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Regiospecific and enantioselective synthesis of methylated metabolites of tea catechins

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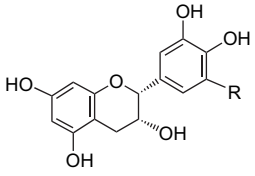
Abstract—The regiospecific and enantioselective syntheses of various methylated regioisomers of *epi*catechin gallate (EGC) and *epi*gallocatechin gallate (EGCG) have been achieved.

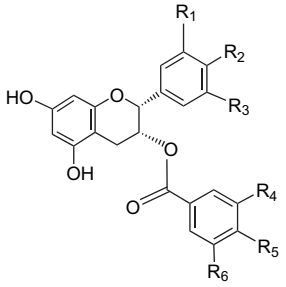
1. Introduction

Tea, produced from the plant *Camellia sinensis*, has been consumed by humans for thousands of years. It is one of the most popular beverages worldwide, second to water. Tea catechins, which are polyphenols, constitute about 30–40% of the water-soluble compounds in brewed green tea. The major tea catechins are: (−)-*epi*catechin (**1**, EC), (−)-*epi*gallocatechin (**2**, EGC), (−)-*epi*catechin gallate (**3**, ECG), and (−)-*epi*gallocatechin gallate (**4**, EGCG).[1] Of these, EGCG is by far the most abundant and has been reported to have various biological activities, which may account for the beneficial effects attributed to green tea.[2,3]

Recently, the metabolic transformations of tea catechins have been investigated. Catechins were found to be substrates of human catechol-*O*-methyltransferase (COMT). In humans, 4′-*O*-methyl-EGC[4] and 4′,4″-di-*O*-methyl-EGCG (**12**)[5] were detected after green tea and catechin consumption. In rats, 4′-*O*-methyl-EGCG (**11**), 4″-*O*-methyl-EGCG (**9**), 3′-*O*-methyl-EGCG, 3″-*O*-methyl-EGCG (**8**), and 4′,4″-dimethyl-EGCG (**12**) were found to be the biliary metabolites of EGCG.[6] Indeed, some of these methylated catechins have been found as minor components in tea infusions.[7] Methylated EGCG has been shown to inhibit type I allergic reactions in mice.[7a,8]



1: R=H, EC
2: R=OH, EGC



3: R_1=H, R_2=R_3=R_4=R_5=R_6=OH; ECG
4: R_1=R_2=R_3=R_4=R_5=R_6=OH; EGCG
5: R_3=H, R_1=R_2=R_4=R_5=OH, R_6=OMe
6: R_3=H, R_1=R_2=R_4=R_6=OH, R_5=OMe
7: R_3=H, R_1=R_2=R_4=OH, R_5=R_6=OMe
8: R_1=R_2=R_3=R_4=R_5=OH, R_6=OMe
9: R_1=R_2=R_3=R_4=R_6=OH, R_5=OMe
10: R_1=R_2=R_3=R_4=OH, R_5=R_6=OMe
11: R_1=R_3=R_4=R_5=R_6=OH, R_2=OMe
12: R_1=R_3=R_4=R_6=OH, R_2=R_5=OMe
13: R_1=R_3=R_4=OH, R_2=R_5=R_6=OMe

Biomethylation of catechins may play a significant role in affecting the biological effects of tea. Recently, it has been reported that among women who carried at least one low activity *COMT* allele, tea drinkers showed a significantly reduced risk of breast cancer compared with nontea drinkers. In contrast, risk of breast cancer did not differ between tea drinkers and nontea drinkers among those who were homozygous for the high activity *COMT* allele.[9] These data suggest that methylation of catechins may reduce the cancer protecting activities of tea polyphenols. EGCG is known to inhibit *COMT*[10] as well as DNA methyltransferase.[11]

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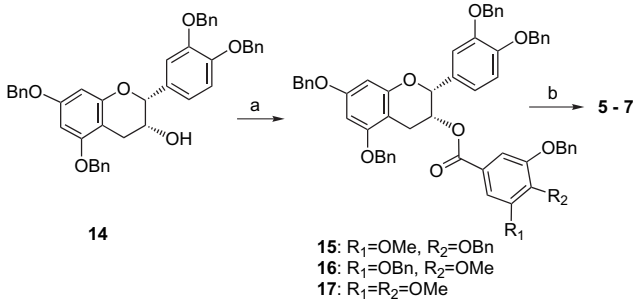
Because of our interest in the synthesis of EGCG[12] and its role as proteasome inhibitors in cancer protection,[13] we became interested in the synthesis of various methylated metabolites of catechins. Previously, (−)-EGCG had been methylated in a nonregiospecific manner to give a mixture of 4″-methyl-EGCG (**9**), 4′,4″-dimethyl-EGCG (**12**), and 4′,3″,4″-trimethyl-EGCG (**13**).[5] Herein, we report a regiospecific and enantioselective synthesis of the various methylated ECG and EGCG (**5**–**13**).

2. Results and discussion

2.1. Syntheses of compounds 5–7

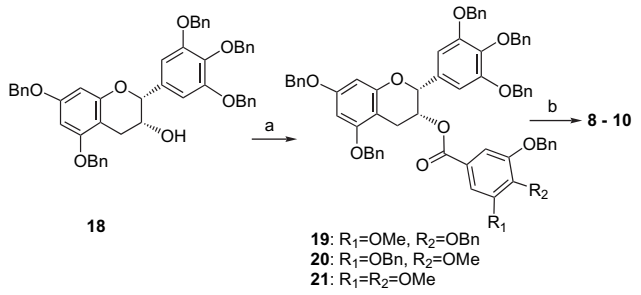
Previously, we had reported on the enantioselective synthesis of the benzylated *epi*catechin **14** [(−)-(2*R*,3*R*)-5,7-Bis(benzyloxy)-2-[3,4-bis(benzyloxy)phenyl]-chroman-3-ol].[12b] The same compound **14** can be obtained by the direct benzylation of (−)-*epi*catechin isolated from nature.[14] Acylation of **14** with 3,4-bis(benzyloxy)-5-methoxybenzoyl chloride, 3,5-bis(benzyloxy)-4-methoxybenzoyl chloride or 3-benzyloxy-4,5-dimethoxybenzoyl chloride gave the protected esters **15**–**17**, respectively. Hydrogenolysis of **15**–**17** afforded compounds **5**–**7** in good yields (Scheme 1). The synthetic compounds **5** and **6** have optical rotations and spectroscopic data similar to those reported for the natural products.[7]



Scheme 1. (a) Acid chloride/DMAP in CH_2Cl_2, rt; (b) H_2/Pd(OH)$_2$/MeOH/THF.

