An Efficient Total Synthesis and Absolute Configuration Determination of Varitriol

Ryan T. Clemens and Michael P. Jennings*

Department of Chemistry, University of Alabama, 500 Campus Dr. Tuscaloosa, AL 35478-0336

jenningm@bama.ua.edu

Supporting Information

General Procedure ^{1}H and ^{13}C NMR spectra were collected on either a 360 (90) MHz or 500 (125) MHz Bruker spectrometer. Chemical shifts were reported in parts per million relative to chloroform ($CHCl_3$, 7.24 ppm) or (acetone, 2.2 ppm) as the internal reference, and coupling constants were reported in Hertz. HRMS determination was performed in the laboratory of mass spectrometry at the University of Alabama. Solvents and reagents were used as purchased without further purification.

Styrene (7)

To a stirred solution of potassium vinyltrifluoroborate (1.35 g, 10.1 mmol, 1.1 equiv), $PdCl_2(dppf){\cdot}CH_2Cl_2$ (0.375 g, 0.46 mmol, 5 % equiv), Et_3N (1.7 mL, 12.0 mmol, 1.3 equiv) in EtOH (60.0 mL) was added triflate **3** (3.0 g, 9.2 mmol). The mixture was allowed to reflux for 4.5 h under an argon environment. The mixture was then cooled to room temperature, diluted with water, and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica, 30% ethyl acetate in hexanes) afforded **7** (R_f = 0.50, 30% ethyl acetate in hexanes) as colorless oil (1.75 g, 93%).[1]

Methoxy Benzyl Ester (8)

Benzyl alcohol (0.13 mL, 1.2 mmol) was added to a suspension of NaH (6 mg, 0.25 mmol) in DMF (5 mL) at 0 ^oC, and the mixture was stirred for 30 minutes while being warmed to ambient temperature. Styrene **7** (25 mg, 0.215 mL in THF, 0.12 mmol) was introduced and allowed to stir for 3 h while TLC showed consumption of starting material. The suspension was neutralized with aqueous 1 M HCl (5 mL), buffered with saturated aqueous $NaHCO_3$, and extracted with ether (3 x 5 mL). The combined ether extracts were washed with water (10 mL) and dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica, 30% ethyl acetate in hexanes) afforded the free phenol (R_f = 0.61, 30% ethyl acetate in hexanes) as colorless oil (0.030 g, 97%). The free phenol (0.509 g, 2.0 mmol) was then dissolved in THF (8 mL) and treated with potassium carbonate (0.689 g, 5.0 mmol, 2.5 equiv), and MeI (0.15 mL, 2.4 mmol, 1.2 equiv) at 0 ^oC. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was then quenched with water, and partitioned between ethyl acetate (15 mL) and water (10 mL). The water layer was washed with additional ethyl acetate (2 x 10 mL). The organic phase was combined and washed with brine (20 mL) and then dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded the methoxy benzyl ester **8** (R_f = 0.55, 30% ethyl acetate in hexanes) as a colorless oil (0.475 g, 88%). NMR (360 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.30 (d, 1H, J = 11.1), 5.42 (s, 2H), 5.74 (d, 1H, J = 17.4), 6.66 (dd, 1H, J = 10.9, 17.6), 6.86 (d, 1H, *J* = 7.5), 7.18 (d, 1H, *J* = 8.0), 7.29-7.43 (m, 4H), 7.47-7.49 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 55.9, 67.0, 110.2, 117.1, 117.6, 120.1, 128.2, 128.3, 130.4, 133.3, 135.7, 136.4, 156.5, 167.8; IR (CH_2Cl_2): 1726, 1574, 1471, 1266, 1070, 1027 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{16}O_3$ $(M)^+$: 268.1104, found: 268.1099.

