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Synthesis and Preliminary Anticancer Activity Studies of C4 and C8-Modified Derivatives of Catechin Gallate (CG) and Epicatechin Gallate (ECG)

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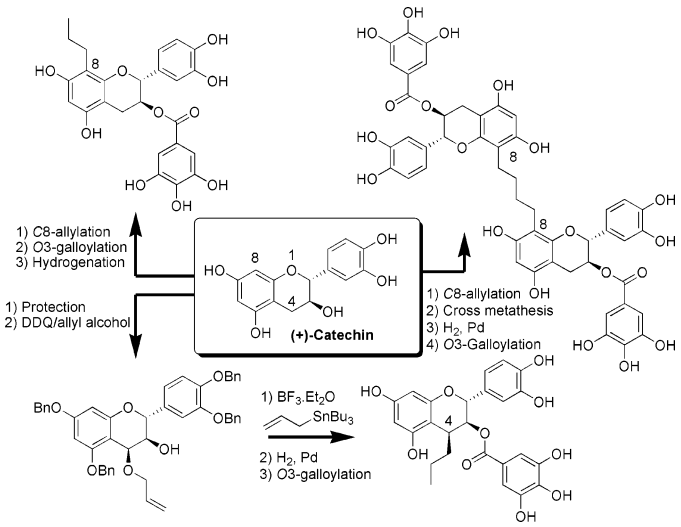

We have developed an improved and reliable method for stereoselective functionalization at C4 of naturally occurring (+)-catechin. Our method utilizes DDQ oxidation followed by trapping of the quinonemethide intermediate with allyl alcohol. The quinonemethide intermediate can be regenerated from the allyl ether by exposure to boron trifluoride diethyl etherate. This reactive intermediate can be trapped with a wide range of external nucleophiles. NBS bromination, lithium halogen exchange, and alkylation gave access to C8-allyl derivatives of (+)-catechin, and this allyl group was used in a series of cross-metathesis experiments to prepare novel dimeric catechin-derived products. Gallate ester derivatives of the novel C4- and C8-substituted catechins were prepared, and these materials were screened for potential anticancer activity in a range of human cancer cell lines. From these preliminary cytotoxicity assays (MTT) we found that C8-propyl-catechin gallate was more active (IC_{50} = 31 μM) than catechin gallate (CG, IC_{50} = 53 μM) or epicatechin gallate (ECG, IC_{50} = 76 μM) against the colorectal adenocarcinoma cell line HCT116. Differential sensitivity in pancreas (Pan1), bladder (RT112), stomach (MGLVA1), liver (HepG2), and fibroblasts (46Br.1G1) cell lines was also observed.

Introduction

There is a high level of interest in the medicinal properties of naturally occurring polyphenolic compounds composed of flavanoid building blocks. These compounds are present in very high concentrations in many plants and the barks and heartwood of a variety of trees.[1] They also enter the human diet and have achieved some attention as beneficial components of a range

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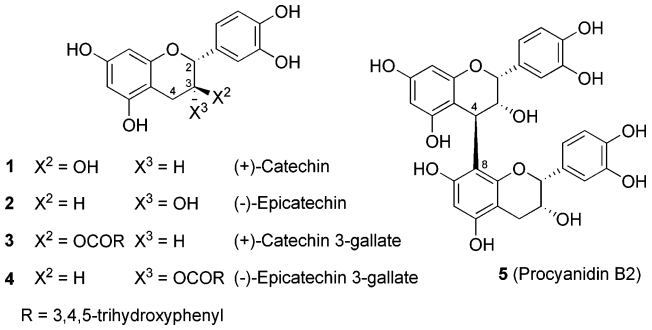


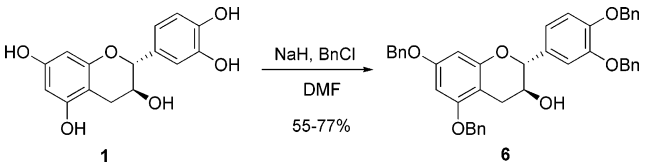
FIGURE 1. Polyphenolic flavanoids.

of foodstuffs including green tea and red wine.[2,3] These include simple flavanoid systems, such as epicatechin 3-gallate **4**, and much more complex oligoflavanoids (so-called tannins), which are often of ill-defined structure. Readily available condensed tannins (procyanidins) have a range of structures made up of many linked flavanoid monomers (such as **1**−**4**, Figure 1) typically via a C4 → 8 interflavanoid bond (e.g., procyanidin B2 **5**).

The inherent biological activities of these compounds are very wide-ranging. For example, members of the procyanidin class of polyphenols, such as **5**, have been identified as possible antiviral, antibacterial, and antitumor agents.[4,5] While some of these biological effects have been attributed to the free-radical scavenging (antioxidant) activity of the polyphenols,[6] recent studies have demonstrated inhibition of essential cellular enzymes (e.g., 20S proteasome;[7] fatty acid synthase (FAS);[8] caspases-3, -7, and -2;[9] P-glycoprotein (P-gp);[10] vascular endothelial growth factor receptor (VEGFR) phosphorylation[11]).

Our recent studies have centered around the synthesis of new catechin analogues based on the structure of the natural flavanoids. We focused our efforts on modifying the C8 and C4 positions of the catechin skeleton, which are the bridging positions of the flavanoid units in procyanidins. We also wanted to access both C3-alcohol stereoisomers, as this allows the opportunity to explore both the catechin and epicatechin basic skeletons. We finally aimed to screen the new compounds for biological activity. We hoped that probing the structure of the simple flavanoids might allow some elucidation of the structural features necessary for biological activity, which as yet are not fully understood. An ultimate goal in this area of study is to tune the inherent biological activity of these polyphenol compounds to a level that is pharmaceutically applicable.

SCHEME 1. O-Benzyl Protection of Catechin 1



Results and Discussion

Synthesis of C4-Substituted Catechin Derivatives. A review of the literature indicated that the phenol protecting group most commonly used during the synthesis of catechin-based polyphenols was the benzyl group.[4,12,13] However, benzylation of electron-rich polyphenols such as catechin often gives a mixture of *O*- and unwanted *C*-benzylated products, leading to difficult separation and low yields. After pursuing a number of different approaches toward 5,7,3′,4′-tetra-*O*-benzlyated catechin **6**,[4,14−17] we obtained the best results using NaH, BnCl, DMF conditions (Scheme 1). It was found that drying the commercially available (+)-catechin hydrate **1** overnight under vacuum was important. In our hands, the reaction worked best on a larger scale (10 g of catechin), reliably producing yields of 55−77% with the desired product isolated by column chromatography. Using this method, large quantities of tetrabenzyl catechin **6** could be prepared, which would provide a common precursor for further elaboration of the catechin scaffold at both the C4 and C8 positions.

A number of related approaches have been reported for the functionalization of catechin at C4. In their extensive studies toward the stereocontrolled synthesis of both natural and unnatural procyanidins, Kozikowski and co-workers introduced an ethylene glycol moiety regioselectively on to tetrabenzylated catechin via a DDQ oxidation at the C4 position. This was then employed as an electrophile in the presence of $TiCl_4$ during condensation reactions to form catechin oligomers.[4,5,18] More recently, Suzuki and co-workers demonstrated the synthetic utility of the C4-acetoxy derivatives of pentabenzylated catechin and epicatechin in stereoselective substitution reactions of the flavan skeleton.[19,20] Unfortunately, despite being synthetically useful intermediates, both the C4-ethylene glycol and the C4-acetoxy derivatives could only be prepared in modest yield (52% and 54%, respectively).

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SCHEME 2. Substitution of 1 at C4

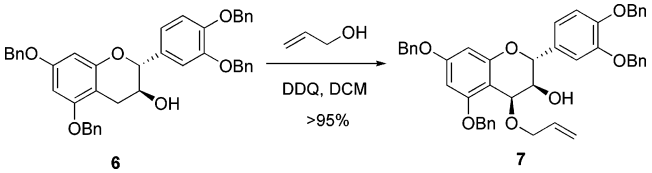
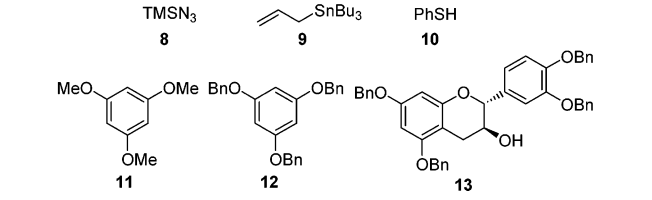


TABLE 1. Lewis Acid Promoted Stereoselective Substitution of 7

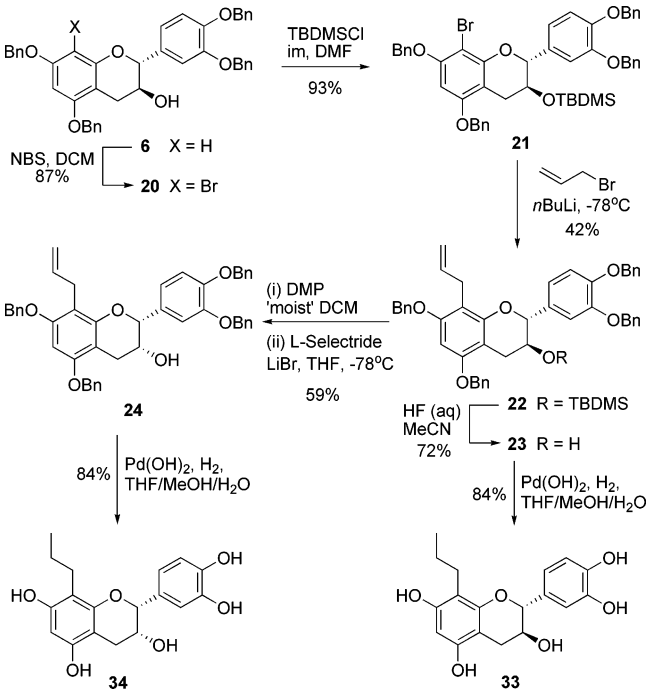
Entry	Reagent	R	Product	Yield/%	α/β
1	**8**	–N_3	**14**	60	β
2	**9**		**15**	45	β
3	**10**	–SPh	**16**	75	β
4	**11**		**17**	80	α
5	**12**		**18**	68	α
6	**13**		**19**	52	α+β (3.5:1)



We re-examined the benzylic DDQ oxidation of tetrabenzylated catechin **6** using allyl alcohol as the nucleophile. We observed the formation of the corresponding C4-*O*-allyl catechin derivative **7** in high yield (>95%) as a single stereoisomer (Scheme 2). The stereochemistry of the new center was determined to be the β-stereoisomer using a combination of NOE (H3 ↔ H4) and coupling constant measurements. The excellent yield of this reaction marks a great improvement on that obtained for the C4-ethylene glycol and the C4-acetoxy derivatives described previously.

We then turned to examining the utility of **7** in substitution reactions at the C4 position. Table 1 shows the results of activation of **7** with a Lewis acid (BF_3·OEt_2) in the presence of the range of nucleophiles **8**−**13**. As reported by Suzuki, in general it was found that the chemical yield of these reactions depended upon the nucleophilicity of the reagents.[19] All reactions appeared to proceed cleanly, and no oligomers due to self-condensation of **7** were observed. We were particularly pleased with the reaction between **7** and allyltributylstannane **9**, as the 45% yield represented a great improvement on the 22% previously reported.[19] For the nonaromatic nucleophiles **8**−**10**, the C4 β-product was obtained as the sole stereoisomer. These selectivities were in good agreement with that observed previously and are generally considered to arise from the energetically favored β-attack on the quinonemethide intermediate.[19] The selectivity is reversed for aromatic nucleophiles **11**−**13**, once again in agreement with previous reports.[19] In these cases the C4 α-product dominates. The basis for this reversal in selectivity remains unclear. Overall, our results demonstrate that C4-*O*-allyl catechin derivative **7** can be used as an effective electrophile for Lewis acid mediated substitution reactions. This allows the introduction of a variety of functional groups at the C4 position of the flavan scaffold. Furthermore, there is no requirement for a C3-alcohol protecting group. This lends itself to further derivatization of the C3-alcohol, which is a common feature among this class of natural products.

