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Enantioselective synthesis of (2*R*,3*S*)-(+)-catechin

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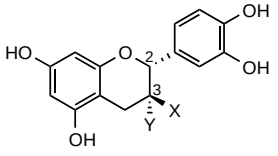
Abstract—A new enantioselective synthetic method for catechin from *trans*-methyl cinnamate derivative was developed via asymmetric dihydroxylation (ADH), the addition of an aryllithium species, followed by the Barton–McCombie reaction and an intramolecular Mitsunobu reaction as key steps. © 2002 Elsevier Science Ltd. All rights reserved.

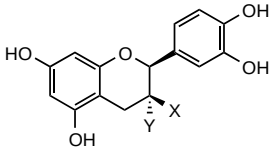
1. Introduction

The catechins are a group of 3-flavanols including catechin **1a**, epicatechin **1b**, enti-catechin **2a**, enti-epicatechin **2b**, and their derivatives. Catechins are widely distributed in a variety of plants. Green tea leaves, *Camellia sinensis* (family *Theaceae*) contain catechin as a major component, comprising up to 30% of the weight of dry leaves.[1] Historically, green tea has been popular in Asia.

Recently, extensive biological activity studies have shown that catechin possesses various important biological activities, such as antitumor activity,[2] antimutagenic activity,[3] and antioxidant properties.[4] As part of our program to find new candidates for anticancer or psychoactive agents, we wanted to perform a structure–activity relationship (SAR) study by catechin modifications. Since a synthetic method for catechin should be established ahead of the SAR study, we first had to develop an efficient synthetic method for catechin.



1a (catechin): X=OH, Y=H
1b (epicatechin): X=H, Y=OH



2a (enti-catechin): X=H, Y=OH
2b (enti-epicatechin): X=OH, Y=H

Thus far, several synthetic methods have been reported: Vercanteren and Brown prepared catechin enantioselectively by chemical resolution.[5] Ferreira's method, using asymmetric dihydroxylation followed by acid-catalyzed cyclization, afforded a mixture of catechin **1a** and the C(2)-epimer **2b** of catechin (in a 3:1 ratio), as a result of C(2)-epimerization under the acidic cyclization conditions.[6] Recently, we reported a new and efficient synthetic method for (2*R*,3*S*)-3-hydroxyflavanone, which has a similar structure to the 3-flavanols, using asymmetric dihydroxylation[7] and an intramolecular Mitsunobu reaction.[8,9] We now describe a highly enantioselective synthetic method (>99% ee) for the catechin **1a** using catalytic asymmetric dihydroxylation[7] and an intramolecular Mitsunobu reaction[8] as key reactions.

2. Results and discussion

Based on the retrosynthetic analysis depicted in Scheme 1, we planned to prepare (2*R*,3*S*)-(+)-catechin **1a** by three steps: the asymmetric dihydroxylation of methyl cinnamate derivative **5**, the addition of a functionalized aryllithium to the chiral dihydroxyaldehydes **4** followed by deoxygenation via Barton–McCombie reaction,[10] and the intramolecular Mitsunobu reaction.[8]

As shown in Scheme 2, the catechol **5** was protected at both phenols with a methoxymethyl (MOM) group by treatment with MOMCl under basic conditions to

