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Stereoselective Total Synthesis of (+)-Varitriol, (−)-Varitriol, 5′-*epi*-(+)-Varitriol, and 4′-*epi*-(−)-Varitriol from D-Mannitol

Subhash Ghosh* and Tapan Kumar Pradhan

Indian Institute of Chemical Technology, Hyderabad 500607, India

subhash@iict.res.in

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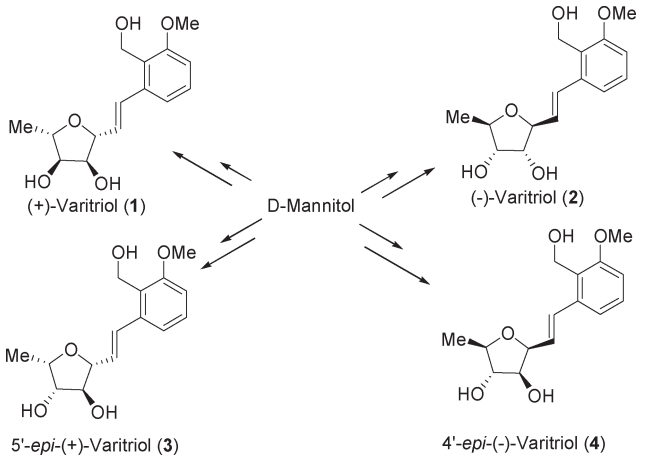

Stereoselective total syntheses of natural (+)-varitriol (**1**), (−)-varitriol (**2**), 5′-*epi*-(+)-varitriol (**3**), and 4′-*epi*-(−)-varitriol (**4**) have been accomplished with use of D-mannitol as a chiral pool material. The Heck reaction was used to assemble the olefinic sugar moiety and the aromatic triflate moiety.

Marine fungi are an important source of a wide range of biologically active compounds. In 2002 Rosales et al. isolated a low molecular weight cytotoxic compound called varitriol from the marine-derived strain of the fungus *Emericella variecolor*.[1] The chemical structure and relative stereochemistry of varitriol was determined by means of detailed NMR studies. Later the absolute stereochemistry was established via total synthesis.[2] The cytotoxic activity of this compound was tested against NCI's 60-cell panel and it showed increased potency toward renal, CNS, and breast cancer cell lines.[1,3] Significant cytotoxic activity and unknown mode of action attracted considerable attention from synthetic organic chemists worldwide, and as a result several total syntheses of (+)- and (−)-varitriol appeared in the literature.[4] The first total synthesis of (−)-varitriol was reported by Jennings et al. using cross metathesis to stitch together the carbohydrate and aromatic moieties.[2] Subsequently Taylor et al. reported the total synthesis of (−)-varitriol, where they used Horner−Wadsworth−Emmons//Ramberg−Bäcklund sequences.[4a] Shaw et al. reported the first total synthesis of naturally occurring (+)-varitriol by applying a cross metathesis approach.[4b] In this strategy D-mannose was used as a chiral pool material for the synthesis of the required olefinic sugar moiety. Very recently Gracza et al. reported another synthetic approach to natural (+)-varitriol by applying Kocieński−Julia olefination.[4c] Some simplified analogues of (+)-varitriol were also reported in the literature.[5] In this paper we wish to report our strategy for the synthesis of (+)-varitriol, (−)-varitriol, and their analogues starting from a single chiral pool material D-mannitol. The Heck reaction[6] was used to introduce the *E*-olefinic moiety in the molecule (Scheme 1).