SCHEME 3. Synthesis of C8-Substituted Catechin and Epicatechin Analogues



Synthesis of C8-Substituted Catechin Derivatives. In 1970 Weinges and co-workers reported the synthesis of a protected procyanidin via condensation between a C8-bromo catechin derivative and a C4-ketone catechin derivative.[21] This reaction involved an initial halogen−lithium exchange followed by nucleophilic attack of the ketone. More recently, Kozikowski and co-workers reinvestigated this halogen−lithium exchange and showed that the C8-bromo catechin derivative could be alkylated with aldehyde or ketone electrophiles.[18] Other groups have reported the synthesis and subsequent elaboration of the C8-aldehyde catechin derivative from tetrabenzyl catechin **6** via a classical Vilsmeier reaction.[14] We chose to further investigate the utility of the C8-bromo catechin derivative, as it possessed the potential to undergo alkylation either via trapping with other electrophiles after halogen−lithium exchange or by a palladium-catalyzed Stille coupling with alkylstannanes.

Following the literature procedure,[4] tetrabenzyl catechin **6** was transformed into the corresponding C8-bromo derivative **20** by treatment with NBS at −78 °C in 87% (Scheme 3). In preparation for the halogen−lithium exchange it was necessary to protect the C3-alcohol and initially the benzyl protecting

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group was chosen. Following the Kozikowski procedure,[18] the C8-bromo pentabenzyl catechin derivative was treated with *t*BuLi followed by electrophile (allyl bromide or acryolyl chloride). Unfortunately in our hands only Br to H exchange was observed, yielding undesired pentabenzyl catechin. When *n*BuLi was used in conjunction with allyl bromide, a low 22% yield of the desired C8-allyl product was isolated. A series of palladium-catalyzed Stille coupling reactions using allyltributylstannane were screened but produced only trace amounts of the desired product.

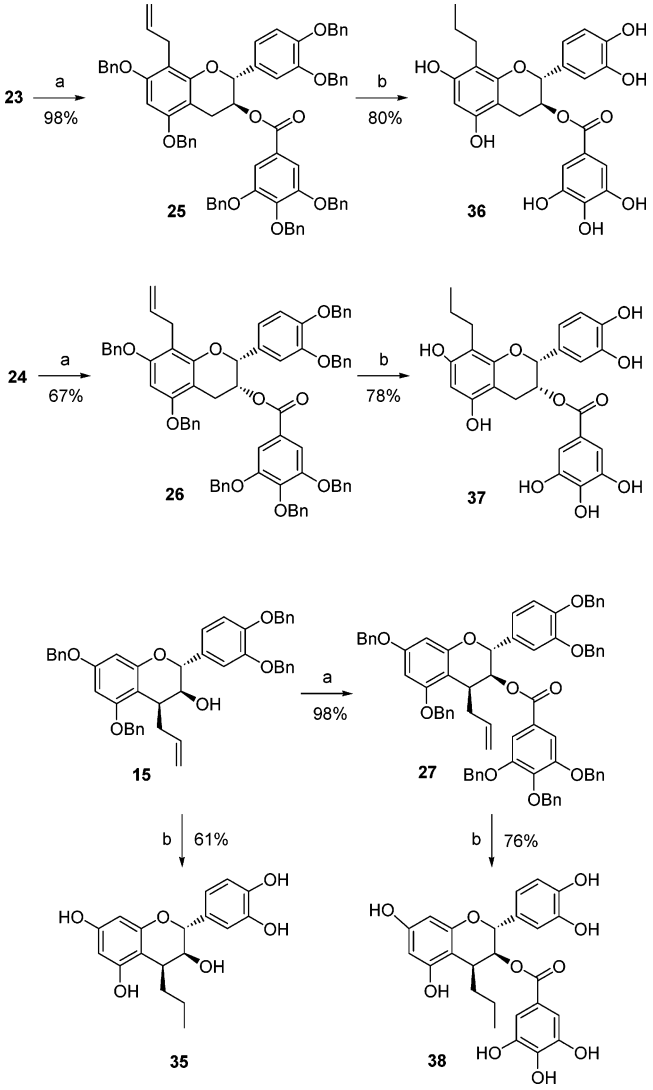
Kozikowski had also shown that the C3-*O*-TBDMS protected epicatechin derivative could undergo halogen−metal exchange reactions.[18] Accordingly, the C3-hydroxyl group of **20** was protected as the corresponding TBDMS ether **21** in excellent 93% yield (Scheme 3). This had the added advantage that we could selectively deprotect the hydroxyl group at a later stage. It would then be available for derivatization as the gallate ester found in natural catechin polyphenols. When the C3-silyl protected catechin **21** was treated with *n*BuLi at −78 °C followed by an excess of freshly distilled allyl bromide (6 equiv), the major product formed was the desired C8-allyl derivative **22**. It was noted that the yield of **22** was higher when the reaction was performed on a medium scale (1−5 g of **21**), giving a reproducible yield of 42% (Scheme 3). Removal of the silyl protecting group was readily effected using aqueous HF in acetonitrile to give alcohol **23** in 72% yield.

So far all of the synthetic precursors prepared exhibited the 2*R*,3*S* stereochemistry of the parent (+)-catechin **1** starting material. As part of our program, we also wanted to prepare analogues possessing the 2*R*,3*R* stereochemistry of the closely related epicatechin **2**, which is another important building block in natural polyphenols. Because commercially available epicatechin is considerably more expensive than catechin, we decided to use the C3-alcohol inversion methodology developed previously.[4] Treatment of **23** with freshly prepared Dess−Martin periodinane[22] in moist DCM[23] afforded the corresponding ketone, which was directly reduced using L-Selectride and LiBr in THF at −78 °C to give the C8-allyl epicatechin derivative **24** in 59% over two steps (Scheme 3).

Gallic Acid Coupling. Recent reports have disclosed the differences in biological activity between polyphenols bearing a gallic acid moiety and those that do not. For example, it is has recently been demonstrated that epicatechin 3-gallate **4** has in vitro proteasome inhibition activity in a system where epicatechin **2** is inactive.[7] For this reason, we were interested in modifying our unnatural catechin derivatives via the formation of gallate esters. The three derivatives **23**, **24**, and **15** were chosen for galloylation onto the available C3-alcohol. Under standard carbodiimide coupling conditions using 3,4,5-tribenzylgallic acid,[24,25] smooth conversion to the desired 3-gallate esters **25**−**27** was observed in 98%, 67%, and 98% yield, respectively (Scheme 4).

Metathesis Dimerization. As mentioned previously, catechin and epicatechin (and the gallate esters thereof) often form the basic building blocks of larger polyphenol oligomeric structures.

SCHEME 4. Synthesis of Galloylated C8- and C4-Substituted Catechin and Epicatechin Analogues[a]



[a] Reagents and conditions: (a) 3,4,5-tri-*O*-benzylgallic acid, DCC, DCM, DMAP; (b) $Pd(OH)_2$, H_2, THF/MeOH/H_2O.

Our advanced precursors **25**−**27** all possessed an allyl group at either the C4- or C8-position. This gave them the potential to be used in a cross-metathesis reaction to form dimeric compounds whose structure would mimic that of the natural procyanidins. Using 10 mol % of Grubbs' second generation catalyst in DCM at reflux, we were pleased to observe homodimerization of both **25** and **26** to form "pseudo" flavanoid dimers **28** and **29** in 55% and 29% yield, respectively (Scheme 5). Both dimers were isolated as a mixture of major and minor products (assumed to be the *E* and *Z* isomers) possessing a C8 → C8 unsaturated linker between the two monomer units.

The C4-allyl catechin gallate derivative **27** was subjected to identical metathesis conditions, but only 10% of the desired C4 → C4 linked homo-dimer was formed, and the isomeric disubstituted alkene **30** was isolated as the major new product (62%) (Scheme 6). This type of isomerization in the presence of Grubbs' catalyst has been reported previously.[26] Initially we

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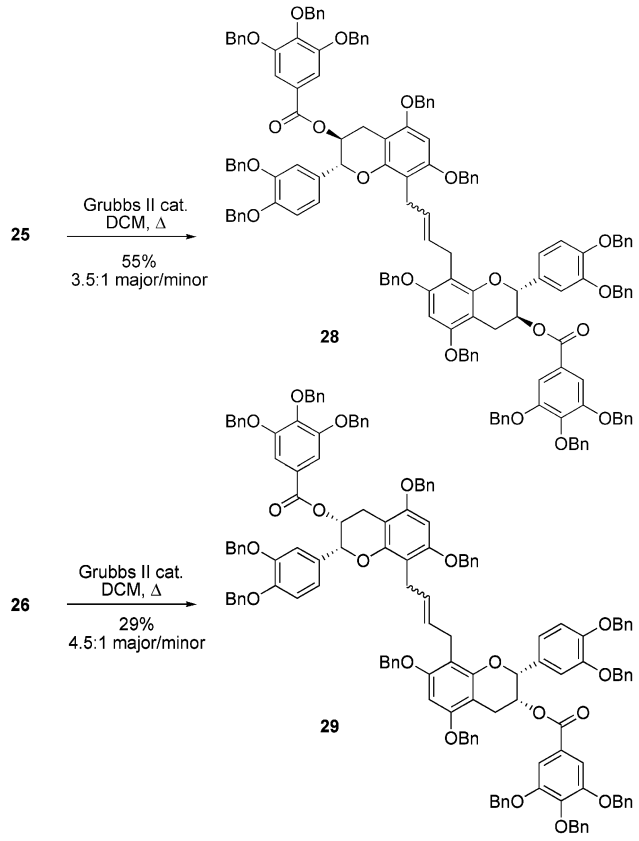
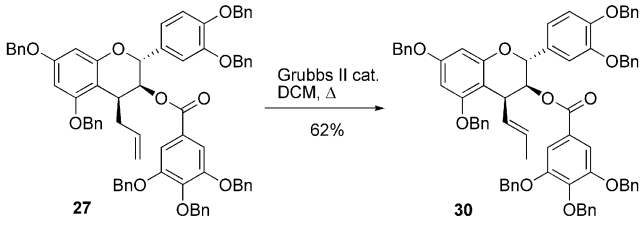
SCHEME 5. Synthesis of C8 → C8 Linked Catechin and Epicatechin Dimers



SCHEME 6. Grubbs' Catalyst Promoted Double Bond Isomerization of 27

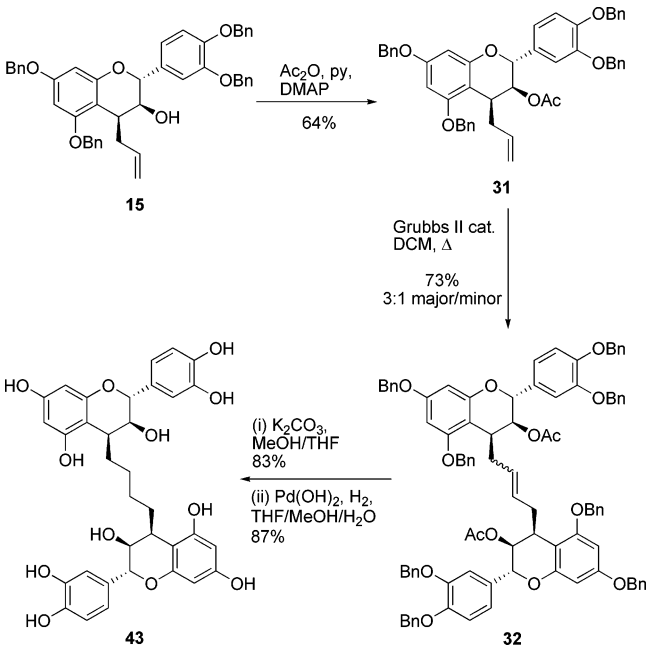


wondered whether steric hindrance from the gallate group was retarding the cross-metathesis reaction, but similar levels of isomerization (56%) were also observed when the less hindered alcohol **15** was subjected to identical conditions.

Interestingly, when the C3-alcohol of **15** was protected as the corresponding acetate **31**, homo-dimerization proceeded in 73% yield, giving **32** as a mixture of double bond isomers (Scheme 7). Hetero-dimerization between **25** and **27** was also attempted with a view to accessing C4 → C8 linked dimers. Unfortunately, the competing homo-dimerization of **25** and isomerization of **27** seemed to dominate, and no hetero-dimer was isolated.

Deprotection of Final Compounds. With a small library of modified catechin- and epicatechin-based monomeric and dimeric derivatives in hand, the final synthetic requirement was the removal of the phenolic protecting groups. The most commonly used method in the literature is hydrogenolysis[5,7,18] Accordingly, all protected compounds (**15**, **18**, **19**, **23**−**29**, and **32**) were hydrogenated over $Pd(OH)_2$ to yield the corresponding polyphenols (**33**−**43**). Obviously, any double bonds present in

SCHEME 7. Synthesis of C4 → C4 Linked Catechin Dimer



the protected derivatives became fully saturated under the hydrogenation conditions. For the C4 → C4 linked homo-dimer **32**, the acetate groups were removed in 83% yield prior to hydrogenolysis using K_2CO_3 in MeOH/THF (Scheme 7). All final compounds were purified by column chromatography.

