol, 82% yield). M.p. 125.6–126.2 °C. IR (KBr): $\tilde{\nu}$ = 3440, 1618, 1592, 1512, 1498, 1454, 1378, 1263, 1142, 1217, 1113, 1026, 735, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 7.47–7.35 (m, 20 H, Ar-H), 7.18 (d, $^4J_{2',6'}$ = 1.2 Hz, 1 H, 2′-H), 7.02 (dd, $^3J_{6',5'}$ = 8.4 Hz, 1 H, 6′-H), 6.99 (d, 1 H, 5′-H), 6.30 (s, 2 H, 6-H, 8-H), 5.21 (s, 2 H, CH_2Ph), 5.17 (s, 2 H, CH_2Ph), 5.07 (s, 2 H, CH_2Ph), 5.03 (s, 2 H, CH_2Ph), 4.93 (s, 1 H, 2-H), 4.23 (m, 1 H, 3-H), 3.02 and 2.95 (ABX, $^2J_{4\alpha,4\beta}$ = 17.2 Hz, $^3J_{4\alpha,3}$ = 1.5 Hz, $^3J_{4\beta,3}$ = 4.3 Hz, 2 H, 4α-H and 4β-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 159.19 (C-7), 158.74 (C-5), 155.69 (C-8a), 149.45 (C-3′), 149.27 (C-4′), 137.68 (CqPh), 137.58 (CqPh), 137.42 (CqPh), 137.35 (CqPh), 131.90 (C-1′), 129.02 (2 CHPh), 128.94 (2 CHPh), 128.92 (2 CHPh), 128.90 (2 CHPh), 128.40 (CHPh), 128.29 (CHPh), 128.27 (CHPh), 128.23 (CHPh), 127.96 (2 CHPh), 127.93 (2 CHPh), 127.69 (2 CHPh), 127.63 (2 CHPh), 119.92 (C-6′), 115.49 (C-5′), 113.95 (C-2′), 101.41 (C-4a), 95.11 (C-8), 94.49 (C-6), 78.79 (C-2), 71.80 (2 CH_2Bn), 70.56 (CH_2Bn), 70.36 (CH_2Bn), 66.76 (C-3), 28.63 (C-4) ppm. MS (LSIMS): *m*/*z* (%) = 673 (31) $[M + Na]^+$, 651 (65) $[M]^+$, 409 (47), 332 (17), 319 (100), 229 (18). HRMS: calcd. for $C_{43}H_{39}O_6$ 651.2747; found 651.2739.

3′,4′,5,7-Tetra-*O*-benzyl-4β-(2-hydroxyethoxy)catechin (3a):[8a] Ethylene glycol (1 mL, 6 equiv.) and DDQ (1.5 g, 2 equiv.) were added to a solution of 3′,4′,5,7-tetra-*O*-benzylcatechin (**2a**) (2.0 g, 3.07 mmol) in dichloromethane (40 mL) at room temperature. A black-green colour appeared instantaneously. After 3 h of vigorous stirring at room temperature, 4-(dimethylamino)pyridine (0.75 g, 2 equiv.) was added. After another 10 min of stirring, the solvent was evaporated. The resulting crude material was purified by chromatography on silica gel (pentane/EtOAc, 1:1) to obtain after evaporation and drying in vacuo the product **3a** as a beige solid (1.51 g, 2.12 mmol, 69% yield). M.p. 120–122 °C. IR (KBr): $\tilde{\nu}$ = 3583, 3063, 3031, 2908, 1635, 1604, 1513, 1499, 1454, 1423, 1380, 1320, 1263, 1216, 1179, 1128, 1027, 735, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 7.62–7.30 (m, 20 H, Ar-H), 7.21 (d, $^4J_{2',6'}$ = 1.5 Hz, 1 H, 2′-H), 7.09 (dd, $^3J_{6',5'}$ = 8.3 Hz, 1 H, 6′-H), 6.97 (d, 1 H, 5′-H), 6.37 (d, $^4J_{6,8}$ = 1.9 Hz, 1 H, 6-H), 6.27 (d, 1 H, 8-H), 5.27 (s, 2 H, CH_2Ph), 5.19 (s, 2 H, CH_2Ph), 5.12 (m, 4 H, 2 CH_2Ph), 5.03 (s, 2 H, CH_2Ph), 4.96 (d, $J_{2,3}$ = 12.0 Hz, 1 H, 2-H), 4.86 (d, $^3J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 3.98–3.83 (m, 3 H, 9-H, 3-H), 3.76–3.58 (m, 2 H, 10-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 161.41 (C-7), 159.11 (C-5), 156.55 (C-8a), 149.88 (C-4′), 149.59 (C-3′), 137.83 (4′-CqPh), 137.79 (3′-CqPh), 137.18 (7-CqPh), 137.00 (5-CqPh), 131.97 (C-1′), 130.06 (2 CHPh), 129.21 (2 CHPh), 129.18 (2 CHPh), 129.03 (2 CHPh), 128.99 (CHPh), 128.77 (CHPh), 128.63 (CHPh), 128.34 (CHPh), 128.22 (2 CHPh), 128.08 (4 CHPh), 127.84 (2 CHPh), 122.02 (C-6′), 115.31 (C-2′), 115.17 (C-5′), 104.62 (C-4a), 94.93 (C-8), 94.22 (C-6), 77.36 (C-2), 73.56 (C-9), 71.89 (CH_2Bn), 71.83 (C-3), 71.71 (CH_2Bn), 71.01 (CH_2Bn), 70.62 (C-4), 70.58 (CH_2Bn), 62.72 (C-10) ppm. MS (LSIMS): *m*/*z* (%) = 710 (3) $[M]^+$, 374 (9), 181 (7), 91 (100), 65 (8). HRMS: calcd. for $C_{45}H_{42}O_8$ 710.2879; found 710.2876.

3′,4′,5,7-Tetra-*O*-benzyl-4β-(2-hydroxyethoxy)epicatechin (3b):[8a] Ethylene glycol (1.22 mL, 22.0 mmol, 20 equiv.) and DDQ (0.558 g, 2.46 mmol, 2 equiv.) were added to a solution of 3′,4′,5,7-tetra-*O*-benzylepicatechin (**2b**) (0.800 g, 1.23 mmol) in dichloromethane (40 mL) at room temperature. A black-green colour appeared instantaneously. After 3 h of vigorous stirring at room temperature, 4-(dimethylamino)pyridine (0.600 g, 4.91 mmol, 4 equiv.) was added. After another 20 min of stirring, the organic layer was washed with a 5% aqueous solution of sodium hydrogen carbonate (2×20 mL) and with brine (20 mL). Then the organic layer was dried with magnesium sulfate and the solvent evaporated. A purple solid was obtained and purified by chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) giving **3b** as a pale pink solid (0.555 g, 0.77 mmol, 63% yield). IR (KBr): $\tilde{\nu}$ = 3583, 1615, 1591, 1511, 1497, 1453, 1377, 1265, 1214, 1151, 1115, 1026, 736, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 7.50–7.20 (m, 20 H, Ar-H), 7.19 (d, $^4J_{2',6'}$ = 1.5 Hz, 1 H, 2′-H), 7.08 (dd, $^3J_{6',5'}$ = 8.3 Hz, $^4J_{6',2'}$ = 1.5 Hz, 1 H, 6′-H), 6.97 (d, $^3J_{5',6'}$ = 8.3 Hz, 1 H,

