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A conventional approach to the total synthesis of (−)-varitriol

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ABSTRACT

The stereoselective total synthesis of (−)-varitriol has been achieved starting from commercially available D-(−)-ribose and *o*-anisic acid. A Mitsunobu reaction, Julia–Kocienski olefination, and one pot reduction of both ester and iodo functionalities with superhydride are the key reactions involved in this synthesis.

1. Introduction

Natural products from marine-derived fungi show a pronounced degree of structural diversity and have been found to display interesting biological and pharmacological properties. This feature has attracted significant interest from synthetic chemists and the pharmaceutical industry.[1] (+)-Varitriol **1**, a novel low molecular weight natural product isolated by Malmstrom et al.[2] from a marine derived strain of fungus *Emericella variecolor* displayed lower potency toward leukemia, ovarian, and colon cell lines with GI_{50} values ranging from 2.52×10^{-5} to 9.59×10^{-5} M and an increased potency toward renal, CNS, and breast cancer cell lines with GI_{50} values ranging from $1.63–2.44 \times 10^{-7}$ M. Since the mode of action of varitriol has not yet been fully established,[3] it is necessary to further investigate and elucidate the mechanism of action. Toward the end, several chemists have taken up the total synthesis[4,5] and analogue synthesis[6] of varitriol for further investigation. The absolute structure of (+)-varitriol was initially determined after accomplishing the total synthesis of its enantiomer (−)-varitriol **1′** (Fig. 1) and later followed by natural (+)-varitriol synthesis. As part of an academic exercise, we have initiated a program to synthesize both enantiomers of the potentially active natural products.[7] We have recently accomplished the total synthesis of (+)-varitriol and the C6′-epimer;[8] herein we report the total synthesis of its enantiomer (−)-varitriol.

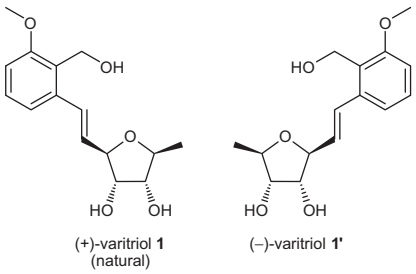

Figure 1. Structures of natural and unnatural varitriols.

The first synthesis of (−)-varitriol was reported by Jennings et al.[4a] which resulted in the reassignment of the absolute structure of natural varitriol; this was followed by Taylor[4b] et al. who used Horner-Wadsworth-Emmons (HWE) and Ramberg Backlund reactions. Several syntheses have since been reported for the synthesis of both natural[5] and unnatural analogues[6] of varitriol.

2. Results and discussion

Our synthetic approach to (−)-varitriol is depicted in Scheme 1. The target molecule can be obtained from the intermediate **2** involving a four step sequence, that is, deprotection of the silyl group, iodination of the resulting alcohol, and a one pot reduction of the ester and iodide functionalities with super hydride, followed by isopropylidene deprotection. Compound **2** can be obtained via a coupling reaction of sulfone **3** and aromatic aldehyde **4** by Julia–Kocienski olefination reaction. Sulfone **3** was synthesized from alcohol five involving a Mitsunobu reaction followed by an oxidation reaction. Alcohol **5** in turn was readily accessible from D-(−)-ribose in five steps. The aromatic aldehyde **4** was synthesized from commercially available *o*-anisic acid in four steps.

The synthesis of sulfone **3** started with D-(−)-ribose as shown in Scheme 2. Alcohol **5** [which we had synthesized earlier from D-(−)-ribose involving five steps[8]] was treated with 1-phenyl-1*H*-tetrazole-5-thiol, triphenylphosphine, diisopropyl azodicarboxylate in THF (Mitsunobu conditions) to provide sulfide **6** in 84% yield.[9] Sulfide **6** upon oxidation with H_2O_2 in the presence of a catalytic amount of ammonium molybdate in EtOH furnished the sulfone **3** in 70% good yield[10].

The other key aromatic fragment **4** was synthesized as shown in Scheme 3. *O*-Anisic acid was converted into compound **7** following earlier known procedures[8] in two steps amidation through acid chloride formation, and finally formylation. Amide **7** was then subjected to acidic hydrolysis to give the hemi acetal **8**, which upon exposure to diazomethane yielded aldehyde **4**.

