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Enantioselective synthesis of afzelechin and *epi*afzelechin

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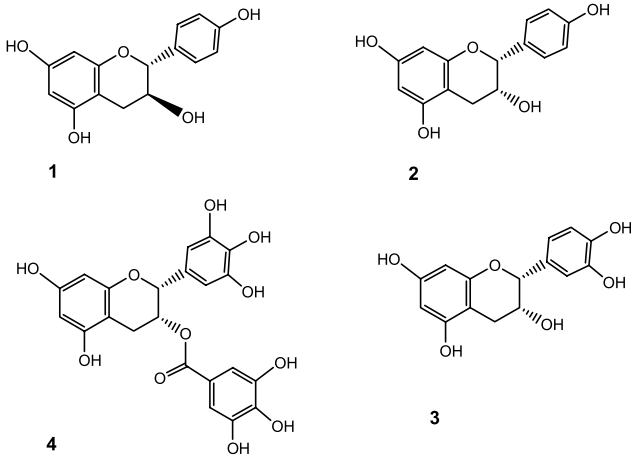
Abstract—The flavonoids afzelechin and *epi*afzelechin as well as their gallate esters were synthesized enantioselectively via Sharpless hydroxylation followed by regioselective cyclization.

1. Introduction

The flavonoids afzelechin (**1**) and *epi*afzelechin (**2**) have been found in numerous plants. Some recent reports of isolation of **1** and **2** include the following species: *Typha capensis* (Rohrb.) N. E. Br, commonly referred to as bulrush in South Africa;[1] *Artocarpus dadah*, known as 'Tampang' in Indonesia;[2] *Celastrus orbiculatus* Thunb. (Celastraceae), a perennial shrub[3] and *Calophyllum apetalum* from India.[4] In addition, many plants contain also proanthocyanidins which are oligomers formed by the condensation of **1** and **2** as well as similar flavonoids.[5] Many of these compounds and their derivatives show a range of biological activities. Potent proliferative effects on MCF-7 and osteoblastic cells have been found for a number of *epi*afzelechin (**2**) derivatives.[6] (−)-*Epi*afzelechin showed selective inhibitory activities against cyclooxygenase-1 (COX-1) over COX-2.[2] Condensed tannin derived from *epi*afzelechin and *epi*-catechin (**3**), isolated from the Chinese herbal drug 'Wen Guan Mu', showed inhibitory effects on HIV-1 protease.[7] Selligueain A, a proanthocyanidin trimer composed of **1** and **2** units, isolated from the rhizomes of *Selliguea feei*, was rated by a taste panel as being ca. 35 times sweeter than a 2% w/v aqueous sucrose solution.[8] Because of our interest in the potential of green tea catechins as cancer preventive agents, we have embarked on a program in preparing synthetic analogs of *epi*gallocatechin-3-gallate (EGCG, **4**).[9] We have engaged in the enantioselective synthesis of **1** and **2** as well as their gallate esters. As far as we are aware, no de novo syntheses of these compounds have been reported in the literature.[10]



2. Results and discussion

The synthesis of afzelechin (**1**) is outlined in Scheme 1. Friedel–Craft alkylation of 3,5-dibenzyloxyphenol (**5**)[11] with **6** under strictly controlled conditions gave the alkylation product **7**. Compound **7** was first protected as the *t*-butyldimethylsilyl ether and then subject to Sharpless hydroxylation with AD-mix α, followed by de-silylation to give the (+)-(1*S*,2*S*)-diol **8**. Direct hydroxylation of **7** without protection did not proceed well under the Sharpless conditions. The assignment of the absolute configurations at the two stereogenic centres in **8** was based on the stereochemical outcome normally formulated according to Sharpless hydroxylation of alkenes.[12] Cyclization of **8** under the orthoformate/acidic conditions followed by base hydrolysis of the formate ester gave the protected flavan-3-ol **9**. The *trans* stereochemistry of **9** was evident from its