2.2. Syntheses of compounds 8–10

Compounds **8**–**10** were prepared from the perbenzylated *epi*-gallocatechin **18**[12a] according to the same acylation and hydrogenolysis sequence (Scheme 2). Compound **8** showed the same optical rotation and spectroscopic data as the natural compound.[6] Compound **9** had been previously synthesized,



Scheme 2. (a) Acid chloride/DMAP in CH_2Cl_2, rt; (b) H_2/Pd(OH)$_2$/MeOH/THF.

but only characterized by its ^{1}H NMR spectrum.[5] With both compounds **8** and **9** at hand, we have assigned their regiochemistry unambiguously by the synthesis.

2.3. Syntheses of compounds 11–13

In order to obtain the methylated compounds **11**–**13**, a total synthesis starting from a properly protected B-ring precursor is used (Scheme 3). 3,5-Bis(benzyloxy)-4-methoxybenzaldehyde (**22**) was converted to the cinnamyl alcohol **24** via a Wittig–Horner reaction followed by DIBAL reduction. Friedel–Craft alkylation of 3,5-dibenzyloxyphenol (**25**) with **24** gave the alkylation product **26**. Compound **26** was first protected as the *tert*-butyldimethylsilyl ether and then dihydroxylated with the Sharpless asymmetric dihydroxylation protocol followed by desilylation to give the optically active diol **27**. The (+)-(1*S*,2*S*)-diol **27** was obtained from AD-mix α in agreement with our previous observation that similar enantioselectivity was obtained in EGCG synthesis.[12a] Cyclization of **27** under the orthoformate/acidic conditions followed by base hydrolysis gave the protected flavan-3-ol **28**. The trans stereochemistry of **28** was evident from its ^{1}H NMR spectrum. Compound **28** was then oxidized by Dess–Martin periodinane to the corresponding ketone **29**. Reduction of the carbonyl function in **29** with L-Selectride at −78 °C gave exclusively the cis-substituted compound **30**. The stereochemistry of **30** was also evident from its ^{1}H NMR where the coupling of H-2 and H-3 hydrogens is distinctly different from that of compound **28**. Esterification of **30** with 3,4-bis(benzyloxy)-5-methoxybenzoyl chloride, 3,5-bis(benzyloxy)-4-methoxybenzoyl chloride or 3-benzyloxy-4,5-dimethoxybenzoyl chloride gave the protected esters **31**–**33**, respectively. Hydrogenolysis of **31**–**33** afforded the methylated compounds **11**–**13**. The spectroscopic data of compounds **11**–**13** are in agreement with those reported previously for the metabolites.[5,6]

The structure–activity relationships (SARs) of these methylated metabolites of tea catechins were also examined as a function of inhibition of a purified 20S proteasome. We found that addition of a methyl group to the B- and/or D-ring led to diminished proteasome-inhibitory activity in vitro and that as the number of methyl groups increased on these catechin molecules, their effectiveness as proteasome inhibitors decreased.[15]

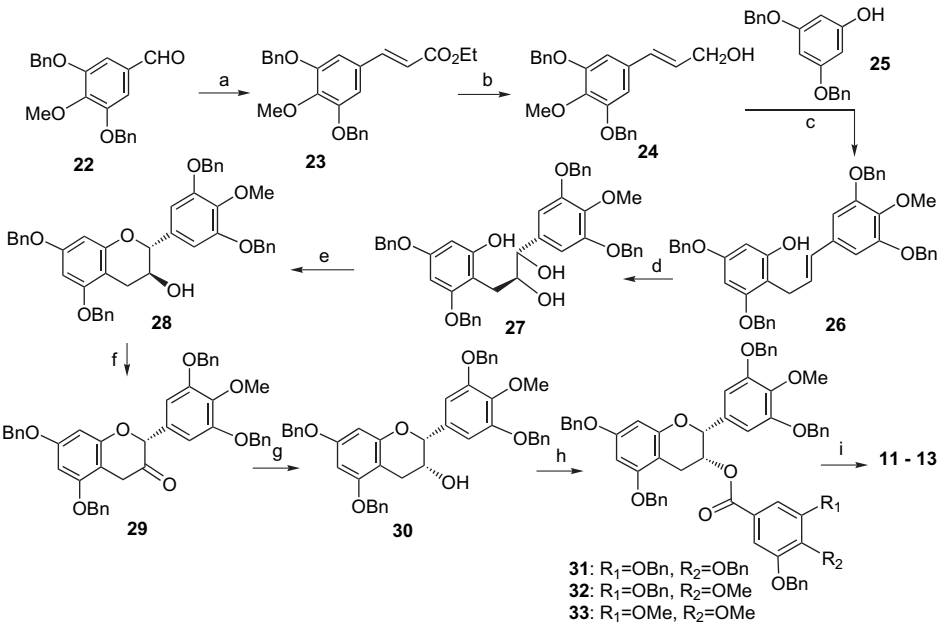
3. Conclusion

We have synthesized nine different methylated catechins, which are metabolites or potential metabolites of tea catechins in biomethylation. The synthesis is regiospecific and enantioselective. These compounds will allow us to evaluate the role of biomethylation in affecting the biological effects of tea consumption.