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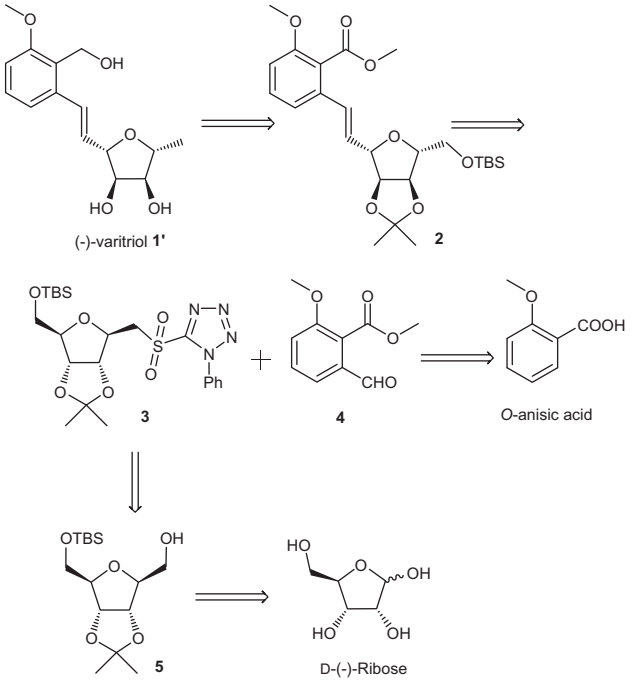
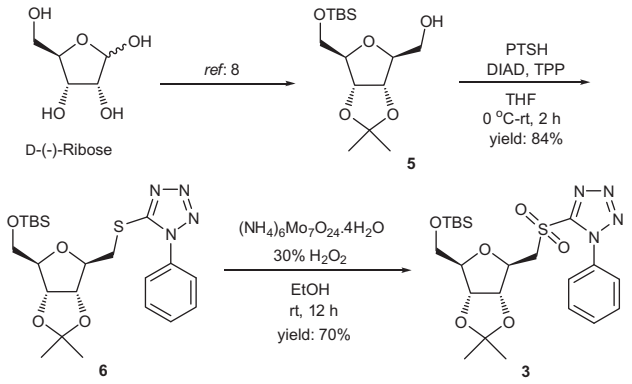
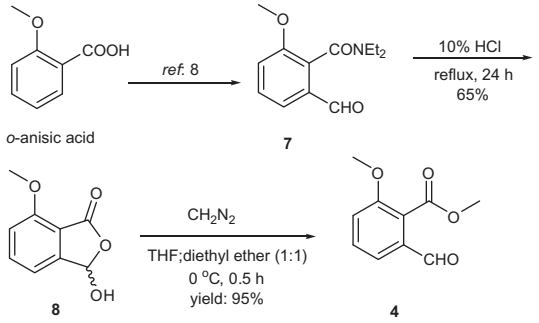


Scheme 1. Retrosynthesis of (−)-varitriol.