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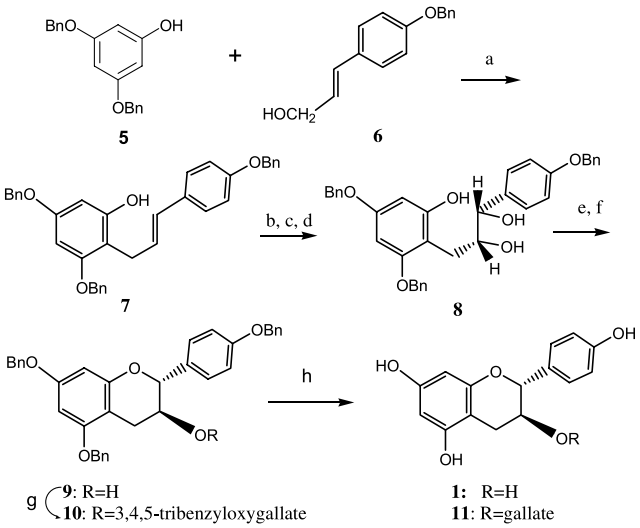
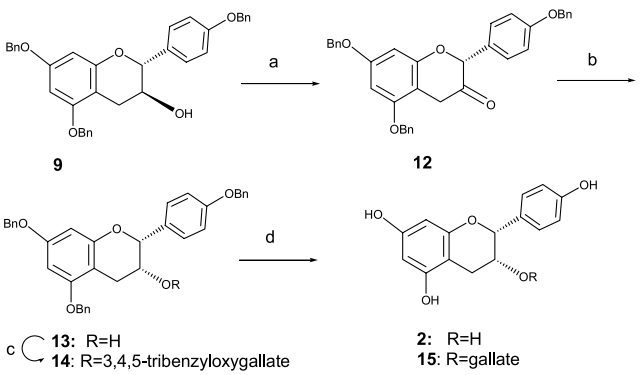


Scheme 1. (a) $H_2SO_4(SiO_2)/CH_2Cl_2$, rt; (b) TBSCl/imidazole/DMF, rt; (c) AD-mix/$CH_3SO_2NH_2/H_2O/t$-BuOH/CH_2Cl_2, 0 °C; (d) TBAF/THF, rt; (e) $CH(OEt)_3$/PPTS/$(CH_2Cl)_2$, rt; (f) K_2CO_3/MeOH/DME, rt; (g) 3,4,5-tris(benzyloxy)benzoyl chloride/DMAP/CH_2Cl_2, rt; (h) $H_2/Pd(OH)_2$ on charcoal/MeOH/THF, rt.

^{1}H NMR spectrum.[13] This is in agreement with a inversion of stereochemistry at C-2 during cyclization, giving the 2*R*,3*S* product. Hydrogenolysis of **9** to remove the benzyl protecting group gave (+)-**1**. The optical activity of the synthetic (+)-**1** was found to be the same as that reported in the literature.[15] Alternately, compound **9** was first acylated with 3,4,5-tribenzyloxybenzoyl chloride to give the corresponding ester **10**, which on hydrogenolysis gave (+)-(2*R*,3*S*)-afzelechin-3-gallate (**11**).

To obtain *epi*afzelechin, compound **9** was first oxidized by Dess–Martin periodinane[14] to the corresponding ketone **12**. Reduction of the carbonyl function with L-selectride at −78 °C gave exclusively the *cis*-substituted compound **13**. The stereochemistry of **13** was also evident from its ^{1}H NMR where the coupling of H-2 and H-3 is distinctly different from that of compound **9**. Hydrogenolysis of **13** gave then (−)-(2*R*,3*R*)-**2** (Scheme 2). The synthetic (−)-**2** had an optical rotation, $[\alpha]_D = -59$ ($c=3$, EtOH), similar to the literature value for the natural compound, $[\alpha]_D = -58.9$ ($c=3$, EtOH).[15] Similarly, the 3-gallate ester **15** was



Scheme 2. (a) Dess-Martin periodinane/CH_2Cl_2, rt; (b) L-Selectride/THF, −78 °C–rt; (c) 3,4,5-Tris(benzyloxy)benzoyl chloride/DMAP/CH_2Cl_2, rt; (d) $H_2/Pd(OH)_2$ on charcoal/MeOH/THF, rt.

obtained after formation of the ester **14** followed by hydrogenolysis.