(+)-Catechin 3-gallate **3** and (−)-epicatechin 3-gallate **4** were also synthesized following known procedures.[4] The biological activity of these compounds is known and therefore they offer ideal standards against which the activity of our modified polyphenols could be compared.

MTT Cell Proliferation Assays. Initially, the effect of compounds **3**, **4**, **36**, **38**, **39**, **41**, and **42** on in vitro proliferation of a colorectal adenocarcinoma cell line, HCT116, was examined. Cells were exposed to a range of concentrations (μM to mM) for 48 h, and cell numbers were measured using a tetrazolium-based MTT assay. Differential sensitivity to the compounds was observed. In Figure 3a, the growth of cells in the presence of each of the compounds is illustrated, with the parent compound **3** [IC_{50} 5.3×10^{-5} M] included for comparison. The log IC_{50} values for each compound achieved with HCT116 cells is also shown (Figure 3b). However, the activities of the parent compounds catechin gallate **3** and epicatechin gallate **4** and the unnatural compounds **36** and **38** were similar, with IC_{50}'s of 5.3, 7.6, 3.1, and 6.0×10^{-5}M, respectively, compound **36** being more active than its parent compound **3**. Compound **39** had slightly lower activity than compound **3** (IC_{50} $= 13.0 \times 10^{-5}$ M compared with 5.3×10^{-5} M). Compounds **41** and **42** had activities considerably lower than that of their parent compound: IC_{50}'s were not achieved within the concentration range assayed, but their projected IC_{50}'s are 2.6 and 1.9 mM, respectively. As (+)-catechin gallate **3** was slightly more potent than (−)-epicatechin gallate **4** at inhibiting HCT116 proliferation (Figure 3a), we chose to use **3** as the control in all subsequent assays. It is interesting to note that 4β-propyl-(+)-catechin gallate **38** maintained the activity of the parent compound (+)-catechin gallate **3**, while 8-propyl-(+)-catechin gallate **36** actually displayed increased potency over that of the parent compound **3**. All other compounds tested showed reduced activity in the HCT116 cell proliferation assay (Figure 3a).

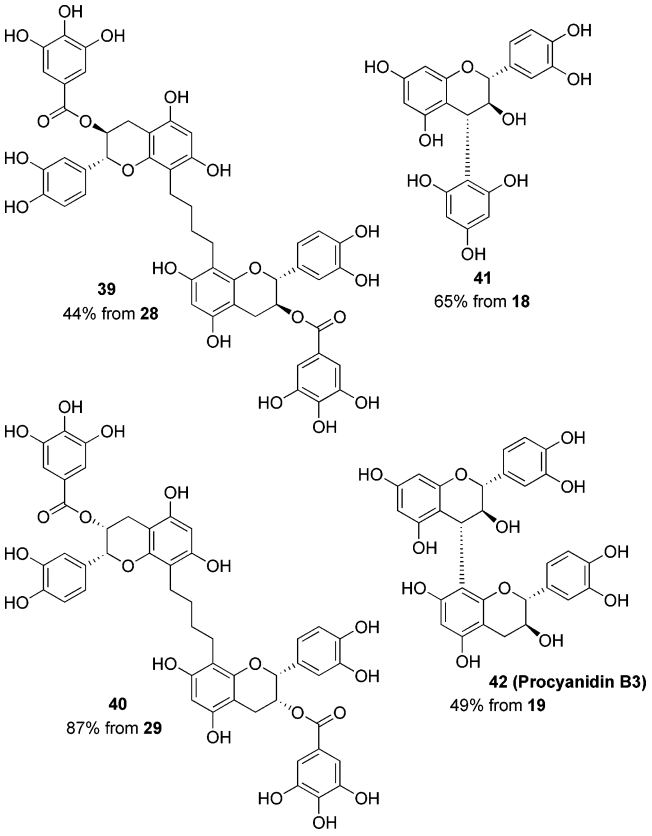


FIGURE 2. Final deprotected compounds **39**−**42**.

Since 8-propyl-(+)-catechin gallate **36** showed increased activity over that of its parent (+)-catechin gallate **3**, these two compounds were selected for testing in a range of human cell lines derived from pancreas (Pan1), bladder (RT112), stomach (MGLVA1), liver (HepG2), and fibroblasts (46Br.1G1) as well as colon. The log IC_{50} for each compound in each cell line is shown in Figure 4.

The cell lines showed differential sensitivity to the compounds, with the colon, liver, and stomach cell lines being more sensitive than the pancreatic and fibroblast cell lines to both compounds ($p < 0.05$). The bladder cell line was more sensitive than the pancreatic and fibroblast cell lines to compound **36** but not to compound **3**. There was significantly increased sensitivity ($p < 0.05$) of the colon, bladder, and fibroblast cell lines to compound **36** compared with compound **3**, suggesting that substitution at C8 of the molecule increases the activity of the compound in these cell lines. These results highlight the need for a more extensive synthetic and biological study of C8-substituted catechins, and we will report our further studies in this area in due course.

Experimental

5,7,3′,4′-Tetra-*O*-benzyl-4β-*O*-allyl-catechin (7). 5,7,3′,4′-Tetra-*O*-benzylcatechin **6** (150 mg, 0.2 mmol) was dissolved in dry DCM (5 mL), and allyl alcohol (500 μL) was added in one portion. The reaction was stirred quite vigorously to ensure good mixing, and DDQ (0.1 g, 0.46 mmol) was added in one portion (the reaction mixture turned from colorless to deep blue-green). Stirring was continued overnight (the reaction mixture turned beige), then DMAP (56 mg, 0.46 mmol) was added in one portion, and stirring was continued for a further 24 h. The reaction mixture was preabsorbed directly onto silica and purified by column chromatography

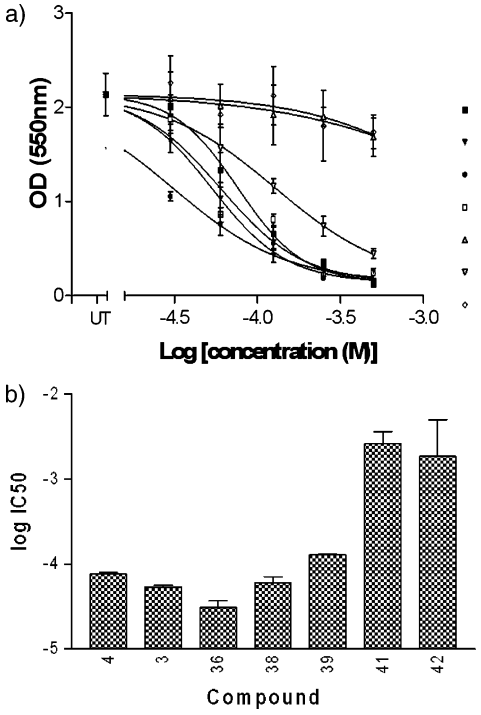


FIGURE 3. (a) Growth of HCT116 colon adenocarcinoma cells in the presence of catechin derivatives. Compounds **4**, **3**, **36**, **38**, **39**, **41**, and **42** were tested at a range of concentrations between 0.03 and 0.5 mM over 48 h, and the effect on cell survival was measured by an MTT. (b) The log IC_{50} values of compounds **4**, **3**, **36**, **38**, **39**, **41**, and **42**.

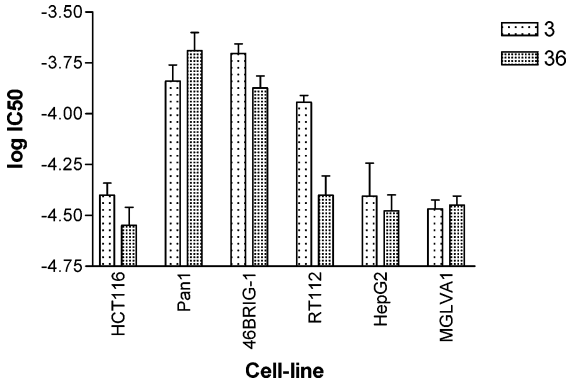


FIGURE 4. The log IC_{50} values of compounds **3** and **36** in a range of human cell lines derived from colon (HCT116), pancreas (Pan1), bladder (RT112), stomach (MGLVA1), liver (HepG2), and fibroblasts (46Br.1G1).

(gradient elution 1:4 → 1:1 EtOAc−petrol to give 5,7,3′,4′-tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (158 mg, 95%) as a pink crystalline solid. Note: the compound was found to be unstable if left standing in $CHCl_3$; R_f 0.35 (2:8 EtOAc−petrol); mp 105−109 °C; $[\alpha]^{25}_D$ +42.1 (*c* 0.92, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3540, 2930, 1615, 1591, 1454; ^1H NMR (400 MHz, $CDCl_3$) 7.48−7.28 (20H, m), 7.10 (1H, br d, J = 2.0), 7.02 (1H, br dd, J = 8.4 and 2.0), 6.98 (1H, br d, J = 8.4), 6.28 (1H, d, J = 2.0), 6.18 (1H, d, J = 2.0), 5.89, (1H, dddd, J = 17.2, 10.4, 6.0 and 5.6), 5.17 (4H, br s), 5.12 (1H, app dt, J = 17.2 and 1.6), 5.07 (1H, d, J = 11.2), 5.06−5.04 (1H, m), 5.02 (1H, d, J = 11.2), 5.00 (2H, br s), 4.97 (1H, d, J = 10.4), 4.85 (1H, d, J = 3.6), 4.27 (1H, app ddt, J = 12.8, 5.6 and 1.6), 4.15 (1H, app ddt, J = 12.8, 6.0 and 1.6), 3.90 (1H, br s) and 2.41 (1H, d, J = 9.2); NOE irradiation at 3.90 (H3) results in enhancement at 4.85 (H4) (9.03%), irradiation at 4.85 (H4) results

in enhancement at 3.90 (H3) (9.78%); ^{13}C NMR (100 MHz, $CDCl_3$) 161.2, 159.0, 156.6, 149.6, 149.4, 137.6, 137.5, 136.9, 136.7, 135.5, 131.9, 128.9, 128.8, 128.7, 128.5, 128.4, 128.1, 128.1, 127.8, 127.5, 121.6, 116.8, 115.1, 114.8, 103.7, 94.7, 93.7, 77.2, 71.8, 71.7, 71.6, 70.8, 70.7, 70.4 and 68.9; *m*/*z* (ES) 729.2 (MNa^+, 100%); found 729.2838; $C_{46}H_{42}O_7Na$ requires 729.2822.

Method 1. General Procedure for C-4 Nucleophilic Substitution of 5,7,3′,4′-Tetra-*O*-benzyl-4β-*O*-allyl-catechin (7). 5,7,3′,4′-Tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (1 equiv) was placed in an oven dried flask under an Argon atmosphere. Nucleophile (3 equiv) was added followed by dry DCM (1 mL per 50 mg **7**), the solution was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (1.5 equiv) was added dropwise to the reaction, and the mixture was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C with saturated aqueous $NaHCO_3$ solution (1 mL), and the reaction was allowed to warm to room temperature. The mixture was diluted with $CHCl_3$ (15 mL) and washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was preabsorbed onto silica and purified by column chromatography.

5,7,3′,4′-Tetra-*O*-benzyl-4β-azido-catechin (14). Following Method 1, 5,7,3′,4′-tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (0.2 g, 0.28 mmol) and azidotrimethylsilane (112 μL, 0.84 mmol) gave a crude product, which was purified by column chromatography (gradient elution 5:95 → 20:80 EtOAc−petrol) to give pure 5,7,3′,4′-tetra-*O*-benzyl-4β-azido-catechin **14** (0.117 g, 60%) as a colorless solid; R_f 0.4 (20:80 EtOAc−petrol); mp 120−122 °C; $[\alpha]^{26}_D$ +62.1 (*c* 0.76, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3578, 2930, 2110, 1617, 1592 and 1454; ^{1}H NMR (400 MHz, $CDCl_3$) 7.48−7.31 (20H, m), 7.09 (1H, br s), 7.02 (1H, br d, *J* = 8.4), 7.99 (1H, br d, *J* = 8.4), 6.32 (1H, d, *J* = 1.6), 6.20 (1H, d, *J* = 1.6), 5.19 (5H, br s), 5.12 (1H, d, *J* = 11.6), 5.06 (1H, d, *J* = 11.6,), 5.01 (2H, br s), 4.85 (1H, d, *J* = 10.0), 3.99−3.96 (1H, m) and 1.99 (1H, d, *J* = 6.4); NOE irradiation at 3.97 (H3) results in enhancement at 5.19 (H4) (5.79%); ^{13}C NMR (100 MHz, $CDCl_3$) 161.5, 158.6, 156.1, 149.9, 149.4, 137.4, 137.3, 136.7, 136.5, 130.4, 128.9, 128.8, 128.8, 128.5, 128.4, 128.1, 128.1, 127.9, 127.8, 127.8, 127.5, 121.6, 115.1, 114.7, 101.2, 94.7, 94.1, 77.4, 71.6, 71.5, 70.7, 70.4, 70.2 and 56.0; *m*/*z* (ES) 692.2 (MH^+, 20%) 649.2 (M−N_3, 100%); found 692.2795; $C_{43}H_{38}N_3O_6$ requires 692.2761.