Styrene (2)

To a stirred solution of benzylic alcohol derived from the reduction of **8** with DIBAL (0.149 g, 0.91 mmol) dissolved in 4 mL of DMF was added TBSCl (0.164 g, 1.1 mmol, 1.2 equiv) and imidazole (0.185 g, 2.7 mmol, 3 equiv). The mixture was allowed to stir for 6 h, by which time TLC (10 % ethyl acetate/hexanes) showed complete conversion of starting material to product. The reaction was then quenched with water and extracted with ether. The ether phases were combined and washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica, 30% ethyl acetate in hexanes) afforded styrene **2** (R_f = 0.60, 30% ethyl acetate in hexanes) as colorless oil (0.244 g, 97%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 3.84 (s, 3H), 4.88(s, 2H), 5.36 (dd, 1H, *J* = 11.0, 1.5), 5.73 (dd, 1H, *J* = 17.5, 1.5), 6.82 (d, 1H, *J* = 7.2), 7.18 (d, 1H), 7.23 (t, 1H), 7,27 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ -5.2, 18.4, 25.9, 55.5, 55.9, 76.6, 76.9, 109.8, 115.8, 118.2, 126.3, 128.5, 135.0, 139.6, 157.3; IR (CH_2Cl_2): 2956, 2929, 2888, 2856, 1576, 1472, 1265, 1063 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{26}O_2Si$ $(M-C_4H_9)$+: 221.0998, found: 221.0999.

β-*C*-furanoside (6)

To a stirred solution of 1-*O*-acetyl-2,3,5,-tri-*O*-benzoyl-β-*C*-furanose **9** (10 g, 19.8 mmol) in CH_2Cl_2 (25 mL) was added cyanotrimethylsilane (5.5 ml, 41.6 mmol, 2.1 equiv). The reaction was then treated slowly with $BF_3{\cdot}OEt_2$ (2.5 mL, 19.8 mmol, 1 equiv). The darkening solution was stirred for 4.5 h at room temperature and then poured slowly into a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The ether layers were combined and washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded the methoxy β-*C*-furanoside **6** as a colorless oil (7.93 g, 85%).[2]

β-*C*-furanoside (10)

A solution of β-*C*-furanoside **6** (3.69 g, 8.4 mmol) in CH_2Cl_2 (30 mL) was added with stirring to an ice-cooled saturated methanolic ammonia solution (54 mL) and was kept at 0 ^{o}C for 4.5 hrs. The solvent was then evaporated *in vacuo*, and the residue was dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$, and then washed with water. The ethyl acetate was dried and evaporated. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded the methoxy β-*C*-furanoside **10** as a white solid (1.81 g, 82%).[2]

β-*C*-furanoside (11)

To a stirred solution of 69-72% perchloric acid (0.30 mL) in 2,2-dimethoxypropane (2.11 mL) and acetone (13 mL) was added β-*C*-furanoside **10** (1.78 g, 6.8 mmol). The resulting mixture was allowed to stir for 2 h at rt. The solution was neutralized with ammonium hydroxide and evaporated to dryness, leaving a residue that was dissolved in CH_2Cl_2 and washed twice with water. The CH_2Cl_2 was then dried and evaporated and the residue crystallized from ether-hexane to afford **11** (2.38g, 95 %).[2]

Hydroxyl β-*C*-furanoside (5)

To a stirred solution of Raney nickel (1 mL, 16.6 mmol), N,N'-diphenylethylenediamine (0.244 g, 0.8 mmol), and sodium hypophosphite (0.488 g, 4.6 mmol) in 4 mL mixture of pyridine, acetic acid, and water (2:1:1) was added **11** (0.244 g, 0.8 mmol). The mixture was allowed to vigorously stirred at room temperature for 1 h and then filtered thru Celite. The solid was washed well with CH_2Cl_2 and the filtrate was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (silica, 15% ethyl acetate in hexanes) afforded the aminal β-*C*-furanoside (0.331 g, 82%) as a colorless oil. The corresponding aminal β-*C*-furanoside (0.500 g, 1.0 mmol) was placed in THF at –78 ^oC and was subsequently added to LAH (3 mL, of a 1 M solution in THF, 3.0 equiv). The mixture was stirred at –78 ^oC for 3 h. Then the mixture was slowly poured into a stirring solution of Rochelle's salt (5 mL), hexanes (10 mL) and ether (10 mL). The mixture was allowed to stir until two layers were clearly visible. The ether phase was collected and the aqueous phase was washed with additional ether (10 mL). The extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded the free hydroxy β-*C*-furanoside **5** (0.364 g, 92%) as white solid.[3]

Aminal β-*C*-furanoside (12)