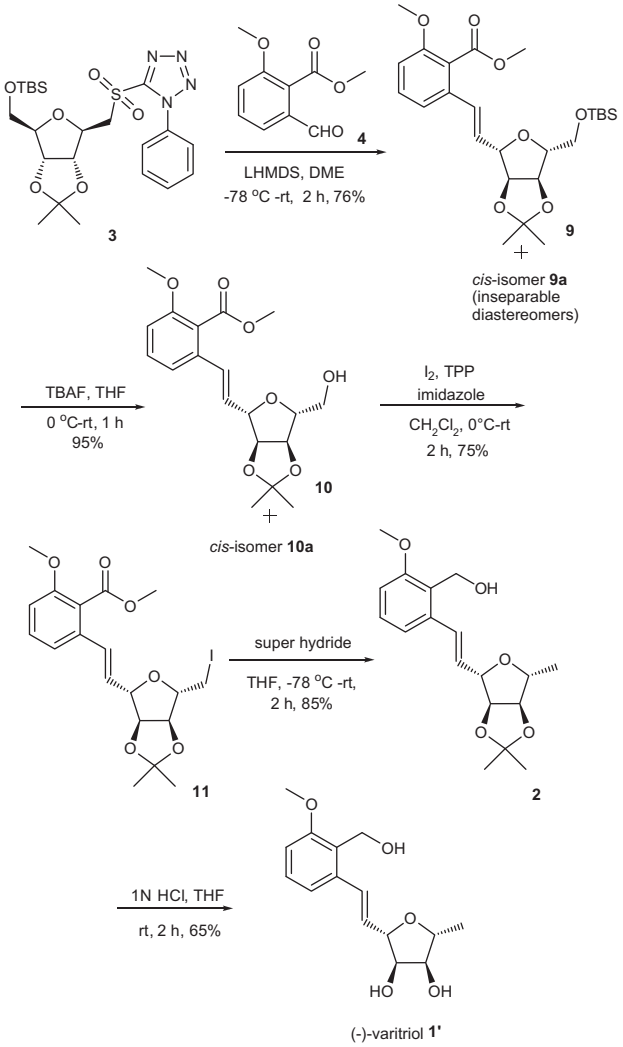


Scheme 2. Synthesis of sulfone **3**.



Scheme 3. Synthesis of Aromatic aldehyde **4**.

Treatment of **3** and **4** with lithium hexamethyl disilazane in THF provided the desired coupling product **9** along with its other diastereomer (*cis*-isomer **9a**) in a 65:35 ratio in 76% yield (Scheme 4).[11] Desilylation of **9** with TBAF provided primary alcohol **10**. Alcohol **10** was converted into the corresponding iodide **11** upon treatment with I_2, TPP, and imidazole at room temperature



Scheme 4. Synthesis of (−)-varitriol **1**′.

in 75% yield.[12] Compound **11** with both ester and halide functionalities then underwent reduction with $LiEt_3BH$ (super hydride) to provide the alcohol **2**. Finally, compound **2** upon isopropylidene deprotection with 1 N Hcl yielded the target product (−)-varitriol **1**'. The analytical data of this synthesized product were found to be identical to those previously reported.[4a]

3. Conclusion

In conclusion, we have accomplished the total synthesis of unnatural (−)-varitriol. The furanoside part was synthesized from readily available inexpensive D-(−)-ribose while the aromatic part was obtained from *o*-anisic acid. The one pot reduction of the two functionalities (ester and alkyl halide) has been achieved with super hydride. The present strategy could be further explored for the synthesis of other analogues to screen their biological activity and is currently being investigated in our laboratory.

4. Experimental

4.1. General

Column chromatography was performed using silica gel 60-120 mesh. All solvents were dried and distilled prior to use. IR spectra were recorded on a Perkin–Elmer Infrared spectrophotometer as

KBr wafers or neat or in $CHCl_3$ as a thin film. ^1H, and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or Varian Inova 500 MHz instrument using TMS as an internal standard. Mass spectra were recorded on Micro mass VG 7070H mass spectrometer for EI, VG Autospec mass spectrometer for FABMS, and micromass Quatro LC triple quadrupole mass spectrometer for ESI analysis. Syringe and septa techniques were used for moisture free reactions.

4.2. Procedures and analytical data

4.2.1. 5-(((3*aR*,4*R*,6*R*,6a*R*)-6-((*tert*-Butyldimethylsilyloxy) methyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylthio)-1-phenyl-1*H*-tetrazole 6

To a solution of compound **5** (3.0 g, 9.4 mmol, 1 equiv) and triphenyl phosphine (3.7 g, 14.2 mmol, 1.5 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (2.5 g, 14.3 mmol, 1.5 equiv) was added dry THF (30 mL). The reaction mixture was then cooled to 0 °C and diisopropyl azo dicarboxylate (2.89 mL, 14.1 mmol, 1.5 equiv) was added dropwise to the reaction mixture at 0 °C over 10 min. The reaction mixture was stirred at same temperature for 20 min, then allowed to warm to room temperature and stirred at the same temperature for 2 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was concentrated under reduced pressure, and purified by column chromatography R_f 0.40 (hexane-EtOAc, 90:10) to give **6** (3.8 g, 84%) as a colorless oil; $[\alpha]_D^{25} = -34.2$ (*c* 1.9, $CHCl_3$); IR υ_{max} (Neat): 2931, 1382, 1251, 1079, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61–7.52 (m, 5H), 4.70 (dd, *J* = 3.0, 6.0 Hz, 1H), 4.51 (dd, *J* = 4.5, 6.8 Hz, 1H), 4.34–4.29 (m, 1H), 4.12 (q, *J* = 2.3, 5.3 Hz, 1H), 3.79–3.59 (m, 4H), 1.51 (s, 3H), 1.33 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 133.6, 130.0, 129.7, 123.8, 113.8, 85.3, 84.2, 82.9, 82.1, 63.7, 36.2, 27.3, 25.9, 25.5, 18.3, −5.4, −5.6; ESIMS: *m*/*z* 479 $[M+H]^+$; HRESIMS: *m*/*z* 479.2164 $[M+H]^+$ (calcd for $C_{22}H_{35}N_4O_4SiS$: *m*/*z* 479.2148).