In conclusion, the natural occurring flavonoids afzelechin (**1**) and *epi*afzelechin (**2**) have been synthesized enantioselectively for the first time in 12 and 7% overall yield, respectively. The biological studies of these synthetic compounds will be reported elsewhere.

3. Experimental

3.1. General

The starting materials and reagents, purchased from commercial suppliers, were used without further purification. Anhydrous THF was distilled under nitrogen from sodium benzophenone ketyl. Anhydrous methylene chloride was distilled under nitrogen from CaH_2. Anhydrous DMF was distilled under vacuum from CaH_2. Reaction flasks were flame-dried under a stream of N_2. All moisture-sensitive reactions were conducted under a nitrogen atmosphere. Flash chromatography was carried out using silica-gel 60 (70–230 mesh). The melting points were uncorrected. ^{1}H NMR and ^{13}C NMR (400 MHz) spectra were measured with TMS as an internal standard when $CDCl_3$ and acetone-d_6 were used as a solvent. High-resolution (ESI) MS spectra were recorded using a QTOF-2 Micromass spectrometer.

3.1.1. (*E*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-(4-benzyloxy)phenyl]propene (7). At rt under an N_2 atmosphere, 25% H_2SO_4/SiO_2 (1.6 g, 4 mmol) was added in one batch to the stirred mixture of 3,5-bis(benzyloxy)phenol (3.06 g, 10 mmol) and (*E*)-4-benzyloxycinnamyl alcohol (2.40 g, 10 mmol) in dry CH_2Cl_2 (50 mL). The resulting mixture was stirred at rt overnight. After filtration and evaporation, the residue was purified by flash chromatography on silica gel (benzene) to afford the desired compound as white solid (2.0 g, 38% yield): mp 132–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.30 (m, 15H), 7.30 (A of AB, $J=8.7$ Hz, 2H), 6.89 (B of AB, $J=8.7$ Hz, 2H), 6.43 (A of AB, $J=15.8$ Hz, 1H), 6.27 (d, $J=2.1$ Hz, 1H), 6.17 (d, $J=2.1$ Hz, 1H), 6.20 (B of ABt, $J=15.8$, 6.3 Hz, 1H), 5.04 (s, 2H), 5.02 (s, 2H), 4.99 (s, 2H), 3.57 (d, $J=6.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.7, 158.0, 157.7, 155.7, 137.0, 136.9, 136.8, 130.2, 129.9, 128.6, 128.5, 128.4, 127.9, 127.8, 127.7, 127.5, 127.4, 127.2, 126.1, 114.8, 106.9, 95.0, 93.6, 77.2. 70.3, 70.0, 69.9, 26.4; HRMS (ESI) calcd for $C_{36}H_{33}O_4$ (M+H) 529.2379, found 529.2385.

3.1.2. (+)-(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-(4-benzyloxyphenyl)propane-1,2-diol ((+)-8). The propene **7** (2.3 g, 4.4 mmol) was dissolved in dry DMF (30 mL), and to this solution imidazole (0.9 g, 13.2 mmol) and TBSCl (1.3 g) were added successively. The resulting mixture was stirred at rt overnight, and then saturated Na_2CO_3 solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatograph on silica gel (*n*-hexane and EtOAc=9:1 v/v) to afford [3,5-bis(benzyloxy)-2-[3-(4-benzyloxyphenyl)allyl]phenoxy]-*tert*-butyldimethylsilane.

