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Total synthesis of (−)-bis-8,8′-catechinylmethane isolated from cocoa liquor

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ABSTRACT

An efficient synthesis of bis-8,8′-catechinylmethane, a dimeric flavanol linked through a methylene bridge, is described. Our strategy involved a regioselective coupling via a trifluoroacetic anhydride condensation reaction followed by ketone reduction to the methylene employing new conditions (lithium aluminum hydride and hexafluorophosphoric acid).

Flavonoids are secondary plant metabolites that have been reported to have numerous health benefits including antioxidant properties, anti-inflammatory, and anti-tumor activities.[1] Epidemiological studies reveal that increased antioxidant levels are associated with the reduction of several diseases involving free radicals.[2] A more recent finding reveals the ability of flavonoids to modulate epigenetic pathways.[3] However, in many cases, no *in vivo* data has been generated partly due to lack of synthetic methods for preparation of pure compound.

Flavonoids are typically isolated in mixtures of other polyphenols, steroids, and a sophisticated separation method is necessary to obtain single components. Unfortunately, enantioselective synthesis of flavonoids still remains a daunting task and few methods provide reasonable yields and purity.[4] This synthetic challenge prompted us to consider methods for the assembly of natural product **1** (Fig. 1). In 2002, a preparation of 420 g of cocoa liquor from fermented beans imported from Ghana resulted in the isolation of 17 phenolic compounds including, 4 mg of flavonoid **1** and 15 mg of catechin **2**.[5] Compound **1** revealed antioxidant activity against H_2O_2-induced impairment in PC12 cells and exhibited DPPH radical-scavenging activity.[6] The DPPH radical scavenging activities of compounds **1** and **3** are SC_{50} = 13 μM and SC_{50} = 15 μM.[7]

Several reports have been published regarding the synthesis of dimeric flavanols linked through a methylene bridge. The polymerization of catechin **2** with formaldehyde[8] and acetaldehyde[9] has been studied but gave moderate yields of dimeric compounds in addition to a complex mixture of higher oligomers. The first synthesis of (−)-bis-8,8′-catechinylmethane (**1**) resulted in a 0.5% overall yield.[8] A recent synthesis trapped a palladium intermediate (generated during hydrogenation) with an electron-rich aromatic to yield 28% of natural product **1** and 19% of the C-8 → C-6 regioisomer **3** as the key step.[10] In order to establish an efficient synthesis of natural product **1**, regioselective C-8 → C-8 coupling had to be achieved. We believed that this step could be completed by a trifluoroacetic anhydride (TFAA) mediated condensation. Unlike a reactive aldehyde that would result in polymerization and regioselectivity issues, a mixed anhydride intermediate in theory should have the desired reactivity.

The synthesis began with the literature preparation of trifluoroketone **4** from (+)-catechin **2**, which included two benzylation steps and a regioselective Friedel–Craft acylation (Fig. 2).[11] Conversion of compound **4** to the acid **5** was accomplished utilizing a hydrate intermediate formed from sodium hydride and water.[12] The acid **5** was then coupled with penta-benzylated flavonol **2b** using trifluoroacetic anhydride to form ketone **6** with one equivalent of trifluoroacetic anhydride in DCM.[13]

With ketone **6** in hand, we hoped that hydrogenolysis would allow for benzyl deprotection and reduction of the ketone.[12] Unfortunately this reaction resulted in ring opening of the chroman

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0040-4039/

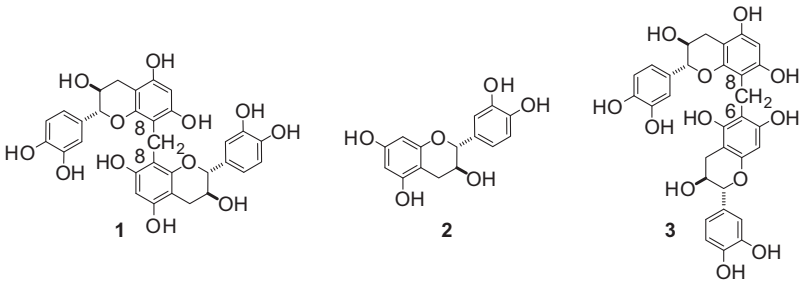

Figure 1. (−)-Bis-8,8′-catechinylmethane (**1**), catechin (**2**), and C-8 → C-6 regioisomer **3**.