4.2.2. 5-(((3a*R*,4*R*,6*R*,6a*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylsulfonyl)-1-phenyl-1*H*-tetrazole 3

To a solution of ammonium molybdate tetrahydrate (1.96 g, 1.59 mmol, 0.2 equiv), in EtOH (20 mL) was added dropwise 30% H_2O_2 (7.94 mL, 79.5 mmol, 10 equiv) at 0 °C over 5 min and the reaction mixture was stirred at room temperature for 15 min; immediately the reaction mixture turned into a light yellow color. To this compound **6** (3.8 g, 7.95 mmol, 1 equiv) in EtOH was added dropwise at 0 °C over 10 min. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 12 h, after which the reaction mixture was quenched by the addition of solid Na_2SO_3 (20.0 g) portionwise at room temperature. The reaction mixture was then stirred at room temperature until the yellow color turned white, then the reaction mixture filtered on a pad of Celite, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography R_f 0.40 (hexane-EtOAc, 90:10) to give **3** (2.8 g, 70%) as a white solid; mp 82–84 °C. $[\alpha]_D^{25} = -46.7$ (*c* 3.1, $CHCl_3$); IR υ_{max} (Neat): 2931, 1352, 1256, 1081, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.64–7.55 (m, 5H), 4.65 (d, *J* = 5.9 Hz, 1H), 4.54–4.53 (m, 1H), 4.49–4.45 (m, 1H), 4.21 (dd, *J* = 8.9, 14.8 Hz, 1H), 4.15 (br s, 1H), 3.85 (dd, *J* = 3.9, 14.8 Hz, 1H), 3.60–3.51 (m, 2H), 1.49 (s, 3H), 1.32 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 133.1, 131.3, 129.3, 125.7, 113.7, 85.8, 84.6, 82.2, 79.9, 64.0, 59.6, 27.1, 25.9, 25.3, 18.4, −5.4, −5.7; ESIMS: *m*/*z* 511 $[M+H]^+$; HRESIMS: *m*/*z* 511.2032 $[M+H]^+$ (calcd for $C_{22}H_{35}N_4O_6SiS$: *m*/*z* 511.2046).

4.2.3. Methyl 2-formyl-6-methoxybenzoate 4

To a solution of *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (3.25 g, 15.19 mmol, 4 equiv), in diethyl ether (40 mL) was added KOH (1.06 g, 18.93 mmol, 5 equiv) in EtOH (15 mL) at room temperature; the reaction mixture was immediately distilled off until the reaction mixture turned yellowish to colorless, which resulted in a yellowish liquid containing CH_2N_2 in diethyl ether (40 mL). This freshly generated CH_2N_2 solution (20 mL) was added dropwise to the compound **8** (0.6 g, 3.8 mmol, 1 equiv) in THF:diethylether (1:1) (10 mL) at 0 °C over 20 min, and the reaction mixture was stirred at same temperature for 1 h. After complete consumption of the starting material, which was monitored by TLC, the reaction mixture was concentrated under reduced pressure to give **4** as a light yellowish oil R_f 0.30 (hexane-EtOAc, 20:80) (0.7 g, 95%); IR υ_{max} (KBr): 2955, 1738, 1698, 1472, 1268 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 167.2, 156.5, 134.1, 131.0, 123.2, 116.9, 56.2, 52.7; ESIMS: *m*/*z* 217 $[M+Na]^+$.