4. Experimental

4.1. General

The starting materials and reagents, purchased commercially, were used without further purification. Literature



Scheme 3. (a) Triethyl phosphonoacetate/NaH/THF, 0 °C–rt; (b) DIBAL/THF, −78 °C–rt; (c) $H_2SO_4/SiO_2/CH_2Cl_2$, rt; (d) (i) TBSCl/imidazole/DMF, rt; (ii) AD-mix α/$CH_3SO_2NH_2/H_2O$/*t*-BuOH/CH_2Cl_2, 0 °C; (iii) TBAF/THF, rt; (e) (i) $CH(OEt)_3$/PPTS/CH_2Cl_2, 60 °C; (ii) K_2CO_3/MeOH/DME, rt; (f) Dess–Martin periodinane/CH_2Cl_2, rt; (g) L-Selectride/THF, −78 °C; (h) acid chloride/DMAP/CH_2Cl_2, rt; (i) H_2/Pd(OH)$_2$/MeOH/THF.

procedures were used for the preparation of 3,5-bis(benzyloxy)phenol,[16] 3,4,5-tris(benzyloxy)benzoic acid,[9] silica gel supported H_2SO_4,[12a] and 3,5-bis(benzyloxy)-4-methoxybenzaldehyde.[17]

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. ^1H and ^{13}C NMR (400 MHz) spectra were measured with TMS as internal standard when $CDCl_3$ and acetone-d_6 were used as solvent. High-resolution electrospray ionization (ESI) mass spectra were recorded using a QTOF-2 Micromass spectrometer.

4.2. Ethyl-(*E*)-3,5-bis(benzyloxy)-4-methoxycinnamate (23)

3,5-Bis(benzyloxy)-4-methoxybenzaldehyde (**22**, 3.48 g, 10.0 mmol) was dissolved in dry THF (100 mL) under a nitrogen atmosphere and cooled in an ice bath. To this solution triethyl phosphonoacetate (3.3 g, 15.0 mmol) was added. Sodium hydride (0.48 g, 60% dispersion in mineral oil, 12.0 mmol) was then added in five batches. The mixture was allowed to be stirred at rt for 2 h. Saturated aqueous $NaHCO_3$ solution was added. The organic phase was separated, and the aqueous layer was extracted with EtOAc. The organic phases were combined, dried ($MgSO_4$), and evaporated to afford a solid. The solid was washed with hexane to remove the mineral oil to yield ethyl-(*E*)-3,5-bis(benzyloxy)-4-methoxycinnamate (3.76 g, 90.0% yield): mp 80–82 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (A of AB, J=15.9 Hz, 1H), 7.42–7.25 (m, 10H), 6.77 (s, 2H), 6.26 (B of AB, J=15.9 Hz, 1H), 5.07 (s, 4H), 4.21 (q, J=7.1 Hz, 2H), 3.89 (s, 3H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 166.6, 152.4, 144.2, 141.2, 136.5, 129.5, 128.3, 127.7, 127.0, 117.2, 107.5, 70.8, 60.7, 60.2, 14.1; HRMS (ESI): calcd for $C_{26}H_{26}O_5Na$ (M+Na) 441.1678, found 441.1697.

4.3. (*E*)-3,5-Bis(benzyloxy)-4-methoxycinnamyl alcohol (24)

To a solution of ethyl-(*E*)-3,5-bis(benzyloxy)-4-methoxycinnamate (**23**, 5.0 g, 11.9 mmol) in dry THF (100 mL) at −78 °C under a nitrogen atmosphere, DIBAL (18 mL, 1 M solution in hexane, 18.0 mmol) was added dropwise. The mixture was stirred at −78 °C for 1 h and then at rt for another 1 h. The mixture was cooled to 0 °C and poured into a stirred mixture of hexane (150 mL) and saturated aqueous Na_2SO_4 solution (5 mL). The resulting mixture was stirred until a large quantity of solid was formed. The mixture was filtered, and the solid was thoroughly washed with EtOAc. The organic solutions were combined and dried ($MgSO_4$). The residue after evaporation of the solvent was washed again with hexane, and the solid was collected and recrystallized in EtOAc and hexane to afford (*E*)-3,5-bis-(benzyloxy)-4-methoxycinnamyl alcohol (4.1 g, 91% yield): mp 99–101 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.27 (m, 10H), 6.62 (s, 2H), 6.39 (A of AB, J=15.8 Hz, 1H), 6.13 (B of ABt, J=15.8, 5.6 Hz, 1H), 5.08 (s, 4H), 4.21 (d, J=5.6 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 152.4, 139.1, 136.9, 132.2, 130.5, 128.4, 128.0, 127.7, 127.1, 106.1, 71.0, 63.3, 60.9; HRMS (ESI): calcd for $C_{24}H_{24}O_4Na$ (M+Na) 399.1572, found 399.1554.

4.4. (*E*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-[3,5-bis(benzyloxy)-4-methoxyphenyl]propene (26)

At rt under a N_2 atmosphere, 25% H_2SO_4/SiO_2 (1.6 g, 4 mmol) was added in one batch to a stirred mixture of

3,5-bis(benzyloxy)phenol (3.06 g, 10 mmol) and (*E*)-3,4-bis(benzyloxy)cinnamyl alcohol (3.76 g, 10 mmol) in dry CH_2Cl_2 (100 mL). The resulting mixture was stirred at rt overnight. After filtration and evaporation, the residue was purified by column chromatography on silica gel (benzene) to afford the desired compound as white solid (3.0 g, 45.1% yield): mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.27 (m, 20H), 6.59 (s, 2H), 6.32 (A of AB, J=15.8 Hz, 1H), 6.26 (d, J=2.0 Hz, 1H), 6.16 (d, J=2.0, 1H), 6.16–6.12 (B of ABt, m, 1H), 5.29 (br s, 1H), 5.07 (s, 4H), 5.01 (s, 2H), 4.96 (s, 2H), 3.85 (s, 3H), 3.54 (d, J=6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.6, 157.9, 155.5, 152.5, 138.6, 137.1, 137.0, 136.8, 133.1, 129.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.5, 127.4, 127.2, 127.1, 106.9, 105.8, 95.0, 93.4, 71.0, 70.2, 70.0, 60.9, 26.2; HRMS (ESI): calcd for $C_{44}H_{40}O_6Na$ (M+Na) 687.2723, found 687.2697.