5,7,3′,4′-Tetra-*O*-benzyl-4β-allyl-catechin (15). Following Method 1, 5,7,3′,4′-tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (0.1 g, 0.14 mmol) and allyltributyltin (132 μL, 0.42 mmol) gave a crude product, which was purified by column chromatography eluting with 10:90 EtOAc−petrol) to give a semi-purified product. The residue was redissolved in MeCN (20 mL) and washed with hexane (2 × 10 mL) to remove any traces of organotin residues. Evaporation of the MeCN layer under reduced pressure yielded pure 5,7,3′,4′-tetra-*O*-benzyl-4β-allyl-catechin **15** (44 mg, 45%) as a colorless solid; R_f 0.55 (20:80 EtOAc−petrol); mp 83−86 °C; $[\alpha]^{25}_D$ +12.2 (*c* 0.80, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3576, 2915, 1615, 1591 and 1454; ^{1}H NMR (400 MHz, $CDCl_3$) 7.49−7.31 (20H, m), 7.08 (1H, br d, *J* = 1.2), 7.00 (1H, br dd, *J* = 8.4 and 1.2), 6.98 (1H, br d, *J* = 8.4), 6.31 (1H, d, *J* = 2.4), 6.21 (1H, d, *J* = 2.4), 5.99 (1H, dddd, *J* = 17.2, 10.0, 7.6 and 6.8), 5.22−5.15 (4H, m), 5.08−5.00 (5H, m), 4.95 (1H, d, *J* = 10.0), 4.94 (1H, m), 4.02 (1H, dd, *J* = 10.0 and 5.6), 3.54−3.50 (1H, m), 2.74−2.67 (1H, m) and 2.54−2.48 (1H, m); NOE irradiation at 4.02 (H3) results in enhancement at 3.52 (H4) (6.24%), irradiation at 3.52 (H4) results in enhancement of at 4.02 (H3) (5.00%); ^{13}C NMR (100 MHz, $CDCl_3$) 159.3, 157.9, 155.1, 149.7, 149.4, 139.2, 137.4, 137.3, 137.1, 131.7, 128.9, 128.8, 128.8, 128.7, 128.3, 128.1, 128.1, 127.9, 127.8, 127.6, 127.5, 121.4, 115.5, 115.2, 114.4, 106.9, 94.4, 93.9, 77.5, 71.9, 71.6, 71.5, 70.3, 70.3, 35.7 and 35.5; *m*/*z* (ES) 691.3 (MH^+, 27%); found 691.3090; $C_{46}H_{43}O_6$ requires 691.3054.

5,7,3′,4′-Tetra-*O*-benzyl-4β-(phenylsulfanyl)-catechin (16). Following Method 1, 5,7,3′,4′-tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (58 mg, 0.08 mmol) and thiophenol (25 μL, 0.24 mmol) gave a crude product, which was purified by column chromatography eluting with 1:10 EtOAc−petrol to yield 5,7,3′,4′-tetra-*O*-benzyl-4β-(phenylsulfanyl)-catechin **16** (47 mg, 75%) as a pale red solid; R_f 0.6 (2:3 EtOAc−petrol); mp 141−143 °C; $[\alpha]^{26}_D$ +85.3 (*c* 0.86, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3574, 2927, 1615, 1591 and 1454; ^{1}H NMR (400 MHz, $CDCl_3$) 7.51−7.27 (21H, m), 7.19−7.10 (5H, m), 7.06 (1H, br dd, *J* = 8.4 and 2.0) 7.00 (1H, br d, *J* = 8.4), 6.32 (1H, d, *J* = 2.0), 6.18 (1H, d, *J* = 2.0), 5.19 (4H, br s), 5.09 (1H, d, *J* = 11.2), 5.04 (1H, d, *J* = 11.2), 5.01 (2H, br s), 4.93 (1H, d, *J* = 9.6), 4.85 (1H, d, *J* = 4.4) and 4.22 (1H, dd, *J* = 9.6 and 4.4); NOE irradiation at 4.22 (H3) results in enhancement at 4.85 (H4) (10.12%), irradiation at 4.85 (H4) results in enhancement at 4.22 (H3) (6.51%); ^{13}C NMR (100 MHz, $CDCl_3$) 160.6, 157.9, 155.3, 149.7, 149.4, 137.5, 137.4, 136.9, 136.6, 136.5, 131.7, 131.0, 129.3, 129.1, 128.9, 128.8, 128.8, 128.7 128.3, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8, 127.8, 127.5, 127.4, 127.2, 121.7, 115.1, 114.9, 103.3, 94.4, 94.3, 78.5, 71.7, 71.5, 70.7, 70.5, 70.4 and 49.3; *m*/*z* (ES) found 781.2588 (MNa^+); $C_{49}H_{42}O_6SNa$ requires 781.2594.

5,7,3′,4′-Tetra-*O*-benzyl-4α-(1,3,5-trimethoxybenzene)-catechin (17). Following Method 1, 5,7,3′,4′-tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (50 mg, 0.07 mmol) and 1,3,5-trimethoxybenzene (36 mg, 0.21 mmol) gave a crude product, which was purified by column chromatography (gradient elution 20:80 → 30:70 EtOAc−petrol) to give pure 5,7,3′,4′-tetra-*O*-benzyl-4α-(1,3,5-trimethoxybenzene)-catechin **17** (46 mg, 80%) as a colorless foam; R_f 0.1 (20:80 EtOAc−petrol); $[\alpha]^{26}_D$ −76.4 (*c* 1.52, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3584, 2936, 2838, 1610, 1591 and 1454; ^{1}H NMR (400 MHz, $CDCl_3$) 7.49−7.25 (18H, m), 7.17 (1H, d, *J* = 2.0), 7.08 (1H, dd, *J* = 8.4 and 2.0), 6.98 (1H, d, *J* = 8.4), 6.94−6.92 (2H, m), 6.27 (1H, d, *J* = 2.4), 6.18 (1H, d, *J* = 2.4), 6.11 (1H, br s), 5.98 (1H, br s), 5.22−5.14 (4H, m), 5.00 (2H, br s), 4.77 (1H, d, *J* = 11.2), 4.65 (1H, d, *J* = 8.8), 4.58 (1H, d, *J* = 11.2), 4.22 (1H, dd, *J* = 9.6 and 8.8), 3.80 (3H, s), 3.47 (3H, s) and 3.42 (3H, s); NOE irradiation at 4.58 (H2) results in enhancement at 4.65 (H4) (2.69%); ^{13}C NMR (100 MHz, $CDCl_3$) 159.7, 159.6, 159.0, 158.1, 157.9, 157.4, 149.4, 149.4, 137.6, 137.5, 137.3, 137.0, 131.9 128.8, 128.7, 128.7, 128.3, 128.2 128.2, 128.1, 128.0, 127.8, 127.8, 127.5, 127.3, 121.3, 115.3, 114.8, 113.3, 109.1, 94.9, 94.5, 92.7, 91.6, 82.5, 73.9, 71.7, 71.6, 70.3, 70.3, 56.3, 56.0, 55.5 and 37.5; *m*/*z* (ES) 839.3 (MNa^+, 32%) found 839.3169; $C_{52}H_{48}O_9Na$ requires 839.3190.

5,7,3′,4′-Tetra-*O*-benzyl-4α-(1,3,5-tribenzylphloroglucinol)-catechin (18). Following Method 1, 5,7,3′,4′-tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (50 mg, 0.07 mmol) and 1,3,5-tribenzylphloroglucinol (84 mg, 0.21 mmol) gave a crude product, which was purified by column chromatography (gradient elution 5:95 → 10:90 EtOAc−petrol) to give pure 5,7,3′,4′-tetra-*O*-benzyl-4α-(1,3,5-tribenzylphloroglucinol)-catechin **18** (50 mg, 68%) as a colorless foam; R_f 0.3 (20:80 EtOAc−petrol); $[\alpha]^{26}_D$ −63.6 (*c* 1.50, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3586, 2872, 1608, 1591, 1454 and 1375; ^{1}H NMR (400 MHz, $CDCl_3$) 7.49−7.14 (34H, m), 7.05 (1H, br s), 6.99−6.92 (3H, m), 6.32 (1H, d, *J* = 2.4), 6.24 (1H, d, *J* = 2.4), 6.16 (1H, d, *J* = 2.4), 6.11 (1H, d, *J* = 2.4), 5.18 (2H, br s), 5.09 (1H, d, *J* = 11.6), 5.02 (2H, br s), 5.02 (1H, d, *J* = 11.6), 4.87 (1H, d, *J* = 12.0), 4.86 (1H, d, *J* = 8.8), 4.80−4.71 (2H, m), 4.75 (1H, d, *J* = 12.0), 4.62 (1H, d, *J* = 11.2), 4.61 (1H, d, *J* = 9.6), 4.52 (1H, d, *J* = 12.0) and 4.37 (1H, dd, *J* = 9.6 and 8.8); ^{13}C NMR (100 MHz, $CDCl_3$) 158.9, 158.5, 158.1, 157.8, 157.5, 157.2, 157.0, 149.2, 149.1, 137.5, 137.4, 137.2, 137.1, 137.1, 137.0, 136.8, 132.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 121.1, 115.0, 113.9, 113.1, 108.7, 94.9, 94.3, 93.9, 93.7, 82.1, 73.0, 71.4, 71.2, 71.0, 70.6, 70.2, 70.2, 70.0, 69.7 and 37.5; *m*/*z* (ES) found 1067.4129 (MNa^+); $C_{70}H_{60}O_9Na$ requires 1067.4129.

5,7,3′,4′-Tetra-*O*-benzyl-4-(5,7,3′,4′-tetra-*O*-benzylcatechin)-catechin (19). Following Method 1, 5,7,3′,4′-tetra-*O*-benzyl-4β-*O*-allyl-catechin **7** (100 mg, 0.14 mmol) and 5,7,3′,4′-tetra-*O*-benzylcatechin (276 mg, 0.42 mmol) gave a crude product, which was purified by column chromatography (gradient elution 20:80 → 25:75 EtOAc−petrol) to give pure 5,7,3′,4′-tetra-*O*-benzyl-4-(5,7,3′,4′-tetra-*O*-benzylcatechin)-catechin **19** (95 mg, 52%, 3.5:1

mixture of 4α:4β stereoisomers) as a colorless foam. The data were identical to those previously reported; R_f 0.15 (20:80 EtOAc−petrol); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3584, 2873, 1608, 1592, and 1454; ^1H NMR (400 MHz, $CDCl_3$, 4α 2:1 mixture of rotamers) major rotamer: 7.47−7.20 (34H, m), 7.16−7.12 (2H, m), 7.00−6.98 (2H, m), 6.93−6.82 (7H, m), 6.80 (1H, dd, J = 8.3 and 2.0), 6.24 (1H, s), 6.17 (1H, d, J = 2.4), 6.10 (1H, d, J = 2.4), 5.20−4.87 (12H, m), 4.83−4.79 (2H, m), 4.71−4.64 (1H, m), 4.67 (1H, d, J = 9.2), 4.54 (1H, d, J = 10.8), 4.50 (1H, d, J = 9.6), 4.29 (1H, dd, J = 9.6 and 8.8), 3.68−3.65 (1H, m), 3.58 (1H, d, J = 8.8), 3.05 (1H, dd, J = 16.4 and 5.6) and 2.38 (1H, dd, J = 16.4 and 5.6); minor rotamer: 7.47−7.20 (35H, m), 7.16−712 (2H, m), 6.93−6.82 (6H, m), 6.71 (1H, d, J = 8.0), 6.59 (1H, d, J = 2.0), 6.44 (1H, dd, J = 8.0 and 2.0), 6.20 (1H, d J = 2.4), 6.10 (1H, s), 6.00 (1H, d, J = 2.4), 5.20−4.87 (12H, m), 4.83−4.79 (2H, m), 4.78 (1H, d, J = 8.4), 4.71−4.64 (2H, m), 4.53−4.50 (1H, m), 4.46 (1H, d, J = 8.4), 4.18 (1H, dd, J = 9.6 and 8.8), 3.68−3.65 (1H, m), 3.17 (1H, dd, J = 16.4 and 6.0) and 2.66 (1H, dd, J = 16.4 and 9.6); ^1H NMR (400 MHz, $CDCl_3$, 4β 2:1 mixture of rotamers) major rotamer: 7.47−7.20 (36H, m), 7.26−7.25 (1H, m), 7.10−7.06 (2H, m), 7.03−7.01 (1H, m), 7.00−6.98 (2H, m), 6.92 (1H, d, J = 8.4), 6.86−6.85 (1H, m), 6.84−6.83 (1H, m), 6.56 (1H, dd, J = 8.4 and 1.6), 6.34 (1H, s), 6.04 (1H, d, J = 2.4), 5.42 (1H, d, J = 2.0), 5.14−5.12 (1H, m), 5.12−4.79 (14H, m), 5.07 (1H, d, J = 6.4), 4.60 (1H, d, J = 11.6), 4.51−4.49 (1H, m), 4.22−4.28 (1H, m), 3.87−3.82 (1H, m), 3.72−3.70 (1H, m), 3.27 (1H, dd, J = 16.8 and 6.8) and 2.66 (1H, dd, J = 16.8 and 9.6); m/z (ES) found 1321.5072 (MNa^+); $C_{86}H_{74}O_{12}Na$ requires 1321.5072.

