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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

J. Am. Chem. Soc., 1996, 118(43), 10660-10661, DOI: [10.1021/ja962163m](https://doi.org/10.1021/ja962163m)

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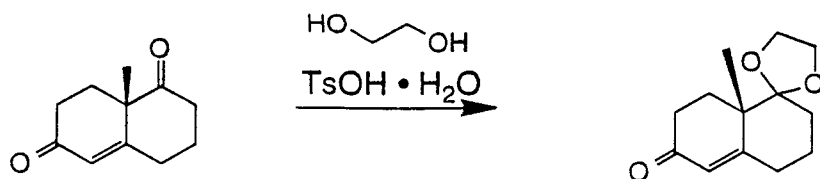
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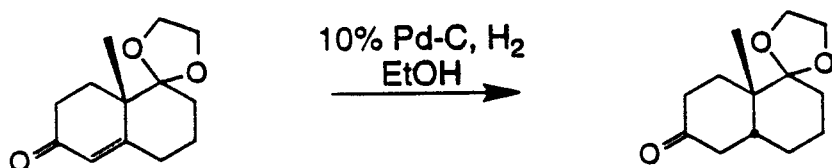
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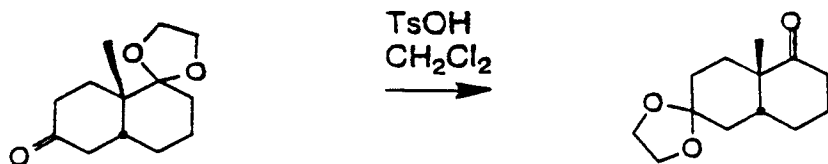
Ethylene glycol (54 mL), and TsOH·H₂O (154 mg, 0.84 mmol) were added to a solution of Miescher-Wieland ketone (15.6 g, 87.5 mmol) in benzene (200 mL). The mixture was refluxed for 40 min under a Dean-Stark water separator. The solution was then cooled to 0 °C, and powdered NaHCO₃ (3.0 g) was added. The mixture was diluted with saturated NaHCO₃ solution (200 mL), and benzene (200 mL). After separation, the aqueous layer was extracted with ether (200 mL x 3). The combined layers were washed with brine (100 mL), and the organic layer was dried over MgSO₄. The solvent was removed, and the residue was purified by silica gel column chromatography (eluant: hexanes/ethyl acetate 4/1 to 1/1). The monoketal (17.3 g, 89%) was obtained as a white solid, mp 56-57 °C

¹H NMR (CDCl₃) δ 5.63 (s, 1H) 4.0-3.9 (m, 4H) 2.5-2.2 (m, 4H) 1.9-1.6 (m, 4H) 1.37 (s, 3H)
¹³C NMR (CDCl₃) δ 198.9, 167.5, 125.5, 112.3, 65.2, 64.9, 44.9, 33.8, 31.3, 29.9, 26.8, 21.6, 20.4
 IR (CHCl₃) 1664, 1519, 1422, 1214, 1158, 770, 754 cm⁻¹
 HRMS Calcd for C₁₃H₁₈O₃ 222.1256; found 222.1260
 [α]²³_D +115.4 (c 0.97, CHCl₃)



The ketal enone (57.2 g, 257 mmol) in EtOH (50 mL) was added to a suspension of 10% Pd-C (3.0 g) in EtOH (300 mL). Hydrogen was bubbled through the suspension until the enone had disappeared (TLC). The catalyst was removed by filtration, and was washed with EtOH (30 mL x 3). The alcohol was removed on a rotary evaporator, and the residue was purified on a silica gel column (eluant: hexanes/ether 1/1) to give the saturated ketone (57.6 g, quant.), as a colorless oil.