Thus our synthesis commenced from the known diol compound **8**, which was prepared from D-mannitol (**7**) according to the reported procedures.[7] The diol compound **8** was converted to compound **9** in two steps: chemoselective tosylation of the primary alcohol gave a tosyl intermediate, which on treatment with LAH in THF at 0 °C furnished secondary alcohol **9** in 95% yield over two steps. Mesylation of **9** with MsCl gave an intermediate mesyl compound, which on treatment with CSA in MeOH:CH_2Cl_2 (1:1) underwent cycloetherification to give tetrahydrofuran compound **10**[8] in 95% yield. The primary hydroxyl group of **10** was then protected as its TBS ether to give compound **11**, which on hydrogenation furnished diol compound **12**. Introduction of the double bond between C4′ and C5′,[9] followed by OsO_4-mediated dihydroxylation furnished compound **13** (dr 10:1 in favor of the required isomer) in 55% yield over two steps. TBS protection of the secondary hydroxyl groups of **13** with TBSOTf followed by selective deprotection of the primary TBS with HF:Py gave primary alcohol **15**, which on DMP[10] oxidation followed by Wittig olefination with $Ph_3P{=}CH_2$ gave olefinic fragment **6**. The crucial Heck coupling[6d] between the olefinic compound and the aromatic triflate[11] was achieved with

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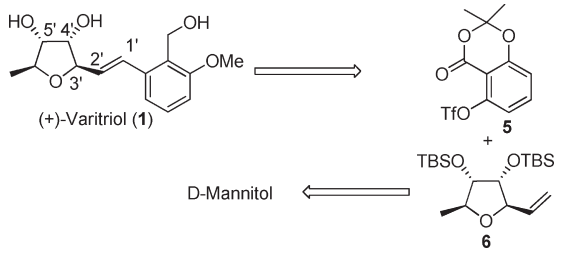
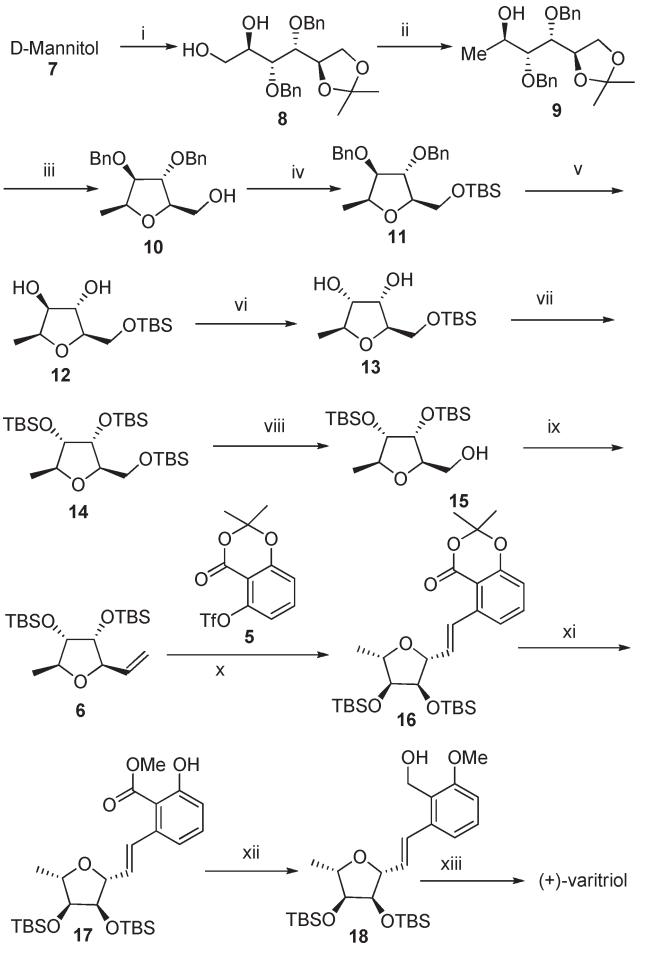
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of (+)-Varitriol[a]