5,7,3′,4′-Tetra-*O*-benzyl-8-allyl-3-(*tert*-butyldimethylsilyl)-catechin (22). 5,7,3′,4′-tetra-*O*-benzyl-8-bromo-3-(*tert*-butyldimethylsilyl)-catechin **21** (5 g, 5.92 mmol) was placed into a flame dried flask under an Argon atmosphere and dissolved in dry THF (50 mL). The solution was cooled to −78 °C, and *n*BuLi was added (7.98 mL, 1.54M solution in hexanes) dropwise to give a pale yellow solution that was stirred for 10 min. Freshly distilled allyl bromide (3.07 mL, 35.5 mmol) was added dropwise, and the reaction was stirred at −78 °C for 1 h. The reaction was quenched with water (5 mL), and the mixture was allowed to warm to room temperature. The THF was evaporated under reduced pressure, and the residue was dissolved in DCM (50 mL). The organic phase was washed with H_2O (40 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give a crude product, which was preabsorbed onto silica and purified by column chromatography eluting with 0.25:0.25:95 EtOAc−DCM−petrol to give pure 5,7,3′,4′-tetra-*O*-benzyl-8-allyl-3-(TBDMS)-catechin **22** (2.01 g, 42%) as a colorless viscous oil; R_f 0.4 (0.5:0.5:9 EtOAc−DCM−petrol); $[\alpha]^{24}_D$ −7.63 (c 0.76, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2929, 2857, 1608, 1497 and 1454; ^1H NMR (400 MHz, $CDCl_3$) 7.47−7.28 (20H, m), 7.10 (1H, s), 6.93 (2H, br s), 6.23 (1H, s), 5.95 (1H, dddd, J = 16.8, 10.0, 6.8 and 6.0), 5.21−5.12 (4H, m), 5.06 (2H, s), 5.03 (2H, s), 4.98 (1H, dd, J = 16.8 and 2.0), 4.92 (1H, dd, J = 10.0 and 2.0), 4.59 (1H, d, J = 8.8), 3.80 (1H, ddd, J = 9.6, 8.8 and 5.6), 3.41 (1H, dd, J = 14.4 and 6.0), 3.35 (1H, dd, J = 14.4 and 6.8), 3.11 (1H, dd, J = 16.0 and 5.6), 2.64 (1H, dd, J = 16.0 and 9.6), 0.76 (9H, s), −0.16 (3H, s) and −0.47 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 155.8, 155.3, 153.3, 149.0, 148.6, 137.6, 137.5, 137.5, 137.4, 133.3, 128.6, 128.6, 128.6, 128.5, 127.8, 127.8, 127.8, 127.6, 127.4, 127.4, 127.2, 126.9, 121.3, 114.9, 114.1, 114.0, 109.2, 103.4, 91.7, 81.9, 71.6, 71.2, 70.8, 70.3, 69.8, 30.6, 27.4, 25.8, −4.8 and −5.3; m/z (ES) found 805.3945 (MH^+); $C_{52}H_{57}O_6Si$ requires 805.3918.

5,7,3′,4′-Tetra-*O*-benzyl-8-allyl-catechin (23). *Caution: HF is corrosive to glass, and therefore the reaction must be performed in a plastic vessel; plastic syringes were also used.* 5,7,3′,4′-Tetra-*O*-benzyl-8-allyl-3-(TBDMS)-catechin **22** (0.30 g, 0.38 mmol) was dissolved in MeCN (3 mL) and HF (269 μL, 7.6 mmol, 48% solution in H_2O) was added dropwise. The reaction was stirred overnight during which time a cream precipitate was formed in the reaction mixture. The reaction was diluted with EtOAc (30 mL) and then poured cautiously onto a saturated aqueous $NaHCO_3$ solution (20 mL). The layers were separated, the organic phase was washed with H_2O (20 mL) and brine (20 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a colorless solid. The crude product was preabsorbed onto silica and purified by column chromatography (gradient elution 1:1:8 → 2:2:6 EtOAc−DCM−petrol) to yield pure 5,7,3′,4′-tetra-*O*-benzyl-8-allyl-catechin **23** (0.22 g, 83%) as a colorless amorphous solid; R_f 0.2 (1:1:8 EtOAc−DCM−petrol); mp 129−130 °C; $[\alpha]^{25}_D$ −31.4 (c 0.87, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3586, 2911, 1607, 1497 and 1454; ^1H NMR (400 MHz, $CDCl_3$) 7.48−7.29 (20H, m), 7.05 (1H, br s), 6.95 (2H, br s), 6.26 (1H, s), 5.95 (1H, dddd, J = 16.5, 10.0, 6.5 and 6.3), 5.18 (2H, br s), 5.16 (2H, br s), 5.05 (2H, br s), 5.01 (2H, br s), 5.01−4.95 (1H, m), 4.94−4.90 (1H, m), 4.67 (1H, d, J = 7.9), 3.91 (1H, ddd, J = 8.8, 8.0 and 5.6), 3.44−3.34 (2H, m), 3.09 (1H, dd, J = 16.4 and 5.6) and 2.67 (1H, dd, J = 16.4 and 8.8); ^{13}C NMR (100 MHz, $CDCl_3$) 156.0, 155.6, 153.0, 149.2, 149.1, 137.5, 137.4, 137.3, 137.2, 137.1, 131.6, 128.6, 128.0, 127.9, 127.5, 127.3, 127.2, 127.2, 120.3, 114.8, 114.2, 113.6, 109.1, 102.6, 91.5, 81.3, 71.4, 71.3, 70.8, 70.2, 68.5, 27.7 and 27.4; m/z (ES) found 691.3072 (MH^+); $C_{46}H_{43}O_6$ requires 691.3054. Anal. calcd for $C_{46}H_{42}O_6$: C, 79.98; H, 6.13. Found: C, 80.07; H, 6.19.

5,7,3′,4′-Tetra-*O*-benzyl-8-allyl-epicatechin (24). 5,7,3′,4′-Tetra-*O*-benzyl-8-allyl-catechin **23** (100 mg, 0.14 mmol) was dissolved in DCM (1 mL), Dess−Martin periodinane (92 mg, 0.21 mmol) was added in one portion followed by dropwise addition of H_2O (15 μL), and the reaction was stirred overnight at room temperature. A further portion of Dess−Martin periodinane was added (30 mg), and stirring was continued for 1.5 h. Saturated aqueous $NaHCO_3$ solution was added (10 mL) followed by 10% aqueous $Na_2S_2O_3$ solution (10 mL), and the mixture was diluted with DCM (20 mL). The organic phase was separated, and the aqueous layer was extracted with DCM (20 mL). The combined organic phases were evaporated under reduced pressure to give a crude residue, which was preabsorbed onto silica and purified by column chromatography eluting with 1:1:8 EtOAc−DCM−petrol to yield pure ketone (78 mg, 81%) as a pale yellow waxy solid. Note: ketone could be stored for up to 3 days in the freezer under an argon atmosphere; R_f 0.55 (1:1:8 EtOAc−DCM−petrol). Lithium bromide (154 mg, 1.7 mmol) was placed in an oven-dried flask under a nitrogen atmosphere. Dry THF (0.64 mL) was added, and the mixture was stirred until all the LiBr was dissolved. The solution was cooled to 0 °C, and L-Selectride (496 μL, 1 M solution in THF) was added dropwise. The mixture was cooled to −78 °C, and a solution of ketone (0.24 g, 0.35 mmol) in THF (2.56 mL) was added dropwise. The reaction was stirred at −78 °C for 135 min, after which the cold bath was removed and 2.5 M NaOH (1.81 mL) was added cautiously. The flask was placed in a room-temperature water bath, and a solution of 35% aqueous H_2O_2 (469 μL) in EtOH (1.4 mL) was added dropwise. The mixture was stirred overnight, then $CHCl_3$ (20 mL) was added, and the layers were separated (a little H_2O was added to make the separation easier). The aqueous phase was extracted with $CHCl_3$ (2 × 15 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which was purified by column chromatography (gradient elution 0.5:10:9.5 → 1:12:7 EtOAc−DCM−petrol) to give pure 5,7,3′,4′-tetra-*O*-benzyl-8-allyl-epicatechin **24** (175 mg, 72%) as a pale yellow oil; R_f 0.4 (1:12:7 EtOAc−DCM−petrol); $[\alpha]^{25}_D$ −29.2 (c 1.07, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3574, 2909, 1609, 1454 and 1380; ^1H NMR (400 MHz, $CDCl_3$) 7.44−7.28 (20H, m), 7.19 (1H, br s), 7.01−6.96 (2H, m), 6.27 (1H, s), 6.04 (1H, dddd, J = 16.8, 10.0, 6.4 and 6.0), 5.20 (2H, br s), 5.17 (2H, br s), 5.05 (1H, br dd, J = 16.8 and 2.0), 5.04 (2H, br s), 5.00 (2H, br s), 4.97 (1H, br dd, J = 10.0 and 2.0), 4.91 (1H, br s), 4.21 (1H, br s), 3.53 (1H, dd, J = 14.4 and 6.4), 3.47 (1H, dd, J = 14.4 and 6.0), 3.05 (1H, dd, J = 17.2 and 1.6), 2.92 (1H, dd, J = 17.2 and 4.4) and 1.70 (1H, br d, J = 4.0); ^{13}C NMR (100 MHz, $CDCl_3$) 156.1, 155.9, 152.8, 149.0, 148.6, 137.5, 137.5, 137.3, 137.2, 131.8, 128.5, 128.5, 127.9, 127.8, 127.8,

127.7, 127.5, 127.4, 127.3, 127.2, 127.1, 127.1, 126.9, 119.0, 115.0, 114.0, 113.2, 109.1, 101.3, 91.7, 78.0, 71.3, 71.2, 70.7, 70.1, 66.1, 28.3 and 27.3; *m*/*z* (ES) 691.3 (MH^+, 100%) found 691.3082 (MH^+); $C_{46}H_{43}O_6$ requires 691.3054.

Method 2. General Procedure for DCC Coupling. Substrate alcohol (1 equiv) and 3,4,5-tri-*O*-benzylgallic acid (2 equiv) were dissolved in dry DCM (10 mL per 100 mg alcohol) and stirred under an argon atmosphere. DCC (2 equiv) and DMAP (0.1 equiv) were added in one portion, and the reaction mixture was stirred for 24 h (the reaction slowly turns cloudy due to the formation of insoluble urea byproduct). The reaction was quenched by the addition of H_2O (10 mL), and the organic phase was separated. The aqueous phase was extracted with DCM (10 mL), the combined organic phases were washed with H_2O (10 mL) and brine (10 mL) and then dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a crude residue, which was preabsorbed onto silica and purified by column chromatography.