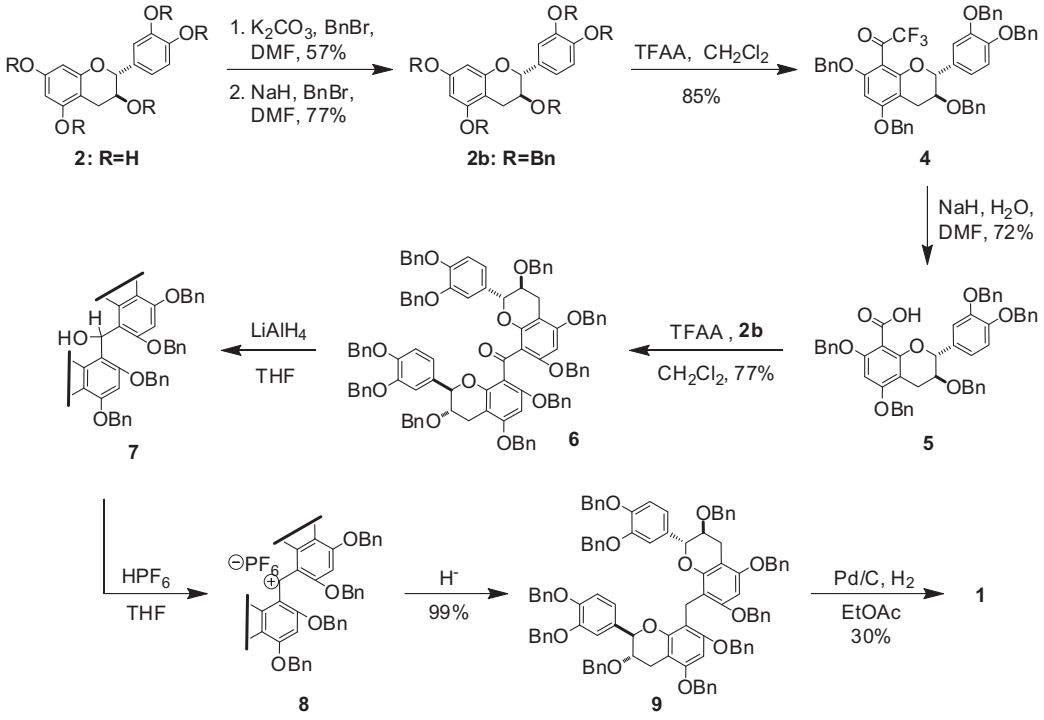

Figure 2. Total synthesis of (−)-bis-8,8′-catechinylmethane (**1**).

rather than reduction of the ketone. In our phloroglucinol model system we achieved over-reduction of the ketone to the methylene with lithium aluminum hydride. Unfortunately, treatment of ketone **6** with the same conditions resulted in formation of a stable, benzyhydryl alcohol. We found that sequential addition of lithium aluminum hydride followed by superacid HPF_6, however, resulted in our desired compound **9**. This reaction sequence presumably proceeds through a benzyhydryl alcohol intermediate **7**, a stable carbocation[14] **8**, which is then trapped by the excess hydride in the reaction. We did not find other one-pot conditions in the literature to over-reduce electron-rich ketones with a superacid and reducing reagent. However, there is an example where HPF_6 and Et_3SiH were used to reduce alcohols to methylenes in hydroxyindolinechromium complexes.[15] Finally, natural product **1** was obtained from the hydrogenolysis of *deca*-benzylated compound **9** under standard conditions. Ring opening of the chroman was again an issue, resulting in 30% yield although a higher yield (70%) was obtained on smaller scale. The final compound **1** was confirmed by 2D NMR studies and in comparison to the original characterization paper.[8,16] Compounds **4**,[11] **5**, **6**, and **9** were characterized by ^1H, ^{13}C, HRMS, IR, and optical rotation.[17]

A regioselective synthesis of bis-8,8′-catechinylmethane has been described. We believe a similar strategy can enable the syntheses of other methylene-linked flavonoids (Fig. 3).[18] It is envisioned that a regioselective coupling with trifluoroacetic anhydride and reduction using lithium aluminum hydride/hexafluorophosphoric acid could be employed in these syntheses.

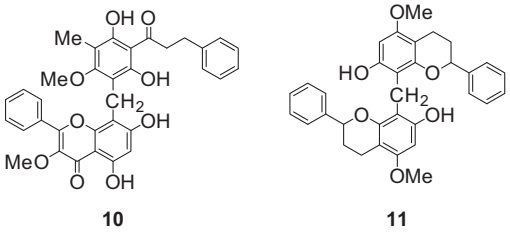

Figure 3. Methylene-containing flavonoids.

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Supplementary data

Supplementary data (copies of all ^{1}H NMR, ^{13}C NMR, and multidimensional NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.011.