[a]Reagents and conditions: (i) ref 7; (ii) (a) TsCl, Et_3N, CH_2Cl_2, DMAP (cat), 0 °C−rt, 2 h; (b) LAH, THF, 0 °C−rt, 10 min, 95% over two steps; (iii) (a) MsCl, Et_3N, CH_2Cl_2, DMAP (cat), 0 °C−rt, 15 min; (b) CSA, MeOH:CH_2Cl_2 (1:1), 0 °C−rt, 2 h, 95%; (iv) TBSCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C−rt, 1 h, 94%; (v) H_2, Pd−C, EtOAc, 10 h, 96%; (vi) (a) TPP, I_2 imidazole, toluene, reflux, 30 min; (b) OsO_4, NMO, methane sulfonamide, acetone:H_2O (1:1), 40 °C, 3−4 h, dr (10:1), 55% over two steps; (vii) TBSOTf, CH_2Cl_2, 2,6-lutidine, 0 °C−rt, 10 min, 87%; (viii) HF:Py, THF, 10 h, 70%; (ix) (a) DMP, CH_2Cl_2, $NaHCO_3$, 0 °C−rt, 10 min; (b) $Ph_3P{=}CH_2$, Et_2O, $(CH_3)_3COK$, 0 °C, 80%; (x) Ar-OTf (**5**), $PdCl_2(PPh_3)_2$, DMF, LiCl, Et_3N, 120 °C, 10 h, 80%; (xi) LiOH, THF: MeOH:H_2O (3:1:1), 0 °C−rt, 30 min, 97%; (xii) (a) MeI, acetone, K_2CO_3, reflux, 2.5 h; (b) DIBAL-H, CH_2Cl_2, −78 °C−rt, 10 min, 90%, over two steps; (xiii) 6 N HCl, THF, 0 °C−rt, 5 h, 88% yield.

use of $Pd(PPh_3)_2Cl_2$, LiCl, and Et_3N in DMF at 120 °C to give the compound **16**,[6b] which on treatment with LiOH in MeOH: THF:H_2O (3:1:1) afforded compound **17** in good yield. Finally *O*-methylation followed by reduction of the ester functionality with DIBAL-H and TBS deprotection furnished (+)-varitriol, whose analytical data were in good agreement with the reported value.[4c]

For the synthesis of 5′-*epi*-(+)-varitriol we started from compound **12**. TBS protection of the secondary hydroxyl groups followed by selective deprotection of the primary TBS furnished primary alcohol **20**. Oxidation of the primary alcohol with DMP[10] gave an aldehyde, which on Wittig olefination with $Ph_3P{=}CH_2$ in ether gave olefinic compound **21**. Heck coupling[6d] between aromatic triflate **5**[11] and olefinic sugar following similar reaction conditions of Scheme 2 afforded compound **22**, which was converted to 5′-*epi*-(+)-varitriol following the same sort of reactions as used for the conversion of **16** to (+)-varitriol (Scheme 3).

For the synthesis of (−)-varitriol, we started from compound **9**, which on benzoylation followed by acetonide deprotection furnished diol compound **26** (Scheme 4). Selective tosylation of the primary hydroxyl group gave tosyl intermediate, which on treatment with K_2CO_3 in methanol gave tetrahydrofuran compound **27** in 86% yield over two steps.[12] TBS protection of the primary alcohol followed by benzyl deprotection via hydrogenation gave diol compound **29**, which was converted to *ent*-**13** in two steps. Finally compound *ent*-**13** was converted to (−)-varitriol (**2**) following the same sort of reactions as were used for the conversion of **13** to (+)-varitriol (**1**).

The synthesis of 4′-*epi*-(−)-varitriol started from compound **29**. Global protection of the secondary hydroxyl groups with TBSOTf gave compound **30**. Selective deprotection of the primary TBS followed by oxidation of the resulting primary alcohol gave an aldehyde, which was reacted with $Ph_3P{=}CH_2$ in ether to afford olefinic compound **32**. Heck coupling[6d] between **32** and **5** afforded compound **33**, which was converted to 4′-*epi*-(−)-varitriol following the same sort of reactions as used earlier for the synthesis of (+)-varitriol (Scheme 5).

In conclusion we have developed a strategy for the stereoselective total synthesis of (+)-varitriol and its stereochemical analogues. Using this strategy currently we are making structural analogues for structure activity relationship studies, which will be reported separately somewhere else.

