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Synthesis of [2-^{13}C, 4-^{13}C]-(2*R*,3*S*)-catechin and [2-^{13}C, 4-^{13}C]-(2*R*,3*R*)-epicatechin

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The first synthesis of doubly labeled, [2-^{13}C, 4-^{13}C]-(2*R*,3*S*)-catechin 15 and [2-^{13}C, 4-^{13}C]-(2*R*,3*R*)-epicatechin 18 starting from labeled 2-hydroxy-4, 6-bis(benzyloxy)acetophenone 3 and labeled 3, 4-bis(benzyloxy)-benzaldehyde 7 are described.

Keywords: flavan-3-ol; [2-^{13}C, 4-^{13}C]-(2*R*, 3*S*)-catechin; [2-^{13}C, 4-^{13}C]-(2*R*, 3*R*)-epicatechin; $CH_3\,{}^{13}CN$; $Me_2N{}^{13}CHO$

Introduction

There is great interest in the role played by the polyphenolic class of compounds in health, nutrition and treatment of disease. In particular, dietary interventions using flavanol-containing foods and beverages have substantiated epidemiological data regarding the improvement of vasodilation[1] and blood pressure.[2] Moreover, numerous investigations have been conducted *in vitro* aimed at elucidating flavanol-mediated bioactivities. These activities include, but are not limited to inhibiting HIV-1 replication *in vitro*,[3] reducing the risk of heart disease,[4] suppressing ulcer formation,[5] possessing antimutagenic,[6] neuroprotective,[7] anti-inflammatory,[8] antibacterial,[9] hypertensive[10] properties, and can inhibit the growth of cancer cells.[11] Moreover, flavanols can affect a host of cellular functions *in vitro* such as signaling pathways,[12] alter cell membrane characteristics[13] and receptor function[14] to imply physiological effects *in vivo*. It should be noted that these *in vitro* studies use the natural form of the flavanols as they appear in nature, whereas the biological effects elicited *in vivo* are the consequences of adsorption (bioavailability), their metabolism and distribution within body organs. Substantial data exists to support the *in vivo* biotransformation and metabolism of flavanols within the gastrointestinal tract by resident microflora[15] as well as their hepatic metabolism.[16]

To validate flavanol activities *in vivo,* isotopic labeling has proved to be an invaluable tool. Multiple approaches have been reported in the literature to include deuterium labeling,[17] ^{14}C-labeling in plants *via* incorporation of $^{14}CO_2$, ^{14}C-acetate and ^{14}C-phenylalanine,[18] and direct synthesis of ^{13}C and ^{14}C-labeled flavanols.[19] These approaches have been applied to small, monomeric flavanols, but little information is available to describe the adsorption, distribution and metabolic fates of higher molecular weight oligomers (procyanidins)[20] which are abundantly present in many foods and beverages. This is in spite of their reported stability during gastric transit,[21] where it was originally thought that the acidic conditions within the stomach would hydrolyze the larger oligomers into smaller species down to the monomers. Additionally, *in vitro* studies with Caco-2 cells have shown dimers and trimers to cross multiple layers of cells.[22]

An intriguing possibility has been raised by the recent plant literature. Several reports have indicated that plant nuclei and histones are the target for flavanols and proanthocyanidins.[23] In one instance[23b] flavanols have been detected in calf small intestinal cell nuclei upon addition to cells *in vitro* raising the possibility that flavanols and accompanying proanthocyanidins may be 'hidden' in other mammalian cell nuclei. Verification of this observation and its extension to other cell lines *in vitro* has not yet been established.

To complement and extend this validation process, we have developed the synthesis for doubly ^{13}C-labeled (2*R*,3*S*)-catechin and (2*R*,3*R*)-epicatechin for more rigorous *in vitro* and *in vivo* studies. These labeled monomers have been developed for use 'as is' and for the synthesis[24] of B-type dimers and trimers up to the multigram level to address the fates of these procyanidins *in vivo*. A doubly labeled target was chosen to accommodate the various types of chemistry active at the C-2 and C-4 positions of the pyran ring to account for the known products of biotransformation and metabolic processes, as well as account for the possible biotransformation sites of higher oligomers. This would include the possible oxidation of B-types to A-types,[25] where doubly linked A-type dimers and trimers could be formed. In this case, all of the cited synthesis steps could be adapted for the ^{14}C-labeled synthesis of the monomers and their resultant B-type dimers and trimers.

As a first step in this process, the first doubly (at C-2 and C-4) ^{13}C-labeled synthesis of (2*R*,3*S*)-catechin **15** and (2*R*,3*R*)-epicatechin **18** (Figure 1) were established. The synthesis developed here for **15** and **18** could then be applied to obtain the other isomers, which are not as abundant in nature as (2*R*, 3*S*)-catechin.

For these applications, we decided to synthesize [2-^{13}C, 4-^{13}C]-(2*R*,3*S*)-catechin **15** and [2-^{13}C, 4-^{13}C]-(2*R*,3*R*)-epicatechin

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18 starting from labeled 2-hydroxy-4, 6-bis(benzyloxy)acetophenone **3** and labeled 3,4-bis(benzyloxy)benzaldehyde **7**.

Results and discussions

Our synthetic approach for the construction of **15** and **18** is depicted in Scheme 3. The requisite starting materials, **3** and **7** are synthesized from commercially available starting materials. The synthesis of **3** was accomplished as outlined in Scheme 1.

The reaction of phloroglucinol **1** with labeled-acetonitrile ($CH_3{}^{13}\mathbf{C}N$) in the presence of $ZnCl_2$ in Et_2O resulted in the formation of 2,4,6-trihydroxyacetophen-[2-^{13}**C**]-one **2** as a yellow solid in 39% yield.[16] The reaction of **2** with BnCl in the presence of K_2CO_3 in DMF at 75–80°C yielded 2-hydroxy-4, 6-bis(benzyloxy)acetophen-[^{13}**C**]-one **3** in 33% yield.

The synthesis of compound **7** was achieved as outlined in Scheme 2.