5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-catechin (25). Following Method 2, 5,7,3′,4′-tetra-*O*-benzyl-8-allyl-catechin **23** (110 mg, 0.15 mmol) and 3,4,5-tri-*O*-benzylgallic acid (140 mg, 0.31 mmol) gave a crude product, which was purified by column chromatography (gradient elution 2.5:97.5 → 5:95 EtOAc−toluene) to yield pure 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-catechin **25** (163 mg, 98%) as a pale yellow solid; R_f 0.8 (10:90 EtOAc−toluene); mp 116−118 °C; $[\alpha]^{26}_D$ +19.0 (*c* 1.03, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2928, 1712, 1592, 1454 and 1121; ^1H NMR (400 MHz, $CDCl_3$) 7.46−7.23 (37H, m), 6.99 (1H, br d, J = 1.6), 6.87 (1H, br dd, J = 8.4 and 1.6), 6.84 (1H, d, J = 8.4), 6.28 (1H, s), 6.00 (1H, dddd, J = 16.0, 10.0, 6.4 and 6.0), 5.47−5.43 (1H, m), 5.19 (1H, d, J = 6.4), 5.10 (2H, br s), 5.08 (2H, br s), 5.06−5.03 (6H, m), 5.02−5.00 (5H, m), 4.92 (1H, br dd, J = 10.0 and 2.0), 3.48−3.46 (2H, m), 2.97 (1H, dd, J = 16.8 and 5.2) and 2.87 (1H, dd, J = 16.8 and 6.0); ^{13}C NMR (100 MHz, $CDCl_3$) 165.2, 156.1, 155.5, 152.6, 152.5, 149.0, 148.9, 137.5, 137.5, 137.4, 137.3, 137.1, 136.7, 131.7, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 127.3, 127.2, 125.2, 119.6, 114.9, 114.3, 113.1, 109.2, 108.9, 101.7, 91.4, 78.0, 75.2, 71.5, 71.4, 71.2, 70.7, 70.2, 70.1, 27.4 and 24.1; *m*/*z* (ES) 1135.4 (MNa^+, 100%) found 1135.4335; $C_{74}H_{64}O_{10}Na$ requires 1135.4391. Anal. calcd for $C_{74}H_{64}O_{10}$: C, 79.83; H, 5.79. Found: C, 79.53; H, 5.98.

5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-epicatechin (26). Following Method 2, 5,7,3′,4′-tetra-*O*-benzyl-8-allyl-epicatechin **24** (50 mg, 0.07 mmol) and 3,4,5-tri-*O*-benzylgallic acid (63 mg, 0.14 mmol) gave a crude product, which was purified by column chromatography eluting with 1:99 EtOAc−toluene and then a second column eluting with 1:1:8 EtOAc−DCM−petrol to yield pure 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-epicatechin **26** (53 mg, 67%) as a pale yellow oil; R_f 0.55 (2:98 EtOAc−toluene); $[\alpha]^{26}_D$ −61.6 (*c* 0.61, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2870, 1713, 1601, 1454 and 1326; ^1H NMR (400 MHz, $CDCl_3$) 7.48−7.25 (38H, m), 7.05 (1H, dd, J = 8.4 and 2.0), 6.94 (1H, d, J = 8.4), 6.35 (1H, s), 6.11 (1H, dddd, J = 16.4, 10.0, 6.4 and 6.0), 5.70 (1H, br s), 5.18−5.15 (4H, m), 5.10 (2H, br s), 5.08−5.05 (8H, m), 5.02 (1H, d, J = 12.0), 4.97 (1H, dd, J = 10.0 and 2.4), 4,93 (1H, d, J = 12.0), 3.61 (1H, br dd, J = 14.4 and 6.0), 3.55 (1H, br dd, J = 14.4 and 6.4) and 3.23−3.13 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 165.1, 156.0, 155.9, 153.3, 152.4, 149.0, 148.8, 142.6, 137.7, 137.5, 137.5, 137.3, 137.1, 137.1, 136.6, 131.7, 128.7, 128.6, 128.5, 128.5, 128.5, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.3, 127.3, 127.3, 127.2, 125.2, 119.5, 114.8, 114.1, 113.5, 109.2, 109.1, 101.1, 91.5, 77.4, 75.2, 71.5, 71.4, 71.3, 71.1, 70.7, 70.2, 68.6, 27.4 and 26.3; *m*/*z* (ES) 1135.4 (MNa^+, 100%) found 1135.4402; $C_{74}H_{64}O_{10}Na$ requires 1135.4391.

5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-4β-allyl-catechin (27). Following Method 2, 5,7,3′,4′-tetra-*O*-benzyl-4β-allyl-catechin **15** (50 mg, 0.07 mmol) and 3,4,5-tri-*O*-benzylgallic acid (64 mg, 0.14 mmol) gave a crude product, which was purified by column chromatography eluting with 5:95 EtOAc−toluene to yield pure 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-4β-allyl-catechin **27** (77 mg, 98%) as a pale yellow solid; R_f 0.8 (10:90 EtOAc−toluene); mp 128−131 °C; $[\alpha]^{26}_D$ +79.0 (*c* 0.82, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2932, 1715, 1615, 1591 and 1454; ^1H NMR (400 MHz, $CDCl_3$) 7.43−7.23 (35H, m), 7.13 (2H, s), 7.02 (1H, br d, J = 2.0), 6.89 (1H, br dd, J = 8.4 and 2.0), 6.81 (1H, d, J = 8.4), 6.29 (1H, d, J = 2.0), 6.20 (1H, d, J = 2.0), 5.73 (1H, dddd, J = 17.2, 10.0, 7.2 and 6.8), 5.37 (1H, dd, J = 10.0 and 5.6), 5.18 (1H, d, J = 10.0), 5.07−5.03 (10H, m), 4.99−4.98 (4H, m), 4.83 (1H, br dd, J = 17.2 and 2.0), 4.74−4.72 (1H, m), 3.73−3.69 (1H, m), 2.64−2.59 (1H, m) and 2.54−2.49 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 164.7, 159.3, 157.8, 152.5, 149.4, 149.2, 142.6 137.8, 137.5, 137.2, 137.1, 136.9, 136.8, 136.7, 131.3, 128.7, 128.7, 128.6, 128.5, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.3, 124.9, 121.3, 115.5, 114.9, 114.2, 109.2, 105.8, 94.3, 94.0, 75.2, 75.2, 73.4, 71.6, 71.3, 70.3, 70.2, 36.0 and 33.9; *m*/*z* (FAB) 1113.7 (M^+, 6%); *m*/*z* (ES) 1135.4 (MNa^+, 100%) found 1135.4416; $C_{74}H_{64}O_{10}Na$ requires 1135.4391. Anal. calcd for $C_{74}H_{64}O_{10}$: C, 79.83; H, 5.79. Found: C, 79.49; H, 5.89.

Method 3. General Procedure for Grubbs Metathesis. Metathesis substrate (1 equiv) was placed in an oven-dried flask under an argon atmosphere. Grubbs' second generation catalyst (0.1 equiv) was added, and the flask was fitted with a condenser. DCM (1.5 mL per 50 mg of substrate) was added, and the reaction was heated at reflux overnight. Note: If necessary, the progress of the reaction can be followed by ^1H NMR by evaporating the solvent under reduced pressure and obtaining a crude spectrum in $CDCl_3$. The crude product was preabsorbed directly onto silica and purified by column chromatography.

Tetra-*O*-benzyl-3-*O*-(tri-*O*-benzylgalloyl)-8-[4′-(tetra-*O*-benzyl-3″-*O*-(tri-*O*-benzylgalloyl)-8″-catechinyl)-butyl]-catechin (28). Following Method 3, 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-catechin **25** (50 mg, 0.04 mmol) gave a crude product, which was purified by column chromatography eluting with 1:1:8 EtOAc−DCM−petrol to yield dimer **28** (22 mg, 50%, 3.5:1 mix of major:minor isomers) as a pale yellow oil; R_f 0.3 (1:1:8 EtOAc−DCM−petrol); $[\alpha]^{25}_D$ +9.95 (*c* 1.20, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2870, 1712, 1592, 1454 and 1327; ^1H NMR (400 MHz, $CDCl_3$, major isomer) 7.37−7.15 (74H, m), 6.91 (2H, d, J = 2.0), 6.83 (2H, dd, J = 8.4 and 2.0), 6.67 (2H, d, J = 8.4), 6.23 (2H, s), 5.73−5.71 (2H, m), 5.40−5.36 (2H, m), 5.04−4.88 (30H, m), 3.46 (4H, m), 3.98 (2H, dd, J = 16.4 and 5.2) and 2.84 (2H, dd, J = 16.4 and 6.8); ^1H NMR (400 MHz, $CDCl_3$, minor isomer) 7.37−7.15 (74H, m), 6.94 (2H, d, J = 2.0), 6.80 (2H, dd, J = 8.4 and 2.0), 6.73 (2H, d, J = 8.4), 6.18 (2H, s), 5.58−5.56 (2H, m), 5.42−5.37 (2H, m), 5.04−4.88 (30H, m), 3.66 (2H, dd, J = 14.0 and 4.8), 3.55 (2H, dd, J = 14.0 and 4.8), 2.96−2.91 (2H, m) and 2.85−2.79 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) 165.2, 156.1, 155.3, 152.6, 152.5, 148.9, 148.7, 142.6, 137.5, 137.5, 137.3, 137.1, 136.7, 131.5, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.7, 127.7, 127.5, 127.3, 127.1, 127.0, 125.2, 119.7, 114.7, 113.4, 110.2, 109.1, 101.7, 91.6, 78.1, 75.2, 71.4, 71.1, 71.1, 70.7, 70.3, 70.1, 26.2 and 24.5; *m*/*z* (ES) 2219.8 (MNa^+, 51%) found 2219.8369; $C_{146}H_{124}O_{20}Na$ requires 2219.8578.

Tetra-*O*-benzyl-3-*O*-(tri-*O*-benzylgalloyl)-8-[4′-(tetra-*O*-benzyl-3″-*O*-(tri-*O*-benzylgalloyl)-8″-epicatechinyl)-butyl]-epicatechin (29). Following Method 3, 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-epicatechin **26** (190 mg, 0.17 mmol) gave a crude product, which was purified by column chromatography (gradient elution 1:1:8 → 2:2:6 EtOAc−DCM−petrol) and then a second column (gradient elution 1:1:8 → 1.5:1.5:7 EtOAc−DCM−petrol) to yield dimer **29** (54 mg, 29%, 4.5:1 mix of major:minor isomers) as a yellow oil; R_f 0.25 (1:1:8 EtOAc−DCM−petrol); $[\alpha]^{25}_D$ −87.76 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2869, 1711, 1593, 1454 and 1115; ^1H NMR (400 MHz, $CDCl_3$, major isomer) 7.38−7.17 (74H, m), 7.03 (2H, d, J = 1.6), 6.89 (2H, dd, J = 8.4 and 1.6), 6.73 (2H, d, J = 8.4), 6.19 (2H, s),

5.74 (2H, br s), 5.59 (2H, br s), 5.03−4.94 (18H, m), 4.91−4.71 (12H, m), 3.50−3.40 (4H, m) and 3.11−2.96 (4H, m); (400 MHz, $CDCl_3$, minor isomer) 7.38−7.17 (74H, m), 7.04 (2H, d, J = 1.6), 6.84 (2H, dd, J = 8.4 and 1.6), 6.72 (2H, d, J = 8.4), 6.16 (2H, s), 5.64 (2H, br s), 5.50 (2H, br s), 5.03−4.94 (18H, m), 4.91−4.71 (12H, m), 3.80 (2H, dd, J = 14.4 and 4.0), 3.66 (2H, dd, J = 14.4 and 3.6) and 3.11−2.96 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) 165.3, 156.0, 155.5, 153.0, 152.3, 148.7, 148.7, 142.5, 137.6, 137.5, 137.3, 137.1, 136.6, 131.5, 128.8, 18.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.3, 127.3, 127.1, 127.0, 125.1, 119.5, 114.5, 113.4, 110.4, 109.1, 101.2, 91.7, 76.7, 75.1, 71.3, 71.1, 71.0, 70.6, 70.1, 68.5, 26.3 and 26.0; *m*/*z* (ES) 2219.8 (MNa^+, 64%) found 2219.8517; $C_{146}H_{124}O_{20}Na$ requires 2219.8578.