5′-H), 6.33 (d, $^4J_{6,8}$ = 2.3 Hz, 1 H, 6-H), 6.30 (d, $^4J_{8,6}$ = 2.3 Hz, 1 H, 8-H), 5.23 (s, 2 H, CH_2Ph), 5.21 (s, 2 H, CH_2Ph), 5.14 (s, 2 H, CH_2Ph), 5.09 (d, $^3J_{2,3}$ = 6.8 Hz, 1 H, 2-H), 4.96 (s, 2 H, CH_2Ph), 4.63 (d, $^3J_{4,3}$ = 2.6 Hz, 1 H, 4-H), 4.00 (dd, $^3J_{3,4}$ = 2.6 Hz, $^3J_{3,2}$ = 5.3 Hz, 1 H, 3-H), 3.98–3.65 (m, 4 H, 9-H and 10-H) ppm. ^{13}C NMR (75,0 MHz, $CDCl_3$, 22 °C): δ = 160.7 (C-7), 159.7 (C-5), 156.1 (C-8a), 149.1 (C-4′), 149.0 (C-3′), 137.3 (4′-CqPh), 137.2 (3′-CqPh), 136.7 (7-CqPh), 136.5 (5-CqPh), 130.9 (C-1′), 128.7 (CHPh), 128.5 (2 CHPh), 128.2 (CHPh), 128.1 (CHPh), 127.9 (2 CHPh), 127.8 (CHPh), 127.6 (2 CHPh), 127.3 (CHPh), 119.8 (C-6′), 115.2 (C-5′), 113.9 (C-2′), 101.9 (C-4a), 94.7 (C-8), 94.5 (C-6), 74.8 (C-2), 71.5 (CH_2Bn), 71.4 (CH_2Bn), 70.7 (C-4), 70.6 (CH_2Bn), 70.6 (C-9), 70.1 (CH_2Bn), 68.2 (C-3), 62.0 (C-10) ppm.

3′,4′,5,7-Tetra-*O*-benzyl-8-bromo-4β-(2-hydroxyethoxy)catechin (4a). (a) From 3′,4′,5,7-Tetra-*O*-benzyl-4β-(2-hydroxyethoxy)catechin (3a): Recrystallized *N*-bromosuccinimide (501 mg, 1 equiv.) dissolved in dichloromethane (15 mL) was added dropwise to a solution of 3′,4′,5,7-tetra-*O*-benzyl-4β-(2-hydroxyethoxy)catechin (**3a**) (2.0 g, 2.81 mmol) in dichloromethane (20 mL) at –78 °C (addition in 5 min). The reaction mixture was warmed to room temperature and stirring was continued at room temperature for 8 h. The mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with brine (3 × 100 mL) and then dried with $MgSO_4$. The solvent was evaporated under reduced pressure and after drying in vacuo, the title product **4a** was obtained as a beige solid (2.17 g, 2.76 mmol, 98% yield).

(b) From 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin (5a): Ethylene glycol (0.5 mL, 6 equiv.) and DDQ (0.62 g, 2 equiv.) were added to a solution of 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin (**5a**) (2.25 g, 3.08 mmol) in dichloromethane (20 mL) at room temperature. A black-green colour appeared instantaneously. After 3.5 h of vigorous stirring at room temperature, 4-(dimethylamino)pyridine (0.34 g, 2.0 equiv.) was added. After another 15 min of stirring, the solvent was evaporated. The resulting crude material was purified by chromatography on silica gel (petroleum ether/EtOAc, 1:1) to obtain after evaporation and drying in vacuo the product **4a** as a white solid (1,09 g, 1.39 mmol, 45% yield). M.p. 149–151 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3385, 3063, 3031, 2924, 2868, 1604, 1578, 1516, 1498, 1454, 1421, 1380, 1346, 1265, 1216, 1185, 1126, 1069, 1028, 885, 855, 812, 782, 735, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 7.53–7.23 (m, 20 H, Ar-H), 7.17 (d, $^4J_{2′,6′}$ = 1.9 Hz, 1 H, 2′-H), 7.05 (dd, $^3J_{6′,5′}$ = 8.3 Hz, 1 H, 6′-H), 6.96 (d, 1 H, 5′-H), 6.28 (s, 1 H, 6-H), 5.23–4.99 (m, 8 H, 4 CH_2Bn), 5.09 (d, $^3J_{2,3}$ = 10.6 Hz, 1 H, 2-H), 4.82 (d, $^3J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 3.86 (m, 2 H, 9-H), 3.77 (m, 1 H, 3-H), 3.66 (m, 2 H, 10-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 156.89 (C-5), 156.60 (C-7), 152.16 (C-8a), 149.03 (C-4′), 148.69 (C-3′), 137.05 (CqPh), 136.95 (CqPh), 136.17 (CqPh), 135.82 (CqPh), 130.70 (C-1′), 128.50 (2 CHPh), 128.41 (2 CHPh), 128.25 (2 CHPh), 128.21 (2 CHPh), 128.14 (CHPh), 127.79 (CHPh), 127.54 (2 CHPh), 127.35 (2 CHPh), 127.29 (2 CHPh), 127.01 (2 CHPh), 126.73 (2 CHPh), 120.80 (C-6′), 114.43 (C-5′), 114.03 (C-2′), 105.21 (C-4a), 92.47 (C-8), 91.90 (C-6), 76.72 (C-2), 72.86 (C-9), 71.38 (C-3), 71.07 (CH_2Bn), 70.99 (CH_2Bn), 70.90 (CH_2Bn), 70.53 (CH_2Bn), 69.63 (C-4), 62.02 (C-10) ppm. MS (LSIMS): *m*/*z* (%) = 813 (100) [M + Na]$^+$, 790 (16) [M + H]$^+$, 749 (5), 729 (24), 571 (46), 549 (25), 457 (20), 361 (12), 329 (65), 307 (43), 289 (27). HRMS: calcd. for $C_{45}H_{41}BrNaO_8$ 811.1883; found 811.1893.