Experimental Section

Synthesis of Compound 16. To a solution of olefinic compound **6** (86 mg, 0.23 mmol) in dry degassed DMF (5 mL) were added LiCl (29 mg, 0.69 mmol) and Et_3N (0.1 mL, 0.69 mmol) sequentially under argon atmosphere. Then aromatic triflate **5** (150 mg, 0.46 mmol) followed by $Pd(PPh_3)_2Cl_2$ (32 mg, 0.046 mmol) were added very quickly and once again the solution was degassed for 10 min. The reaction mixture was heated to 120 °C and heating was continued for 10 h. Meanwhile the color of the reaction mixture became dark brown. After completion of the reaction, it was quenched with H_2O (5 mL). The organic layer was extracted with EtOAc (50 mL), washed with brine (5 mL), dried over (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (4−5% ethyl acetate in petroleum ether was eluant) to afford compound **16** (101 mg, 80%) as a colorless liquid. $[\alpha]^{32}_D$ +44.69 (*c* 0.91 in $CHCl_3$); IR (neat) 2929, 2857, 2361, 2334, 1737, 1578, 1472, 1382, 1371, 1264, 1211, 1080, 1042, 837 cm^{-1}; ^1H NMR

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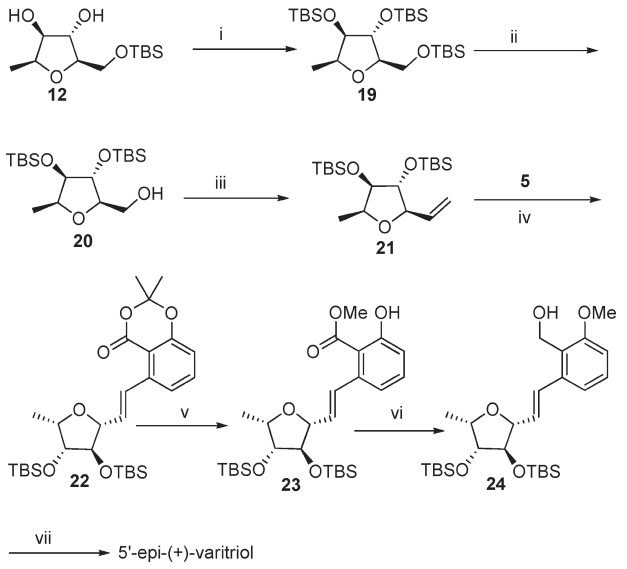
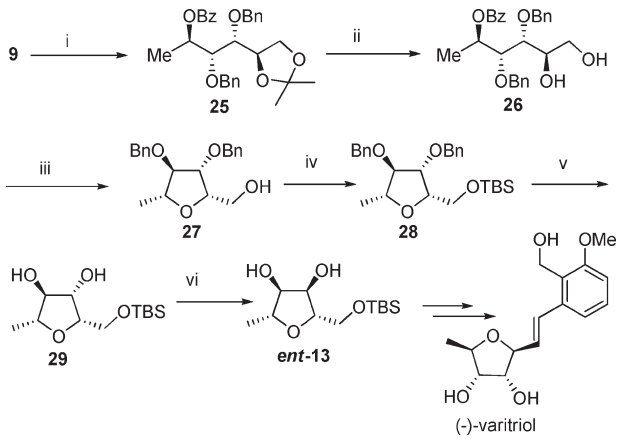
SCHEME 3. Synthesis of 5′-*epi*-(+)-Varitriol[a]



[a]Reagent and conditions: (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 98%; (ii) HF:Py, THF, 10 h, 72%; (iii) (a) DMP, CH_2Cl_2, $NaHCO_3$, 0 °C−rt, 20 min; (b) $Ph_3P{=}CH_2$, Et_2O, $(CH_3)_3COK$, 0 °C, 80%; (iv) **5**, $PdCl_2(PPh_3)_2$, DMF, LiCl, Et_3N, 120 °C, 10 h, 85%; (v) LiOH, THF:MeOH:H_2O (3:1:1), 0 °C−rt, 1 h, 97%; (vi) (a) MeI, acetone, K_2CO_3, reflux, 6−7 h; (b) DIBAL-H, CH_2Cl_2, −78 °C−rt, 10 min, 88%; over two steps (vii) 6 N HCl, THF, 10 h, 75% yield.