The reaction of 4-bromo veratrole **4** with BBr_3 in CH_2Cl_2 resulted in 4-bromo-catechol **5** in quantitative yield. The reaction of **5** with BnBr in the presence of K_2CO_3 in DMF resulted in the formation of 3, 4-bis(benzyloxy)bromobenzene **6** in 27% yield after chromatography. The treatment of **6** with Mg metal in refluxing THF and in the presence of a catalytic amount of 2, 4-dibromoethane followed by reaction with *N*, *N*-dimethyl-[^{13}**C**]-formamide yielded 3, 4-bis(benzyloxy)benz-[**2**-^{13}**C**]-aldehyde **7** as an off-white solid.

Once the synthesis of key starting materials was achieved, our efforts were directed to the target compounds. The syntheses of **15** and **18** are based upon our and other research.[19,26] The synthesis of these compounds was achieved as depicted in Scheme 3. The syntheses of **15** and **18** were accomplished from a common intermediate **12** in high optical purity. This key intermediate was obtained from commercially available starting materials **1** and **4** in gram quantities.

As depicted in Scheme 3, the base-catalyzed condensation between labeled 2-hydroxy-4, 6-bis(benzyloxy)acetophenone **3** and labeled 3,4-bis(benzyloxy)benzaldehyde **7** furnished the corresponding doubly labeled chalcone **8** *via* a Claisen-Schmidt reaction in 86% yield.[19d,e] Attempts to reduce the conjugated ketone **8** to alkene **9** using ethyl chloroformate and $NaBH_4$ as reported by Kijima[27] either at low temperature or elevated temperature did not produce alkene **9** and the starting material was recovered. Alternatively, the selective reduction of the conjugated ketone **8** with $NaBH_4$ in the presence of cerium chloride ($CeCl_3 \cdot 7H_2O$) in a mixture of ethanol and THF at 0–5°C provided the alkene **9** after chromatography in 84% yield. Performing the reaction at low temperature was essential to obtain the high yield of **9** since elevated temperatures resulted in the formation of by-products. This newly developed method to obtain **9** was an improvement over the reported procedure by Li.[26] The phenolic hydroxyl group of **9** was protected with TBDMSC1 and imidazole in DMF to yield compound **10** in quantitative yield. The asymmetric dihydroxylation of compound **10** under Sharpless dihydroxylation conditions using AD-mix-α and methanesulfonamide in a mixture of t-butanol, H_2O and THF yielded compound **11** in good yield.[19b] The use of co-solvent THF, resulted in a short reaction time and high enantio-selectivity. Use of other co-solvents such as CH_2Cl_2, EtOAc or toluene resulted in longer reaction times, low yield and purity of the desired compound. The reaction of compound **11** with nBu_4NF in THF resulted in the deprotection of the TBMDS group to produce **12**.[26] However, chiral HPLC indicated the presence of isomers due to the isomerization of **12,** possibly at the C-2 position. Alternatively, when a cold mixture of equimolar amounts of nBn_4NF and glacial acetic acid in THF was reacted at 0–5°C with **11,** the triol **12** was produced in 88% yield after chromatography. Chiral HPLC indicated <2% isomerization of **12** under these newly developed conditions. Thus, these deprotection conditions of the TBDMS group avoided the isomerization at the C-2 position.

The reaction of triol **12** with triethylorthoformate in PPTS in 1, 2-dichloromethane at 60°C resulted in **13a** in 68% yield and 84% *ee*. Alternatively, when triol **12** was reacted with triethylorthopropionate [$EtC(OEt)_3$] in place of triethylorthoformate, and PPTS in 1,2-dichloroethane at 60°C for 2–3 h, these conditions afforded [2-^{13}**C**, 4-^{13}**C**]-3-*O*-propyl ester 5,7,3′,4′-tetra-*O*-benzyl-(2*R*,3*S*)-catechin **13** in quantitative yield with 98% *ee*.[26] The use of triethylorthopropionate in place of triethylorthoformate avoided the isomerization of **13** under these conditions as determined by ^{1}H NMR and chiral HPLC.[26] The ester **13** was then hydrolyzed using K_2CO_3 in methanol at ambient temperature to produce **14** in 82% yield. The optical purity of **14** was further improved upon crystallization from toluene. The reaction of **14** with palladium hydroxide on carbon in EtOAc at room temperature under hydrogen atmosphere resulted in the formation of [2-^{13}**C**, 4-^{13}**C**]-(2*R*,3*S*)-catechin **15** as an off-white solid in quantitative yield.

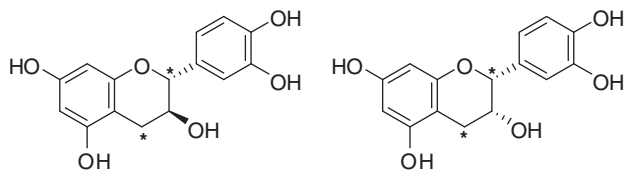
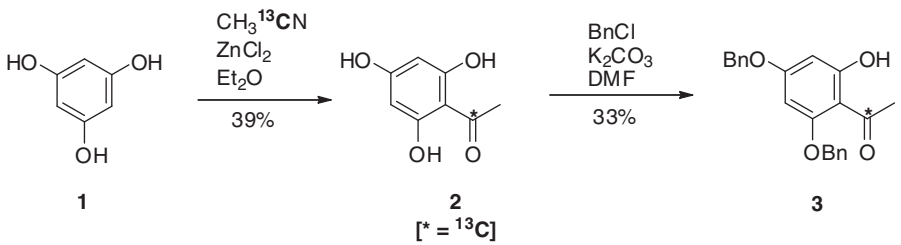
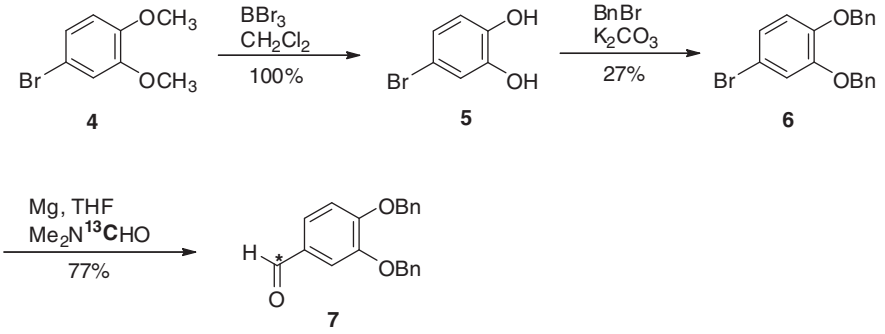