4.2.4. Methyl 2-((*E*)-2-((3a*S*,4*S*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinyl)-6-methoxybenzoate 10

To a solution of compound **4** (0.68 g, 3.52 mmol, 1 equiv) and compound **3** (1.44 g, 2.82 mmol, 0.8 equiv) in 1.2-dimethoxy ethane (20 mL) was added dropwise 1 M LiHMDS (5.28 mL, 1.5 equiv) at −78 °C over 15 min, then the reaction mixture was allowed to warm to room temperature over 1 h, and stirred at the same temperature for 12 h. After the reaction mixture was quenched with saturated aq NH_4Cl (20 mL), the reaction mixture was diluted with EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified on column chromatography R_f 0.70 (hexane-EtOAc, 80:20) to give a mixture of inseparable diastereomers **9** and **9a** in a 65:35 ratio (**LCMS**) (1.02 g, 76%) as a yellow oil.

To the solution of the inseparable diastereomeric mixture **9** and **9a** (1.02 g, 2.13 mmol, 1 equiv) in dry THF (10 mL) was added dropwise a 1.0 M TBAF solution in THF (3.19 mL, 1.5 equiv) over 10 min. at 0 °C. The reaction mixture was then allowed to warm to room temperature while stirring for 2 h. After complete consumption of the starting material, the reaction mixture was quenched with saturated aq. NH_4Cl (5 mL), and diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give crude material, which was purified by column chromatography R_f 0.30 (hexane-EtOAc, 60:40) to give separable diastereomers **10** and **10a** (0.73 g, 95%) as a colorless oil; **10**: $[\alpha]_D^{25} = -19.5$ (*c* 2.2, $CHCl_3$); IR υ_{max} (Neat): 3456, 2940, 1730, 1472, 1272, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (t, *J* = 8.4 Hz, 1H) 7.11 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* = 5.6, 15.9 Hz, 1H), 4.69–4.67 (m, 1H), 4.53–4.49 (m, 2H), 4.14–4.12 (m, 1H), 3.91 (s, 3H), 3.86–3.83 (m, 1H), 3.83 (s, 3H), 3.70 (dd, *J* = 4.7, 7.5 Hz, 1H), 2.02 (br s, 1H), 1.57 (s, 3H) 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 156.5, 135.2, 130.5, 130.3, 128.4, 122.6, 117.9, 114.6, 110.2, 85.2, 85.1, 84.6, 81.6, 62.9, 55.9, 52.4, 27.3, 25.3; ESIMS: *m*/*z* 387 $[M+Na]^+$; HRESIMS: *m*/*z* 387.1432 $[M+Na]^+$ (calcd for $C_{19}H_{24}O_7Na$: *m*/*z* 387.1419).

4.2.5. Methyl 2-((*E*)-2-((3a*S*,4*S*,6*S*,6a*S*)-6-(iodomethyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinyl)-6-methoxybenzoate 11

To a solution of compound **10** (0.26 g, 0.72 mmol, 1 equiv), triphenyl phosphine (0.37 g, 1.44 mmol, 2 equiv) and imidazole (0.14 g, 2.17 mmol, 3 equiv) in dry CH_2Cl_2 (8 mL) was added

molecular I_2 (0.40 g, 1.59 mmol, 2.2 equiv) at 0 °C. The reaction mixture was then stirred at the same temperature for 15 min, after which the reaction mixture was allowed to warm to room temperature, and stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC) the reaction mixture was quenched with a saturated aq. $Na_2S_2O_3 \cdot 5H_2O$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with brine (5 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude material, which was purified by column chromatography R_f 0.80 (hexane-EtOAc, 60:40) to give **11** (0.25 g, 75%) as a colorless oil; $[\alpha]_D^{25} = -39.6$ (*c* 6.3, $CHCl_3$); IR υ_{max} (Neat): 2927, 1731, 1467, 1269, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (t, *J* = 8.3 Hz, 1H) 7.12 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 5.3, 15.9 Hz, 1H), 4.58–4.51 (m, 3H), 4.04-4.00 (m, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.37–3.27 (m, 2H), 1.56 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 156.4, 135.0, 130.4, 130.0, 128.6, 122.8, 117.9, 114.7, 110.2, 85.2, 85.1, 85.0, 83.0, 55.9, 52.4, 27.2, 25.4, 6.9; ESIMS: *m*/*z* 475 $[M+H]^+$; HRESIMS: *m*/*z* 475.0634 $[M+H]^+$ (calcd for $C_{19}H_{24}O_6I$: *m*/*z* 475.0617).