3′,4′,5,7-Tetra-*O*-benzyl-8-bromo-4β-(2-hydroxyethyloxy)epicatechin (4b):[29] The title compound was prepared following the same procedure as that described for the synthesis of 3′,4′,5,7-tetra-*O*-benzyl-8-bromo-4β-(2-hydroxyethoxy)catechin (**4a**) using 3′,4′,5,7-tetra-*O*-benzyl-4β-(2-hydroxyethoxy)epicatechin (**3b**) (0.902 g, 1.27 mmol). After work up, the product **4b** was obtained without further purification as a pale pink solid (0.990 g, 1.25 mmol, 99% yield). M.p. 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 7.53–7.26 (m, 20 H, Ar-H), 7.24 (d, $^4J_{2′,6′}$ = 1.5 Hz, 1 H, 2′-H), 7.05 (dd, $^3J_{6′,5′}$ = 8.3 Hz, $^4J_{6′,2′}$ = 1.5 Hz, 1 H, 6′-H), 6.99 (d, $^3J_{5′,6′}$ = 8.3 Hz, 1 H, 5′-H), 6.29 (s, 1 H, 6-H), 5.24–5.05 (m, 8 H, 4 CH_2Ph), 5.03 (d, $^3J_{2,3}$ = 6.8 Hz, 1 H, 2-H), 4.65 (d, $^3J_{4,3}$ = 2.6 Hz, 1 H, 4-H), 4.05 (m, 1 H, 3-H), 3.84–3.66 (m, 4 H, 9-H and 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 158.7 (C-7), 157.0 (C-5), 152.6 (C-8a), 149.4 (C-4′), 149.0 (C-3′), 137.5 (4′-CqPh), 137.4 (3′-CqPh) 136.7 (7-CqPh), 136.4 (5-CqPh), 130.6 (C-1′), 129.0–127.3 (CHPh), 119.4 (C-6′), 115.5 (C-5′), 113.7 (C-2′), 103.8 (C-4a), 93.1 (C-8), 93.0 (C-6), 75.5 (C-2), 71.6–71.0 (CH_2Bn), 70.6 (C-9), 68.1 (C-3), 62.2 (C-10), 29.8 (C-4) ppm. MS (LSIMS): *m*/*z* (%) = 813 (100) [M + Na]$^+$, 790 (45) [M + H]$^+$, 727 (52), 637 (15), 547 (19), 479 (10), 457 (83), 413 (28), 381 (38), 361 (41), 329 (60), 289 (53). HRMS: calcd. for $C_{45}H_{41}BrNaO_8$ 811.1883 found 811.1893.

3′,4′,5,7-Tetra-*O*-benzyl-8-bromocatechin (5a):[8a] Recrystallized *N*-bromosuccinimide (547 mg, 1 equiv.) dissolved in dichloromethane (15 mL) was added dropwise to a solution of 3′,4′,5,7-tetra-*O*-benzyl-(+)-catechin (**2a**) (2.00 g, 3.07 mmol) in dichloromethane (25 mL) at –78 °C (addition in 25 min). The reaction mixture was warmed to room temperature and stirring was continued at room temperature for 7 h. The mixture was extracted with ethyl acetate (50 mL), washed with brine (40 mL) and then dried with $MgSO_4$. The solvent was evaporated under reduce pressure and after drying in vacuo the title compound **5a** was purified by recrystallization in diethyl ether, giving a white solid (1.97 g, 2.70 mmol, 88% yield). M.p. 121.7–122.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 7.56–7.29 (m, 20 H, Ar-H), 7.07 (s, 1 H, 2′-H), 6.96 (s, 2 H, 5′-H and 6′-H), 6.28 (s, 1 H, 6-H), 5.19 (s, 4 H, 2 CH_2Bn), 5.14 (s, 2 H, CH_2Bn), 5.01 (s, 2 H, CH_2Bn), 4.84 (d, $^3J_{2,3}$ = 7.5 Hz, 1 H, 2-H), 4.00 (m, 1 H, 3-H), 3.02 and 2.71 (ABX, $^2J_{4α,4β}$ = 16.6 Hz, $^3J_{4α,3}$ = 5.6 Hz, $^3J_{4β,3}$ = 8.3 Hz, 2 H, 4α-H and 4β-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 156.34 (C-7), 154.82 (C-5), 151.67 (C-8a), 149.16 (C-4′), 148.97 (C-3′), 137.20 (CqPh), 137.01 (CqPh), 136.69 (CqPh), 136.57 (CqPh), 130.69 (C-1′), 128.59 (4 CHPh), 128.52 (2 CHPh), 128.48 (2 CHPh), 128.04 (CHPh), 127.95 (CHPh), 127.84 (2 CHPh), 127.47 (2 CHPh), 127.23 (2 CHPh), 127.14 (2 CHPh), 127.07 (2 CHPh), 119.88 (C-6′), 114.92 (C-5′), 113.46 (C-2′), 103.95 (C-4a), 92.90 (C-6), 92.80 (C-8), 81.60 (C-2), 71.36 (CH_2Bn), 71.25 (CH_2Bn), 71.21 (CH_2Bn), 70.24 (CH_2Bn), 67.79 (C-3), 27.21 (C-4) ppm. MS (LSIMS): *m*/*z* (%) = 753 (100) [M + Na]$^+$, 730 (63) [M + H]$^+$, 661 (16), 421 (16), 409 (18), 397 (72), 329 (40), 307 (39), 289 (27). HRMS: calcd. for $C_{43}H_{37}BrO_6$ 728.1774; found 728.1781.

3′,4′,5,7-Tetra-*O*-benzyl-8-iodocatechin (6a): *N*-Iodosuccinimide (450 mg, 1 equiv.) dissolved in DMF (6 mL) was added dropwise to a solution of 3′,4′,5,7-tetra-*O*-benzyl-(+)-catechin (**2a**) (1.30 g, 2.0 mmol) in DMF (14 mL) (addition in 15 min). Stirring was continued at room temperature for 24 h. The mixture was diluted with ethyl acetate (50 mL) and washed with water (5 × 40 mL). The organic layer was washed with water and then dried with $MgSO_4$. After evaporation of the solvent under reduce pressure and purification by recrystallization in diethyl ether, the title compound **6a** was obtained as a yellow solid (1.48 g, 1.91 mmol, 95% yield). M.p. 149.4–150.4 °C. IR (KBr): $\tilde{\nu}$ = 3583, 3420, 2923, 1600, 1595, 1513, 1498, 1454, 1381, 1262, 1167, 1221, 1119, 1026, 735, 696, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): δ = 7.41–7.22 (m, 20 H, Ar-H), 6.99 (s, 1 H, 2′-H), 6.85 (s, 2 H, 5′-H and 6′-H), 6.15 (s, 1 H, 6-H), 5.10 (s, 2 H, CH_2Bn), 5.06 (s, 2 H, CH_2Bn), 5.03 (s, 2 H,

CH_2Bn), 4.91 (s, 2 H, CH_2Bn), 4.75 (d, $^3J_{2,3}$ = 7.3 Hz, 1 H, 2-H), 3.88 (m, 1 H, 3-H), 2.89 and 2.57 (ABX, $^2J_{4\alpha,4\beta}$ = 16.6 Hz, $^3J_{4\alpha,3}$ = 5.3 Hz, $^3J_{4\beta,3}$ = 8.0 Hz, 2 H, 4α-H and 4β-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 158.43 (C-8a), 157.64 (C-7), 154.23 (C-5), 149.42 (C-3′), 149.35 (C-4′), 137.66 (CqPh), 137.50 (CqPh), 137.12 (CqPh), 137.04 (CqPh), 131.30 (C-1′), 129.04 (2 CHPh), 129.01 (2 CHPh), 128.97 (2 CHPh), 128.93 (2 CHPh), 128.48 (CHPh), 128.32 (CHPh), 128.27 (2 CHPh), 127.92 (2 CHPh), 127.70 (2 CHPh), 127.59 (2 CHPh), 127.49 (2 CHPh), 120.23 (C-6′), 115.24 (C-5′), 113.82 (C-2′), 103.91 (C-4a), 92.62 (C-6), 82.17 (C-2), 71.71 (CH_2Bn), 71.66 (CH_2Bn), 71.61 (CH_2Bn), 70.65 (CH_2Bn), 68.39 (C-8), 67.79 (C-3), 27.65 (C-4) ppm. MS (LSIMS): *m*/*z* (%) = 800 (10) $[M + Na]^+$, 777 (59) $[M + H]^+$, 650 (13), 445 (100), 319 (50).