Figure 1. Structures of (2*R*, 3*S*)-catechin **15** and (2*R*, 3*R*)-epicatechin **18**



Scheme 1. Synthesis of 2-hydroxy-4,6-bis(benzyloxy)acetophen-[^{13}C]-one (**3**)



Scheme 2. Synthesis of 3,4-bis(benzyloxy)benz-[^{13}C]-aldehyde (**7**)

The oxidation of the C-3 hydroxyl group of **14** with Dess-Martin periodinane (DMP)[28] in wet CH_2Cl_2 resulted in **16** in 90% yield. The presence of water in the reaction was required to accelerate the reaction rate.[24,28] The reaction of **16** with $Al(O^iPr)_3$ and 2-propanol in refluxing toluene under Meerwein–Ponndorf–Verley reduction conditions resulted in the formation of **17** in 74% yield after crystalization.[24] The treatment of **17** with palladium hydroxide on carbon in ethyl acetate at room temperature under hydrogen atmosphere using a balloon produced **18** in 77% yield.

The optical rotation of **15** and **18** were consistent with those reported in the literature.[29]

Experimental

General

All the solvents were purchased from Aldrich Chemical Company in Sure/Seal™ bottles and were used as received. The labeled *N*, *N*-dimethyl-[^{13}**C**]-formamide (99 atom % ^{13}C) and $CH_3{}^{13}$**C**N (99 atom % ^{13}C) were purchased from Cambridge Isotope Laboratory and were used as received. Phloroglucinol dihydrate and 4-bromo veratrole were purchased from Alfa Aesar. ^{1}H NMR spectra were recorded on a 300 MHz Bruker, whereas ^{13}C NMR spectra were recorded on a 75 MHz Bruker NMR and TMS was used as an internal standard. In ^{13}C NMR, only the chemical shift of the ^{13}**C**-labeled position-values in the molecule were reported. Specific rotations were determined for solutions by irradiating with the sodium D line (= 589 nm) using a Perkin Elmer 341 polarimeter: specific rotation, $[\alpha]_D$ values are given in units 10^{-1}deg · cm^{2}g^{-1} where the concentration *c* is given in g/100 mL. The chemical purity (Method A) was determined by standard HPLC (containing a PDA detector) using a Phenomenex Synergi 4 μ Fusion-RP 80 Å (150 mm × 4.6 mm) column at wavelength of 280 nm, using a gradient of 5–90% of acetonitrile (containing 0.01% TFA) with water (containing 0.01% TFA) up to 20 min, the column temperature was 25°C, and the flow rate was 1 mL/min. The enantiomeric purity (Method B) was determined by chiral HPLC equipped with a PDA detector using a Chiralpak AD-RH 5 μ (150 mm × 4.6 mm) column. The solvent for isocratic programs were acetonitrile/water (65/35, v/v) containing 0.01% TFA, run time 40 min, detection wavelength was 210 nm, column temperature was 60°C, and the flow rate was 1 mL/min. All the compounds were monitored against reference materials including the starting materials.

2, 4, 6-Trihydroxyacetophen-[^{13}C]-one (2)

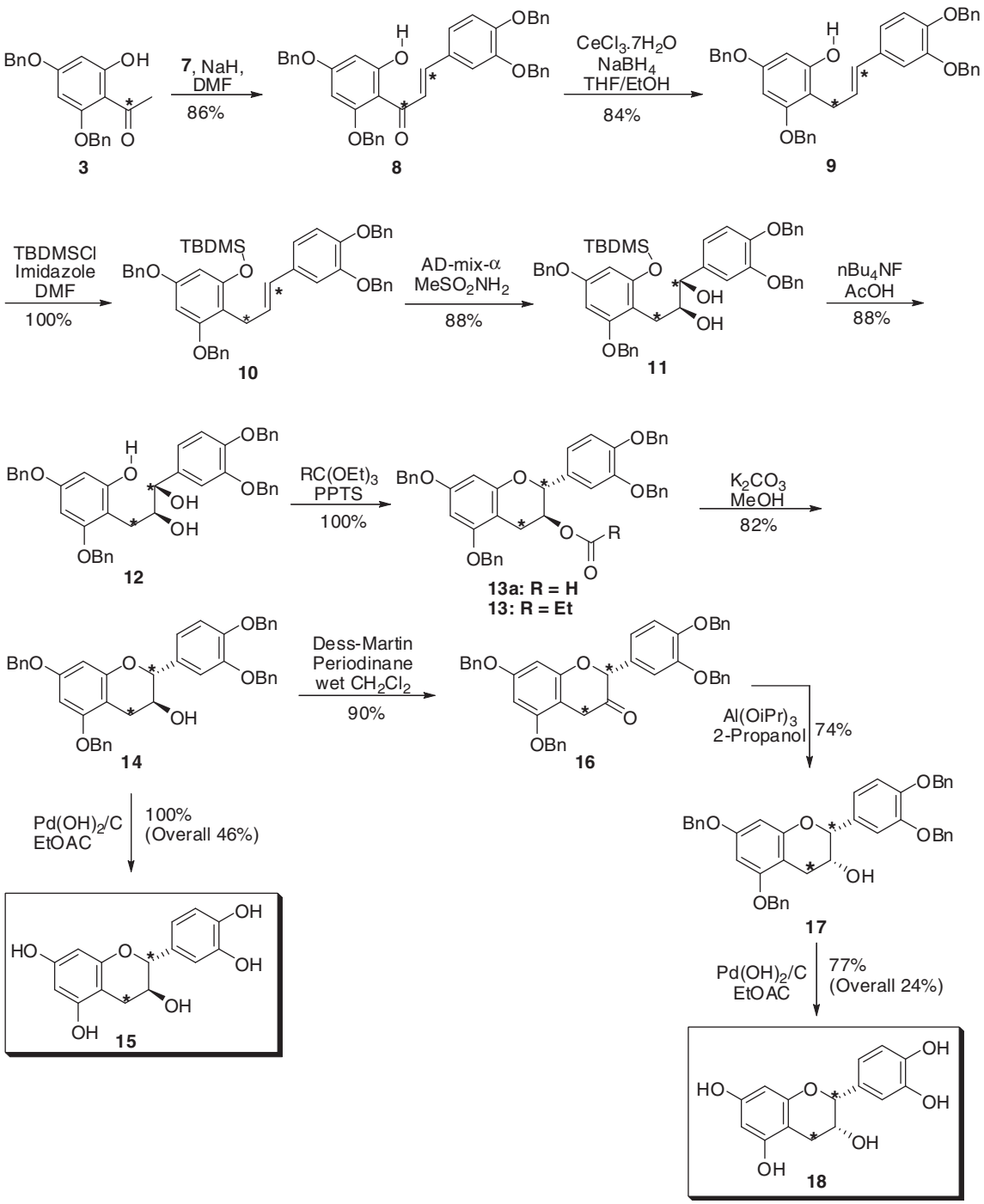
Phloroglucinol dihydrate (9.98 g, 61.6 mmol, 1 eq.) was dried under high vacuum at 125 ± 3°C to a constant weight (Note: It took ~ 72 h at this scale to achieve a constant weight. After this time, only ~ 1.3% water content remained in the compound). Under N_2 atmosphere, a 2 M solution of $ZnCl_2$ in Et_2O (80 mL) was added and the mixture was stirred at room temperature for 0.5 h. A clear solution was obtained. Then, $CH_3{}^{13}$**C**N (5 g, 121.8 mmol, 1.98 eq.) was added and the resulting mixture was stirred for 188 h at RT. The solids were suction filtered. The solids were dissolved in H_2O (80 mL) and refluxed for 4 h. The reaction mixture was cooled to RT. The solids were suction filtered and dried under high vacuum at RT for 20 h to give 5.16 g (39% yield) of **2** as a yellow solid. HPLC analysis using Method A showed the product to be 100% pure with a retention time of 7.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.53$ (d, $J = 5.8$ Hz, 3H), 5.8 (s, 2H), 10.26 (br s, 1H), 11.2 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 202.4$.