¹H NMR (CDCl₃) δ 3.98 (m, 4H) 2.65 (dd, 1H, *J* = 5.6, 3.2 Hz) 2.5-2.3 (m, 2H) 2.2-2.0 (m, 2H) 1.8-1.4 (m, 5H) 1.21 (s, 3H) 1.4-1.2 (m, 1H)
¹³C NMR (CDCl₃) δ 211.9, 112.3, 65.0, 64.8, 44.0, 42.6, 37.8, 29.6, 29.0, 28.2, 22.1, 17.7
 IR (neat) 2946, 2884, 1713, 1090, 1032 cm⁻¹
 HRMS Calcd for C₁₃H₂₀O₃ 224.1412; found 224.1413
 [α]²²_D +35.6 (c 0.46, CHCl₃)



Anhydrous TsOH (220 mg, 1.16 mmol) was added to a solution of the monoketal (2.60 g, 11.59 mmol) in CH₂Cl₂ (20 mL). The resulting mixture was stirred for 20 h. Powdered NaHCO₃ (1.0 g) was added, the mixture was diluted with CH₂Cl₂ (200 mL), and saturated NaHCO₃ solution was added. The aqueous layer was extracted with CH₂Cl₂ (100 mL x 3), and the combined layers were washed with brine (100 mL). After the extract had been dried over MgSO₄, the solvent was removed under vacuum, and the residue was chromatographed on a silica gel column (eluant: hexanes/ether 7/3-1/1) to give the isomeric ketal (2.21 g, 85%) as a colorless oil.

¹HNMR (CDCl₃) δ 3.96 (s, 4H) 2.55 (ddd, 1H, *J* = 15.2, 4.8, 10.4 Hz) 2.3-2.1 (m, 4H) 1.90 (m, 2H) 1.7-1.4 (m, 6H) 1.24 (s, 3H)

¹³CNMR (CDCl₃) δ 214.9, 109.4, 64.2, 42.7, 37.8, 37.4, 31.8, 25.9, 22.4

IR (neat) 2934, 2880, 1704, 1089, 1076 cm⁻¹

HRMS Calcd for C₁₃H₂₀O₃ 224.1412; found 224.1407

[α]_D²³ -25.8 (c 0.96, CHCl₃)



To a solution of ketone (1.6 g, 7.13 mmol) and Et₃N (7.5 mL, 53.5 mmol) in DMF (10 mL), TMSCl (3.6 mL, 28.5 mmol) was added. The whole mixture was stirred at 120 °C for 48 h, under Ar. The reaction mixture was then cooled to 0 °C, followed by addition of hexanes (100 mL). The organic layer was washed with saturated NaHCO₃ solution (40 mL x 2), and the aqueous layer was extracted with hexanes (100 mL x 2). The combined extracts were washed with brine (50 mL) and were dried over MgSO₄. The solvent was removed, and the residue was purified by silica gel column chromatography (eluant: hexanes/ether 9/1 - 4/1) to give the TMS enol ether (2.00 g, 95%) as a colorless oil.

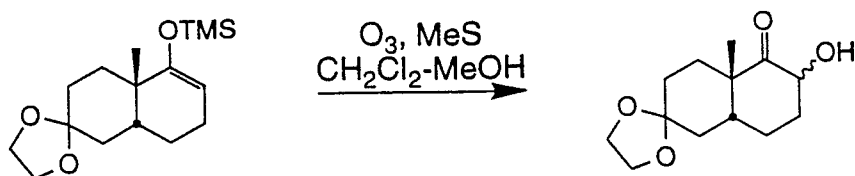
¹HNMR (CDCl₃) δ 4.60 (t, 1H, *J* = 4.4Hz) 3.94 (s, 4H) 2.2-1.9 (m, 2H) 1.9-1.6 (m, 3H) 1.6-1.2 (m, 6H) 1.08 (s, 3H) 0.17 (s, 9H)

¹³CNMR (C₆D₆) δ 154.3, 109.7, 101.1, 64.2, 39.7, 38.1, 36.5, 32.6, 32.5, 27.9, 24.0, 21.5, 0.39

IR (neat) 2950, 2882, 1658, 1442 cm⁻¹

HRMS Calcd for C₁₆H₂₈O₃Si 296.1808; found 296.1820

[α]_D²⁴ +62.6 (c 1.05, toluene)



Ozone was bubbled through a solution of the TMS enol ether (43.3 g, 146.05 mmol) in CH_2Cl_2 (200 mL) and MeOH (200 mL), at $-78\text{ }^\circ\text{C}$, until the reaction mixture showed a light blue color. Oxygen was then bubbled in to remove excess ozone, and Me_2S (20 mL) was added. The reaction mixture was allowed to come slowly to room temperature, and was stirred at room temperature for 12 h. After evaporation of the solvent, the residue was chromatographed on a silica gel column (eluant: hexanes/ethyl acetate 4/1) to give the mixture of epimeric α -hydroxy ketones (28.0 g, 80%), as a colorless oil.