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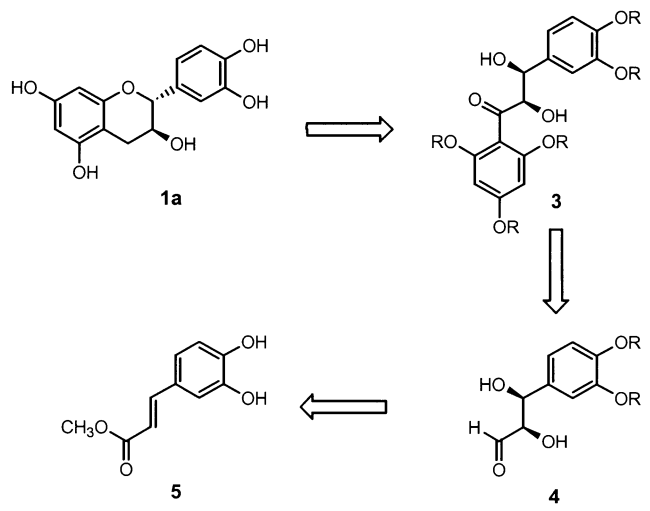
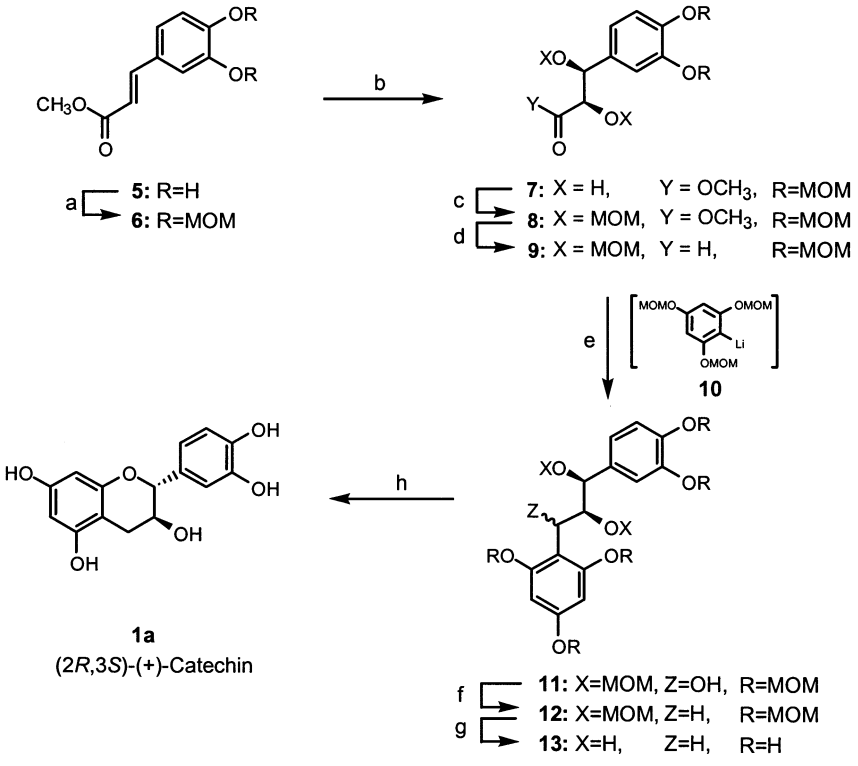


Scheme 1.

afford **6** (99%). Sharpless asymmetric dihydroxylation[7] of the ester **6** with AD-mix-α and methanesulfonamide in *tert*-butanol–H_2O (1:1) led to the diasteromerically pure (2*R*,3*S*)-dihydroxy ester **7** (quant., >99% ee). The enantiomeric excess was determined by ^1H NMR analysis of the diastereomeric Mosher's esters[11] of **7**.[12] The absolute configuration was assigned as 2*R*,3*S* from the enantioselectivity mnemonic of the ADH reactions.[7] The two hydroxy groups at C(2) and C(3) of **7** were protected by treating **7** with MOMCl and diisopropylethylamine to give **8** (89%). Compound **11** was prepared by the addition of aryllithium **10** derived from 1,3,5-tris(methoxymethoxy)benzene and *n*-butyllithium to **9**, obtained by reduction of **8** with diisobutylaluminum hydride (87%). The deoxygenation could be accomplished by a Barton–McCombie reaction. Treatment of **11** with sodium hydride, carbon disulfide, and imidazole in THF produced the xanthate, which was reduced to **12** by using tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) (91%). Removal of all MOM groups was carried out using 2% HCl in methanol to afford **13** (49%).

For the final cyclization, in order to avoid the epimerization accompanying Ferreira's method using acidic cyclization conditions, we chose the intramolecular Mitsunobu reaction. Compound **13** was submitted to the intramolecular Mitsunobu reaction using triphenylphosphine and diethyl azodicarboxylate in THF to afford the (2*R*,3*S*)-(+)-catechin, **1a** [50%; >99% ee; $[\alpha]_D^{22}$ +16.0 (*c* 0.1, acetone)]. The absolute configuration of the new stereogenic center *C*(2) of **1a** could be assigned as *R* by the anti-relationship between C(2)H and C(3)H ($J=7.3$ Hz), which is in accord with the S_N2 mechanism of the Mitsunobu reaction, as expected.