To a stirred solution of **5** (0.585 g, 1.5 mmol) in dry pyridine (12.0 mL) at 0 °C was added *p*-toluenesulfonyl chloride (0.591 g, 3.1 mmol, 2.1 equiv). The mixture was allowed to stir overnight at room temperature. The reaction was then quenched with saturated NH_4Cl, washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica, 15% ethyl acetate in hexanes) afforded the tosylate (0.772 g, 95%) as white solid. The tosylate (0.479 g, 0.87 mmol) in THF (10.0 mL) was then treated with LAH (2.61 mL, 3 equiv of a 1 M solution in THF) at –78 °C. The reaction was then allowed to warm to room temperature and then refluxed for 3 hours. The reaction was poured directly (slowly) into a solution of Rochelle's salt (5 mL) and hexanes (17 mL) and allowed to stir until two layers were distinguishable. The mixture was then extracted with ether twice (10 mL) and the extracts were filtered thru a short plug of silica gel. The organics were then dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded **12** (R_f = 0.64, 30% ethyl acetate in hexanes) as white solid (0.612 g, 92%). $[a]^{25}_D$ -31.8° (c 0.128, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.24(d, 3H, *J* = 6.4), 1.26 (s, 3H), 1.41 (s, 3H), 3.62-3.68 (m, 2H), 3.71-3.83 (m, 2H), 3.90 (m, 1H, *J* = 6.3, 12.6), 4.03 (dd, 1H, *J* = 4.8, 6.9), 4.30 (d, 1H, *J* = 4.7), 4.64 (dd, 1H, *J* = 4.8, 6.8), 5.54 (s, 1H), 6.76-6.82 (m, 4H), 6.87 (s, 1H), 6.89 (s, 1H), 7.24-7.31 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 18.8, 25.7, 27.5, 46.5, 47.2, 74.5, 79.7, 81.2, 85.2, 85.8, 113.5, 113.5, 114.4, 117.7, 129.3, 146.4, 146.6; IR (CH_2Cl_2): 3049, 2984, 1597, 1502, 1265, 1077, 739 cm^{-1}; HRMS(EI) calcd for $C_{23}H_{28}N_2O_3$ $(M)^+$: 380.2100, found: 380.2104.

β-*C*-furanoside (4)

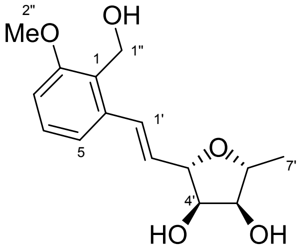
A solution of *p*-toluenesulfonic acid monohydrate (0.125 g, 0.66 mmol, 2.5 equiv) in acetone (2 mL) was added with stirring to an ice-cooled solution of **12** (0.100 g, 0.26 mmol) in methylene chloride (5 mL). After 5 min at 0 °C, the mixture was allowed to warm to room temperature over 40 min. T.L.C. showed a trace of starting material so an additional 50 mg of *p*-toluenesulfonic acid monohydrate was added. After 15 min, the reaction was completed and the mixture was filtered. The precipitate was washed with methylene chloride and the combined filtrates were evaporated *in vacuo* without heating. The residue was dissolved in methylene chloride, and washed three times with cold water, dried with $MgSO_4$, and evaporated again without heat. The volatility of the aldehyde was suspect, and was immediately added to a solution was immediately added to a solution of prepared methylene Wittig reagent in ether. After stirring overnight, the reaction mixture was filtered to remove the solid and the solid was washed with additional ether. The filtrate and washing were combined and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded β-*C*-furanoside **4** ($R_f = 0.50$, 30% ethyl acetate in hexanes) as clear oil (0.013 g, 56%).

$[\alpha]^{25}_D$ -18.3° (c 6.3 x 10^{-2}, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, 3H, *J* = 6.3), 1.30 (s, 3H), 1.51 (s, 3H), 3.96 (m, 1H), 4.22-4.26 (m, 2H), 4.41 (t, 1H, *J* = 5.1), 5.18 (d, 1H, *J* = 10.9), 5.34 (d, 1H, *J* = 17.4), 5.87 (m, 1H, *J* = 6.3, 10.3, 14.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 25.4, 27.3, 80.1, 84.9, 85.3, 86.1, 114.8, 117.1, 135.9; IR (CH_2Cl_2): 2983, 2934, 2875, 2250, 1383, 1212, 1080 cm^{-1}; HRMS(EI) calcd for $C_{10}H_{16}O_3$ (M^+): 184.1099, found: 184.1104.