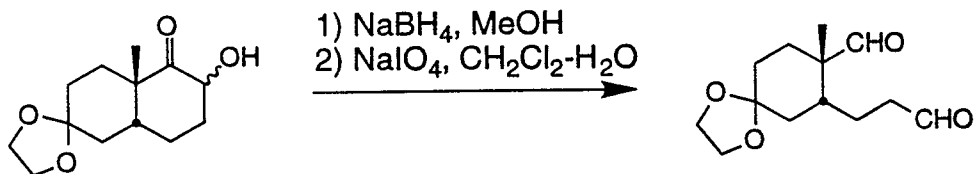
major ketol isomer

$^1\text{H NMR}$ (CDCl_3) δ 3.93 (m, 4H) 2.57 (ddd, 1H, $J = 10.4, 12.2, 1.8$ Hz) 2.3-2.1 (m, 4H) 1.89 (m, 2H) 1.7-1.4 (m, 6H) 1.24 (s, 3H)

$^{13}\text{C NMR}$ (CDCl_3) δ 215.6, 107.6, 71.7, 64.3, 64.1, 47.6, 43.9, 35.4, 35.0, 30.3, 29.1, 25.5, 19.2

IR (neat) 1721, 1471, 1111 cm^{-1}

HRMS Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_4$ 240.1361; found 240.1366



To a solution of α -hydroxy ketone (5.4 g, 21.22 mmol) in MeOH (30 mL), NaBH_4 (1.6 g, 42.44 mmol) was added in several portions, at $0\text{ }^\circ\text{C}$. The mixture was stirred at room temperature for 2 h. After evaporation of the MeOH, water (30 mL) was added to the residue, and the aqueous layer was extracted with CH_2Cl_2 (100 mL \times 3). The combined layers were washed with brine (40 mL), and dried over MgSO_4 . The solvent was removed. To a solution of the crude diol in CH_2Cl_2 (90 mL) and water (70 mL), NaIO_4 (9.4 g, 31.83 mmol) was added at $0\text{ }^\circ\text{C}$, with vigorous stirring. After 30 min, the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (200 mL \times 2), and the combined extracts were washed with brine (50 mL). After drying over MgSO_4 , the solvent was removed, and purification by silica gel column chromatography gave the dialdehyde (4.8 g, 94%) as a colorless oil.

glycol (major isomer)

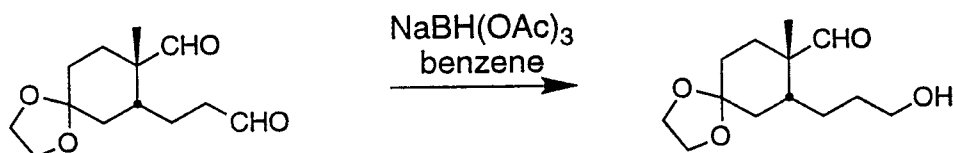
$^1\text{H NMR}$ (CDCl_3) δ 4.42 (ddd, 1H, $J = 3.6, 6.8, 10.0$ Hz) 4.0-3.9 (m, 4H) 3.7 (d, 1H, $J = 3.6$ Hz) 2.42 (m, 1H) 2.35 (m, 1H) 2.2-1.3 (m, 9H) 1.27 (s, 3H)
 MS 243 M^{+1} , 225 $\text{M}^{+1}(-\text{H}_2\text{O})$, 224 $\text{M}^{+1}(-\text{H}_2\text{O})$

glycol (minor isomer)

$^1\text{H NMR}$ (CDCl_3) 4.42 (ddd, 1H) 3.93 (m, 4H) 2.3-2.1 (m, 2H) 1.8-1.1 (m, xH) 1.29 (s, 3H)