Scheme 2. *Reagents and conditions*: (a) MOMCl (5.0 equiv.), NaH (5.0 equiv.), DMF, rt, 1 h, 99%; (b) AD-mix-α (1.4 g/mmol), methanesulfonamide (1.0 equiv.), *t*-BuOH–H_2O (1:1), rt, 5 h, 100%; (c) MOMCl (10.0 equiv.), *i*-Pr_2NEt (2.5 equiv.), CH_2Cl_2, rt, 20 h, 89%; (d) DIBAL-H (1.3 equiv.), toluene, −78°C, 1 h, 87%; (e) 1,3,5-tris(methoxymethoxy)benzene (1.9 equiv.), *n*-BuLi (1.5 equiv.), THF, −78°C, 10 min, 53%; (f) (i) NaH (5.0 equiv.), imidazole, CS_2, CH_3I, THF, 60°C, 1 h, 99%, (ii) *n*-Bu_3SnH (3.0 equiv.), AIBN (cat.), benzene, 80°C, 2 h, 91%; (g) 2% HCl (17.0 equiv.), MeOH, 50°C, 30 min, 49%; (h) PPh_3 (1.5 equiv.), DEAD (1.5 equiv.), THF, rt, 1.5 h, 50%.

3. Conclusion

The highly enantioselective synthesis of catechin **1a** has been accomplished by employing the asymmetric dihydroxylation, the addition of aryllithium followed by the Barton–McCombie reaction, and the intramolecular Mitsunobu reaction as the crucial steps, in eight steps from 3′,4′-dihydroxymethyl cinnamate **5** (9%, >99% ee). The efficient synthetic route can be applied to the synthesis of other catechins, **1b** and **2a**,**b** by the combination of the (*E*)- or (*Z*)-α,β-unsaturated ester and the AD-mix-α or AD-mix-β. We believe that this method will be very useful to prepare various derivatives of catechins for SAR studies to find new candidates for anticancer and psychoactive drugs.

4. Experimental

4.1. General

Optical rotations were measured with a JASCO DIP-1000 digital polarimeter. Infrared spectra were taken on a Perkin–Elmer 1710 FT-IR spectrometer. Mass spectra were obtained on a VG Trio-2 GC-MS instrument. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-LA 300, a JEOL JNM-GCX 400, using TMS as the internal standard. All reactions were carried out under an argon atmosphere using anhydrous solvents except for those involving hydrolysis. Most reagents were obtained from commercial suppliers and used without further purification unless noted. Tetrahydrofuran was distilled from Na and benzophenone, and methylene chloride from CaH_2.

4.2. Methyl 3′,4′-bis(methoxymethoxy)cinnamate 6

To a suspension of NaH (95% in mineral oil, 3.0 g, 0.12 mol) and methyl 3′,4′-dihydroxycinnamate (4.73 g, 0.024 mol) in anhydrous DMF (100 mL) was added dropwise MOMCl (9.24 mL, 0.12 mol) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was quenched by the addition of water and then the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes:EtOAc = 1:1) to afford the desired product **6** as a yellow oil (6.80 g, 99% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.51 (s, 3H), 3.53 (s, 3H), 3.80 (s, 3H), 5.25 (s, 2H), 5.27 (s, 2H), 6.33 (d, 1H, J = 15.8 Hz), 7.15 (s, 2H), 7.36 (s, 1H), 7.62 (d, 1H, J = 15.8 Hz); IR (neat) 1714, 2958 cm^{-1}; LRMS (EI) 282 [M]$^+$.