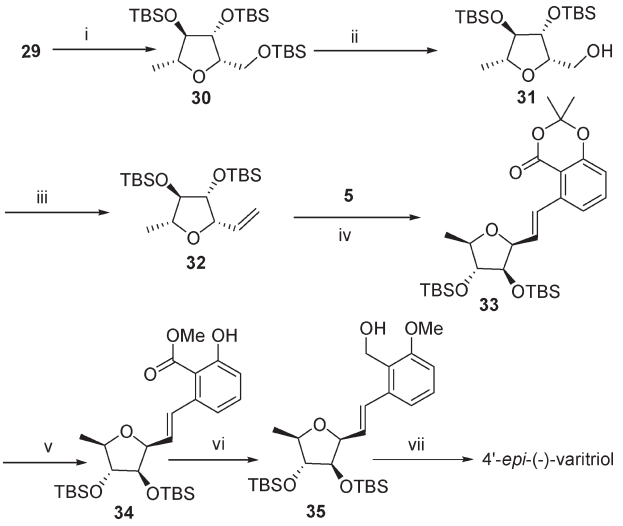
SCHEME 4. Synthesis of (−)-Varitriol[a]



[a]Reagent and conditions: (i) (a) BzCl, Et_3N, CH_2Cl_2, DMAP (cat), 0 °C−rt, 8 h,70%, starting material recovered; (ii) CSA, MeOH:CH_2Cl_2 (1:1), 0 °C−rt, 10 h, 90%; (iii) (a) TsCl, Et_3N, CH_2Cl_2, DMAP (cat), 0 °C−rt, 2 h ; (b) K_2CO_3, MeOH, 30 min, 86%; (iv) TBSCl, Et_3N, CH_2Cl_2, DMAP, 0 °C−rt, 4 h, 93%; (v) H_2, Pd−C, EtOAc, 3 h, 92%; (vi) (a) TPP, I_2 imidazole, toluene, reflux, 30 min; (b) OsO_4, NMO, methane sulfonamide, acetone:H_2O (1:1), 40 °C, 3−4 h, dr (9:1), 56% over two steps.

(500 MHz, $CDCl_3$) δ 7.69 (d, J = 15.8 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.09 (dd, J = 15.8, 6.3 Hz, 1H), 4.49 (ddd, J = 6.3, 3.9, 1.5 Hz, 1H), 4.04 (dq, J = 6.3, 6.1 Hz, 1H), 3.90 (t, J = 3.9 Hz, 1H), 3.73 (dd, J = 6.1, 4.1 Hz, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.31 (d, J = 6.3 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.07 (br s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.9, 156.7, 141.5, 135.1, 132.8, 129.9, 121.5, 116.3, 110.9, 105.2, 84.1, 78.2, 77.5, 77.3, 25.8 (2C), 25.3, 19.1, 18.1, −4.2, −4.3, −4.4, −4.6; MS (ESI) m/z (%) 549 (20) $[M + H]^+$, 566 (80) $[M + NH_4]^+$, 571 (65) $[M + Na]^+$; HRMS (ESI) calcd for $C_{29}H_{48}O_6NaSi_2$ $[M + Na]^+$ 571.2887, found 571.2892.

SCHEME 5. Synthesis of 4′-*epi*-(−)-Varitriol[a]



[a]Reagent and conditions: (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 85%; (ii) HF:Py, THF, 7 h, 75%; (iii) (a) DMP, CH_2Cl_2, $NaHCO_3$, 0 °C−rt, 20 min; (b) $Ph_3P{=}CH_2$, Et_2O, $(CH_3)_3COK$, 0 °C, 80%; (iv) **5**, $PdCl_2(PPh_3)_2$, DMF, LiCl, Et_3N, 120 °C, 16 h, 87%; (v) LiOH, THF:MeOH:H_2O (3:1:1), 0 °C−rt, 30 min, 92%; (vi) (a) MeI, acetone, K_2CO_3, reflux, 1 h; (b) DIBAL-H, CH_2Cl_2, −78 °C−rt, 10 min, 85%, over two steps; (vii) 6 N HCl, THF, 3 h, 83% yield.