3′,4′,5,7-Tetra-*O*-benzyl-4β-(2-hydroxyethoxy)-8-iodocatechin (7a): 3′,4′,5,7-Tetra-*O*-benzyl-8-iodocatechin (**6a**) (2.0 g, 2.6 mmol) was dissolved in dichloromethane (40 mL). Ethylene glycol (0.86 mL, 6 equiv.) and DDQ (1.17 g, 2 equiv.) were then added at room temperature. A black-green colour appeared instantaneously. After 2 h of vigorous stirring at room temperature, 4-(dimethylamino)pyridine (0.63 g, 2 equiv.) was added. The solvent was evaporated and the resulting crude material was purified by chromatography on silica gel (petroleum ether/EtOAc, 1:1) to obtain after evaporation and drying in vacuo the product **7a** as an orange solid (914 mg, 1.09 mmol, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): δ = 7.34–7.14 (m, 20 H, Ar-H), 7.07 (d, $^4J_{2',6'}$ = 1.9 Hz, 1 H, 2′-H), 6.93 (dd, $^3J_{6',5'}$ = 8.3 Hz, 1 H, 6′-H), 6.84 (d, 1 H, 5′-H), 6.11 (s, 1 H, 6-H), 5.08–4.88 (m, 8 H, 4 CH_2Bn), 5.08 (d, $^3J_{2,3}$ = 5.7 Hz, 1 H, 2-H), 3.72 (d, $^3J_{4,3}$ = 3.5 Hz, 1 H, 4-H), 3.73 (m, 2 H, 9-H), 3.63 (m, 1 H, 3-H), 3.53 (m, 2 H, 10-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 159.61 (C-7), 159.16 (C-5), 154.95 (C-8a), 149.56 (C-3′), 149.33 (C-4′), 137.71 (CqPh), 137.63 (CqPh), 136.79 (CqPh), 136.45 (CqPh), 131.35 (C-1′), 129.13 (CHPh), 129.02 (CHPh), 128.88 (2 CHPh), 128.86 (3 CHPh), 128.78 (CHPh), 128.35 (CHPh), 128.16 (CHPh), 127.99 (3 CHPh), 127.88 (3 CHPh), 127.63 (2 CHPh), 127.35 (2 CHPh), 121.29 (C-6′), 114.99 (C-5′), 114.49 (C-2′), 105.35 (C-4a), 91.93 (C-6), 77.48 (C-8), 73.55 (C-2), 72.27 (C-9), 71.67 (CH_2Bn), 71.63 (CH_2Bn), 71.55 (CH_2Bn), 71.17 (CH_2Bn), 70.16 (C-4), 67.84 (C-3), 62.70 (C-10) ppm. MS (LSIMS): *m*/*z* (%) = 859 (100) $[M + Na]^+$, 676 (13), 649 (25), 557 (14), 527 (29), 505 (34), 487 (13). HRMS: calcd. for $C_{45}H_{41}O_8INa$ 859.1743; found 859.1741.

3′,4′,5,7-Tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (9a): $TiCl_4$ (1 M in CH_2Cl_2) (1.5 mL, 2 equiv.) was added dropwise with ice cooling to 3′,4′,5,7-tetra-*O*-benzylcatechin (**2a**) (500 mg, 0.77 mmol) and 3′,4′,5,7-tetra-*O*-benzyl-8-bromo-4β-(2-hydroxyethoxy)catechin (**4a**) (728 mg, 1.2 equiv.) in THF (5 mL) and dichloromethane (5 mL). The resulting dark-red solution was stirred at room temperature for 3 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL). The $TiO_2{\cdot}xH_2O$ precipitate was removed by filtration and rinsed with dichloromethane and water. The organic layer was washed with brine and the aqueous phases were extracted with dichloromethane. The organic phases were then dried with $MgSO_4$. After evaporation of the solvents, the resulting dark-red oil was purified by flash chromatography on silica gel (pentane/EtOAc, 4:1) to obtain after evaporation and drying in vacuo the title compound **9a** as a beige solid (710 mg, 0.515 mmol, 67% yield). M.p. 74–76 °C. IR (KBr): $\tilde{\nu}$ = 3568, 3062, 3029, 2865, 1600, 1509, 1498, 1454, 1419, 1380, 1339, 1263, 1213, 1172, 1114, 1026, 909, 847, 808, 734, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 22 °C): (two rotamers: maj/min, 63:37): δ = 7.56–7.24 (m, Ar-H, min and maj), 7.19–6.76 (2′B-H, 2′E-H, 5′B-H, 5′E-H, 6′B-H, 6′E-H, min and maj), 6.32 (s, 6D-H, maj), 6.26 (s, 6A-H, min), 6.24 (s, 6A-H, maj), 6.15 (s, 6D-H, min), 5.34–4.49 (m, CH_2Bn, min and maj), 4.88 (d, $^3J_{4C,3Cmin}$ = 8.3 Hz, 4C-H, min), 4.80 (d, $^3J_{4C,3Cmaj}$ = 9.0 Hz, 4C-H, maj), 4.62 (d, $^3J_{2C,3C}$ = 9.8 Hz, 2C-H, min and maj), 4.44 (d, $^3J_{2F,3Fmin}$ = 8.7 Hz, 2F-H, min), 4.32 (m, 3C-H, maj), 4.19 (m, 3C-H, min), 3.73 (m, 3F-H, min and maj), 3.72 (d, $^3J_{2F,3Fmaj}$ = 12.1 Hz, 2F-H, maj), 3.26 and 2.70 (ABX, $^2J_{4F\alpha,4F\beta min}$ = 16.6 Hz, $^3J_{4F\alpha,3Fmin}$ = 5.8 Hz, $^3J_{4F\beta,3Fmin}$ = 9.4 Hz, 4Fα-H and 4Fβ-H, min), 3.11 and 2.46 (ABX, $^2J_{4F\alpha,4F\beta maj}$ = 16.2 Hz, $^3J_{4F\alpha,3Fmaj}$ = 4.9 Hz, $^3J_{4F\beta,3Fmaj}$ = 8.5 Hz, 4Fα-H and 4Fβ-H, maj) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 157.57 (C-7A, min), 156.88 (C-7A, maj), 156.77 (C-7D, min), 156.24 (C-7D, maj), 156.15 (C-5D, min), 156.06 (C-5D, maj), 154.74 (C-5A, maj), 154.69 (C-5A, min), 154.50 (C-8aA, maj), 154.24 (C-8aA, min), 154.00 (C-8aD, maj), 153.43 (C-8aD, min), 149.77–148.61 (C-3′B, C-3′E, C-4′B, C-4′E, min and maj), 137.23–136.97 (CqPh, min and maj), 132.31 (C-1′E, maj), 132.15 (C-1′B, min), 132.07 (C-1′B, maj), 130.61 (C-1′E, min), 130.19–127.46 (CHPh, min and maj), 121.62 (C-6′B, maj), 121.09 (C-6′B, min), 120.71 (C-6′E, maj), 120.30 (C-6′E, min), 116.09 (C-5′B, min), 115.39 and 115.18 (C-5′B and C-5′E, maj), 115.07 (C-5′E, min), 114.51 (C-2′B and C-2′E, min), 114.10 (C-2′B and C-2′E, maj), 112.17 (C-8D, min), 111.90 (C-8D, maj), 111.23 (C-4aA, maj), 111.13 (C-4aA, min), 104.04 (C-4aD, min), 103.04 (C-4aD, maj), 94.39 (C-8A, min), 94.33 (C-8A, maj), 94.06 (C-6A, maj), 93.83 (C-6A, min), 92.31 (C-6D, min), 91.79 (C-6D, maj), 82.76 (C-2C, maj), 82.33 (C-2C, min), 81.93 (C-2F, min), 81.28 (C-2F, maj), 73.82 (C-3C, min), 73.60 (C-3C, maj), 71.90–70.46 (CH_2Bn, min and maj), 69.27 (C-3F, min), 68.97 (C-3F, maj), 38.04 (C-4C, min), 37.94 (C-4C, maj), 29.07 (C-4F, min), 28.58 (C-4F, maj) ppm. MS (LSIMS): *m*/*z* (%) = 1401 (87) $[M + Na]^+$, 1378 (58) $[M]^+$, 1309 (16), 1045 (25), 937 (26), 727 (35), 647 (21), 395 (64), 307 (42), 211 (100). HRMS: calcd. for $C_{86}H_{73}O_{12}BrNa$ 1399.4183; found 1399.4160.