4.5. (+)-(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-[3′,4′-bis(benzyloxy)-4′-methoxyphenyl]propane-1,2-diol ((+)-27)

The propene **26** (3.0 g, 4.5 mmol) was dissolved in dry DMF (30 mL), and to this solution imidazole (1.0 g, 14.7 mmol) and TBSCl (1.1 g, 7.2 mmol) 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 chromatography on silica gel (*n*-hexane/EtOAc, 6/1 v/v) to afford [3,5-bis(benzyloxy)]-2-[3′-[3″,5″-bis(benzyloxy)-4″-methoxyphenyl]allyl]phenoxy-*tert*-butyldimethylsilane (3.1 g). This material was used in the next step without further purification.

AD-mix α (12.8 g) and methanesulfonamide (0.85 g) were dissolved in a solvent mixture of *t*-BuOH (60 mL) and H_2O (60 mL). The resulting mixture was stirred at rt for 5 mm, then the mixture was cooled to 0 °C, and a solution of [3,5-bis(benzyloxy)-2-[3′-[3″,5″-bis(benzyloxy)-4″-methoxyphenyl]allyl]phenoxy-*tert*-butyldimethylsilane (3.1 g) in dichloromethane (60 mL) was added. After the mixture had been stirred overnight, a total of four batches of AD-mix α (6.4 g each) and methanesulfonamide (0.43 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% aqueous $Na_2S_2O_3$ 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 purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 4/1 v/v). The product was redissolved in THF (30 mL) and then TBAF (10 mL, 1 M in THF) was added. The resulting mixture was stirred at rt for 4 h, and saturated $NaHCO_3$ solution was added. The mixture was extracted with EtOAc and the organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAc/CH_3Cl) and then recrystallized in EtOAc to give a white solid (2.2 g, 69.7% yield): mp 125–127 °C; $[\alpha]_D$ +7.0 (*c* 3, CH_3Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.14 (m, 20H), 6.57 (s, 2H), 6.26 (d, J=2.1 Hz, 1H), 6.21 (d, J=2.1 Hz, 1H), 4.97 (s, 2H), 4.96 (s, 2H), 4.93 (s, 2H), 4.87 (s, 2H), 4.39 (d, J=5.6 Hz, 1H), 3.90–3.85 (m, 1H), 3.81 (s, 3H), 2.89 (A of AB, J=14.6, 3.6 Hz, 1H), 2.73 (B of AB, J=14.6, 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.9, 157.7, 157.1, 152.2, 138.6, 136.8, 136.7, 136.1, 128.5, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 127.2, 127.0, 126.9, 126.4, 105.1, 95.7, 93.3, 76.4, 70.8, 69.9, 60.7, 26.6; HRMS (ESI): calcd for $C_{44}H_{42}O_8Na$ (M+Na) 721.2777, found 721.2759.

4.6. (+)-(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-ol ((+)-28)

To a suspension of compound (+)-**27** (3.0 g, 4.3 mmol) in 1,2-dichloroethane (50 mL) was added triethyl orthoformate (2 mL), followed by PPTS (500 mg, 2.0 mmol). The mixture was stirred at rt for 20 min and the solid was dissolved. The mixture was heated to 50 °C for 5 h until TLC showed the reaction had been completed. After evaporation of the solvent, the residue was redissolved in DME (30 mL) and MeOH (30 mL), K_2CO_3 (600 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 (2.1 g, 71.8% yield): mp 123–125 °C; $[\alpha]_D$ +5.5 (*c* 7.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.23 (m, 20H), 6.67 (s, 2H), 6.26 (s, 1H), 6.20 (s, 1H), 5.05 (s, 2H), 5.04 (s, 2H), 4.97 (s, 2H), 4.95 (s, 2H), 4.54 (d, J=8.1 Hz, 1H), 3.90–3.86 (m, 1H), 3.85 (s, 3H), 3.05 (A of ABq, J=16.4, 5.4 Hz, 1H), 2.61 (B of ABq, J=16.4, 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.6, 157.6, 155.0, 152.4, 139.2, 136.7, 133.2, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 127.0, 126.9, 106.5, 102.1, 94.2, 93.7, 81.6, 70.8, 69.9, 69.7, 67.8, 60.7, 27.4; HRMS (ESI): calcd for $C_{44}H_{40}O_7Na$ (M+Na) 703.2672, found 703.2684.

4.7. (+)-(2*R*)-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-one ((+)-29)

Dess–Martin periodinane (19.7 mL, 15% g/mL in CH_2Cl_2, 4.6 mmol) was added in one batch to a stirred solution of (+)-**28** (2.1 g, 3.1 mmol) in CH_2Cl_2 (30 mL) under a 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 (40 mL) and 10% aqueous $Na_2S_2O_3$ solution (40 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 (1.8 g, 85.7%): mp 149–151 °C; $[\alpha]_D$ +20.2 (*c* 7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.23 (m, 20H), 6.63 (s, 2H), 6.35 (d, J=0.6 Hz, 1H), 6.33 (d, J=0.6 Hz, 1H), 5.18 (s, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 4.98 (s, 2H), 4.97 (s, 2H), 3.84 (s, 3H), 3.58–3.35 (AB, J=21.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 204.4, 159.3, 156.9, 154.1, 152.5, 139.3, 136.7, 136.4, 136.2, 130.0, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.3, 127.2, 127.0, 106.0, 101.6, 95.5, 94.8, 82.8, 70.8, 70.0, 69.9, 60.7, 33.3; HRMS (ESI): calcd for $C_{44}H_{39}O_7$ (M+H) 679.2696, found 679.2700.

4.8. (−)-(2*R*,3*R*)-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-ol ((−)-30)

Under a N_2 atmosphere, the ketone (+)-**29** (1.8 g, 2.6 mmol) was dissolved in dry THF (30 mL), and the solution was cooled to −78 °C. Then L-Selectride (4.0 mL, 1 M solution in THF, 4.0 mmol) was added dropwise. The resulting solution was stirred at −78 °C overnight. When TLC showed the reaction was completed, saturated aqueous $NaHCO_3$ solution (30 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 chromatography on silica gel (EtOAc/hexane, 1/3 v/v) and then recrystallized with EtOAc and *n*-hexane to afford the desired product (1.6 g, 88.8%) as a white solid: mp 107–109 °C; $[\alpha]_D$ −21.2 (*c* 4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.26 (m, 20H), 6.76 (s, 2H), 6.26 (s, 2H), 5.11 (s, 4H), 4.98 (s, 4H), 4.81 (s, 1H), 4.13 (br s, 1H), 3.88 (s, 3H), 2.96 (A of AB, *J*=17.1 Hz, 1H), 2.87 (B of ABq, *J*=17.1, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.6, 158.1, 155.0, 152.5, 139.1, 136.9, 136.8, 136.7, 133.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.4, 127.3, 127.2, 127.0, 126.9, 106.0, 100.8, 94.5, 93.9, 78.3, 70.9, 69.9, 69.7, 66.1, 60.7, 27.9; HRMS (ESI): calcd for $C_{44}H_{40}O_7Na$ (M+Na) 703.2672, found 703.2659.