4.3. Methyl (2*R*,3*S*)-2,3-dihydroxy-3-[3′,4′-bis(methoxymethoxy)phenyl]propionate 7

To a solution of AD-mix-α (2.22 g) and methanesulfonamide (148 mg, 1.56 mmol) in *tert*-BuOH–H_2O (1:1 v/v, 15 mL) was added the methyl cinnamate derivative **6** (439 mg, 1.56 mmol). The resulting solution was stirred vigorously for 5 h at room temperature. Excess sodium sulfite was added to the reaction and the mixture was allowed to stir for an additional 10 min. The mixture was diluted with EtOAc and the layers were separated. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel chromatography (hexanes:EtOAc = 1:2) afforded the desired product **7** as a white solid (493 mg, 100% yield): $[\alpha]_D^{21}$ +3.9 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.65 (d, 1H, J = 7.1 Hz), 3.07 (d, 1H, J = 5.8 Hz), 3.51 (s, 3H), 3.53 (s, 3H), 3.87 (s, 3H), 4.36 (dd, 1H, J = 5.8, 2.7 Hz), 4.97 (dd, 1H, J = 7.1, 2.7 Hz), 5.23 (s, 2H), 5.24 (s, 2H), 7.02 (dd, 1H, J = 8.5, 2.2 Hz), 7.16 (d, 1H, J = 8.5 Hz), 7.22 (d, 1H, J = 2.2 Hz); IR (neat) 1741, 2954, 3469 cm^{-1}; LRMS (EI) 316 [M]$^+$.

4.4. Methyl (2*R*,3*S*)-2,3-bis(methoxymethoxy)-3-[3′,4′-bis(methoxymethoxy)phenyl]propionate 8

To a solution of diol **7** (1.25 g, 4.88 mmol) and *i*-Pr_2NEt (2.12 mL, 12.2 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise MOMCl (3.7 mL, 48.8 mmol) at 0°C. The resulting solution was stirred for 10 min at the same temperature and allowed to warm to room temperature while stirring for 20 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes:EtOAc = 2:1) to afford the desired product **8** as a colorless oil (1.79 g, 89%): $[\alpha]_D^{20}$ +110.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.00 (s, 3H), 3.32 (s, 3H), 3.50 (s, 6H), 3.76 (s, 3H) 4.31 (d, 1H, J = 3.4 Hz), 4.49 (d, 1H, J = 6.8 Hz), 4.58 (s, 2H), 4.65 (d, 1H, J = 6.8 Hz), 5.09 (d, 1H, J = 3.4 Hz), 5.21 (s, 4H), 7.01 (dd, 1H, J = 8.6, 2.0 Hz), 7.12 (d, 1H, J = 8.6 Hz), 7.24 (d, 1H, J = 2.0 Hz); IR (neat) 1715, 2953 cm^{-1}; LRMS (EI) 404 [M]$^+$.

4.5. (2*R*,3*S*)-2,3-Bis(methoxymethoxy)-3-[3′,4′-bis-(methoxymethoxy)phenyl]propionaldehyde 9

To a solution of compound **8** (4.2 g, 10.4 mmol) in anhydrous toluene (80 mL) at −78°C was added DIBAL-H dropwise (13.5 mL, 13.5 mmol, 1.0 M in toluene). The resulting solution was stirred for 1 h at −78°C. The reaction was quenched by dropwise addition of sat. NH_4Cl, and was diluted with ethyl ether (250 mL). After allowing the reaction mixture to reach room temperature, a saturated solution of Rochelle salt (250 mL) was added and the mixture was stirred for 18 h. The layers were separated and the organic phase was washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was purified by silica gel chromatography (hexanes:EtOAc = 1:1) to afford the desired product **9** as a colorless oil (3.39 g, 87%): $[\alpha]_D^{21}$ +131.6 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.20 (s, 3H), 1.33 (s, 3H), 3.51 (s, 6H), 4.09 (dd, 1H, J = 3.2, 1.0 Hz), 4.44 (d, 1H, J = 7.0 Hz), 4.56 (s, 2H), 4.69 (d, 1H, J = 7.0 Hz), 5.08 (d, 1H, J = 3.2 Hz), 5.23 (s, 4H), 6.99 (dd, 1H, J = 8.3, 2.0 Hz), 7.14 (d, 1H, J = 8.3 Hz), 7.23 (d, 1H, J = 2.0 Hz), 9.77 (d, 1H, J = 1.0 Hz); IR (neat) 1734, 2953 cm^{-1}; LRMS (EI) 374 [M]$^+$.

4.6. Methyl (2*S*,3*R*)-2,3-dihydroxy-3-[3′,4′-bis(methoxymethoxy)phenyl]propionate 7′

To a solution of AD-mix-β (967 mg) and methanesulfonamide (656 mg, 0.69 mmol) in *tert*-BuOH–H_2O (1:1 v/v, 6 mL) was added compound **6** (195 mg, 0.69 mmol). The resulting solution was stirred vigorously for 5 h at room temperature. Excess sodium sulfite was added to the reaction mixture and the mixture was allowed to stir for an additional 10 min. The mixture was diluted with EtOAc and the layers were separated. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The purification of the residue by silica gel chromatography (hexanes:EtOAc = 1:2) afforded the desired product **7′** as a white solid (213 mg, 98%).