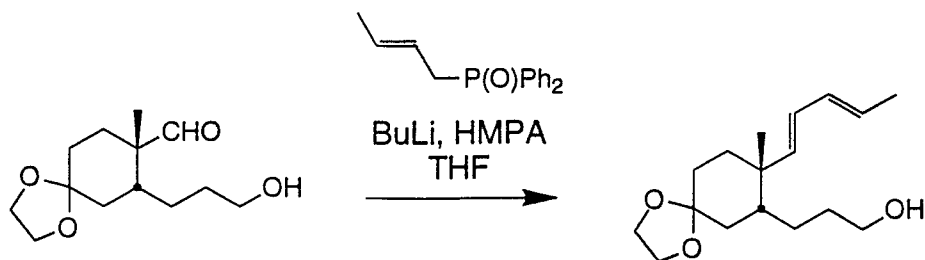
dialdehyde

$^1\text{H NMR}$ (CDCl_3) δ 9.69 (t, 1H, $J = 2.0$ Hz) 9.52 (s, 1H) 3.85 (m, 4H) 2.46 (m, 1H) 2.33 (m, 1H) 1.97 (m, 1H) 1.84 (m, 1H) 1.8-1.5 (m, 7H) 1.07 (s, 3H)
 $^{13}\text{C NMR}$ (C_6D_6) δ 204.7, 200.7, 108.6, 64.3, 64.2, 48.3, 42.2, 41.9, 36.9, 32.3, 32.0, 22.1, 21.4
 IR (neat) 2942, 2882, 1722, 1082 cm^{-1}
 $[\alpha]_{\text{D}}^{22} -188$ (c 0.48, CHCl_3)
 MS 240 M^{+}



$\text{NaBH}(\text{OAc})_3$ (13.6 g, 64.09 mmol) was added in several portions, at 0 °C, to a solution of dialdehyde (14.0 g, 58.26 mmol) in benzene (400 mL). After 12 h, the reaction was quenched with saturated NaHCO_3 solution, the aqueous layer was extracted with CH_2Cl_2 (200 mL \times 3). The combined layers were washed with brine (100 mL), and the organic layer was dried over MgSO_4 . The solvent was evaporated, and the residue was chromatographed on a silica gel column (eluant: hexanes/ethyl acetate 1/1-1/4) to give the hydroxy aldehyde (9.0 g, 67%).

$^1\text{H NMR}$ (CDCl_3) δ 9.56 (s, 1H) 3.85 (s, 4H) 3.55 (m, 2H) 2.0-1.2 (m, 11H) 1.03 (s, 3H)
 $^{13}\text{C NMR}$ (C_6D_6) δ 205.0, 108.9, 64.3, 64.2, 62.5, 48.3, 42.6, 37.5, 32.6, 32.2, 31.6, 26.2, 21.6
 IR (neat) 3402, 2945, 2362, 1716, 1082, 1025, 947 cm^{-1}
 HRMS Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_4$: 242.1518; found 242.1527
 $[\alpha]_{\text{D}}^{23} -10.4$ (c 0.62, CHCl_3)



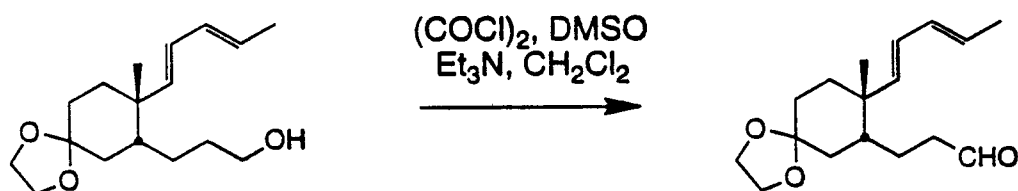
BuLi (1.21 mL, 2.23 N hexane solution, 0.269 mmol) was added dropwise at 0 °C, under Ar, to a solution of (*E*)-butenyldiphenylphosphine oxide (690 mg, 0.269 mmol) and HMPA (0.94 mL, 0.538 mmol) in THF (3 mL). After 20 min, the ketal aldehyde (193.7 mg, 0.799 mmol) in THF (2 mL) was added slowly, at 0 °C, to the red reaction mixture. The flask was rinsed with THF (1 mL x 2). The mixture was stirred at 0 °C for 2 h, then at room temperature for 9 h. The reaction mixture was quenched with saturated NH₄Cl solution (20 mL), and the aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined layers were washed with saturated NaHCO₃ solution (20 mL) and brine (20 mL). After drying over MgSO₄, the solvent was removed, and the residue was purified by silica gel column chromatography to give the diene (172.6 mg, 77%) which was obtained as a colorless oil.