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16. *Bis(8-catechinyl)methane (**1**):* Palladium on carbon (93 mg, 0.087 mmol) was added to a solution of **9** (260 mg, 0.174 mmol) in EtOAc (12 mL). The suspension was de-gassed under vacuum and then stirred for 3 h under hydrogen atmosphere (using a balloon). The catalyst was filtered through Celite, washed with EtOAc, and the solvent was evaporated in vacuo. The residue was purified by RP-HPLC, 20% to 100% MeOH/water + 0.05% TFA to yield **1** (31 mg, 0.052 mmol, 30.1% yield). ^{1}H NMR (400 MHz, Acetone): δ 6.94 (2H, s), 6.80 (4H, s), 5.97 (2H, s), 4.68 (2H, d, 2 Hz), 4.10–3.98 (2H, m), 3.95 (2H, s), 2.91 (2H, dd, J1 = 1 Hz, J2 = 6 Hz), 2.54 (2H dd, J1 = 2 Hz, J2 = 4 Hz). .^{1}H NMR (500 MHz, DMSO): δ 9.01–8.62 (8H, –OH), 6.70 (2H, H-2′), 6.59 (2H, H-5′), 6.44 (2H, H-6′), 5.90 (2H, H-6), 4.78 (2H, –OH), 4.39 (2H, H-2), 3.77 (2H, H-3), 3.57 (s, 2H, CH_2), 2.59 (1H, H-4β), 2.32 (1H, H-4α). ^{13}C NMR (125 MHz, DMSO): δ 153.2 (C-7), 153.2 (C-5), 152.3 (C-9), 144.5 (C-3′, C-4′), 130.3 (C-1′), 117.9 (C-6′), 114.8 (C-5′), 114.2 (C-2′), 104.5 (C-8), 99.2 (C-4a), 95.0 (C-6), 80.8 (C-2), 66.0 (C-3), 27.7 (C-4), 15.5 (CH_2, methane) . IR ($CDCl_3$, cm^{-1}): 3600–2700 (br s), 1606. HRMS (ESI-TOF) *m/z* calcd for $C_{31}H_{29}O_{12}$ $[M+H]^+$ 593.1659, found 593.1661. $[\alpha]_D^{25}$ −104.1 (*c* 1.5, MeOH).
17. *3,5,7,3′,4′-Penta-O-benzyl-8-(2,2,2-trifluoroacetyl)flavan (**4**):* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.25 (m, 23H), 7.10–7.07 (m, 2H), 6.99 (br s, 1 H, H-2′), 6.94 (d, *J* = 8.3 Hz, 1H, H-5′), 6.88 (d, *J* = 8.0 Hz, 1H, H-6′), 6.20 (s, 1H, H-6), 5.21–5.03 (m, 8H), 4.89 (d, *J* = 7.3 Hz, 1H, H-2), 4.29,4.18 (AB, *J* = 11.9 Hz, 2H), 3.70 (m, 1H, H-3), 2.93 (dd, *J* = 16.5, 5.3 Hz, 1H, H-4β), 2.70 (dd, *J* = 16.5, 8.0 Hz, 1H, H-4α). ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.4, 160.5, 157.7, 154.3, 149.0, 138.0, 137.5, 137.4, 137.3, 136.3, 136.2, 131.5, 128.8–127.2, 120.2, 115.8, 115.0, 113.6, 105.7, 103.1, 91.1, 80.1, 74.1, 71.8, 71.5, 71.2, 71.1, 70.4, 25.7. IR ($CDCl_3$, cm^{-1}): 3066, 3034, 2919, 2873, 1715, 1606. HRMS (ESI-TOF) *m/z* calcd for $C_{52}H_{43}F_3O_7$ $[M+H]^+$ 837.3039, found: 837.3040. $[\alpha]_D^{25}$ +3.7 (*c* 2.0, $CDCl_3$).
*3,5,7,3′,4′-Penta-O-benzyl-8-carboxycatechin (**5**):* Compound **4** (950 mg, 1.1 mmol) was dissolved in DMF (7.5 ml) and water (0.020 ml) then stirred at room temperature for 2 min. NaH (0.454 g, 11. mmol) was added and the solution was heated to 60 °C for 1.5 h. The reaction mixture was then quenched with 1 N HCl, extracted with EtOAc, washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was then chromatographed (EtOAc–hexane, 2:8 → 6:4) to yield 655 mg (72%) of **5** as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.15 (m, 23H), 7.02–6.99 (m, 2H), 6.94 (s, 1H, H-2′), 6.82 (s, 2H, H-5′, H-6′), 6.14 (s, 1H, H-6), 5.08–4.94 (m, 8H), 4.89 (d, *J* = 7.3 Hz, 1H, H-2), 4.24,4.14 (AB, *J* = 11.9 Hz, 2H), 3.67 (m, 1H, H-3), 2.82 (dd, *J* = 16.6, 5.2 Hz, 1H, H-4β), 2.62 (dd, *J* = 16., 7.8 Hz, 1H, H-4α). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 159.4, 158.3, 154.2, 149.0, 137.8, 137.3, 137.2, 136.3, 136.2, 131.3, 128.7–127.1, 119.9, 115.0, 113.5, 103.3, 103.2, 92.3, 80.2, 73.6, 71.7, 71.6, 71.4, 71.1, 70.3, 25.4. IR ($CDCl_3$, cm^{-1}): 3500–2800 (br s), 3064, 3033, 2931, 1730, 1695, 1606. HRMS (ESI-TOF) *m/z* calcd for $C_{51}H_{45}O_8$ $[M+H]^+$ 785.3114, found 785.3113. $[\alpha]_D^{25}$ +5.4 (*c* 1.3, $CDCl_3$).
*Bis(3,5,7,3′,4′-Penta-O-benzyl-8-catechinyl)methanone (**6**):* To a solution of **5** (69.2 mg, 0.088 mmol) in anhydrous CH_2Cl_2 were added TFAA (14.71 µl, 0.106 mmol) and 3,5,7,3′,4′-Penta-*O*-benzylcatechin[11] (65.3 mg, 0.088 mmol). After three hours, the solution was poured into ice-H2O and was extracted with CH_2Cl_2. The organic layers were washed with satd $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated in vacuo. The residue was then chromatographed (EtOAc–hexane, 1:9 → 5:5) to yield 105 mg (77%) of **6**. ^{1}H NMR (500 MHz, DMSO): δ 7.48–7.13 (m, 46H), 6.95 (4H), 6.86 (2H), 6.70 (2H), 6.61 (2H), 6.44 (2H, H-6), 5.16 (2H), 5.10 (2H), 5.04 (2H), 4.88 (2H), 4.22 (2H, H-2), 3.95 (2H), 3.52 (2H, H-3), 2.90 (1H, H-4β), 2.40 (1H, H-4α). ^{13}C NMR (125 MHz, DMSO): δ 189.5 (C-carbonyl), 157.6, 157.3, 153.1, 148.0, 138.3, 137.2, 137.0, 131.9, 128.5–127.2, 120.2, 114.9, 114.8, 110.0, 102.0, 91.3, 79.0, 74.2, 70.6, 70.2, 69.9, 69.8, 69.5, 26.2. IR ($CDCl_3$, cm^{-1}): 3065, 3033, 2902, 1730, 1655, 1606. HRMS (ESI-TOF) *m/z* calcd for $C_{101}H_{87}O_{13}$ $[M+H]^+$ 1507.6205, found 1507.6138. $[\alpha]_D^{25}$ +18.3 (*c* 1.1, $CDCl_3$).
*Bis(3,5,7,3′,4′-Penta-O-benzyl-8-catechinyl)methane (**9**):* A solution of **6** (326 mg, 0.216 mmol) in anhydrous THF (2162 µl) was cooled to −78 °C and $LiAlH_4$ (16.4 mg, 0.432 mmol) was added. The mixture was stirred for 30 min while slowly being warmed to room temperature. 2 equiv of HPF_6 (1 M in THF) was added portionwise (~0.5 equiv each time) at room temperature over 3 h. The solution was extracted with EtOAc, washed with brine, dried with Na_2SO_4, and evaporated in vacuo to give 320 mg (99%) of **9** as an orange oil. ^{1}H NMR (500 MHz, DMSO): δ 7.41–7.14 (m, 46H), 6.94 (4H), 6.83 (2H), 6.76 (2H), 6.54 (2H), 6.35 (2H, H-6), 5.04 (2H), 5.03 (2H), 4.87 (2H), 4.71 (2H), 4.24 (2H, H-2), 3.97 (2H), 3.77 (s, 2H, CH_2), 3.51 (2H, H-3), 2.87 (1H, H-4β), 2.43 (1H, H-4α). ^{13}C NMR (125 MHz, DMSO): δ 155.55 (C-7), 154.2 (C-5), 152.9 (C-9), 147.9 (C-3′, C-4′), 138.3 (Bn-C), 137.6 (Bn-C), 137.1 (Bn-C), 132.4 (C-1′), 128.4–127.2 (Bn-CH), 120.1 (C-6′), 113.9 (C-5′), 113.2 (C-2′), 109.7 (C-8), 101.5 (C-4a), 91.4 (C-6), 78.6 (C-2), 74.4 (C-3), 70.4 (CH_2), 70.3 (CH_2), 69.9 (CH_2), 69.5 (CH_2), 69.3 (CH_2), 25.9 (C-4), 17.0 (CH_2, methane). IR ($CDCl_3$, cm^{-1}): 3065, 3033, 2919, 2873, 1606. HRMS (ESI-TOF) *m/z* calcd for $C_{101}H_{87}O_{12}$ $[M+H]^+$ 1493.6354, found 1493.6344. $[\alpha]_D^{25}$ −4.40 (*c* 1.0, $CDCl_3$).
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