2-Hydroxy-4, 6-bis(benzyloxy)acetophen-[^{13}C]-one (3)

To preheated (internal temperature ~ 35°C) DMF (130 mL) was added 2,4,5-trihydroxyacetophenone (13.6 g, 72.84 mmol, 1 eq.) and the solution was degassed for 15 min by bubbling with N_2. K_2CO_3 (22.1 g, 160.2 mmol, 2.2 eq.) was added and the internal temperature rose to ~ 55°C. To this was added, BnCl (20.28 g, 160.2 mmol, 2.2 eq.) in one portion and the mixture was stirred at 55 ± 2°C with stirring for 3–3.5 h. The reaction mixture was cooled to room temperature and the solids were suction filtered. The filtrate was diluted with EtOAc (600 mL) and washed with H_2O (2 × 250 mL). The combined aqueous layer was extracted with EtOAc (1 × 100 mL). The organic layers were combined and washed with 10% aqueous brine (4 × 100 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography using CH_2Cl_2/heptane (1/1, v/v) as the eluent to give 9.3 g (33% yield) of **3** as an off-white solid. HPLC analysis using Method A showed the product to be 99% pure with a retention time of 10.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.53$ (d, J^{13}C–H = 5.8 Hz, 3H), 5.02 (s, 4H), 6.1 (d, 1H, $J = 1.4$ Hz), 6.22 (d, 1H, $J = 2.3$ Hz), 7.2–7.55 (m, 10H), 14.02 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 203.2$.

4-Bromocatechol (5)

BBr_3 (1 M solution in CH_2Cl_2, 130.3 mL, 130.3 mmol, 1.45 eq.) was added slowly to 4-bromo veratrole (19.5 g, 89.86 mmol, 1 eq.) with stirring at 0°C under N_2. The resulting mixture was heated



Scheme 3. Synthesis of [2-^{13}C, 4-^{13}C]-(2*R*, 3*S*)-catechin **15** and [2-^{13}C, 4-^{13}C]-(2*R*, 3*R*)-epicatechin **18**

at reflux for 18–20 h. The reaction mixture was cooled to (< 5°C) and H_2O (15 mL) was added and stirred for 15 min. To this was added, 1 N aqueous sodium hydroxide solution (220 mL). The mixture was stirred for 1 h at room temperature (pH of the solution was ~9.0 as judged by pH paper). The reaction mixture was then acidified with 1 N hydrochloric acid (120 mL, pH ~ 0 to 1). The reaction mixture was then extracted with *tert*-butyl methyl ether (3 × 300 mL). The organic layers were combined and washed with H_2O (3 × 250 mL), brine (1 × 250 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give 25.3 g (100% yield) of **5** as an oil. HPLC analysis using Method A showed the product to be 98.3% pure with a retention time of 8.1 min. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 5.88$ (br s, 1H), 6.5 (br s, 1H), 6.72 (d, 1H, $J = 8.5$ Hz), 6.9 (dd, 1H, $J = 2.3$, 8.5 Hz), 7.0 (d, 1H, $J = 2.3$ Hz). Note: The crude material was used in the next step without further purification, as it was unstable at room temperature. However, it was stable at–20°C.