¹HNMR (CDCl₃) δ 6.00 (m, 2H) 5.78 (m, 1H) 5.62 (m, 1H) 3.94 (s, 4H) 3.62 (bs, 2H) 1.74 (d, 3H, *J* = 6.4 Hz) 1.8-1.3 (m, 10H) 1.06 (s, 3H) 0.95 (m, 1H)

¹³CNMR (CDCl₃) δ 133.9, 132.2, 129.3, 127.4, 109.3, 64.2, 64.2, 63.2, 44.3, 38.3, 37.5, 36.6, 31.2, 31.1, 26.8, 26.4, 18.0

IR (neat) 3429, 3017, 2935, 1123, 1090, 991, 945 cm⁻¹

HRMS: Calcd for C₁₇H₂₈O₃ 280.2038; found 280.2046



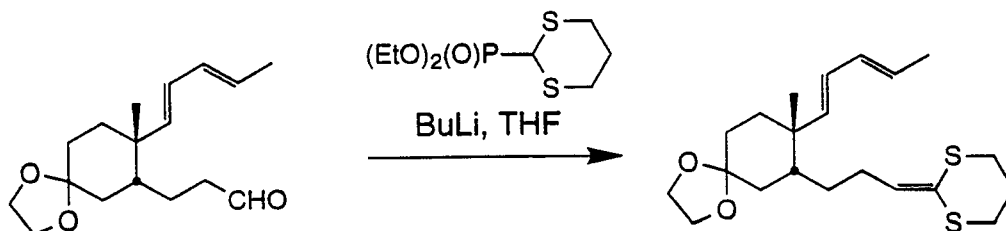
To a solution of (COCl)₂ (1.6 mL, 2 M solution in CH₂Cl₂, 3.21 mmol), DMSO (0.31 mL, 4.28 mmol) in CH₂Cl₂ (3 mL) was added slowly at -78 °C, under Ar. After 5 min, alcohol (300 mg, 1.07 mmol) in CH₂Cl₂ (3 mL) was added slowly. The flask was rinsed with CH₂Cl₂ (1 mL x 2). After stirring the mixture at -78 °C for 15 min, triethylamine (2 mL) was added. The temperature was allowed to rise slowly to 0 °C. ~~The reaction was quenched with saturated NH₄Cl solution (10 mL). The aqueous layer~~ was extracted with ethyl acetate (30 mL x 4), and the combined layers were washed with brine (20 mL). After drying over MgSO₄, the solvent was removed, and the residue

was purified by silica gel column chromatography (eluant: hexanes/ether 7/3). The aldehyde (261.5 mg, 78%) was obtained as a colorless oil.

$^1\text{H NMR}$ (CDCl_3) δ 9.75 (s, 1H) 6.05 (m, 2H) 5.79 (m, 1H) 5.64 (m, 1H) 3.94 (s, 4H) 2.5-1.2 (m, 11H) 1.74 (d, 3H, $J = 6.4\text{Hz}$) 1.09 (s, 3H)

IR (neat) 2955, 1722 cm^{-1}

HRMS: Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3$: 278.1882; found: 278.1875

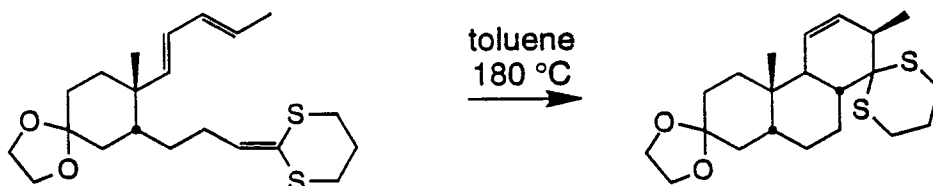


BuLi (11 mL, 1.47 N in hexanes, 16.20 mmol) was added, at $-78\text{ }^\circ\text{C}$ under Ar, to a solution of the thioacetene phosphonate (4.53 g, 17.67 mmol) in THF (50 mL). The reaction mixture was then warmed to $0\text{ }^\circ\text{C}$, and stirred for 15 min. A THF solution (40 mL) of the diene aldehyde (4.1 g, 14.73 mmol) was then added, and the flask was rinsed with THF (10 mL). After stirring the mixture at $0\text{ }^\circ\text{C}$ for 1 h, saturated NH_4Cl solution (100 mL) was added. The aqueous layer was extracted with ether (100 mL \times 3). The combined layers were washed with brine (100 mL). After drying over MgSO_4 , the solution was concentrated and the residue was purified by silica gel column chromatography (eluant: hexanes/ether 7/ 3). The thioacetene acetal (5.1 g, quant.) was obtained as a pale yellow oil.