4.7. Methyl 2,3-dihydroxy-3-[3′,4′-bis(methoxymethoxy)phenyl]propionate 7″

To a solution of NMO (1.41 g, 3.20 mmol) in *tert*-BuOH–H_2O (1:1 v/v, 5 mL) was added dropwise osmium tetroxide (1.5 mL, 0.32 mmol, 0.2 M in toluene). After stirring for 10 min, compound **6** (900 mg, 3.20 mmol) was added. The resulting solution was stirred vigorously for 15 h at room temperature. Excess sodium sulfite was added to the reaction and the mixture was allowed to stir for an additional 10 min. The mixture was diluted with EtOAc and the layers were separated. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The purification of the residue by silica gel chromatography (hexanes:EtOAc = 1:2) afforded the desired product **7″** as a white solid (677 mg, 67%).

4.8. Methyl (2*R*,3*S*)-2,3-bis[(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy]-3-[3′,4′-bis(methoxymethoxy)phenyl]propionate 14

To a solution of diol **7** (35 mg, 0.11 mmol) and DMAP (68 mg, 0.55 mmol) in anhydrous THF (1 mL) was added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl] (103 μL, 0.55 mmol). The resulting mixture was stirred for 1 h at room temperature. After filtration of the reaction mixture, the filtrate was concentrated in vacuo to afford the desired product **14** as a colorless oil (66 mg, 80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.43 (s, 3H), 3.44 (s, 3H), 3.51 (s, 3H), 3.53 (s, 3H), 3.67 (s, 3H), 5.01 (dd, 2H, J = 6.8, 2.0 Hz), 5.19 (s, 2H), 5.45 (d, 1H, J = 2.6 Hz), 6.45 (d, 1H, J = 2.6 Hz), 6.73 (dd, 1H, J = 8.3, 2.0 Hz), 6.90 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 2.0 Hz), 7.24–7.55 (m, 10H).

4.9. Methyl (2*S*,3*R*)-2,3-bis[(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy]-3-[3′,4′-bis(methoxymethoxy)phenyl]propionate 14′

To a solution of diol **7′** (89 mg, 0.28 mmol) and DMAP (172 mg, 1.41 mmol) in anhydrous THF (3 mL) was added (*S*)-MTPACl (263 μL, 1.41 mmol). The resulting mixture was stirred for 1 h at room temperature. After filtration of the reaction mixture, the filtrate was concentrated in vacuo to afford the desired product **14′** as a colorless oil (200 mg, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.37 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.52 (s, 3H), 3.72 (s, 3H), 5.02 (d, 1H, J = 6.6 Hz), 5.10 (d, 1H, J = 6.6 Hz), 5.23 (s, 2H), 5.50 (d, 1H, J = 2.9 Hz), 6.51 (d, 1H, J = 2.9 Hz), 6.84 (dd, 1H, J = 6.6, 2.9 Hz), 7.07–7.12 (m, 2H), 7.25–7.42 (m, 10H).

4.10. Methyl 2,3-bis[(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetoxy]-3-[3′,4′-bis(methoxymethoxy)phenyl]-propionate 14″

To a solution of diol **7″** (40 mg, 0.13 mmol) and DMAP (77 mg, 0.63 mmol) in anhydrous THF (1.5 mL) was added (*S*)-MTPACl (118 μL, 0.63 mmol). The resulting mixture was stirred for 2 h at room temperature. After filtration of the reaction mixture, the filtrate was concentrated in vacuo to afford the desired product **14″** as a colorless oil (90 mg, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.37–3.44 (m, 6H), 3.51–3.56 (m, 6H), 3.67 (s, 1.5H), 3.72 (s, 1.5H), 5.01–5.11 (m, 2H), 5.20 (s, 1H), 5.23 (s, 1H), 5.47 (dd, 1H, J = 6.6, 2.9 Hz), 6.47 (dd, 1H, J = 6.6, 2.7 Hz), 6.73–7.06 (m, 3H), 7.25–7.59 (m, 10H).