3, 4-Bis(benzyloxy)bromobenzene (6)

To an ice cold solution (< 5°C) of **5** (25.3 g, 89.86 mmol, 1 eq.) in DMF (250 mL) was added K_2CO_3 (31 g, 224.64 mmol, 2.5 eq.) and

stirred for 15 min. To this was added, BnBr (30.8 g, 180 mmol, 2 eq.) slowly and the reaction mixture was stirred at room temperature for 1820 h. HPLC indicated the completion of the reaction. The reaction –mixture was diluted with EtOAc (600 mL) and the solids were suction filtered. The filtrate was washed with H_2O (3 × 500 mL), brine (1 × 500 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to furnish the crude product. The crude product was triturated with EtOH (175 mL) at room temperature with stirring for 2 h. The solids were filtered. The filtered solids were again re-dissolved in hot EtOAc (25 mL) and ethanol (75 mL). The solution was then cooled to room temperature with stirring. The solids were suction filtered and washed with EtOH (2 × 25 mL) and dried under high vacuum at room temperature for 20 h to give 13.11 g (27% yield) of **6** as an off-white solid. HPLC analysis using Method A showed the product to be 98.8% pure with a retention time of 13.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 5.1$ (s, 4H), 6.78 (d, 1H, $J = 5.8$ Hz), 6.98 (dd, 1H, $J = 2.3$, 8.6 Hz), 7.05 (d, 1H, $J = 8.6$ Hz), 7.26–7.47 (m, 10H).

3. 4-Bis(Benzyloxy)benz-[^{13}C]-aldehyde (7)

In a flame dried flask under positive nitrogen atmosphere, was added Mg (234 mg, 9.76 mmol, 1.24 eq.) in dry THF (50 mL) and the resulting mixture was heated at 50 ± 3°C (bath temperature). To this, was slowly added a solution of 3, 4-bis(benzyloxy)-bromobenzene (2.9 g, 7.86 mmol, 1 eq.) and 1,2-dibromoethane (0.2 mL) in dry THF (10 mL). The bath temperature was raised to 65 ± 3 °C and maintained for 3–4h until all of the magnesium was dissolved. The reaction mixture was cooled (< 5 °C) and then $Me_2N^{13}CHO$ (1 g, 5.78 mmol, 0.74 eq.) was added and the resulting reaction mixture stirred at this temperature for 1 h. The reaction mixture was quenched with a cold solution (< 5 °C) of 10% aqueous hydrochloric acid (15 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (1 50 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography using CH_2Cl_2/heptane (1/1, v/v) as the eluent to furnish 1.3 g (77% yield) of **7** as an off-white solid. HPLC analysis using Method A showed the product to be 99.2% pure with a retention time of 14.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 5.2$ (s, 2H), 5.22 (s, 2H), 6.98 (d, 1H, $J = 8.2$ Hz), 7.26–7.54 (m, 12H), 9.82 (d, J^{13}C–H = 144 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 190.8$.

(E)-1-(2, 4-Bis(benzyloxy)-6-hydroxyphenyl)-3-(3′, 4′-bis(benzyloxy)phenyl)prop-2-[^{13}C]en-1-[^{13}C]-one (8)

A suspension of NaH (60% dispersion in oil, 0.845 g, 21.13 mmol, 1.2 eq.) in DMF (20 mL) was cooled in an ice bath (~5°C) under N_2. To this was added a solution of **3** (6.13 g, 17.61 mmol, 1 eq.) in DMF (20 mL). The reaction mixture was stirred for 0.5 h at this temperature. Then, a solution of **7** (5.6 g, 17.61 mmol, 1 eq.) in DMF (25 mL) was slowly added. The cooling bath was removed and the resulting reaction mixture was allowed to warm to room temperature and stirred for 3.5 4 h. The reaction mixture was poured into a mixture of ice (100 g) and 1N HCl (50 mL) and stirred for 15 min. The solids were suction filtered and washed with CH_3OH (2 × 50 mL). The solids were dissolved in EtOAc (250 mL) and washed with H_2O (1 × 100 mL), brine (1 × 100 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give the crude product. The crude product was triturated with CH_3OH (100 mL) at room temperature for 15 min. The solids were filtered and washed with CH_3OH (2 × 50 mL) and dried under high vacuum at room temperature to give 9.71 g (86% yield) of **8** as a yellow solid. HPLC analysis using Method A showed the product to be 98% pure with a retention time of 8.9 min. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 4.9$ (s, 2H), 5.01 (s, 2H), 5.02 (s, 2H), 5.2 (s, 2H), 6.1 (br s, 1H), 6.2 (d, 1H, $J = 2.1$ Hz), 6.6–6.7 (m, 1H), 6.72 (d, 1H, $J = 8.4$ Hz), 6.81 (dd, 1H, $J = 1.6$, 4.6 Hz), 7.1–7.5 (m, 20H), 7.6–8.0 (m, 1H), 14.4 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 142.7$, 192.6.

(E)-[1-^{13}C, 3-^{13}C]-2,4-Bis(benzyloxy)-2-(3-(3′, 4′-bis(benzyloxy)phenyl)allyl)phenol (9)

A solution of **8** (9.7 g, 14.97 mmol, 1 eq). in THF (225 mL) and EtOH (45 mL) was cooled to 0–2°C. Then, $CeCl_3 \cdot 7H_2O$ (13.94 g, 37.42 mmol, 2.5 eq). was added to the reaction mixture and stirring continued until a clear solution was obtained. Solid $NaBH_4$ (1.42 g, 37.42 mol, 2.5 eq.) was added in portions over a period of 1 h while keeping the internal temperature ≤ 4°C for an additional 1.5–2 h. (*Note*: *The color of the reaction mixture turned to light brown from light yellow and the evolution of hydrogen gas was observed*). HPLC indicated the consumption of the starting material and the formation of the desired product (84% AUC) and a by-product (14% AUC). The reaction mixture was quenched with 5% aqueous citric acid solution (50 mL) while keeping the internal temperature < 5°C for 15 min. (*Note: The reaction mixture solution turned turbid*). The reaction mixture was diluted with EtOAc (250 mL) and the solids were removed by suction filtration. The filtrate was washed with H_2O (1 × 75 mL), brine (1 × 100 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to furnish the crude product. The crude product was triturated with CH_2Cl_2/heptane (1/1, v/v) at 50°C (bath temperature) for 10–15 min. The mixture was cooled to room temperature and the solids were suction filtered to give crude **9**. The combined filtrate was concentrated *in vacuo* and purified by silica gel chromatography using CH_2Cl_2/heptane (1/1–4/1, v/v) as the eluent to give 8.01 g (84% yield) of **9**. HPLC analysis using Method A showed the product to be 98.8% pure with a retention time of 13.9 min. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 3.28$–3.36 (m, 1H), 3.7–3.8 (m, 1H), 4.95 (s, 2H), 4.98 (s, 2H), 5.06 (s, 1H), 5.08 (s, 2H), 5.12 (s, 2H), 6.1 (d, 1H, $J = 6$ Hz), 6.14 (d, 1H, $J = 2.1$ Hz), 6.26 (d, 1H, $J = 2.1$ Hz), 6.75–6.78 (m, 2H), 6.94 (d, 1H, $J = 3.3$ Hz), 7.26–7.5 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 26.7$, 128.6.