(-)-Varitriol (1)

To a stirred solution of styrene **2** (26 mg, 0.01 mmol) and β-*C*-furanoside **4** (17 mg, 0.01 mmol) in 3 mL of DCM was added Grubbs 2nd generation catalyst **14** (5 % mol). The mixture was allowed to reflux at 40 ^{o}C for 18 hr. The reaction was then cooled to rt and concentrated by reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded protected natural product **15** (R_f = 0.60, 30% ethyl acetate in hexanes) as brown oil (19 mg, 59%). The protected natural product **15** was then dissolved in 2 mL of THF and added to 2 mL of 1 M HCl. The reaction was allowed to stir at room temperature for 3 hr. The reaction was then quenched with saturated Na_2CO_3 and extracted with ethyl acetate. The extracts were combined, dried of $MgSO_4$, and concentrated. Preparatory TLC (60 % dichloromethane in acetone) afforded pure (-)-varitriol (R_f = 0.20, 60% methylene chloride in acetone) as a clear oil (9 mg, 75%). $[\alpha]^{25}_{D}$ -18.2^{O} (c 3.3 x 10^{-3}, MeOH); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 1.27 (d, 3H, *J* = 6.2), 3.62 (t, 2H, *J* = 5.7), 3.74 (q, 1H, *J* = 5.6), 3.82 (s, 3H), 3.85 (quint., 3H, *J* = 6.0), 3.93 (q, 1H, *J* = 5.5), 4.02 (d, 1H, *J* = 5.6), 4.24 (d, 1H, *J* = 5.5), 4.29 (t, 1H, *J* = 5.5), 4.71 (d, 2H, *J* = 5.7), 6.20 (dd, 1H, *J* = 15.8, 6.6), 6.89 (d, 1H, *J* = 8.0), 7.11 (d, 1H, *J* = 6.6), 7.14 (d, *J* = 15.8, 1H), 7.22 (t, 1H, *J* = 8.0); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 19.6, 55.6, 56.2, 76.6, 77.3, 80.1, 85.5, 110.8, 119.4, 128.1, 129.3, 129.4, 132.6, 139.1, 159.1); IR (CH_2Cl_2): 3055, 2987, 2306, 1264 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{20}O_5$ (M^{+}): 280.1311, found: 280.1313.

^{1}H and ^{13}C NMR tabular comparison between the natural and synthetic varitriol in d_6-acetone.



Chemical Shift (ppm) -- natural	Proton	Chemical Shift (ppm) --synthetic
7.22	H-4	7.22
7.14	H-1’	7.14
7.13	H-5	7.11
6.89	H-3	6.89
6.19	H-2’	6.20
4.72	H-1’’	4.71
4.62	OH-C-4’	4.24
4.41	OH-C-5’	4.02
4.32	H-3’	4.29
3.94	H-4’	3.93
3.84	H-6’	3.85
3.82	H-2’’	3.82
3.80-3.70	OH-C-1’’	3.62
3.74	H-5’	3.74
1.27	H-7’	1.27

Chemical Shift (ppm) -- natural	Carbon	Chemical Shift (ppm) --synthetic
158.9	C-2	159.1
139.0	C-6	139.1
132.3	C-2’	132.6
129.4	C-1’	129.4
129.3	C-4	129.3
127.9	C-1	128.1
119.3	C-5	119.4
110.7	C-3	110.8
85.2	C-3’	85.5
80.1	C-6’	80.1
77.2	C-5’	77.3
76.5	C-4’	76.6
56.0	C-2’’	56.2
55.5	C-1’’	55.6
19.5	C-7’	19.6

References:

1. S. Bolshakov, J. L. Leighton, *Org. Lett.*, 2005, **7**, 3809.

2. H. P. Albrecht, D. B. Repke, J. G. Moffatt, *J. Org. Chem.*, 1973, **38**, 1836.

3. M. J. Robins, J. M. R. Parker, *Can. J. Chem.*, 1983, **61**, 317.