4.9. (−)-(2*R*,3*R*)-5,7-Bis(benzyloxy)-2-[3,4-bis(benzyloxy)-phenyl]chroman-3-yl-3,4-dibenzyloxy-5-methoxybenzoate ((−)-15)

Under a N_2 atmosphere, a solution of 3,4-dibenzyloxy-5-methoxybenzoic acid (246 mg, 0.67 mmol) was refluxed with oxalyl (1 mL) in dry CH_2Cl_2 (10 mL) and one drop of DMF for 3 h. The excess oxally chloride and solvent were removed by distillation and the residue was dried under vacuum for 3 h and dissolved in CH_2Cl_2 (2 mL). This solution was added dropwise to a solution of (−)-**14** (220 mg, 0.34 mmol)[12b] and DMAP (75 mg, 0.62 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at rt overnight, then saturated aqueous $NaHCO_3$ 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 (*n*-hexane/EtOAc, 3/1 v/v) to afford the desired compound (300 mg, 88.9% yield). Recrystallization in $CHCl_3$ and ether gave a white powder: mp 129–131 °C; $[\alpha]_D$ −37.5 (*c* 2.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.26 (m, 30H), 7.22 (s, 1H), 7.16 (s, 1H), 6.88 (AB, *J*=8.2 Hz, 2H), 6.34 (s, 1H), 6.30 (s, 1H), 5.60 (br s, 1H), 5.08 (s, 4H), 5.01 (s, 6H), 4.97 (s, 2H), 4.77 (AB, *J*=11.7 Hz, 2H), 3.76 (s, 3H), 3.08 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.9, 158.6, 157.8, 155.5, 153.2, 151.9, 148.7, 141.7, 137.2, 136.9, 136.8, 136.7, 136.6, 136.3, 130.9, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.2, 127.0, 124.9, 119.8, 114.4, 113.5, 108.6, 107.1, 100.7, 94.4, 77.3, 74.8, 71.1, 70.9, 70.7, 69.9, 69.7, 56.0, 25.8; HRMS (ESI): calcd for $C_{65}H_{56}O_{10}Na$ (M+Na) 1019.3771, found 1019.3782.

4.10. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′-bis-(benzyloxy)phenyl]chroman-3-yl-3″,5″-bis(benzyloxy)-4″-methoxybenzoate (16)

Following the procedure for the preparation of **15**, the esterification of (−)-**14** with 3,5-dibenzyloxy-4-methoxybenzoic acid gave the product **16** (86% yield): mp 126–128 °C; $[\alpha]_D$ −76.5 (*c* 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.21 (m, 31H), 7.00 (d, *J*=1.8 Hz, 1H), 6.86 (A of ABq, *J*=8.3, 1.6 Hz, 1H), 6.81 (B of AB, *J*=8.3 Hz, 1H), 6.37 (d, *J*=2.0 Hz, 1H), 6.32 (d, *J*=2.0 Hz, 1H), 5.60 (br s, 1H), 5.10–4.98 (m, 12H), 4.61 (AB, *J*=11.6 Hz, 2H), 3.83 (s, 3H), 3.12 (A of ABq, *J*=17.7, 4.4 Hz, 1H), 3.05 (B of AB, *J*=17.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.8, 158.7, 157.9, 155.6, 151.9, 148.9, 148.8, 143.5, 137.1, 136.9, 136.7, 136.4, 130.9, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 124.6, 119.9, 114.6, 113.5, 109.1, 100.8, 94.5, 93.8, 77.6, 77.2, 71.1, 71.0, 70.9, 70.1, 69.9, 68.4, 60.8, 26.1; HRMS (ESI): calcd for $C_{65}H_{57}O_{10}$ (M+H) 997.3952, found 997.3923.

4.11. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′-bis-(benzyloxy)phenyl]chroman3-yl-3″-benzyloxy-4″, 5″-dimethoxybenzoate (17)

Following the procedure for the preparation of **15**, the esterification of (−)-**14** with 3-benzyloxy-4,5-dimethoxybenzoic acid gave the product **17** (83% yield): mp 72–74 °C; $[\alpha]_D$ −72.0 (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.25 (m, 25H), 7.16 (s, 1H), 7.06 (s, 1H), 6.88 (AB, *J*=8.3 Hz, 2H), 6.36 (s, 1H), 6.31 (s, 1H), 5.61 (br s, 1H), 5.08–5.00 (m, 10H), 4.75 (AB, *J*=11.6 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.09 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 165.0, 158.8, 157.9, 155.6, 153.0, 151.6, 148.9, 148.8, 142.8, 137.1, 136.9, 136.8, 136.4, 131.0, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 124.8, 120.0, 114.6, 113.6, 108.8, 107.1, 100.8, 94.5, 93.8, 77.5, 71.2, 71.1, 70.8, 70.1, 69.9, 68.6, 60.8, 56.1, 26.0; HRMS (ESI): calcd for $C_{59}H_{53}O_{10}$ (M+H) 921.3639, found 921.3677.