(E)-[1-^{13}C, 3-^{13}C)-(3, 5-Bis(benzyloxy)-2-(3-(3′, 4′-bis(benzyloxy)phenyl)allyl)phenoxy)(tert-butyldimethyl-silane (10)

To a solution of **9** (7.91 g, 12.48 mmol, 1 eq). and imidazole (2.55 g, 37.44 mmol, 1 eq.) in DMF (60 mL) at room temperature was added TBDMSCl (3.76 g, 24.95 mmol, 2 eq). under N_2. The resulting solution was stirred at room temperature for 20 h. Water (150 mL) was added to the reaction mixture. The reaction mixture was extracted with EtOAc (2 × 200 mL). The organic layers were combined and washed with H_2O (2 × 100 mL), brine (1 × 100 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography using CH_2Cl_2/heptane (1/1–4/1, v/v) as the eluent to give 9.88 g (100% yield) of **10** as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.22$ (s, 6H), 1.02 (s, 9H), 3.32 (t, 1H, 6 Hz), 3.78 (t, 1H, $J = 6$ Hz), 5.04 (s, 2H), 5.06 (s, 2H), 5.16 (s, 2H), 5.18 (s, 2H), 6.5 (m, 1H), 6.21 (m, 2H), 6.35 (d, 1H, $J = 2.1$ Hz), 6.78–6.9 (m, 2H), 6.94–7.0 (m, 1H), 7.28–7.5 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 26.8$, 128.6.

(1*S*, 2*S*)-[1-^{13}C, 3-^{13}C]-3-(2, 4-bis(benzyloxy)-6-(tert-butyldimethylsilyloxy)phenyl)-1-(3′,4′-bis(benzyloxy)-phenyl)propane-1, 2-diol (11)

A cold solution (0–2°C) of *tert*-butanol (130 mL), H_2O (130 mL) and AD-mix-α (48.9 g, 5 eq. by weight) was added to a solution of **10** (9.78 g, 13.07 mmol, 1 eq.) in THF (150 mL) under N_2. The internal temperature rose to 10°C. The reaction mixture was then cooled to 0°C and methanesulfonamide (1.62 g, 17 mmol, 1.3 eq.) was added; followed by stirring for ~42 h at 0–2°C. 10% Aqueous sodium bisulfite solution (w/v, 150 mL) was added slowly with stirring and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc (200 mL) and H_2O (200 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (1 × 200 mL). The organic layers were combined and washed with H_2O (1 × 150 mL), brine (1 × 150 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography using EtOAc/heptane (2/8, v/v) as the eluent to give 9 g (88% yield) of **11** as an off-white solid. HPLC analysis using Method A showed the product to be 100% pure with a retention time of 17.9 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.18 (s, 6H), 0.78 (s, 9H), 1.98 (br s, 1H, OH), 2.4 (d, 2H, *J* = 3.5 Hz), 2.82 (d, 1H, *J* = 5.6 Hz), 3.03 (t, 1H, *J* = 2.6 Hz), 3.6–3.76 (m, 1H), 4.8 (s, 2H), 4.82 (s, 2H), 4.93 (s, 2H), 4.97 (s, 2H), 5.95 (d, 1H, *J* = 2 Hz), 6.14 (d, 1H, *J* = 2 Hz), 6.68 (s, 2H), 6.83 (d, 1H, *J* = 3.2 Hz), 7.08–7.3 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.2, 76.8.

(1*R*, 2*R*)-[1-^{13}C, 3-^{13}C]-3-(2, 4-bis(benzyloxy)-6-hydroxy phenyl)-1-(3′, 4′-bis(benzyloxy)-phenyl)propane-1, 2-diol (12)

To an ice cold solution (0–5°C) of **11** (8.9 g, 11.35 mmol, 1 eq.) in THF (50 mL) was slowly added a premixed solution of nBu_4NF (1M solution in THF, 22.7 mL, 22.7 mol, 2 eq.) and glacial AcOH (1.36 g, 22.7 mol, 2 eq.) under N_2. The resulting reaction mixture was stirred at this temperature for 0.5 h as HPLC indicated the completion of the reaction. The solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (1 × 100 mL), brine (1 × 100 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give the crude product. The crude product was triturated with EtOAc/heptane (1/9, v/v, 100 mL) at room temperature for 0.5 h. The solids were suction filtered, washed with cold EtOAc/heptane (~5°C, 1/9, v/v, 2 × 25 mL), and dried under high vacuum at room temperature for 18 h to give 6.7 g (88% yield) of **12** as an off-white solid. HPLC analysis using Method A showed the product to be 99.9% pure with a retention time of 8.7 min. The *ee* was determined using chiral HPLC analysis (Method B) and was found to be 98.6% *ee*. $[\alpha]_D^{25} = -21.6$ [*c* 1, Acetone]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.74 (br s, 2H), 4.08 (br s, 1H), 4.52 (br s, 1H), 4.86 and 5.1 (each br s, 1H), 4.95 (s, 2H), 4.98 (s, 2H), 5.03 (s, 2H), 5.07 (s, 2H), 6.1 (d, 1H, *J* = 1.7 Hz), 6.21 (d, 1H, *J* = 1.7 Hz), 6.78 (d, 1H, *J* = 7.3 Hz), 6.96 (d, 1H, *J* = 8.3 Hz), 7.04 (br s, 1H), 7.2–7.5 (m, 20H), 9.3 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.9, 75.5 (d, *J* = 7.5 Hz).