3′,4′,5,7-Tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylepicatechin) (9b): The title compound was prepared after coupling 3′,4′,5,7-tetra-*O*-benzyl-8-bromo-4β-(2-hydroxyethoxy)-catechin (**4a**) (582 mg, 0.74 mmol, 1.2 equiv.) and 3′,4′,5,7-tetra-*O*-benzylepicatechin (**2b**) (400 mg, 0.61 mmol, 1 equiv.) following the same procedure as that described for 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9a**). The resulting dark-red solution was stirred at room temperature for 5 h. After work up and purification on silica gel (pentane/EtOAc, 4:1), the protected B4 dimer **9b** was isolated (449 mg, 0.33 mmol, 53% yield). M.p. 73–75 °C. IR (KBr): $\tilde{\nu}$ = 3422, 3062, 3030, 2925, 2856, 1600, 1512, 1498, 1454, 1418, 1382, 1340, 1265, 1216, 1173, 1116, 1027, 910, 848, 786, 735, 696, 620 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): (two rotamers: maj/min 85:15): δ = 7.49–6.80 (m, 40 H, Ar-H), 7.22–6.67 (m, 6 H, 2′B-H, 5′B-H, 6′B-H, 2′E-H, 5′E-H, 6′E-H), 6.22 (s, 1 H, 6D-H), 6.18 (s, 1 H, 6A-H), 5.24–4.38 (m, 16 H, CH_2Bn), 4.83 (d, $^3J_{4C,3C}$ = 8.3 Hz, 1 H, 4C-H), 4.58 (d, $^3J_{2C,3C}$ = 9.6 Hz, 1 H, 2C-H), 4.19 (m, 1 H, 3C-H), 3.88 (m, 1 H, 3F-H), 3.78 (s, 1 H, 2F-H), 2.88 and 2.57 (ABX, $^2J_{4F\alpha,4F\beta}$ = 17.1 Hz, $^3J_{4F\alpha,3F}$ = 4.4 Hz, $^3J_{4F\beta,3F}$ < 1 Hz, 2 H, 4Fα-H and 4Fβ-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 22 °C): δ = 156.58 (C-5A), 156.48 (C-5D), 155.63 (C-7D), 154.38 (C-7A), 153.87 (C-8aD), 153.65 (C-8aA), 149.24, 149.05, 148.77, 148.56 (C-3′B, C-3′E, C-4′B, C-4′E), 138.20–136.50 (CqPh), 132.29 (C-1′E), 131.63 (C-1′B), 129.10–127.00 (CHPh), 121.25 (C-6′B), 118.95 (C-6′E), 115.43, 114.78 (C-5′B, C-5′E), 113.58 (C-2′B), 113.18 (C-2′E), 111.49 (C-8D), 110.97 (C-4aA), 100.98 (C-4aD), 94.04 (C-8A), 93.89 (C-6A), 91.36 (C-6D), 82.43 (C-2C), 77.49 (C-2F), 73.14 (C-3C), 71.90–69.80 (CH_2Bn), 66.23 (C-3F), 37.35 (C-4C), 28.42 (C-4F) ppm (chemical shifts and coupling constants *J* are only given

for the major rotamer). MS (LSIMS): *m/z* (%) = 1401 (100) [M + Na]$^+$, 1379 (38) [M]$^+$, 1309 (18), 1045 (13), 727 (7), 647 (21), 381 (30), 353 (14), 329 (24), 307 (16), 289 (15), 211 (7). HRMS: calcd. for $C_{86}H_{73}O_{12}BrNa$ 1399.4183; found 1399.4215.