4.11. (2*R*,3*S*)-3-[3″,4″-Bis(methoxymethoxy)]phenyl-2,3-bis(methoxymethoxy)-1-[2′,4′,6′-tris(methoxymethoxy)]-phenylpropanol 11

To a solution of 1,3,5-tris(methoxymethoxy)benzene (4.22 g, 16.3 mmol) in anhydrous THF (50 mL) was added dropwise *n*-BuLi (8.13 mL, 13.0 mmol, 1.6 M in hexane). The mixture was stirred for 2 h at 50°C before a solution of aldehyde **9** (3.25 g, 8.7 mmol) in anhydrous THF (40 mL) was added dropwise at −78°C. After the addition was completed, the reaction was stirred for 10 min at −78°C, and then quenched by addition of water. The solvent was removed in vacuo and the residue was diluted with EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel chromatography (hexanes:EtOAc = 1:2) to afford the desired product **11** as a colorless oil (2.92 g, 53%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.45 (s, 3H), 3.48 (s, 3H), 3.50 (s, 9H), 3.51 (s, 6H), 3.73 (d, 1H, J = 6.8 Hz), 3.95 (d, 1H, J = 6.8 Hz), 4.74 (d, 1H, J = 6.4 Hz), 4.81 (d, 1H, J = 6.4 Hz), 5.12–5.15 (m, 4H), 5.20–5.22 (m, 8H), 5.31 (s, 1H), 5.43–5.46 (m, 1H), 6.55 (s, 2H), 7.04–7.14 (m, 3H); IR (neat) 2954, 3545 cm^{-1}; LRMS (CI) 615 [M−17]$^+$.

4.12. (2*S*,3*S*)-3-[3″,4″-Bis(methoxymethoxy)]phenyl-2,3-bis(methoxymethoxy)-[2′,4′,6′-tris(methoxymethoxy)]-phenylpropane 12

To a suspension of NaH (460 mg, 18.2 mmol, 95% in mineral oil) and imidazole (100 mg, 1.47 mmol) in anhydrous THF (35 mL) was added a solution of alcohol **11** (2.29 g, 3.63 mmol) in anhydrous THF (35 mL) at room temperature. After stirring for 30 min, the

reaction mixture was cooled to 0°C, and then carbon disulfide (8.0 mL) was added to the mixture dropwise. The resulting mixture was stirred for 2 h at 60°C, and the temperature was cooled to 0°C. Methyl iodide (1.4 mL) was added and the resulting solution was allowed to warm to room temperature while stirring for 1 h. The reaction mixture was quenched by addition of water and the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel chromatography (hexanes:EtOAc = 1:1) to afford the desired xanthate as a yellow oil (2.59 g, 99%). To a solution of xanthate (844 mg, 1.17 mmol) and AIBN (19 mg, 0.12 mmol) in anhydrous benzene was added *n*-Bu_3SnH (0.9 mL, 3.50 mmol) at ambient temperature. The resulting solution was stirred for 2 h at 80°C. The solvent was removed in vacuo and the residue was purified on silica gel chromatography (hexanes:EtOAc = 1:1) to afford 658 mg (91%) of the desired product **12** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.62 (dd, 1H, J = 13.7, 3.6 Hz), 2.95–3.01 (m, 1H), 3.39 (s, 3H), 3.46 (s, 6H), 3.47 (s, 6H), 3.53 (d, 6H, J = 3.6 Hz), 4.15–4.19 (m, 1H), 4.48 (dd, 2H, J = 9.3, 6.7 Hz), 4.62 (d, 1H, J = 5.4 Hz), 4.66 (dd, 2H, J = 13.7, 6.7 Hz), 5.14 (d, 6H, J = 9.3 Hz), 5.23 (s, 4H), 6.51 (s, 2H), 6.98 (dd, 1H, J = 8.3, 1.7 Hz), 7.12 (d, 1H, J = 8.3 Hz), 7.22 (d, 1H, J = 1.7 Hz); IR (neat) 1026, 1152, 1507, 3565 cm^{-1}; LRMS (CI) 616 $[M]^+$.