This material was used in next step without further purification.

AD-mixα (11.4 g) and methanesulfonamide (0.76 g) were dissolved in a solvent mixture of *t*-BuOH (50 mL) and H_2O (50 mL). The resulting mixture was stirred at rt for 5 min, then the mixture was cooled to 0 °C and a solution of the above [3,5-bis(benzyloxy)-2-[3-(4-benzyloxyphenyl)allyl-phenoxy]-*tert*-butyldimethylsilane in dichloromethane (50 mL) was added. After the mixture had been stirred overnight, a total of four batches of AD-mixα (5.7 g each) and methanesulfonamide (0.38 g each) were added in 24 h intervals. After another 24 h of stirring at 0 °C, TLC showed that the reaction was completed. Then a 10% $Na_2S_2O_3$ solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic phases were combined, dried ($MgSO_4$) and evaporated. The residue was redissolved in THF (30 mL), and TBAF (10 mL, 1 M in THF) was added. The resulting mixture was stirred at rt for 4 h, and the saturated $NaHCO_3$ solution was added. The mixture was extracted with EtOAc, and the organic layers were combined, dried (MgSO4) and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAc in CH_3Cl) and then recrystallized in EtOAc to give a white solid (1.3 g, 53% yield): mp 150–152 °C; $[\alpha]_D=+2.1$ ($c=0.9$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.19 (m, 15H), 7.10 (A of AB, $J=8.6$ Hz, 2H), 6.84 (B of AB, $J=8.6$ Hz, 2H), 6.27 (d, $J=2.2$ Hz, 1H), 6.19 (d, $J=2.2$ Hz, 1H), 4.98 (s, 2H), 4.94 (s, 2H), 4.85 (AB, $J=11.7$ Hz, 2H), 4.48 (d, $J=7.4$ Hz, 1H), 4.03–3.98 (m, 1H), 2.93 (A of ABt, $J=14.7$, 3.1 Hz, 1H), 2.74 (B of ABt, $J=14.7$, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 159.0, 158.7, 157.7, 157.5, 136.9, 136.8, 136.7, 132.5, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 127.4, 126.8, 114.8, 106.1, 95.9, 93.3, 77.2, 70.0, 69.9, 69.8, 26.3; HRMS (ESI) calcd for $C_{36}H_{34}O_6Na$ (M+Na) 585.2253, found 585.2246.

3.1.3. (+)-(2*R*,3*S*)-*trans*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)chroman-3-ol ((+)-9). To a suspension of (1*S*,2*S*)-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-1-(4-benzyloxy-phenyl)propane-1,2-diol (1.3 g, 2.3 mmol) in 1,2-dichloro-ethane (30 mL) was added triethyl orthoformate (1 mL), followed by PPTS (340 mg, 1.4 mmol). The mixture was stirred at rt for 20 min and the solid dissolved, then heated the mixture to 60 °C for 5 h until TLC showed the reaction had been completed. After evaporation of the solvent, the residue was redissolved in DME (20 mL) and MeOH (20 mL), K_2CO_3 (400 mg) was added, and the mixture was stirred at rt overnight. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexane=1:3 v/v) to afford the desired product as white solid (0.95 g, 75% yield): mp 134–136 °C; $[\alpha]_D=+5.8$ ($c=2.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.32 (m, 17H), 7.01 (d, $J=8.5$ Hz, 2H), 6.26 (s, 1H), 6.21 (s, 1H), 5.06 (s, 2H), 5.01 (s, 2H), 4.97 (s, 2H), 4.69 (d, $J=8.2$ Hz, 1H), 4.08 (m, 1H), 3.15 (A of ABt, $J=16.3$, 5.6 Hz, 1H), 2.69 (B of ABt, $J=16.3$, 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 159.0, 158.7, 157.7, 155.3, 136.9, 136.8, 136.7, 130.1, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.5, 127.4, 127.0, 115.1, 102.2, 94.3, 93.7, 81.4, 70.0, 69.9, 69.8, 68.1, 27.9; HRMS (ESI) calcd for $C_{36}H_{33}O_5$ (M+H) 545.2328, found 545.2319.