3′,4′,5,7-Tetra-*O*-benzyl-8-bromoepicatechin-4β,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (9c): The title compound was prepared after coupling 3′,4′,5,7-tetra-*O*-benzyl-8-bromo-4β-(2-hydroxyethoxy)-epicatechin (**4b**) (0.467 g, 0.591 mmol, 1.2 equiv.) and 3′,4′,5,7-tetra-*O*-benzylcatechin (**2a**) (0.321 g, 0.493 mmol, 1 equiv.) following the same procedure as described for 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9a**). The resulting dark-red solution was stirred at room temperature for 3 h. After work up and purification on silica gel (cyclohexane/ethyl acetate, 7:3) the protected B1 dimer **9c** was isolated (0.321 g, 0.232 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 22 °C): (two rotamers: maj/min 77:23): δ = 7.50–7.26 (m, Ar-H), 7.21–6.80 (2′B/E-H, 5′B-H, 6′B/E-H, 5′E-H, maj and min), 6.64 (d, $^4J_{2',6'}$ = 1.5 Hz, 2′E/B-H, maj), 6.35 (s, 6D-H, maj), 6.32 (dd, $^3J_{6',5'}$ = 8.3 Hz, $^4J_{6',2'}$ = 1.9 Hz, 6′E/B-H, maj), 6.20 (s, 6A-H, min), 6.17 (s, 6D-H, min), 6.05 (s, 6A-H, maj), 5.45 (s, 2C-H, maj), 5.38 (s, 2C-H, min), 5.17–4.76 (m, CH_2Bn, maj and min), 4.85 (d, $^3J_{3C,4Cmaj}$ = 1.1 Hz, 4C-H, maj), 4.73 (d, J < 1 Hz, 4C-H, min), 4.62 (d, $^3J_{2F,3Fmin}$ = 3.4 Hz, 2F-H, min), 4.07 (d, $^3J_{3C,4Cmaj}$ = 1.1 Hz, 3C-H, maj), 3.93 (m, J < 1 Hz, 3C-H, min), 3.69 (dd, $^3J_{3F,4F\alpha/\beta maj}$ = 8.7 Hz, $^3J_{3F,4F\alpha/\beta maj}$ = 7.5 Hz, 3F-H, maj), 3.58 (d, $^3J_{2F,3Fmaj}$ < 1 Hz, 2F-H, maj), 3.23 (dd, $^2J_{4F\alpha,4F\beta maj}$ = 16.7 Hz, $^3J_{4F\beta,3Fmaj}$ = 6.4 Hz, 4Fβ-H, maj), 3.14 (dd, $^2J_{4F\beta,4F\beta min}$ = 16.2 Hz, $^3J_{4F\beta,3Fmin}$ = 5.3 Hz, 4Fβ-H, min), 2.68 (dd, $^2J_{4F\alpha,4F\beta min}$ = 16.2 Hz, $^3J_{4F\alpha,3Fmin}$ = 9.0 Hz, 4Fα-H, min), 2.55 (dd, $^3J_{4F\alpha,4F\beta maj}$ = 16.7 Hz, $^3J_{4F\alpha,3Fmaj}$ = 9.8 Hz, 4Fα-H, maj) ppm. ^{13}C NMR (75.0 MHz, $CDCl_3$, 22 °C): δ = 156.0 (C-5D), 155.8 (C-7D), 155.6 (C-5A), 154.3 (C-7A and C-8aD), 151.4 (C-8aA), 149.8, 149.4, 149.2, 148.6 (C-3′B, C-3′E, C-4′B, C-4′E), 137.6–136.9 (CqPh), 131.8, 129.5 (C-1′B, C-1′E), 128.6–126.8 (CHPh), 120.3, 119.1 (C-6′B, C-6′E), 115.2, 114.3 (C-5′B, C-5′E), 113.1, 111.3 (C-2′E, C-2′B), 110.8 (C-8D), 106.8 (C-4aA), 104.3 (C-4aD), 93.4 (C-8A), 92.5 (C-6D), 92.4 (C-6A), 81.6 (C-2F, maj), 81.4 (C-2F, min), 77.2 (C-2C, min), 75.9 (C-2C, maj), 72.1–69.5 (CH_2Bn, C-3C, maj and min), 68.5 (C-3F, maj), 68.2 (C-3F, min), 35.8 (C-4C, maj and min), 29.7 (C-4F, maj), 28.9 (C-4F, min) ppm. MS (LSIMS): *m/z* (%) = 1417.3 (18) [M + K]$^+$, 1401.3 (100) [M + Na]$^+$, 1103.3 (6), 901.3 (6), 887.3 (15), 873.3 (25), 859.3 (23), 722.2 (13). HRMS: calcd. for $C_{86}H_{73}BrO_{12}$ 1376.4285 found 1376.4270.

3′,4′,5,7-Tetra-*O*-benzyl-8-bromoepicatechin-4β,8-(3′,4′,5,7-tetra-*O*-benzylepicatechin) (9d):[29] The title compound was prepared after coupling 3′,4′,5,7-tetra-*O*-benzyl-8-bromo-4β-(2-hydroxyethoxy)-epicatechin (**4b**) (0.502 g, 0.636 mmol, 1.2 equiv.) and 3′,4′,5,7-tetra-*O*-benzylepicatechin (**2b**) (0.345 g, 0.530 mmol, 1 equiv.) following the same procedure as described for 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9a**). The resulting dark-red solution was stirred at room temperature for 3 h. After work up and purification on silica gel (cyclohexane/ethyl acetate, 7:3) the protected B2 dimer **9d** was isolated (0.314 g, 0.228 mmol, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): (two rotamers: maj/min 67:33): δ = 7.52–7.25 (m, Ar-H), 7.22–6.74 (m, 2′B-H, 2′E-H, 5′B-H, 5′E-H, 6′E/B-H), 6.35 (s, 6D-H, maj), 6.28 (d, $^3J_{2',6'}$ = 8.3 Hz, 6′B/E-H), 6.23 (s, 6A-H, min), 6.20 (s, 6D-H, min), 6.13 (s, 6A-H, maj), 5.57 (s, 2F-H, maj), 5.37 (s, 2F-H, min), 5.25–4.96 (m, CH_2Bn, 2F-H, min), 4.89 (s, 2F-H, maj), 4.33 (m, 3F-H, maj), 4.12 (s, 3C-H, min), 4.00 (s, 3C-H, maj), 3.81 (d, ^3J = 3.6 Hz, 3F-H, min), 3.00–2.84 (m, 4Fα-H and 4Fβ-H, maj and min) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 156.8 (C-5D), 156.1 (C-7D), 155.9 (C-5A), 154.6 (C-7A), 154.5 (C-8aA), 151.7 (C-8aD), 149.5, 149.3, 148.8, 148.7 (C-3′B, C-3′E,C-4′B, C-4′E), 137.9–136.7 (CqPh), 132.0, 130.9 (C-1′B, C-1′E), 128.9–127.0 (CHPh), 119.5, 118.4 (C-6′B, C-6′E), 115.4 (C-5′B and C-5′E), 113.3 (C-2′E and C-2′B), 111.5 (C-8D), 107.4 (C-4aA), 102.5 (C-4aD), 93.3 (C-6D), 93.0 (C-8A), 91.8 (C-6A), 79.1 (C-2F, maj), 78.4 (C-2F, min), 76.4 (C-2C, maj), 76.3 (C-2C, min), 72.5–69.6 (CH_2Bn, C-3C, maj and min), 66.7 (C-3F, maj), 65.4 (C-3F, min), 36.1 (C-4C, maj), 35.9 (C-4C, min), 28.9 (C-4F, min), 28.7 (C-4F, maj) ppm. MS (LSIMS): *m/z* (%) = 1417.3 (14) [M + K]$^+$, 1401.3 (100) [M + Na]$^+$, 712.3 (5). HRMS: calcd. for $C_{26}H_{76}BrO_{12}$ 1399.4183; found 1399.4234.