$^1\text{H NMR}$ (CDCl_3)

δ 6.0-5.8 (m, 3H) 5.75-5.7 (m, 1H) 5.6-5.5 (m, 1H) 3.88 (s, 4H) 2.8-2.7 (m, 4H) 2.2-2.0 (m, 4H) 1.77 (d, 1H, $J = 4\text{ Hz}$) 1.6-1.1 (m, 9H) 0.98 (s, 3H)

MS 382 $\text{M}^{+}+2$, 381 $\text{M}^{+}+1$



The triene (950.3 mg, 2.47 mmol) in toluene (20 mL) was heated to $180\text{ }^\circ\text{C}$ in a

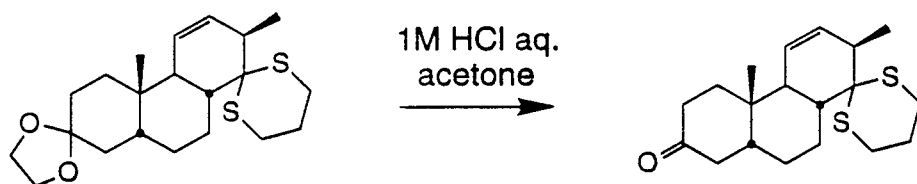
sealed tube for 36 h. After evaporation of the solvent, the crude material was purified by silica gel column chromatography (eluant: hexane/ether/CH₂Cl₂ 8/1/1) to give desired tricyclic compound (580.5 mg, 61%).

¹HNMR (CDCl₃)

δ 5.77 (ddd, 1H, *J* = 10.4, 2.0, 5.2 Hz), 5.59 (d, 1H, *J* = 10.4 Hz) 3.94 (s, 4H) 3.13 (m, 1H,) 3.02 (m, 1H) 2.85 (m, 1H) 2.69 (m, 2H) 2.59 (m, 1H) 2.1-1.3 (m, 11H) 1.14 (d, 3H, *J* = 7.2 Hz) 0.87 (s, 3H)

MS 380 M⁺

IR (neat) 2934 cm⁻¹



The thioacetal (971.0 mg, 2.52 mmol) was dissolved in THF (1 mL), and acetone (20 mL) and 1 N HCl (4 mL) were added. The reaction mixture was stirred at room temperature for 12 h, after which it was poured into saturated NaHCO₃ solution, and the aqueous layer was extracted with CH₂Cl₂ (60 mL x 3). The combined layers were dried over MgSO₄, and evaporated to give a colorless oil which was purified by silica gel column chromatography (eluant: hexanes/ether/CH₂Cl₂ 8/1/1) to give the ketone (732 mg, 80%).

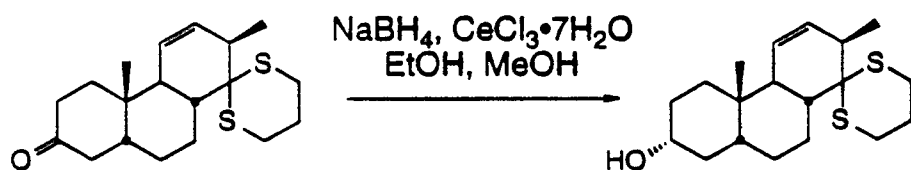
¹HNMR (CDCl₃)

δ 5.85 (ddd, 1H, *J* = 10.0, 6.0, 1.2 Hz) 5.62 (d, 1H, *J* = 10.1 Hz) 3.16 (m, 1H) 3.06 (m, 1H) 2.84 (m, 1H) 2.70 (m, 2H) 2.42 (m, 1H) 2.2-1.4 (m, 14H) 1.17 (d, 3H, *J* = 6.8 Hz) 0.95 (s, 3H)

MS 336 M⁺

IR (CHCl₃) 2930, 1710 cm⁻¹

[α]_D²² -20.8 (c 1.03, CHCl₃)