4.2.6. (2-Methoxy-6-((*E*)-2-((3a*S*,4*S*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinyl)phenyl)methanol 2

To a solution of compound **11** (0.10 g, 0.21 mmol, 1 equiv) in dry THF (3 mL) was added 1 M $LiEt_3BH$ (1.68 mL, 8 equiv) in THF at −78 °C, over 10 min; then the reaction mixture was allowed to warm to room temperature. After complete consumption of the starting material, the reaction mixture was quenched with saturated $NaHCO_3$ (10 mL) at 0 °C followed by 30% H_2O_2 (3 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred at the same temperature for 5 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the product which was purified by column chromatography R_f 0.35 (hexane-EtOAc, 50:50) to give **2** (0.057 g, 85%) as a colorless oil; $[\alpha]_D^{25} = -36.6$ (*c* 1.5, $CHCl_3$); IR υ_{max} (Neat): 3452, 2932, 1579, 1467, 1262, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.9 Hz, 1H) 7.09–7.04 (m, 2H), 6.82 (d, *J* = 8.9 Hz, 1H), 6.15 (dd, *J* = 6.9, 15.9 Hz, 1H), 4.78 (s, 2H), 4.54 (dd, *J* = 4.9, 6.9 Hz, 1H), 4.45 (t, *J* = 5.9 Hz, 1H), 4.33 (dd, *J* = 3.9, 5.9 Hz, 1H), 4.04 (qt, *J* = 5.9, 10.9 Hz, 1H), 3.86 (s, 3H), 1.57 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 137.3, 130.7, 129.4, 128.8, 126.4, 119.3, 115.0, 119.7, 86.3, 85.5, 84.8, 80.3, 56.8, 55.6, 27.4, 25.5, 19.1; ESIMS: *m*/*z* 343 $[M+Na]^+$; HRESIMS: *m*/*z* 343.1512 $[M+Na]^+$ (calcd for $C_{18}H_{24}O_5Na$: *m*/*z* 343.1521).

4.2.7. (2*S*,3*R*,4*S*,5*R*,*E*)-2-(2-(Hydroxymethyl)-3-methoxystyryl)-5-methyl-tetrahydrofuran-3,4-diol 1′

To a solution of compound **2** (0.025 g, 0.078 mmol, 1 equiv) in THF (3 mL) was added 1N HCl (3 mL) and then the reaction mixture was stirred at room temperature for 3 h. After complete conversion of the starting material, the reaction mixture was quenched with solid $NaHCO_3$ (2.0 g), diluted with EtOAc (5 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude product, which was purified by column chromatography R_f 0.30 (hexane-EtOAc, 20:80) to give (−)-varitriol **1′** (0.013 g, 65%) as a white solid; mp 102–104 °C, $[\alpha]_D^{25} = -29.2$ (*c* 0.7, MeOH); lit.[4a] $[\alpha]_D^{rt} = -18.2$ (*c* 0.0033 g ml^{-1}, MeOH); IR υ_{max} (KBr): 3405, 2926, 1469, 1249, 1094 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 7.22 (t, *J* = 7.9 Hz, 1H), 7.15 (br s, 1H), 7.11 (d, *J* = 5.5, Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.20 (dd, *J* = 6.6, 15.9 Hz, 1H), 4.70 (br s, 2H), 4.30-4.27 (m, 1H), 3.92–3.88 (m, 1H), 3.85–3.78 (m, 1H), 3.82 (s, 3H), 3.70–3.67 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 159.9, 139.9, 133.4, 130.3, 130.2, 128.9, 120.3, 111.6, 86.3, 80.9, 78.1, 77.4, 57.0, 56.4, 20.5; ESIMS: *m*/*z* 303 $[M+Na]^+$; HRESIMS: *m*/*z* 303.1197 $[M+Na]^+$ (calcd for $C_{15}H_{20}O_5Na$: *m*/*z* 303.1208).

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