Catechin-4α,8-catechin (10a):[30] In a reaction flask washed with aqueous hydrogen carbonate, 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9a**) (40 mg, 29 μmol) was dissolved in ethyl acetate (2 mL) and methanol (2 mL). Pearlman's catalyst $Pd(OH)_2$/C (40 mg) and triethylamine (40 μL, 287 μmol) were added and the mixture was then stirred under H_2 at room temperature for 18 h. After filtration through Celite, washing with ethyl acetate and evaporation of the solvents, the B3 dimer was obtained accompanied by the triethylamine hydrobromide salt. Rapid filtration through silica gel (acetone/4% methanol) followed by evaporation and drying in vacuo gave the B3 dimer **10a** as a white solid in quantitative yield. M.p. 218–220 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3375, 1610, 1522, 1451, 1375, 1283, 1207, 1144, 1106, 1092, 1061, 870, 818, 780, 668, 621 cm^{-1}. ^{1}H NMR (400 MHz, H_2O/10% D_2O, 22 °C): (two rotamers: maj/min 95:5): δ = 6.87 (d, $^3J_{5'E,6'E}$ = 8.2 Hz, 1 H, 5′E-H), 6.83 (d, $^3J_{5'B,6'B}$ = 8.2 Hz, 1 H, 5′B-H), 6.80 (d, $^4J_{2'B,6'B}$ < 1 Hz, 1 H, 2′B-H), 6.61 (d, $^4J_{2'E,6'E}$ < 1 Hz, 1 H, 2′E-H), 6.61 (dd, 1 H, 6′B-H), 6.46 (dd, 1 H, 6′E-H), 6.15 (s, 1 H, 6D-H), 6.00 (s, 1 H, 6A-H), 5.71 (s, 1 H, 8A-H), 4.58 (d, $^3J_{2F,3F}$ = 7.9 Hz, 1 H, 2F-H), 4.39 (d, $^3J_{2C,3C}$ = 10.0 Hz, 1 H, 2C-H), 4.36 (d, $^3J_{4C,3C}$ = 10.5 Hz, 1 H, 4C-H), 4.29 (m, 1 H, 3C-H), 3.92 (m, 1 H, 3F-H), 2.85 and 2.49 (ABX, $^2J_{4F\alpha,4F\beta}$ = 15.8 Hz, $^3J_{4F\alpha,3F}$ = 5.3 Hz, $^3J_{4F\beta,3F}$ = 8.5 Hz, 2 H, 4Fα-H and 4Fβ-H) ppm. ^{13}C NMR (100.6 MHz, H_2O/10% D_2O, 22 °C): δ = 156.83 (C-8aA), 155.24 (C-5A), 154.73 (C-7A), 154.07 (C-7D), 153.15 (C-8aD), 153.02 (C-5D), 144.73 (C-3′B), 144.08 (C-3′E), 144.03 (C-4′E), 143.91 (C-4′B), 130.84 (C-1′E), 130.65 (C-1′B), 120.54 (C-6′B), 120.17 (C-6′E), 116.40 (C-5′E), 116.04 (C-2′B), 115.84 (C-5′B), 115.16 (C-2′E), 109.25 (C-8D), 107.27 (C-4aA), 101.51 (C-4aD), 96.89 (C-6A), 95.65 (C-6D), 95.61 (C-8A), 82.04 (C-2C), 80.57 (C-2F), 72.85 (C-3C), 67.28 (C-3F), 37.07 (C-4C), 27.52 (C-4F) ppm. MS (LSIMS): *m/z* (%) = 579 (15) [M]$^+$, 473 (13), 449 (22), 433 (14), 413 (21), 329 (30), 306 (23), 289 (27), 284 (100), 247 (27). HRMS: calcd. for $C_{30}H_{26}NaO_{12}$ 601.1322; found 601.1319.

Catechin-4α,8-epicatechin (10b):[10a,30] This title compound was prepared following the same procedure as described for catechin-4α,8-catechin (**10a**) except that 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4β,8-(3′,4′,5,7-tetra-*O*-benzylepicatechin) (**9b**) was used in place of 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9a**). The B4 dimer **10b** was quantitatively isolated as a white solid. M.p. 178–180 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3385, 1617, 1602, 1522, 1458, 1450, 1384, 1283, 1205, 1145, 1095, 1062, 819, 783 cm^{-1}. ^{1}H NMR (400 MHz, D_2O/[D_6]ethanol, 88:12, 22 °C): (two rotamers: maj/min 76:24): δ = 6.68 (d, $^3J_{5'E,6'E}$ = 8.2 Hz, 1 H, 5′E-H), 6.63 (d, $^3J_{5'B,6'B}$ = 8.2 Hz, 1 H, 5′B-H), 6.57 (d, $^4J_{2'B,6'B}$ = 1.6 Hz, 1 H, 2′B-H), 6.55 (d, $^4J_{2'E,6'E}$ = 1.8 Hz, 1 H, 2′E-H), 6.34 (dd, 1 H, 6′B-H), 6.29 (dd, 1 H, 6′E-H), 6.02 (s, 1 H, 6D-H), 5.89 and 5.82 (AM, $^4J_{6A,8A}$ = 2.0 Hz, 2 H, 6A-H and 8A-H), 4.70 (d, $^3J_{2F,3F}$ < 1 Hz, 1 H, 2F-H), 4.31 (d, $^3J_{2C,3C}$ = 9.7 Hz, 1 H, 2C-H), 4.28 (d, $^3J_{4C,3C}$ = 8.5 Hz, 1 H, 4C-H), 4.13 (dd, 1 H, 3C-H), 4.00 (m, 1 H, 3F-H), 2.78 and 2.55 (ABX, $^2J_{4F\alpha,4F\beta}$ = 17.2 Hz, $^3J_{4F\alpha,3F}$ = 4.7 Hz, $^3J_{4F\beta,3F}$ < 1 Hz, 2 H, 4Fα-H and 4Fβ-H) ppm. ^{13}C NMR (100.6 MHz, D_2O/[D_6]ethanol, 88:12, 22 °C): δ

= 156.89 (C-5A), 155.49 (C-7A), 155.01 (C-5D), 154.25 (C-7D), 153.83 (C-8aA), 153.52 (C-8aD), 144.65 (C-4′B), 144.12 (C-3′B), 143.81 and 143.77 (C-3′E and C-4′E), 131.24 (C-1′E), 130.94 (C-1′B), 120.43 (C-6′B), 119.81 (C-6′E), 116.40 (C-5′B), 116.25 (C-2′B), 115.64 (C-5′E), 114.78 (C-2′E), 109.14 (C-4aA), 107.53 (C-8D), 100.83 (C-4aD), 97.19 (C-6A), 96.31 (C-8A), 96.00 (C-6D), 82.26 (C-2C), 78.32 (C-2F), 72.69 (C-3C), 66.22 (C-3F), 37.30 (C-4C), 27.99 (C-4F) ppm (chemical shifts and coupling constants *J* are only given for the major rotamer). MS (LSIMS): *m/z* (%) = 601 (4) $[M + Na]^+$, 413 (15), 376 (7), 357 (10), 329 (58), 306 (19), 301 (16), 289 (13), 241 (53), 219 (100), 212 (33). HRMS: calcd. for $C_{30}H_{26}NaO_{12}$ 601.1322; found 601.1319.