To a solution of CeCl₃·7H₂O (297 mg, 0.796 mmol) in MeOH (2 mL), NaBH₄ (26 mg, 0.674 mmol) was added in several portions at 0 °C. After 5 min, the above

$\text{NaBH}_4\text{-CeCl}_3\cdot 7\text{H}_2\text{O}$ solution was added at 0 °C to a solution of the tricyclic ketone (206.1 mg, 0.612 mmol) in EtOH (20 mL). The flask was rinsed with MeOH (1 mL x 2), and, after 20 min, brine (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (40 mL x 3). The combined layers were dried over MgSO_4 , and concentrated. The residue was chromatographed on a silica gel column (eluant: hexanes/ethyl acetate 9/1 - 4/1) to give β -alcohol (19.5 mg, 9.4%), and α -alcohol (168.0 mg, 81%).

α -alcohol

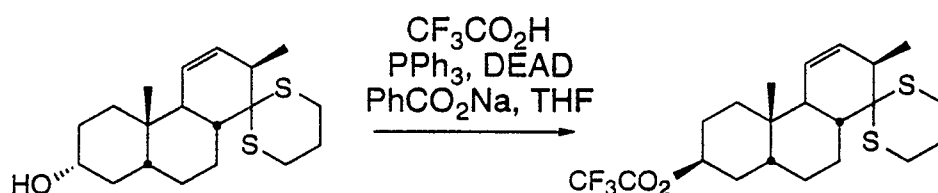
$^1\text{H NMR}$ (CDCl_3)

δ 5.78 (m, 1H) 5.59 (d, 1H, $J = 10.8\text{Hz}$) 3.64 (m, 1H) 3.17 (m, 1H) 3.02 (m, 1H) 2.85 (m, 1H) 2.67 (m, 2H) 2.1-1.1 (m, 15H) 1.14 (d, 3H, $J = 7.6\text{Hz}$) 0.85 (s, 3H)

MS 338 M^+

IR (CHCl_3) 3352, 2863 cm^{-1}

$[\alpha]_{\text{D}}^{22}$ -24.3 (c 0.84, CHCl_3)

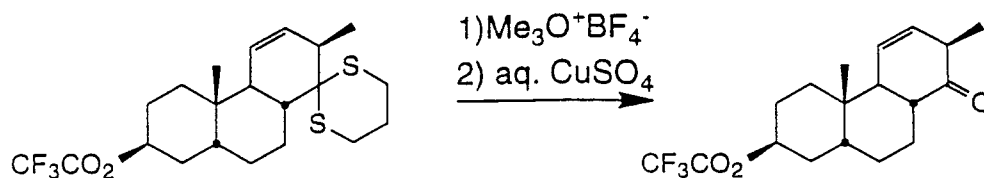


To a solution of α -alcohol (213.0 mg, 0.629 mmol), DEAD (0.13 mL, 0.818 mmol), and PPh_3 (215 mg, 0.818 mmol) in THF (5 mL), $\text{CF}_3\text{CO}_2\text{H}$ (0.052 mL, 0.818 mmol) was added dropwise at 0 °C. After 5 min, NaOBz (118 mg, 0.818 mmol) was added, and the reaction mixture was warmed to room temperature. After stirring the mixture for 16 h, the solvent was removed under vacuum. The residue was purified by silica gel chromatography (eluant: hexanes/ether 10/1) to give the trifluoroacetate of the 3β -alcohol (256 mg, 94%).

$^1\text{H NMR}$ (CDCl_3) δ 5.79 (m, 1H) 5.58 (d, 1H, $J = 10.4\text{ Hz}$) 5.30 (m, 1H) 3.15 (m, 1H) 3.03 (m, 1H) 2.86 (m, 1H) 2.72 (m, 2H) 2.53 (m, 1H) 2.1-1.2 (m, 14H) 1.15 (d, 3H, $J = 6.8\text{ Hz}$) 0.92 (s, 3H)

HRMS Calcd for $\text{C}_{21}\text{H}_{29}\text{F}_3\text{O}_2\text{S}_2$: 434.1562; found: 434.1553.