4.12. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′,5′-tris-(benzyloxy)phenyl]chroman-3-yl-3″,4″-bis(benzyloxy)-5″-methoxybenzoate (19)

Following the procedure for the preparation of **15**, the esterification of (−)-**18**[12a] with 3,4-dibenzyloxy-5-methoxybenzoic acid gave the product **19** (82% yield): mp 120–121 °C; $[\alpha]_D$ −41.7 (*c* 2.3, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.25 (m, 35H), 7.20 (s, 2H), 6.75 (s, 2H), 6.37 (s, 1H), 6.32 (s, 1H), 5.65 (br s, 1H), 5.03–4.96 (m, 9H), 4.90 (s, 2H), 4.78 (AB, *J*=11.5 Hz, 4H), 3.74 (s, 3H), 3.09 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.8, 158.7, 157.8, 155.5, 153.3, 152.7, 152.0, 141.9, 138.3, 137.6, 137.3, 136.8, 136.7, 136.6, 136.2, 133.2, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.1, 124.9, 108.7, 107.3, 106.4, 100.8, 94.5, 93.8, 77.7, 75.0, 74.8, 71.1, 70.9, 70.0, 69.9, 68.3, 56.1, 26.0; HRMS (ESI): calcd for $C_{72}H_{62}O_{11}Na$ (M+Na) 1125.4190, found 1125.4204.

4.13. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′,5′-tris(benzyloxy)phenyl]chroman-3-yl-3″,5″-bis(benzyloxy)-4″-methoxybenzoate (20)

Following the procedure for the preparation of **15**, the esterification of (−)-**18** with 3,5-dibenzyloxy-4-methoxybenzoic acid gave the product **20** (87% yield): mp 49–51 °C; $[\alpha]_D$ −54.7 (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.20 (m, 37H), 6.70 (s, 2H), 6.40 (s, 1H), 6.34 (s, 1H), 5.65 (br s, 1H), 5.04–4.94 (m, 11H), 4.67 (AB, *J*=11.5 Hz, 4H), 3.77 (s, 3H), 3.11 (A of ABq, *J*=17.6, 4.2 Hz, 1H), 3.04 (B of AB, *J*=17.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.6, 158.8, 158.0, 155.6, 152.8, 152.0, 151.9, 147.1, 143.6, 138.3, 137.7, 136.8, 136.7, 136.3, 133.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.2, 124.6, 109.1, 106.6, 100.9, 77.9, 77.2, 75.0, 71.0, 70.9, 70.1, 69.9, 68.1, 60.8, 26.2; HRMS (ESI): calcd for $C_{72}H_{63}O_{11}$ (M+H) 1103.4370, found 1103.4425.

4.14. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′,5′-tris(benzyloxy)phenyl]chroman-3-yl-3″-benzyloxy-4″,5″-dimethoxybenzoate (21)

Following the procedure for the preparation of **15**, the esterification of (−)-**18** with 3-benzyloxy-4,5-dimethoxybenzoic acid gave the product **21** (82% yield): mp 57–59 °C; $[\alpha]_D$ −52.5 (*c* 2.5, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.41–7.21 (m, 32H), 6.74 (s, 2H), 6.38 (d, *J*=2.0 Hz, 1H), 6.32 (d, *J*=2.0 Hz, 1H), 5.65 (br s, 1H), 5.06–4.93 (m, 9H), 4.76 (AB, *J*=11.5 Hz, 4H), 3.76 (s, 6H), 3.10–3.09 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.8, 158.8, 158.0, 155.6, 153.1, 152.8, 151.7, 143.0, 138.4, 137.7, 136.8, 136.7, 136.3, 133.2, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 124.8, 108.9, 107.2, 106.7, 100.9, 94.6, 93.9, 77.8, 75.1, 71.3, 71.2, 70.9, 70.1, 69.9, 68.3, 60.8, 56.2, 26.1; HRMS (ESI): calcd for $C_{65}H_{59}O_{11}$ (M+H) 1027.4057, found 1027.4100.

4.15. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-yl-3″,4″,5″-tris(benzyloxy)benzoate (31)

Following the procedure for the preparation of **15**, the esterification of (−)-**30** with 3,4,5-tris(benzyloxy)benzoic acid gave the product **31** (88% yield): mp 57–59 °C; $[\alpha]_D$ −54.2 (*c* 5.0, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.38–7.23 (m, 37H), 6.70 (s, 2H), 6.38 (d, *J*=1.6 Hz, 1H), 6.33 (d, *J*=1.6 Hz, 1H), 5.64 (br s, 1H), 5.02–4.99 (m, 9H), 4.91 (s, 2H), 4.74 (AB, *J*=11.7 Hz, 4H), 3.80 (s, 3H), 3.08 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.7, 158.7, 157.9, 155.5, 152.5, 152.2, 142.6, 139.4, 137.3, 136.8, 136.6, 136.3, 132.9, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.3, 127.2, 127.1, 124.8, 109.0, 106.7, 100.8, 94.5, 93.9, 77.8, 74.9, 71.0, 70.9, 70.0, 69.8, 60.7, 26.1; HRMS (ESI): calcd for $C_{72}H_{62}O_{11}Na$ (M+Na) 1125.4190, found 1125.4181.

4.16. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-yl-3″,5″-bis(benzyloxy)-4″-methoxybenzoate (32)

Following the procedure for the preparation of **15**, the esterification of (−)-**30** with 3,5-dibenzyloxy-4-methoxybenzoic acid gave the product **32** (85% yield): mp 65–67 °C; $[\alpha]_D$ −49.8 (*c* 2.7, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.38–7.21 (m, 32H), 6.68 (s, 2H), 6.38 (s, 1H), 6.34 (s, 1H), 5.63 (br s, 1H), 5.04–4.98 (m, 9H), 4.70 (AB, *J*=11.7 Hz, 4H), 3.79 (s, 3H), 3.77 (s, 3H), 3.08–3.05 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.5, 158.7, 157.9, 155.5, 152.4, 151.8, 143.5, 139.3, 136.8, 136.6, 136.2, 132.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.3, 127.1, 127.0, 124.5, 109.0, 106.6, 100.8, 94.5, 93.8, 77.8, 70.9, 70.8, 70.0, 69.8, 68.0, 60.7, 26.1; HRMS (ESI): calcd for $C_{66}H_{59}O_{11}$ (M+H) 1027.4057, found 1027.4054.