Synthesis of Compound 22. 22 was prepared following the same procedure as used earlier for the synthesis of **16**: $[\alpha]^{27}_D$ +45.23 (*c* 0.21 in $CHCl_3$); IR (neat) 2929, 2857, 2361, 2334, 1737, 1578, 1472, 1382, 1371, 1264, 1211, 1157, 1103, 1080, 1042, 837, 778 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, J = 16.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 6.82 (dd, J = 8.1, 1.0 Hz, 1H), 6.27 (dd, J = 16.0, 8.6 Hz, 1H), 4.36 (d, J = 8.6 Hz, 1H), 4.22 (dq, J = 2.5, 6.3 Hz, 1H), 3.96 (br s, 1H), 3.76 (dd, J = 2.7, 1.3 Hz, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.25 (d, J = 6.3 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 156.7, 141.5, 134.9, 134.2, 129.0, 121.4, 116.1, 110.8, 105.1, 88.0, 84.2, 80.1, 77.6, 26.2, 25.7, 25.0, 18.0, 17.8, 14.5, −4.4, −4.5, −4.7, −4.9; MS (ESI) m/z (%) 549 (10) $[M + H]^+$, 566 (90) $[M + NH_4]^+$, 571 (75) $[M + Na]^+$; HRMS (ESI) calcd for $C_{29}H_{48}O_6NaSi_2$ $[M + Na]^+$ 571.2883, found 571.2890.

Synthesis of Compound 33. 33 was prepared following the same procedure as used earlier for the synthesis of **16**: $[\alpha]^{27}_D$ +23.65 (*c* 1.23 in $CHCl_3$); IR (neat) 2930, 2893, 2857, 1737, 1577, 1471, 1383, 1316, 1265, 1209, 1113, 1083, 1050, 933, 836, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 16.2 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.32 (dd, J = 8.0, 1.0 Hz, 1H), 6.85 (dd, J = 8.0, 1.0 Hz, 1H), 6.33 (dd, J = 16.2, 8.1 Hz, 1H), 4.64 (dd, J = 8.1, 3.0 Hz, 1H), 3.95 (dd, J = 3.0, 1.4 Hz, 1H), 3.91 (dq, J = 1.4, 6.6 Hz, 1H), 3.80 (t, J = 1.4 Hz, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 156.7, 141.4, 135.0, 131.3, 130.8, 121.4, 116.2, 110.9, 105.1, 84.1, 83.1, 82.8, 81.7, 25.8, 25.7 (2C), 25.3, 19.8, 18.0, 17.9, −4.5, −4.7, −4.8; MS (ESI) m/z (%) 549 (40) $[M + H]^+$, 566 (90) $[M + NH_4]^+$, 571 (65) $[M + Na]^+$; HRMS (ESI) calcd for $C_{29}H_{48}O_6NaSi_2$ $[M + Na]^+$ 571.2880, found 571.2885.

Synthesis of (+)-Varitriol (1). To a stirred solution of compound **18** (14 mg, 0.02 mmol) in THF (2 mL) was added 6 N HCl

(2 mL) in a dropwise manner at 0 °C. After being stirred for 7 h at room temperature the reaction was quenched slowly with saturated $NaHCO_3$ solution (3−4 mL) at 0 °C and the organic layer was extracted with $CHCl_3$ (4 × 50 mL), washed with H_2O (2 × 5 mL) and brine (5 mL), dried over (Na_2SO_4), and filtered. After concentration in vacuum, it was subjected to chromatographic purification (preparative TLC, 20% acetone in CH_2Cl_2 (2 times)) to afford compound **1** (6.7 mg, 88%) as a white solid. $[\alpha]^{28}_D$ +40.00 (*c* 0.21 in MeOH); IR (neat) 3375, 2960, 2922, 1587, 1575, 1469, 1456, 1439, 1255, 1089, 1004, 974, 799, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 8.1 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 16.1 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.09 (dd, J = 16.1, 7.3 Hz, 1H), 4.82 (d, J = 11.7 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.29 (t, J = 6.6 Hz, 1H), 3.95−3.81 (m, 5H), 3.69 (t, J = 5.5 Hz, 1H), 3.62 (br s, 1H), 3.08 (br s, 1H), 2.81 (br s, 1H), 1.32 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 137.3, 131.0, 129.4, 128.9, 125.8, 119.0, 109.7, 84.0, 79.9, 76.1, 75.3, 56.4, 55.6, 19.2; MS (ESI) m/z (%) 281 (10) $[M + H]^+$, 303 (100) $[M + Na]^+$; HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ 303.1208, found 303.1198.