[2-^{13}C, 4-^{13}C]-3-*O*-propiolate ester-5,7,3′,4′-tetra-*O*-benzyl-(2*S*,3*S*)-catechin (13)

To a suspension of **12** (6.6 g, 9.85 mmol, 1 eq.) in 1,2-dichloroethane (130 mL) was added $EtC(OEt)_3$ (3.13 g, 17.73 mmol, 1.8 eq.) and PPTS (1.34 g, 5.32 mmol, 0.54 eq.) and the resulting reaction mixture was heated at ~65°C (bath temperature) for 5 h. The reaction mixture was cooled to room temperature and passed through a silica gel plug. The silica gel plug was eluted with CH_2Cl_2 (4 × 50 mL). The combined filtrate was concentrated *in vacuo* to give 6.97 g (100% yield) of **13** as an oil. HPLC analysis using Method A showed the product to be 92.3% pure with a retention time of 14.2 min. The *ee* was determined using chiral HPLC analysis (Method B) and was found to be 98% *ee*. $[\alpha]_D^{25} = +29.5$ [*c* 1, Acetone]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.95 (t, 3H, *J* = 7.6 Hz), 2.1 (q, 2H, *J* = 7.6 Hz), 4.69 (d, J^{13}C–H = 15 Hz), 5.2 (d, J^{13}_{C-H} = 30 Hz, 1H), 5.0 (s, 2H), 5.08 (s, 2H), 5.12 (s, 2H), 5.26–5.38 (m, 1H), 6.25 (dd, 1H, *J* = 2 8 Hz), 6.88 (br s, 2H), 6.95 (d,1H, *J* = 3.7 Hz), 7.2–7.5 (m, 22H), 7.7–7.83 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.2, 78.4.

5,7,3′,4′-Tetra-O-benzyl-[2-^{13}C, 4-^{13}C]-(2*R*,3*S*)-catechin (14)

To a solution of **13** (8.9 g, 12.08 mol, 1 eq.) in CH_2Cl_2 (100 mL) and CH_3OH (50 mL) was added K_2CO_3 (1.63 g, 16.63 mol, 1.5 eq.) and the resulting suspension was stirred at room temperature for 6–8 h. The reaction mixture was concentrated *in vacuo* keeping the bath temperature ≤ 26°C. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (1 × 50 mL). The organic layer was passed through a silica gel plug (150 g). The silica gel plug was washed with CH_2Cl_2 (2 × 50 mL). The filtrates were combined and the solvent was removed *in vacuo* to give an off-white solid (~14 g). The solid was dissolved in hot toluene (250 mL) at ~45°C (bath temperature). The solution was allowed to cool to room temperature and kept at room temperature for 65–72 h. The solid obtained was suction filtered. The solids were dried under high vacuum at room temperature for 20 h to give 7.3 g (82% yield) of **14** as an off-white solid. HPLC analysis using Method A showed the product to be 99.8% pure with a retention time of 12.9 min. The *ee* was determined using chiral HPLC analysis (Method B) and was found to be 97% *ee*. $[\alpha]_D^{25} = -59.8$ [*c* 1, Acetone]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.6 (t, 1H, *J* = 4.5 Hz), 2.33–2.48 and 3.22–3.4 (each m, 2H, J^{13}C–H = 54 MHz), 2.76–2.95 (m, 1H), 3.97 (br s, 1H), 4.32 and 4.86 (each dd, 1H, *J* = 2.6, 8.2 Hz, J^{13}C–H = 300 MHz), 5.02 (s, 2H), 5.08 (s, 2H), 5.12 (s, 4H), 6.22 (d, 1H, *J* = 2 Hz), 6.28 (d,1H, *J* = 2 Hz), 6.95 (s, 2H), 7.04 (d, 1H, *J* = 3.6 Hz), 7.1–7.5 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.3, 81.6.

[2-^{13}C, 4-^{13}C]-(2*R*,3*S*)-catechin (15)

To a solution of **14** (350 mg, 0.54 mmol) in EtOAc (5 mL) was added 20% $Pd(OH)_2$/C (50% wet, 70 mg, 20 weight %). The resulting suspension was stirred at RT under H_2 atmosphere using a balloon for ~2 h. The reaction mixture was filtered through a 0.45-micron filter. The filter was washed with EtOAc (5 mL). The filtrates were combined and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (2 mL) and diluted with H_2O (HPLC grade, 15 mL) and lyophilized to give 160 mg (100% yield) of **15** as an off-white solid. HPLC analysis using Method A showed the product to be 100% pure with a retention time of 8.7 min. The *ee* was determined using chiral HPLC analysis (Method B) and was found to be 99% *ee*. $[\alpha]_D^{25} = +36.6$ [*c* 1, Acetone]. ^{1}H NMR (300 MHz, Acetone-d_6) δ = 2.62–2.8 (m, 2H), 3.06–3.2 (m, 1H), 3.85–3.95 (m, 1H), 3.96–4.1 (m, 1H), 4.28–4.37 and 4.75–4.85 (each m, 1H), 5.84 (d, 1H, *J* = 2.4 Hz), 6.02 (d, 1H, *J* = 2.4 Hz), 6.7–6.83 (m, 1H), 6.85–6.92 (m, 1H), 7.84 (br s, 1H), 7.95 (br s, 1H), 8.13 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 29.3, 82.8. MS = 293.1 [M^++H, 99%].