4.17. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-yl-3″-benzyloxy-4″,5″-dimethoxybenzoate (33)

Following the procedure for the preparation of **15**, the esterification of (−)-**30** with 3-benzyloxy-4,5-dimethoxybenzoic acid gave the product **33** (86% yield): mp 51–53 °C; $[\alpha]_D$ −47.1 (*c* 3.5, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.38–7.21 (m, 26H), 7.17 (s, 1H), 6.72 (s, 2H), 6.35 (s, 1H), 6.32 (s, 1H), 5.63 (br s, 1H), 5.05–5.01 (m, 7H), 4.79 (AB, *J*=11.6 Hz, 4H), 3.81 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.08 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.7, 158.7, 157.8, 155.4, 153.0, 152.4, 151.6, 142.9, 139.4, 136.8, 136.6, 136.2, 132.9, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.3, 127.1, 127.0, 124.7, 108.8, 107.1, 106.7, 100.7, 94.4, 93.8, 77.6, 71.0, 70.8, 70.0, 69.8, 68.2, 60.7, 60.6, 56.1, 26.0; HRMS (ESI): calcd for $C_{60}H_{55}O_{11}$ (M+H) 951.3744, found 951.3757.

4.18. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′-dihydroxyphenyl)-chroman-3-yl-3″,4″-dihydroxy-5″-methoxybenzoate (5)

Under a H_2 atmosphere, $Pd(OH)_2/C$ (20%, 200 mg) was added to a solution of **15** (280 mg, 0.28 mmol) in a solvent mixture of THF/MeOH (1/1 v/v, 25 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 chromatography on silica gel (10% MeOH/CH_2Cl_2, then 20% MeOH/CH_2Cl_2) to afford **5** (100 mg, 80% yield): mp 248–250 °C (decomposed); $[\alpha]_D$ −167 (*c* 1, EtOH), lit. 168 (*c* 1, EtOH);[18] ^1H NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 7.22 (d, *J*=1.7 Hz, 1H), 7.18 (d, *J*=1.8 Hz, 1H), 7.11 (d, *J*=1.7 Hz, 1H), 7.02 (A of ABq, *J*=8.2, 1.8 Hz, 1H), 6.90 (B of AB, *J*=8.2 Hz, 1H), 6.14 (AB, *J*=2.0 Hz, 2H), 5.54 (br s, 1H), 5.22 (br s, 1H), 3.90 (s, 3H), 3.16 (A of ABq, *J*=17.3, 4.1 Hz, 1H), 3.04 (B of AB, *J*=17.3 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 166.9, 157.3, 157.2, 156.7, 148.6, 145.5, 145.3, 145.2, 140.1, 131.0, 120.9, 118.9, 115.9, 114.8, 111.6, 105.9, 98.7, 96.4, 95.5, 77.8, 70.3, 56.6, 26.3; HRMS (ESI): calcd for $C_{23}H_{20}O_{10}Na$ (M+Na) 479.0954, found 479.0960.

4.19. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′-dihydroxyphenyl)-chroman-3-yl-3″,5″-dihydroxy-4″-methoxybenzoate (6)

Following the preparation procedure for **5**, the hydrogenolysis of **16** afforded **6** (88% yield): mp 248–250 °C

(decomposed); $[\alpha]_D$ −161.3 (*c* 4.0, Me_2CO), lit. 160.1 (*c* 1.1, Me_2CO);[18] ^1H NMR (acetone-d_6, 400 MHz): δ 7.25 (d, *J*=1.8 Hz, 1H), 7.17 (s, 2H), 7.07 (A of ABq, *J*=8.2, 1.8 Hz, 1H), 6.95 (B of AB, *J*=8.2 Hz, 1H), 6.24 (d, *J*=2.2 Hz, 1H), 6.22 (d, *J*=2.2 Hz, 1H), 5.73 (br s, 1H), 5.31 (br s, 1H), 3.98 (s, 3H), 3.23 (A of ABq, *J*=17.4, 4.5 Hz, 1H), 3.11 (B of ABq, *J*=17.4, 1.8 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 163.5, 155.4, 155.1, 154.7, 148.8, 143.2, 143.1, 138.1, 129.0, 124.1, 116.8, 113.4, 112.5, 107.6, 96.6, 94.2, 93.5, 75.6, 67.5, 58.3, 24.2; HRMS (ESI): calcd for $C_{23}H_{20}O_{10}Na$ (M+Na) 479.0954, found 479.0965.

4.20. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′-dihydroxyphenyl)-chroman-3-yl-3″-hydroxy-4″,5″-dimethoxybenzoate (7)

Following the preparation procedure for **5**, the hydrogenolysis of **17** afforded **7** (86% yield): mp 239–241 °C (decomposed); $[\alpha]_D$ −135.9 (*c* 4.0, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.25 (AB, *J*=1.9 Hz, 2H), 7.18 (d, *J*=1.9 Hz, 1H), 7.07 (A of ABq, *J*=8.2, 1.9 Hz, 1H), 6.94 (B of AB, *J*=8.2 Hz, 1H), 6.20 (AB, *J*=2.2 Hz, 2H), 5.70–5.68 (m, 1H), 5.34 (br s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.23 (A of ABq, *J*=17.5, 4.4 Hz, 1H), 3.15 (B of ABq, *J*=17.5, 2.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.6, 156.6, 156.2, 155.7, 152.5, 149.8, 144.4, 144.2, 140.2, 130.1, 125.1, 117.7, 114.4, 113.5, 110.0, 104.6, 97.5, 95.2, 94.4, 76.6, 68.9, 55.0, 25.1; HRMS (ESI): calcd for $C_{24}H_{22}O_{10}Na$ (M+Na) 493.1111, found 493.1107.

4.21. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′,5′-trihydroxyphenyl)chroman-3-yl-3″,4″-dihydroxy-5″-methoxybenzoate (8)

Following the preparation procedure for **5**, the hydrogenolysis of **19** afforded **8** (83% yield): mp 221–223 °C (decomposed); $[\alpha]_D$ −160 (*c* 1, EtOH), lit. 162 (*c* 1, EtOH);[18] ^1H NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 7.17 (d, *J*=1.9 Hz, 1H), 7.07 (d, *J*=1.9 Hz, 1H), 6.71 (s, 2H), 6.09 (AB, *J*=2.2 Hz, 2H), 5.47 (br s, 1H), 5.10 (br s, 1H), 3.85 (s, 3H), 3.07 (A of ABq, *J*=17.4, 4.3 Hz, 1H), 3.01 (B of AB, *J*=17.4 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 167.0, 157.3, 157.2, 156.6, 148.6, 146.2, 145.5, 140.1, 133.0, 130.6, 121.0, 111.6, 106.5, 106.0, 98.7, 96.4, 95.5, 77.8, 70.5, 56.6, 26.3; HRMS (ESI): calcd for $C_{23}H_{20}O_{11}Na$ (M+Na) 495.0903, found 495.0920.