Analytical data of (−)-varitriol (2): $[\alpha]^{30}_D$ −42.2 (*c* 0.135 in MeOH) in good agreement with the value reported by Taylor[4a] and Gracza et al.,[4c] not with the value reported by others;[1,2] HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ 303.1210, found 303.1209.

Analytical data of compound 5′-*epi*-(+)-varitriol: $[\alpha]^{30}_D$ +58.75 (*c* 0.08 in $CHCl_3$); IR (neat, cm^{-1}) 3334, 2922, 2853, 2363, 2333, 1740, 1708, 1576, 1464, 1260, 1081, 1044, 992; ^1H NMR (600 MHz, CD_3CN) δ 7.22 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 15.8 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.19 (dd, J = 15.8, 7.3 Hz, 1H), 4.63 (dd, J = 11.7, 5.8 Hz, 1H), 4.62 (dd, J = 11.7, 5.8 Hz, 1H), 4.11 (ddd, J = 7.3, 3.8, 1.1 Hz, 1H), 4.06 (dq, J = 4.0, 6.4 Hz, 1H), 3.85 (dt, J = 2.0, 4.1 Hz, 1H), 3.82 (ddd, J = 5.4, 3.8, 2.0 Hz, 1H), 3.80 (s, 3H), 3.48 (d, J = 4.3 Hz, 1H), 3.01 (d, J = 5.4 Hz, 1H), 2.91 (t, J = 5.8 Hz, 1H), 1.19 (d, J = 6.4 Hz, 1H); ^{13}C NMR (150 MHz, CD_3CN) δ 158.8, 138.7, 132.8, 129.7, 128.8, 127.5, 119.2, 110.7, 86.6, 84.1, 80.0, 77.8, 56.2, 55.4, 14.5; MS (ESI) m/z (%) 303 (100) $[M + Na]^+$; HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ 303.1210, found 303.1202.

Analytical data of compound 4′-*epi*-(−)-varitriol: $[\alpha]^{26}_D$ −35.9 (*c* 0.22 in MeOH); ^1H NMR (300 MHz, CD_3CN) δ 7.26 (t, J = 8.0 Hz, 1H), 7.16 (dd, J = 7.9, 1.1 Hz, 1H), 7.05 (dd, J = 15.9, 1.1 Hz, 1H), 6.91 (dd, J = 8.0, 1.1 Hz, 1H), 6.22 (dd, J = 15.9, 6.9 Hz, 1H), 4.68 (s, 2H), 4.52 (ddd, J = 6.9, 4.3, 1.2 Hz, 1H), 3.97 (dd, J = 4.3, 2.0 Hz, 1H), 3.84 (s, 3H), 3.78−3.69 (m, 2H), 1.31 (d, J = 6.2 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 158.4, 138.4, 130.0, 129.4, 129.3, 127.0, 118.9, 110.4, 83.9, 82.4, 81.2, 80.6, 55.8, 55.0, 19.3; MS (ESI) m/z (%) 303 (100) $[M + Na]^+$; HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ 303.1220, found 303.1225.

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Supporting Information Available: Experimental procedures, and spectral data for compounds **9**−**15**, **6**, **17**−**32**, **34**, and **35** and the copies of ^1H and ^{13}C NMR spectra for compounds **9**−**15**, **6**, **16**−**18**, **1**, **19**−**24**, **3**, **25**−**35**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.