Epicatechin-4β,8-catechin (10c):[30] This title compound was prepared following the same procedure as described for catechin-4α,8-catechin (**10a**) except that 3′,4′,5,7-tetra-*O*-benzyl-8-bromoepicatechin-4β,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9c**) (0.430 g, 0.312 mmol, 1 equiv.) was used in place of 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9a**). The B1 dimer **10c** was quantitatively obtained as a beige solid (0.179 g, 0.310 mmol). M.p. 204–205 °C (dec.). ^{1}H NMR (400 MHz, H_2O/D_2O 90:10, 22 °C): (two rotamers: maj/min 95:5): δ = 7.01 (d, 2′B-H), 6.89 (d, 5′B-H), 6.80 (d, 5′B-H and 6′E-H), 6.66 (d, J = 2.3 Hz, 2′E-H), 6.56 (d, 6′E-H), 6.24 (s, 6D-H), 5.86 (s, 6A-H), 5.37 (s, 8A-H), 5.18 (d, $^3J_{2C,3C}$ = 1.1 Hz, 2C-H), 4.40 (m, 4C-H), 4.01 (m, $^3J_{3F,2F}$ = 9.1 Hz, $^3J_{3F,4F\alpha}$ = 5.6 Hz, $^3J_{3F,4F\beta}$ = 9.8 Hz, 3F-H), 3.97 (m, 3C-H), 3.92 (m, 2F-H), 3.07 (m, $^3J_{3F,4F\beta}$ = 9.8 Hz, 4Fβ-H), 2.46 (m, 4Fα-H) ppm. ^{13}C NMR (100.6 MHz, H_2O/D_2O 90:10, 22 °C): δ = 155.3 (C-8aA), 154.5 (C-7A), 154.2 (C-5A), 153.1 (C-8aD), 153.1 (C-5D), 153.1 (C-7D), 143.9 (C-4′E), 143.8 (C-3′B), 143.6 (C-4′B), 143.5 (C-3′E), 131.2 (C-1′B), 130.0 (C-1′E), 120.7 (C-6′E), 119.1 (C-6′B), 115.9 (C-5′B), 115.5 (C-5′E), 115.0 (C-2′E), 114.5 (C-2′B), 107.7 (C-8D), 102.9 (C-4aA), 101.7 (C-4aD), 95.8 (C-6D), 94.8 (C-6A), 94.6 (C-8A), 81.2 (C-2F), 75.2 (C-2C), 71.4 (C-3C), 67.4 (C-3F), 35.5 (C-4C), 28.8 (C-4F) ppm. MS (LSIMS): *m/z* (%) = 601 (2) $[M + Na]^+$, 409 (4), 381 (12), 353 (15), 329 (48), 311 (5), 242 (100), 212 (14). HRMS: calcd. for $C_{30}H_{26}O_{12}Na$ 601.1322; found 601,1319.

Epicatechin-4β,8-epicatechin (10d):[10a,30] The title compound was prepared following the same procedure as described for catechin-4α,8-catechin (**10a**) except that 3′,4′,5,7-tetra-*O*-benzyl-8-bromoepicatechin-4β,8-(3′,4′,5,7-tetra-*O*-benzylepicatechin) (**9d**) (0.260 g, 0.189 mmol) was used in place of 3′,4′,5,7-tetra-*O*-benzyl-8-bromocatechin-4α,8-(3′,4′,5,7-tetra-*O*-benzylcatechin) (**9a**). The B2 dimer **10d** was obtained as a beige solid (0.107 g, 0.187 mmol, 99%). M.p. 197–198 °C (dec.). Compact form (55%): ^{1}H NMR (500 MHz, H_2O/D_2O 90:10, 5 °C):[31] δ = 7.08 (d, $^4J_{2'B,6'B} < 1$ Hz, 2′B-H), 6.93 (m, 6′B-H), 6.92 (m, 5′B-H and 5′E-H), 6.72 ($^4J_{2'E,6'E} < 1$ Hz, 2′E-H), 6.52 (m, 6′E-H), 6.26 (s, 6D-H), 5.82 (s, 6A-H), 5.67 (s, 8A-H), 5.42 (d, $^3J_{2C,3C}$ = 1.1 Hz, 2C-H), 4.47 (m, 4C-H), 4.32 (m, 2F-H), 4.06 (m, 3C-H), 4.02 (m, $^3J_{3F,4F\beta}$ = 4.5 Hz, $^3J_{3F,4F\alpha} < 1$ Hz, $^3J_{3F,2F} < 1$ Hz, 1 H, 3F-H), 2.86 (dd, $^3J_{4F\alpha,4F\beta}$ = 16.9 Hz, $^3J_{3F,4F\beta}$ = 4.5 Hz, 4Fβ-H), 2.71 (br. d, $^3J_{4F\alpha,4F\beta}$ = 16.9 Hz, 4Fα-H) ppm. ^{13}C NMR (125.1 MHz, H_2O/D_2O 90:10, 5 °C): δ = 158.0 (C-7D), 157.7 (C-8aA), 157.0 (C-8aD), 156.9 (C-5D), 156.5 (C-7A), 156.1 (C-5A), 146.7 (C-4′B), 146.5 (C-3′B), 146.0 (C-4′E), 145.8 (C-3′E), 134.2 (C-1′E), 133.5 (C-1′B), 122.2 (C-6′E), 122.1 (C-6′B), 118.7 (C-5′B), 118.7 (C-5′E), 118.0 (C-2′E), 117.4 (C-2′B), 110.6 (C-8D), 105.9 (C-4aA), 103.0 (C-4aD), 98.6 (C-6D), 97.8 (C-8A), 97.7 (C-6A), 81.3 (C-2F), 78.1 (C-2C), 74.6 (C-3C), 68.4 (C-3F), 38.7 (C-4C), 31.1 (C-4F) ppm. Extended form (45%): ^{1}H NMR (500 MHz, H_2O/D_2O 90:10, 5 °C): δ = 7.14 (2′E-H), 6.98 (2′B-H), 6.89 (6′E-H), 6.77 (d, 2 H, 5′B-H and 5′E-H), 6.60 (6′B-H), 6.15 (s, 8A-H), 6.12 (s, 6A-H), 6.06 (s, 6D-H), 5.20 (d, 1 H, 2C-H), 4.82 (m, 2F-H), 4.67 (m, 4C-H), 4.30 (m, 3F-H), 3.98 (m, 3C-H), 2.84 (dd, 4Fβ-H), 2.76 (m, 4Fα-H) ppm. ^{13}C NMR (125,1 MHz, H_2O/D_2O 90:10, 5 °C): δ = 158.6 (C-8aD), 158.5 (C-5A), 157.8 (C-5D), 157.7 (C-8aA), 157.2 (C-7A), 155.9 (C-7D), 146.8 (C-4′E), 146.6 (C-3′E), 146.4 (C-4′B), 146.3 (C-3′B), 133.8 (C-1′E), 133.6 (C-1′B), 121.8 (C-6′B), 121.2 (C-6′E), 117.7 (C-5′E), 117.7 (C-5′B), 117.2 (C-2′B), 116.9 (C-2′E), 109.7 (C-8D), 105.0 (C-4aA), 102.3 (C-4aD), 99.7 (C-6D), 98.2 (C-6A), 97.6 (C-8A), 80.5 (C-2F), 78.4 (C-2C), 74.2 (C-3C), 68.1 (C-3F), 37.9 (C-4C), 30.8 (C-4F) ppm (coupling constants *J* are only given for the major rotamer). MS (LSIMS): *m/z* (%) = 599.5 (18) $[M + Na]^+$, 577.5 (100) $[M]^+$, 425.5 (17), 407.7 (11), 289.5 (15). HRMS: calcd. for $C_{30}H_{23}O_{12}$ 575.1190; found 575.1160.

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