Tetra-*O*-benzyl-4β-[4′-(tetra-*O*-benzyl-4″β-catechinyl)-butyl]-catechin (32). 5,7,3′,4′-Tetra-*O*-benzyl-4β-allyl-catechin **15** (79 mg, 0.11 mmol) was dissolved in dry pyridine (0.75 mL), dry acetic anhydride (1.5 mL) under an argon atmosphere. DMAP (2 mg, 0.01 mmol) was added, and the mixture was stirred overnight. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in EtOAc (20 mL). The organic phase was washed with 2 M HCl (15 mL) and H_2O (15 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a crude product. The crude residue was preabsorbed onto silica and purified by column chromatography (gradient elution 1:9 → 2:8 EtOAc−petrol) to give pure 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-acetyl-4β-allyl-catechin **31** (68 mg, 82%) as a pale yellow oil; R_f 0.2 (1:1:8 EtOAc−DCM−petrol); $[\alpha]^{25}_D$ +32.4 (*c* 0.90, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2935, 1738, 1591, 1454 and 1373; ^{1}H NMR (400 MHz, $CDCl_3$) 7.49−7.30 (20H, m), 7.05 (1H, br d, J = 1.6), 6.96 (1H, br dd, J = 8.0 and 1.6), 6.94 (1H, br d, J = 8.0), 6.29 (1H, d, J = 2.0), 6.19 (1H, d, J = 2.0), 5.82 (1H, dddd, J = 17.3, 10.4, 7.2 and 6.8), 5.27 (1H, dd, J = 10.4 and 5.6), 5.18 (2H, br s), 5.16 (2H, br s), 5.07 (1H, d, J = 10.4), 5.07−5.00 (2H, m), 5.03−4.96 (2H, m), 5.00−4.94 (1H, m), 4.92−4.89 (1H, m), 3.60−3.56 (1H, m), 2.59 (1H, app dq, J = 14.4 and 7.2), 2.54−2.48 (1H, m) and 1.77 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 169.6, 159.2, 157.7, 154.7, 149.2, 148.9, 138.2, 137.2, 136.8, 136.7, 131.1, 128.6, 128.5, 128.1, 128.0, 127.9, 127.9, 127.7, 127.5, 127.4, 121.1, 115.1, 114.8, 114.2, 106.0, 94.2, 93.9, 75.0, 72.3, 71.4, 71.3, 70.2, 70.1, 36.2, 33.8 and 20.8.

Following Method 3, 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-acetyl-4β-allyl-catechin **31** (145 mg, 0.19 mmol) gave a crude product, which was purified by column chromatography (gradient elution 10:90 → 25:75 EtOAc−petrol) to yield dimer **32** (100 mg, 73%, 3:1 mix of major:minor isomers) as a yellow oil; R_f 0.45 (25:75 EtOAc−petrol); $[\alpha]^{25}_D$ +48.0 (*c* 1.31, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 2931, 1738, 1615, 1591 and 1373; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) 7.45−7.24 (40H, m), 7.02 (2H, br d, J = 1.6), 6.93−6.88 (4H, m), 6.21 (2H, d, J = 2.0), 6.16 (2H, d, J = 2.0), 5.38−5.36 (2H, m), 5.23 (2H, d, J = 10.4 and 5.6), 5.16 (4H, br s), 5.13 (4H, br s), 5.02−4.80 (10H, m), 3.47 (2H, app q, J = 5.6), 2.48−2.44 (2H, m), 2.21−2.17 (2H, m) and 1.71 (6H, s); ^{1}H NMR (400 MHz, $CDCl_3$, minor isomer) 7.45−7.24 (40H, m), 6.99 (2H, br d, J = 1.6), 6.93−6.88 (4H, m), 6.24 (2H, d, J = 2.0), 6.17 (2H, d, J = 2.0), 5.38−5.36 (2H, m), 5.24−5.20 (2H, m), 5.16 (4H, br s), 5.11 (4H, br s), 5.02−4.85 (10H, m), 3.49−3.46 (2H, m), 2.44−2.28 (4H, m) and 1.62 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) 169.4, 159.2, 157.6, 154.8, 149.3, 149.0, 137.3, 136.9, 131.3, 130.0, 128.7, 128.6, 128.5, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 121.2, 114.8, 114.2, 106.0, 94.3, 94.0, 75.0, 72.3, 71.4, 71.3, 70.1, 70.0, 34.7, 33.8 and 20.8; *m*/*z* (ES) 1459.5 (MNa^+, 93%) found 1459.5754; $C_{94}H_{84}O_{14}Na$ requires 1459.5753.

Method 4. General Procedure for *O*-Benzyl Deprotection. Deprotection substrate (1 equiv) was dissolved in a mixture of THF−MeOH−H_2O (20:1:1, 5 mL total volume), and $Pd(OH)_2$ (15 mg per 40 mg of substrate, ca. 20% Pd on carbon) was added. The reaction flask was fitted with a three-way tap with a H_2 balloon attached. The flask was carefully evacuated using a water aspirator to remove any dissolved gases from the solvent, and then the flask was charged with H_2 from the balloon. This process was repeated twice, and then the reaction was stirred overnight under a H_2 atmosphere. The reaction was monitored by TLC to observe the consumption of the starting material. Once complete, the reaction mixture was filtered through celite, washing with THF−MeOH (20:1, 75 mL), and the solvent was removed under reduced pressure. The crude residue was preabsorbed onto silica and purified by column chromatography.

8-Propyl-catechin (33). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-8-allyl-catechin **23** (40 mg, 0.05 mmol) gave a crude product, which was purified by column chromatography eluting with 10:90 MeOH−DCM containing 2% AcOH to yield pure 8-propyl-catechin **33** (16.2 mg, 84%) as a yellow-brown oil; R_f 0.35 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{25}_D$ −20.3 (*c* 1.65, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.84 (1H, d, J = 2.0), 6.75 (1H, dd, J = 8.0 and 2.0), 6.71 (1H, d, J = 8.0), 5.96 (1H, s), 4.53 (1H, d, J = 7.6), 3.93−3.87 (1H, m), 2.86 (1H, dd, J = 16.0 and 5.2), 2.51 (1H, dd, J = 16.0 and 8.4), 2.49−2.44 (2H, m), 1.50−1.44 (2H, m) and 0.85 (3H, t, J = 7.6); ^{13}C NMR (100 MHz, CD_3OD) 155.2, 154.7, 154.4, 146.2, 146.1, 132.7, 119.9, 116.0, 115.2, 109.0, 100.7, 96.1, 82.7, 69.1, 28.9, 25.7, 23.8 and 14.4; *m*/*z* (ES) 333.1 (MH^+, 17%) found 333.1328; $C_{18}H_{21}O_6$ requires 333.1333.

8-Propyl-epicatechin (34). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-8-allyl-epicatechin **24** (40 mg, 0.05 mmol) gave a crude product, which was purified by column chromatography eluting with 10:90 MeOH−DCM containing 2% AcOH to yield pure 8-propyl-epicatechin **34** (16.2 mg, 84%) as a yellow-brown oil; R_f 0.35 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{25}_D$ −47.6 (*c* 1.65, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.98 (1H, d, J = 1.6), 6.81 (1H, dd, J = 8.0 and 1.6), 6.76 (1H, d, J = 8.0), 5.98 (1H, s), 4.80 (1H, s), 4.18 (1H, br s), 2.88 (1H, dd, J = 16.8 and 4.4), 2.74 (1H, dd, J = 16.8 and 2.8), 2.63−2.49 (2H, m), 1.51−1.43 (2H, m) and 0.90 (3H, t, J = 7.6); ^{13}C NMR (100 MHz, CD_3OD) 155.0, 154.9, 154.9, 145.9, 145.6, 132.7, 119.0, 115.9, 115.0, 109.3, 99.8, 96.2, 79.4, 67.3, 29.4, 25.8, 23.9 and 14.5; *m*/*z* (ES) 333.1 (MH^+, 27%) found 333.1307; $C_{18}H_{21}O_6$ requires 333.1333.

4β-Propyl-catechin (35). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-4β-allyl-catechin **15** (55 mg, 0.08 mmol) gave a crude product, which was purified by column chromatography eluting with 10:90 MeOH−DCM containing 2% AcOH and then a second column (gradient elution 5:95 → 10:90 MeOH−DCM containing 2% AcOH) to yield pure 4β-propyl-catechin **35** (16 mg, 61%) as a brown oil; R_f 0. 5 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{25}_D$ +32.2 (*c* 1.16, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.83 (1H, d, J = 2.0), 6.75 (1H, d, J = 8.0), 6.72 (1H, dd, J = 8.0 and 2.0), 5.90 (1H, d, J = 2.0), 5.79 (1H, d, J = 2.0), 4.72 (1H, d, J = 10.0), 3.86 (1H, dd, J = 10.0 and 4.8), 3.14 (1H, app dt, J = 7.6 and 4.8), 1.88−1.82 (1H, m), 1.54−1.46 (2H, m), 1.45−1.36 (1H, m) and 0.91 (3H, t, J = 7.2); ^{13}C NMR (100 MHz, CD_3OD) 157.8, 157.4, 156.2, 146.3, 146.2, 133.4, 120.7, 115.9, 115.7, 107.2, 96.2, 95.4, 79.2, 72.8, 36.9, 34.6, 22.9 and 15.1; *m*/*z* (ES) 333.1 (MH^+, 13%) found 333.1316; $C_{18}H_{21}O_6$ requires 333.1333.

8-Propyl-catechin-3-gallate (36). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-catechin **25** (40 mg, 0.03 mmol) gave a crude product, which was purified by column chromatography eluting with 15:85 MeOH−DCM containing 2% AcOH and then a second column eluting with 10:90 MeOH−DCM containing 2% AcOH to yield pure 8-propyl-catechin-3-gallate **36** (13.5 mg, 80%) as a pale yellow oil; R_f 0.15 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{24}_D$ +21.9 (*c* 1.35, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.95 (2H, s), 6.83 (1H, s), 6.70 (2H, s), 5.99 (1H, s), 5.32−5.28 (1H, m), 5.03 (1H, d, J = 6.4), 2.85 (1H, dd, J = 16.4 and 5.2), 2.71 (1H, dd, J = 16.4 and 5.2), 2.52 (2H, t, J = 7.6), 1.54−1.48 (2H, m) and 0.88 (3H, t, J = 7.6); ^{13}C NMR (100 MHz, CD_3OD) 167.6, 155.5, 154.5, 154.3, 146.4, 146.3, 146.1, 131.9, 121.5, 119.3, 116.1, 114.5, 110.2, 109.1, 99.5, 96.3, 79.4, 71.4, 25.7, 25.0, 23.9 and 14.5; *m*/*z* (ES) 507.1 (MNa^+, 87%) found 507.1276; $C_{25}H_{24}O_{10}Na$ requires 507.1262.

8-Propyl-epicatechin-3-gallate (37). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-8-allyl-epicatechin **26** (40 mg, 0.03 mmol) gave a crude product, which was purified by column chromatography (gradient elution 10:90 → 15:85 MeOH−DCM containing 2% AcOH) and then a second column eluting with 10:90 MeOH−DCM containing 2% AcOH to yield pure 8-propyl-epicatechin-3-gallate **37** (13.3 mg, 78%) as a grey oil; R_f 0.15 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{20}_D$ −70.5 (*c* 1.38, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.96 (1H, d, *J* = 2.0), 6.91 (2H, s), 6.81 (1H, dd, *J* = 8.0 and 2.0), 6.70 (1H, d, *J* = 8.0), 5.99 (1H, s), 5.52 (1H, br s), 5.01 (1H, s), 3.01 (1H, dd, *J* = 17.6 and 4.8), 2.85 (1H, dd, *J* = 17.6 and 2.0), 2.67−2.52 (2H, m), 1.62−1.51 (2H, m) and 0.93 (3H, t, *J* = 7.6); ^{13}C NMR (100 MHz, CD_3OD) 167.7, 155.2, 154.9, 154.7, 146.2, 145.9, 145.7, 131.9, 121.5, 119.1, 115.9, 114.9, 110.2, 109.3, 99.1, 96.3, 78.2, 69.9, 27.0, 25.7, 24.0 and 14.5; *m*/*z* (ES) 485.1 (MH^+, 12%) found 485.1429; $C_{25}H_{25}O_{10}$ requires 485.1442.

4*β*-Propyl-catechin Gallate (38). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-4*β*-allyl-catechin **27** (40 mg, 0.03 mmol) gave a crude product, which was purified by column chromatography eluting with 15:85 MeOH−DCM containing 2% AcOH and then a second column eluting with 10:90 MeOH−DCM containing 2% AcOH to yield pure 4*β*-propyl-catechin gallate **38** (12.9 mg, 76%) as a pale yellow oil; R_f 0.3 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{23}_D$ +42.6 (*c* 1.29, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.93 (2H, s), 6.85 (1H, d, *J* = 1.6), 6.74 (1H, dd, *J* = 8.0 and 1.6), 6.68 (1H, d, *J* = 8.0), 5.95 (1H, d, *J* = 2.0), 5.84 (1H, d, *J* = 2.0), 5.22 (1H, dd, *J* = 10.0 and 5.6), 5.06 (1H, d, *J* = 10.0), 3.35 (1H, app q, *J* = 5.6), 1.90−1.83 (1H, m), 1.63−1.57 (1H, m), 1.47−1.40 (2H, app sex, *J* = 7.6) and 0.87 (3H, t, *J* = 7.6); ^{13}C NMR (100 MHz, CD_3OD) 167.0, 158.2, 157.7, 156.1, 146.4, 146.4, 146.2, 139.9, 131.8, 121.3, 120.6, 116.0, 115.2, 110.1, 106.0, 96.6, 95.4, 76.6, 74.9, 35.8, 34.7, 23.1 and 14.9; *m*/*z* (ES) 507.1 (MNa^+, 55%) found 507.1257; $C_{25}H_{24}O_{10}Na$ requires 507.1262.