3.1.4. (+)-Afzelechin ((+)-1). Under an H_2 atmosphere, $Pd(OH)_2$/C (20%, 200 mg) was added to a solution of (+)-**9** (300 mg, 0.55 mmol) in a sovent mixture of THF/MeOH (1:1 v/v, 30 mL). The resulting reaction mixture was stirred at rt under H_2 for 6 h, TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatograph on silica gel (20% MeOH in CH_2Cl_2) to afford (+)-afzelechin (44 mg, 81% yield): mp 252–254 °C (decompose); $[\alpha]_D=+20$ ($c=4$, Me_2CO); lit. $[\alpha]_D=+20.6$ ($c=5$, Me_2CO);[15] ^{1}H NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 7.34 (A of AB, $J=8.5$ Hz, 2H), 6.95 (B of AB, $J=8.5$ Hz, 2H), 6.14 (d, $J=2.2$ Hz, 1H), 5.97 (d, $J=2.2$ Hz, 1H), 4.73 (d, $J=8.0$ Hz, 1H), 4.14 (dd, $J=8.0$, 2.8 Hz, 1H), 3.01 (A of ABt, $J=16.1$, 5.5 Hz, 1H), 2.66 (B of ABt, $J=16.1$, 8.5 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz) δ 151.7, 151.3, 151.0, 150.5, 124.9, 123.6, 109.8, 94.6, 90.2, 89.3, 76.2, 62.1, 22.7; HRMS (ESI) calcd for $C_{15}H_{15}O_5$ (M+H) 275.0919, found 275.0910.

3.1.5. (+)-(2*R*,3*S*)-*trans*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate ((+)-10). Under an N_2 atmosphere, a solution of 3,4,5-tris(benzyloxy)benzoic acid (200 mg, 0.45 mmol) was refluxed with $(COCl)_2$ (1 mL) in dry CH_2Cl_2 (10 mL) and one drop of DMF for 3 h. The excess of $(COCl)_2$ and the solvent were removed by distillation and the residue was dried under vacuum for 3 h and dissolved in CH_2Cl_2 (5 mL). This solution was added dropwise to a solution of (+)-**9** (120 mg, 0.3 mmol) and DMAP (75 mg, 0.22 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at rt overnight, then saturated $NaHCO_3$ aqueous solution was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAc/benzene) to afford the desired compound (170 mg, 80%). Recrystallization from $CHCl_3$ and ether gave a white powder: mp 131–132 °C; $[\alpha]_D=+5.1$ ($c=2.0$, CH_3Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.19 (m, 34H), 6.92 (d, $J=8.6$ Hz, 2H), 6.29 (s, 2H), 5.50 (bs, 1H), 5.12 (d, $J=7.0$ Hz, 1H), 5.08 (s, 2H), 5.03 (s, 4H), 5.00 (s, 2H), 4.99 (s, 4H), 3.15 (A of ABt, $J=16.7$, 5.1 Hz, 1H), 2.87 (B of ABt, $J=16.7$, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 165.0, 158.9, 158.7, 157.6, 155.0, 152.3, 142.3, 137.3, 136.7, 136.5, 130.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.2, 124.9, 114.8, 108.9, 101.4, 94.3, 93.7, 78.4, 77.2, 75.0, 71.0, 70.1, 69.9, 24.5; HRMS (ESI) calcd for $C_{64}H_{55}O_9$ (M+H) 967.3846, found 967.3854.