(2*R*)-[2-^{13}C, 4-^{13}C]-5, 7-bis(benzyloxy)-2-(3′, 4′-bis(benzyloxy)chroman-3-one (16)

To a solution of **14** (2.3 g, 3.53 mmol, 1 eq.) in CH_2Cl_2 (50 mL) was added DMP reagent (1.75 g, 4.13 mmol, 1.17 eq.) under N_2 at room temperature. Water (0.1 mL) was added to the reaction mixture which was continuously stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the pH was adjusted to ~8 (pH paper). The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined and washed with H_2O (1 × 50 mL), and brine (1 × 50 mL). The organic layer was passed through a silica gel plug (1.5″ diameter) and the plug was washed with CH_2Cl_2 (4 × 50 mL). The combined filtrates were concentrated *in vacuo* to give 2.06 g (90% yield) of **16** as an off-white solid. HPLC analysis using Method A showed the product to be 97% pure with a retention time of 9.9 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.3 (dd, 1H, *J* = 21.5, 48 Hz), 3.74 (dd, 1H, *J* = 21.5, 48 Hz), 4.96–5.05 (m, 5H), 5.08 (s, 2H), 5.11 (s, 2H), 6.33 (d, 1H, *J* = 2.5 Hz), 6.82 (br s, 2H), 6.94 (d, 1H, *J* = 2.5 Hz), 7.27–7.52 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 33.6 (d, *J* = 7.5 Hz), 83.0 (d, *J* = 7.5 Hz).

5,7,3′,4′-tetra-*O*-benzyl-[2-^{13}C, 4-^{13}C]-(2*R*,3*R*)-epicatechin (17)

A suspension of **16** (2.3 g, 3.54 mmol, 1 eq.), $Al(O^iPr)_3$ (1.45 g, 7.08 mmol, 2 eq.) and IPA (18 mL) in toluene (60 mL) was heated at 110–115°C (bath temperature) using a Dean–Stark unit (*to remove the acetone formed during the reaction in order to complete the reaction*) under N_2 with stirring for ~1.5–2 h. The reaction mixture was cooled to room temperature, poured into ice (100 g) and the pH of the mixture was adjusted to ~1 (pH paper) with 1 N H_2SO_4. The layers were separated. The aqueous layer was extracted with EtOAc (1 × 50 mL). The organic layers were combined and washed with H_2O (1 × 100 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography (75 g) using CH_2Cl_2/heptane/EtOAc (7/7/1, v/v/v) as the eluent. The fractions containing the desired compound were combined and the solvent was removed *in vacuo* to give the desired compound (**17**, 95% *ee* as judged by chiral HPLC Method B).

The product was further purified by dissolving the compound in CH_2Cl_2 (10 mL) followed by the addition of CH_3OH (20 mL). The solution was allowed to stand at ambient temperature for ~0.5 h. The solids were suction filtered and washed with cold (<5°C) CH_3OH (2 × 3 mL) and dried under high vacuum at room temperature to give 1.7 g (74% yield) of **17** as an off-white solid. HPLC analysis using Method A showed the product to be 100% pure with a retention time of 12.8 min. The *ee* was determined using chiral HPLC analysis (Method B) and was found to be 98.7% *ee*. $[\alpha]_D^{25}$ = 19.8 [*c* 1, Acetone]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.68 (br s, 1H), 2.66–2.8 (m, 1H), 3.08–3.27 (m, 1H), 4.2 (br s, 1H), 5.01 (s, 4H), 5.1–5.23 (m, 5H), 6.28 (s, 2H), 6.92–7.08 (m, 2H), 7.15 (br s, 1H), 7.24–7.53 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.3, 78.4.

[2-^{13}C, 4-^{13}C]-(2*R*,3*R*)-epicatechin (18)

A suspension of **17** (1.65 g, 2.53 mol) and 20% palladium hydroxide (50% wet, 0.33 g, 20% by weight) in ethyl acetate (HPLC grade, 25 mL) was stirred under hydrogen atmosphere using a balloon at room temperature for 1 h. Following the workup similar to **15** provided 573 mg (77% yield) of **18** as a white fluffy solid. HPLC analysis using Method A showed the product to be 98.5% pure with a retention time of 9.2 min. The *ee* was determined using chiral HPLC analysis (Method B) and was found to be 98.7% *ee*. $[\alpha]_D^{25}$ = -33.9 [*c* 1, Acetone]. ^{1}H NMR (300 MHz, Acetone-d_6) δ = 2.42–2.74 (m, 1H), 2.88–3.16 (m, 1H), 3.47–3.68 (m, 1H), 4.2 (br s, 1H), 4.66 (br s, 1H), 5.12 (br s, 1H), 5.9 (d, 1H, *J* = 2.1 Hz), 6.02 (br s, 1H, *J* = 2.1 Hz), 6.75–6.88 (m, 2H), 7.0–7.08 (m, 1H), 7.72 (br s, 1H), 7.9 (br s, 1H), 8.06 (br s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ = 28.8, 79.7 (d, *J* = 7.5 Hz). MS = 293.1 [M^+ + 1, 99%].

Conclusions

The synthesis of doubly labeled [2-^{13}**C**, 4-^{13}**C**]-(2*R*,3*S*)-catechin **15** and [2-^{13}**C**, 4-^{13}**C**]-(2*R*,3*R*)-epicatechin **18** were achieved for the first time in 46 and 24% overall yield, respectively, with high chemical purity and *ee* in milligram quantities. The incorporation of labeled ^{13}**C** at the C-2 and C-4 positions was accomplished using commercially available acetonitrile ($CH_3{}^{13}$**C**N) and *N*, *N*-dimethylformaide ($Me_2N{}^{13}$**C**HO). The reduction of chalcone **8** to alkene **9** was accomplished under Luche conditions resulting in the desired alkene **9** in excellent yield. Use of glacial AcOH with nBu_4NF for the deprotection of the TBDMS group was accomplished and it avoided isomerization at the C-2 position. Replacement of triethylorthoformate with triethylorthopropionate for the synthesis of **13** from **12** resulted in shorter reaction time along with minimal isomerization (<2 %) either at C-2 and/or C-3 positions as determined by ^{1}H NMR and chiral HPLC.[26] The oxidation of the C-3 hydroxyl group of **14** was performed with wet DMP reagent. The presence of a small amount of water (~0.1–0.2 mL) in the reaction mixture allowed the reaction to proceed with ease of operation and complete conversion. The synthetic methodology developed here could not only be applicable for the synthesis of the corresponding radiolabeled analogs, but also applied to obtain gram quantities of other epimers of **15** and **18,** as well as higher oligomers.

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