4.22. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′,5′-trihydroxyphenyl)chroman-3-yl-3″,5″-dihydroxy-4″-methoxybenzoate (9)

Following the preparation procedure for **5**, the hydrogenolysis of **20** afforded **9** (89% yield): mp 226–228 °C (decomposed); $[\alpha]_D$ −158.9 (*c* 1, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.14 (s, 2H), 6.78 (s, 2H), 6.20 (AB, *J*=2.2 Hz, 2H), 5.72 (br s, 1H), 5.23 (br s, 1H), 3.97 (s, 3H), 3.20 (A of ABq, *J*=17.3, 4.6 Hz, 1H), 3.07 (B of AB, *J*=17.4, 2.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.5, 156.5, 156.1, 155.7, 149.8, 144.9, 139.1, 131.8, 129.3, 125.1, 108.6, 105.3, 97.6, 95.1, 94.5, 76.6, 68.3, 59.2, 25.2; HRMS (ESI): calcd for $C_{23}H_{20}O_{11}Na$ (M+Na) 495.0903, found 495.0914.

4.23. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′,5′-trihydroxyphenyl)chroman-3-yl-3″-hydroxy-4″,5″-dimethoxybenzoate (10)

Following the preparation procedure for **5**, the hydrogenolysis of **21** afforded **10** (83% yield): mp 229–231 °C (decomposed); $[\alpha]_D$ −128.3 (*c* 1.5, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.24 (d, *J*=1.9 Hz, 1H), 7.18 (d, *J*=1.9 Hz, 1H), 6.81 (s, 2H), 6.20 (s, 1H), 6.19 (s, 1H), 5.69 (br s, 1H), 5.27 (br s, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.19 (A of ABq, *J*=17.4, 4.2 Hz, 1H), 3.12 (B of ABq, *J*=17.4, 2.2 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 163.5, 155.0, 154.9, 154.7, 154.0, 151.1, 148.3, 143.5, 138.8, 130.2, 127.9, 127.8, 123.6, 108.6, 103.6, 103.1, 95.7, 93.6, 92.7, 75.1, 67.8, 58.0, 53.6, 23.6; HRMS (ESI): calcd for $C_{24}H_{22}O_{11}Na$ (M+Na) 509.1060, found 509.1069.

4.24. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,5′-dihydroxy-4′-methoxyphenyl)chroman-3-yl-3″,4″,5″-trihydroxybenzoate (11)

Following the preparation procedure for **5**, the hydrogenolysis of **31** afforded **11** (90% yield): mp 219–221 °C (decomposed); $[\alpha]_D$ −128.4 (*c* 2.0, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.18 (s, 2H), 6.79 (s, 2H), 6.20 (AB, *J*=2.2 Hz, 2H), 5.72 (br s, 1H), 5.24 (br s, 1H), 3.89 (s, 3H), 3.19 (A of ABq, *J*=17.4, 4.4 Hz, 1H), 3.07 (B of ABq, *J*=17.4, 2.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.5, 156.2, 155.9, 155.4, 149.4, 144.4, 137.3, 134.1, 133.8, 120.2, 108.4, 105.4, 97.5, 95.0, 94.3, 76.4, 67.6, 59.0, 25.1; HRMS (ESI): calcd for $C_{23}H_{20}O_{11}Na$ (M+Na) 495.0903, found 495.0924.

4.25. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,5′-dihydroxy-4′-methoxyphenyl)chroman-3-yl-3″,5″-dihydroxy-4″-methoxybenzoate (12)

Following the preparation procedure for **5**, the hydrogenolysis of **32** afforded **12** (90% yield): mp 228–230 °C (decomposed); $[\alpha]_D$ −131.1 (*c* 2.0, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.15 (s, 2H), 6.80 (s, 2H), 6.21 (AB, *J*=2.2 Hz, 2H), 5.75 (br s, 1H), 5.26 (br s, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.19 (A of ABq, *J*=17.4, 4.4 Hz, 1H), 3.11 (AB, *J*=17.4, 1.8 Hz, 1H); ^{13}C NMR(acetone-d_6, 400 MHz): δ 164.1, 156.1, 155.8, 155.2, 149.4, 149.3, 138.8, 134.0, 133.7, 124.7, 108.2, 105.1, 97.2, 94.9, 94.1, 76.1, 67.9, 58.9, 24.9; HRMS (ESI): calcd for $C_{24}H_{22}O_{11}Na$ (M+Na) 509.1060, found 509.1046.

4.26. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,5′-dihydroxy-4′-methoxyphenyl)chroman-3-yl-3″-hydroxy-4″,5″-dimethoxybenzoate (13)

Following the preparation procedure for **5**, the hydrogenolysis of **33** afforded **13** (89% yield): mp 199–201 °C (decomposed); $[\alpha]_D$ −139.0 (*c* 1.2, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.24 (d, *J*=1.9 Hz, 1H), 7.17 (d, *J*=1.9 Hz, 1H), 6.82 (s, 2H), 6.18 (AB, *J*=2.2 Hz, 2H), 5.65 (br s, 1H), 5.26 (br s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.17 (A of ABq, *J*=17.4, 4.3 Hz, 1H), 3.14 (B of ABq, *J*=17.4, 2.5 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 163.9, 155.7, 155.3, 154.5. 151.7, 148.9, 139.3, 133.4, 133.3, 124.2, 109.1, 104.4, 103.6, 96.3, 94.2,

93.3, 75.5, 68.1, 58.6, 58.5, 58.4, 58.3, 54.2, 54.1, 24.1; HRMS (ESI): calcd for $C_{25}H_{24}O_{11}Na$ (M+Na) 523.1216, found 523.1203.

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