8-[4′-(8″-Catechinyl)-butyl]-catechin (39). Following Method 4, **28** (45 mg, 0.02 mmol) gave a crude product, which was purified by column chromatography (gradient elution 15:85 → 20:80 MeOH−DCM containing 2% AcOH) and then a second column (gradient elution 10:90 → 20:80 MeOH−DCM containing 2% AcOH) to yield pure dimer **39** (8.4 mg, 44%) as a pale yellow oil; R_f 0.15 (20:80 MeOH−DCM containing 2% AcOH); $[\alpha]^{25}_D$ +27.8 (*c* 0.84, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.92 (4H, s), 6.81 (2H, s), 6.65 (4H, s), 5.95 (2H, s), 5.28−5.23 (2H, m), 4.96 (2H, d, *J* = 6.4), 2.84 (2H, dd, *J* = 16.4 and 5.2), 2.66 (2H, dd, *J* = 16.4 and 6.4), 2.51 (4H, br s) and 1.49 (4H, br s); ^{13}C NMR (100 MHz, CD_3OD) 167.6, 155.2, 154.3, 154.2, 146.3, 146.1, 146.0, 139.8, 131.8, 121.4, 149.5, 116.2, 114.5, 110.1, 109.6, 99.7, 96.4, 79.3, 71.5, 30.9, 25.1 and 23.8; *m*/*z* (ES) found 961.2148 (MNa^+); $C_{48}H_{42}O_{20}Na$ requires 961.2162.

8-[4′-(8″-Epicatechinyl)-butyl]-epicatechin (40). Following Method 4, dimer **29** (45 mg, 0.02 mmol) gave a crude product, which was purified by column chromatography (gradient elution 10:90 → 20:80 MeOH−DCM containing 2% AcOH) to yield pure 8-propyl-epicatechin-3-gallate dimer **40** (16.4 mg, 67%) as a purple oil; R_f 0.15 (20:80 MeOH−DCM containing 2% AcOH); $[\alpha]_D^{22}$ −27.8 (*c* 0.84, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.91 (2H, d, *J* = 1.6), 6.89 (4H, s), 6.77 (2H, dd, *J* = 8.0 and 1.6), 6.65 (2H, d, *J* = 8.0), 5.95 (2H, s), 5.48 (2H, br s), 4.91 (2H, br s), 2.96 (2H, br s, *J* = 17.6 and 2.0), 2.81 (2H, dd, *J* = 17.6 and 4.4), 2.76−2.53 (4H, m) and 1.57 (4H, br s); ^{13}C NMR (100 MHz, CD_3OD) 167.7, 153.0, 154.7, 154.4, 146.2, 145.7, 145.6, 139.7, 131.9, 121.5, 119.3, 116.1, 114.8, 110.2, 109.9, 99.3, 96.4, 78.0, 69.9, 30.8, 26.9 and 23.7; *m*/*z* (ES) found 961.2131 (MNa^+); $C_{48}H_{42}O_{20}Na^+$ requires 961.2162.

4α-Phloroglucinol-catechin (41). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-4α-(1,3,5-tribenzylphloroglucinol)-catechin **18** (30 mg, 0.02 mmol) gave a crude product, which was purified by column chromatography (gradient elution 10:90 → 20:80 MeOH−DCM containing 2% AcOH) to yield pure 4α-phloroglucinol-catechin **41** (8.1 mg, 69%) as a pale brown oil; R_f 0.4 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{25}_D$ −20.8 (*c* 1.13, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.91 (1H, d, *J* = 2.0), 6.78 (1H, dd, *J* = 8.0 and 2.0), 6.73 (1H, d, *J* = 8.0), 5.88 (1H, br s), 5.82 (1H, d, *J* = 2.4), 5.79 (1H, d, *J* = 2.4), 5.78 (1H, br s), 4.45 (1H, dd, *J* = 9.6 and 8.0), 4.38 (1H, d, *J* = 8.0) and 4.33 (1H, d, *J* = 9.6); ^{13}C NMR (100 MHz, CD_3OD) 158.5, 158.1, 157.4, 157.3, 146.3, 143.0, 132.3, 120.9, 116.1, 115.9, 107.7, 106.7, 97.4, 96.3, 84.3, 73.4 and 38.5; *m*/*z* (ES, negative mode) 413.0 (M − H, 100%) found 413.0872; $C_{21}H_{17}O_9$ requires 413.0878.

Procyanidin B3 (42). Following Method 4, 5,7,3′,4′-tetra-*O*-benzyl-4-(5,7,3′,4′-tetra-*O*-benzylcatechin)-catechin **19** (100 mg, 0.07 mmol) gave a crude product, which was purified by column chromatography eluting with 10:90 MeOH−DCM containing 2% AcOH to yield procyanidin B3 **42** (31 mg, 69%, 3.5:1 mixture of 4α:4*β* stereoisomers) as a yellow oil. The data were identical to those reported previously;[28] R_f 0.5 (10:90 MeOH−DCM containing 2% AcOH); ^{1}H NMR (400 MHz, CD_3OD, 4α 2:1 mixture of rotamers) major rotamer: 6.71 (1H, d, *J* = 1.6), 6.64 (1H, d, *J* = 8.4), 6.55 (1H, d, *J* = 2.0), 6.43 (1H, dd, *J* = 8.0 and 2.0), 6.22 (1H, dd, *J* = 8.0 and 2.0), 6.04 (1H, s), 5.86 (1H, d, *J* = 2.4), 5.76 (1H, d, *J* = 2.4), 4.52 (1H, d, *J* = 7.6), 4.38 (1H, d, *J* = 7.6), 4.34−4.30 (1H, m), 4.22 (1H, d, *J* = 9.6), 3.78−3.73 (1H, m), 2.73 (1H, dd, *J* = 16.4 and 5.6) and 2.45 (1H, dd, *J* = 16.4 and 8.0); minor rotamer: 6.92 (2H, br s), 6.80−6.77 (2H, m), 6.74 (2H, m), 5.93 (1H, s), 5.80 (1H, d, *J* = 2.0), 5.77 (1H, d, *J* = 2.0), 4.71 (1H, d, *J* = 7.2), 4.38 (1H, d, *J* = 7.6), 4.34−4.30 (1H, m), 4.22 (1H, d, *J* = 9.6), 4.06 (1H, m), 2.81 (1H, dd, *J* = 16.4 and 5.6) and 2.54 (1H, dd, *J* = 16.4 and 8.0); *m*/*z* (ES, negative mode) 578.1 (M^-, 100%) found 578.1423; $C_{30}H_{26}O_{12}$ requires 578.1419.

4*β*-[4′-(4″*β*-Catechinyl)-butyl]-catechin (43). Metathesis dimer **32** (90 mg, 0.062 mmol) was dissolved in MeOH (1.1 mL) and THF (0.9 mL). K_2CO_3 (8.6 mg) was added in one portion, and the reaction mixture was stirred at room temperature for 5 h. After a further addition of K_2CO_3 (4 mg), the reaction was stirred for 12 h until TLC indicated the absence of any starting material. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in H_2O (10 mL) and EtOAc (10 mL). The layers were separated, the aqueous phase was extracted with EtOAc (10 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a crude product. The crude product was preabsorbed onto silica and purified by column chromatography eluting with 1.5:1.5:7 → 3:3:4 EtOAc−DCM−petrol to yield the corresponding diol (70 mg, 83%, 2.5:1 mix of major:minor isomers) as a pale brown oil; R_f 0.35 (1.5:1.5:7 EtOAc−DCM−petrol); $[\alpha]^{25}_D$ +20.5 (*c* 0.73, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ soln) 3574, 2913, 1615, 1591 and 1454; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) 7.45−7.25 (40H, m), 7.05 (2H, br s), 6.97−6.88 (4H, m), 6.27 (2H, d, *J* = 1.6), 6.20−6.18 (2H, m), 5.62 (2H, br s), 5.15 (4H, br s), 5.12 (4H, br s), 5.04−4.88 (8H, m), 4.84 (2H, d, *J* = 10.0), 3.99 (2H, dd, *J* = 10.0 and 5.6), 3.54−3.43 (2H, m) and 2.58−2.38 (4H, m); ^{1}H NMR (400 MHz, $CDCl_3$, minor isomer) 7.45−7.25 (40H, m), 7.05 (2H, br s), 6.97−6.88 (4H, m), 6.28 (2H, d, *J* = 1.6), 6.20−6.18 (2H, m), 5.53 (2H, br s), 5.15 (4H, br s), 5.12 (4H, br s), 5.04−4.88 (10H, m), 4.01−3.98 (2H, m), 3.54−3.52 (2H, m) and 2.58−2.38 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) 159.0, 157.5, 154.8, 137.3, 137.2, 137.0, 136.9, 131.6, 131.0, 128.7, 128.6, 128.6, 128.5, 128.5, 128.1, 127.9, 127.9, 127.7, 127.6, 121.4, 127.3, 121.2, 115.0, 114.3, 107.2, 94.2, 93.8, 77.3, 72.0, 71.3, 71.3, 71.2, 70.1, 70.0, 35.4 and 34.9.

Following Method 4, a sample of the diol (25 mg, 0.018 mmol) was deprotected to give a crude product, which was purified by column chromatography eluting with 10:90 MeOH−DCM contain-

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ing 2% AcOH and then a second column (gradient elution 10:90 → 15:85 MeOH−DCM containing 2% AcOH) to yield pure dimer **43** (10.2 mg, 87%) as a pale brown oil; R_f 0.5 (10:90 MeOH−DCM containing 2% AcOH); $[\alpha]^{24}_D$ +42.1 (*c* 0.33, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 6.80 (2H, s), 6.73−6.71 (4H, m), 5.87 (2H, d, J = 2.4), 5.76 (2H, d, J = 2.4), 4.70 (2H, d, J = 10.0), 3.83 (2H, dd, J = 10.0 and 5.2), 3.12−3.09 (2H, m), 1.90−1.84 (2H, m) and 1.57−1.38 (6H, m); ^{13}C NMR (100 MHz, CD_3OD) 157.8, 157.4, 156.2, 133.4, 128.6, 127.9, 127.0, 120.6, 115.9, 115.6, 107.2, 96.2, 95.4, 79.1, 72.8, 37.1, 32.2 and 30.6; *m*/*z* (ES, negative mode) 633.2 (M − H, 40%) found 633.2000; $C_{34}H_{33}O_{12}$ requires 633.1967.

Cell Culture. All cell lines were routinely cultured in RPMI 1640 culture medium (Gibco, Paisley, U.K.) containing 10% (v/v) heat inactivated fetal bovine serum (FBS, Sigma, Poole, U.K.) at 37 °C in 5% CO_2 and humidified conditions. HCT116 (poorly differentiated human colon carcinoma), RT112 (human bladder carcinoma), HepG2 (Human hepatocyte carcinoma), and 46Br.1G1 (transformed human skin fibroblast) cell lines were obtained from ECACC (ref nos. 91091005, 85061106, 85011430, and 92091814, respectively). PAN-1 is a human pancreatic cell line derived from a poorly differentiated human pancreatic adenocarcinoma within the Academic Unit of Cancer Studies, University of Nottingham, U,K. MGLVA1 is an ascitic variant of the gastric cell line, MKN 45G.[27]

MTT Assay. Cell numbers were measured using a standard methyl thiazoyl tetrazolium (MTT) assay. Briefly, 8×10^3 cells were plated out into 96-well plates and incubated overnight in growth medium. The following day, the medium was replaced by normal growth medium or medium supplemented with the test compounds at 0.03−0.5 mM, and the cells were grown for a further 48 h. The medium was replaced by fresh medium containing MTT at 1 mg/mL and incubated for 4 h. The incorporated MTT was then dissolved in DMSO, and the optical density at 550 nm was read. The IC_{50}'s of the compounds were calculated using nonlinear regression. Significant difference between reactivity of different compounds in the same cell line or the same compound in different cell lines was determined by comparison of the 95% confidence intervals for the log IC_{50} values generated by the nonlinear regression analysis.

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Supporting Information Available: Copies of ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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