3.1.6. (+)-Afzelechin gallate ((+)-11). Under an H_2 atmosphere, $Pd(OH)_2$/C (20%, 200 mg) was added to a solution of (+)-**10** (360 mg, 0.24 mmol) in a sovent mixture of THF/MeOH (1:1 v/v, 30 mL). The resulting reaction mixture was stirred at rt under H_2 for 6 h. TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatograph on silica gel (20% MeOH in CH_2Cl_2) to afford

(+)-afzelechin gallate (130 mg, 82% yield): mp 257–259 °C (decompose); $[\alpha]_D$=45.5 (c=0.5, Me_2CO); ^1H NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 7.39 (A of AB, J=7.3 Hz, 2H), 7.12 (s, 2H), 6.92 (B of AB, J=7.3 Hz, 2H), 6.17 (s, 1H), 6.06 (s, 1H), 5.45 (bs, 1H), 5.20 (d, J=6.8 Hz, 1H), 3.08 (A of ABt, J=16.4, 4.9 Hz, 1H), 2.84 (B of ABt, J=16.4, 6.8 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 160.0, 151.2, 151.0, 150.6, 150.5, 149.5, 139.3, 132.7, 123.4, 122.3, 114.3, 109.4, 103.3, 92.6, 89.9, 88.7, 18.5; HRMS (ESI) calcd for $C_{22}H_{19}O_9$ (M+H) 427.1029, found 427.1024.

3.1.7. (+)-(2*R*)-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)-chroman-3-one ((+)-12). Dess-Martin periodinane (6.3 mL, 15% g/mL in CH_2Cl_2, 2.2 mmol) was added in one batch to a stirred solution of (+)-**9** (600 mg, 1.1 mmol) in CH_2Cl_2 (30 mL) under an N_2 atmosphere. The mixture was stirred at rt for about 2 h till TLC showed the absence of starting material. Subsequently, saturated $NaHCO_3$ solution (15 mL) and 10% $Na_2S_2O_3$ aqueous solution (15 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (benzene) and then recrystallized in $CHCl_3$ and ether to afford the desired compound (448 mg, 75%): mp 141–143 °C, $[\alpha]_D$=+46 (c=1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.30 (m, 15H), 7.27 (A of AB, J=8.7 Hz, 2H), 6.95 (B of AB, J=8.7 Hz, 2H), 6.37 (d, J=2.1 Hz, 1H), 6.34 (d, J=2.1 Hz, 1H), 5.26 (s, 1H), 5.03 (s, 2H), 5.01 (s, 2H), 4.99 (s, 2H), 3.68 (AB, J=21.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 205.3, 159.3, 158.9, 156.9, 154.6, 136.7, 136.5, 136.4, 128.6, 128.5, 128.1, 128.0, 127.9, 127.5, 127.3, 127.1, 114.9, 102.0, 95.7, 95.0, 83.1, 70.1, 70.0, 69.9, 33.8; HRMS (ESI) calcd for $C_{36}H_{31}O_5$ (M+H) 543.2171, found 543.2190.

3.1.8. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)-chroman-3-ol ((−)-13). Under an N_2 atmosphere, the ketone ((+)-**12**) (280 mg, 0.51 mmol) was dissolved in dry THF (10 mL), and the solution was cooled to −78 °C. Then L-selectride (1 mL, 1 M solution in THF, 1 mmol) was added dropwise. The resulting solution was stirred at −78 °C overnight. When TLC showed the reaction was completed, saturated $NaHCO_3$ aqueous solution (10 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatograph on silca gel (5% EtOAC/benzene) and then recrystallized with ethanol and EtOAC to afford the desired product (200 mg, 71%) as a white solid: mp 110–111 °C, $[\alpha]_D$=−5.7 (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.22 (m, 17H), 6.93 (d, J=8.7 Hz, 2H), 6.18 (s, 2H), 4.98 (s, 2H), 4.92 (s, 2H), 4.90 (s, 2H), 4.87 (d, J=4.4 Hz, 1H), 4.16 (bs, 1H), 2.95 (A of ABt, J=17.4, 1.8 Hz, 1H), 2.87 (B of ABt, J=17.4, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 158.7, 158.5, 158.2, 155.3, 136.9, 136.8, 130.5, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 127.4, 127.1, 114.8, 100.9, 94.6, 93.9, 78.3, 70.0, 69.9, 69.8, 66.2, 28.3; HRMS (ESI) calcd for $C_{36}H_{33}O_5$ (M+H) 545.2328, found 545.2320.