4.13. 2-[(2*S*,3*S*)-3-(3″,4″-Dihydroxyphenyl)-2,3-dihydroxypropyl]-1,3,5-benzenetriol 13

A solution of compound **12** (41 mg, 0.066 mmol) in 2% HCl–MeOH (2 mL) was stirred for 30 min at 40°C. The reaction mixture was diluted with EtOAc and washed with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by silica gel chromatography (CH_2Cl_2:MeOH = 10:1) afforded the desired product **13** as a white solid (10 mg, 49%). ^{1}H NMR (CD_3OD, 400 MHz) δ 2.52 (dd, 1H, J = 16.0, 8.3 Hz), 2.83–2.89 (m, 1H), 3.98–4.01 (m, 1H), 4.58 (d, 1H, J = 8.3 Hz), 5.95 (s, 2H), 6.72–6.85 (m, 3H); IR (neat) 1636, 1684, 2361, 2916 cm^{-1}; LRMS (EI) 308 $[M]^+$.

4.14. (2*R*,3*S*)-(+)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-2*H*-chromene-3,5,7-triol, (+)-catechin 1a

To a solution of compound **13** (78 mg, 0.252 mmol) and triphenylphosphine (99 mg, 0.378 mmol) in anhydrous THF (2.5 mL) was added DEAD (59 μL, 0.378 mmol) dropwise. After stirring for 1.5 h at room temperature, the reaction mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by silica gel chromatography (CH_2Cl_2:MeOH = 10:1) afforded the desired product **1a** as a white solid (37 mg, 50%). $[\alpha]_D^{22}$ +16.0 (*c* 0.1, acetone); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.33 (dd, 1H, J = 15.9, 7.9 Hz), 2.64 (dd, 1H, J = 16.0, 5.2 Hz), 3.74–3.85 (m, 1H), 4.46 (d, 1H, J = 7.3 Hz), 4.84 (br s, 1H), 5.67 (d, 1H, J = 2.2 Hz), 5.87 (d, 1H, J = 2.2 Hz), 6.56–6.70 (m, 3H), 8.79 (s, 1H), 8.84 (s, 1H), 8.91 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.3, 66.7, 81.4, 94.3, 95.5, 99.5, 114.9, 115.5, 118.9, 131.0, 145.2, 146.0, 155.8, 156.6, 156.9; IR (KBr) 1469, 1521, 1625, 3345 cm^{-1}; LRMS (EI) 290 $[M]^+$.

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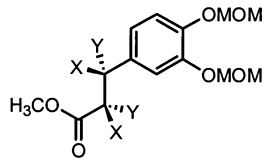
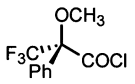
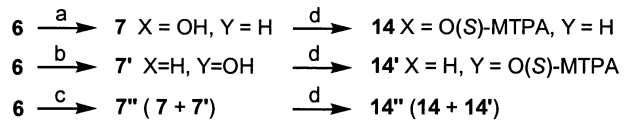
12. The enantiomeric excess was determined by the ^{1}H NMR analysis of the corresponding Mosher's esters **14**, **14′**, and **14″** derived from **7**, **7′**, and **7″**, respectively, as shown in Scheme 3. It was based on the peaks at δ 3.67 (CH_3OCO of **14**) and δ 3.72 (CH_3OCO of **14′**). Compounds **14** and **14′** were prepared from **7** (vide supra) and **7′**, which was obtained by treatment of **6** with AD-mix-β, using (*S*)-(−)-methylphenylacetyl chloride [(*S*)-MTPACl] and 4-dimethylaminopyridine (DMAP) in DMF (80 and 98%, respectively). Compound **14″** was also obtained by the same method from **7″** in a 95% yield, which was derived from the treatment of **6** with osmium tetroxide (OsO_4) and 4-methylmorpholine-*N*-oxide (NMO) (67%). In the case of (*R*)-MTPACl, the corresponding Mosher esters could not be formed.





15 (*S*)-MTPACl



Scheme 3. *Reagents and conditions*: (a) vide supra (Scheme 2); (b) AD-mix-β (1.4 g/mmol), methanesulfonamide (1.0 equiv.), *t*-BuOH–H_2O (1:1), rt, 5 h, **7′** (98%); (c) OsO_4 (0.1 equiv.), NMO (1.0 equiv.), *t*-BuOH–H_2O (1:1), rt, 15 h, **7″** (67%); (d) (*S*)-MTPACl (5.0 equiv.), DMAP (5.0 equiv.), THF, rt, 0.5 h, **14** (80%), **14′** (98%), **14″** (95%).