3.1.9. (−)-*epi*Afzelechin ((−)-2). The compound was prepared following the synthetic method of (+)-afzelechin with (−)-**13** as the starting marterial. The yield was 82%; mp 196–198 °C; $[\alpha]_D$=−59 (c=3, Me_2CO); lit. $[\alpha]_D$=−58.9 (c=3, EtOH);[15] ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (A of AB, J=8.6 Hz, 2H), 6.91 (B of AB, J=8.6 Hz, 2H), 6.12 (d, J=2.3 Hz, 1H), 6.02 (d, J=2.3 Hz, 1H), 5.00 (bs, 1H), 4.32 (bs, 1H), 2.95 (A of ABt, J=16.6, 4.5 Hz, 1H), 2.77 (B of ABt, J=16.6, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 150.4, 150.2, 150.0, 124.2, 122.8, 122.3, 108.8, 106.3, 93.2, 93.1, 89.5, 88.8, 72.4, 59.8, 21.7; HRMS (ESI) calcd for $C_{15}H_{15}O_5$ (M+H) 275.0919, found 275.0932.

3.1.10. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)-chroman-3-yl 3,4,5-tris(benzyloxy)benzoate ((−)-14)). Following the preparation procedure for (+)-**10**, compound (−)-**14** was synthesized with (−)-**13** as starting material. The yield was 82%; mp 134–135 °C; $[\alpha]_D$=−51.3 (c=1.0, CH_3Cl); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.25 (m, 32H), 6.85 (d, J=8.7 Hz, 2H), 6.37 (d, J=2.2 Hz, 1H), 6.30 (d, J=2.2 Hz, 1H), 5.5 (bs, 1H), 5.10 (d, J=4.9 Hz, 1H), 5.08 (s, 2H), 5.03 (s, 2H), 5.02 (s, 2H), 5.01 (s, 2H), 4.99 (s, 2H), 4.97 (s, 2H), 3.08 (bs, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 165.1, 158.7, 158.4, 157.9, 155.6, 152.1, 142.1, 137.8, 136.8, 136.7, 136.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 124.9, 114.5, 108.9, 100.8, 94.5, 93.7, 77.3, 75.0, 70.8, 70.0, 69.8, 68.7, 25.9; HRMS (ESI) calcd for $C_{64}H_{55}O_9$ (M+H) 967.3846, found 967.3862.

3.1.11. (−)-*epi*Afzelechin gallate ((−)-15). The compound was prepared following the synthetic method of (+)-afzelechin gallate with (−)-**14** as the starting material. The yield was 80%; mp 242–244 °C (decompose); $[\alpha]_D$=−177 (c=0.9, Me_2CO); lit. −181.9 (c=0.9, Me_2CO);[15] ^1H NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 7.49 (A of AB, J=8.6 Hz, 2H), 7.13 (s, 2H), 6.92 (B of AB, J=8.6 Hz, 2H), 6.16 (d, J=2.2 Hz, 1H), 6.12 (d, J=2.2 Hz, 1H), 5.56 (bs, 1H), 5.25 (bs, 1H), 3.16 (A of ABt, J=17.4, 4.5 Hz, 1H), 3.02 (B of AB, J=17.4 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 160.3, 151.0, 150.7, 150.2, 139.3, 132.6, 123.6, 122.3, 114.5, 109.1, 103.4, 92.2, 89.9, 89.0, 71.4, 63.3, 19.9; HRMS (ESI) calcd for $C_{22}H_{19}O_9$ (M+H) 427.1029, found 427.1045.

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