IR (CHCl_3) 2936, 1779 cm^{-1}



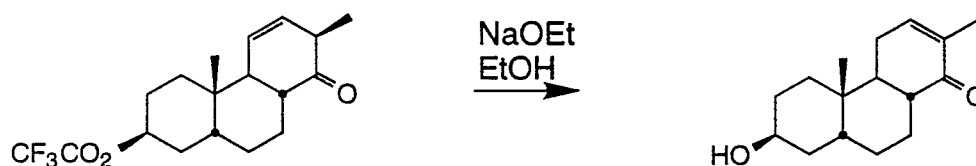
To a solution of thioketal (15.5 mg, 0.0357 mmol) in CH_2Cl_2 (2 mL), trimethyloxonium tetrafluoroborate (53 mg, 0.357 mmol) was added all at once. The reaction mixture was stirred at room temperature for 3 h, and 5% CuSO_4 solution (3 mL) was added. After 10 h, the reaction mixture was diluted with water, and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The organic layer was dried over MgSO_4 and evaporated. The residue was purified by silica gel column chromatography (eluant: hexanes/ether 9/1) to yield the ketone (10.0 mg, 81%).

$^1\text{H NMR}$ (CDCl_3) δ 5.74 (bs, 2H) 5.29 (bs, 1H) 2.75 (m, 1H) 2.53 (bs, 2H) 2.0-1.3 (m, 11H) 1.22 (d, 3H, $J = 7.6$ Hz) 1.01 (s, 3H)

MS 344 M^+ ; HRMS: Calcd for $\text{C}_{18}\text{H}_{23}\text{O}_3\text{F}_3$ 344.1599, found 344.1582.

IR (CHCl_3) 2937, 1780, 1714

$[\alpha]_D^{22}$ -111.5 (c 0.98 CHCl_3).



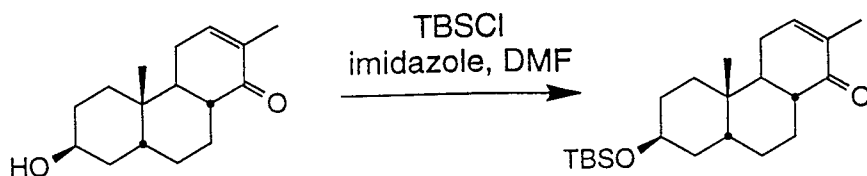
To a solution of the β,γ -unsaturated ketone (135 mg, 0.392 mmol) in EtOH (5 mL), was added a solution of NaOEt in EtOH (0.82 mL, 1 M, 0.82 mmol) freshly prepared from Na and EtOH). After stirring the mixture for 15 min at room temperature, saturated NH_4Cl solution (30 mL) was added, and the aqueous layers were extracted with CH_2Cl_2 (30 mL x 4). The combined layers were dried over MgSO_4 , and evaporated. The residue was purified by flash silica gel column chromatography (eluant: hexanes/ethyl acetate 7:3) to give the conjugated enone (84.0 mg, 86%) as an oil.

$^1\text{H NMR}$ (CDCl_3) δ 6.72 (bs, 1H) 4.11 (bs, 1H) 2.3-1.8 (m, 8H) 1.76 (s, 3H) 1.7-1.2 (m, 7H) 1.00 (s, 3H)

IR (CHCl_3) 3250, 1660 cm^{-1}

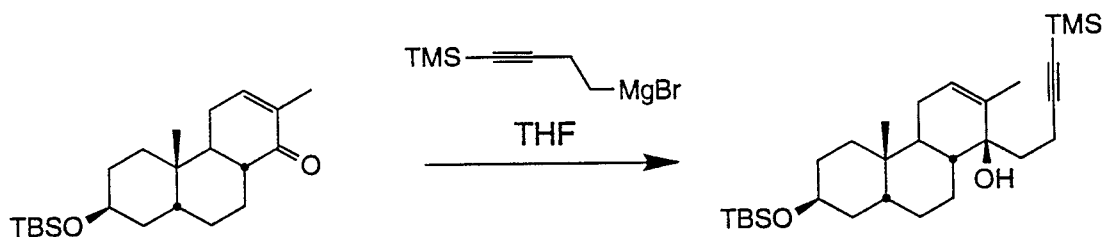
MS 248 M^+ , 230 M^+ -18 (H_2O)

$[\alpha]_D^{22}$ +23.7 (c 0.93, CHCl_3)



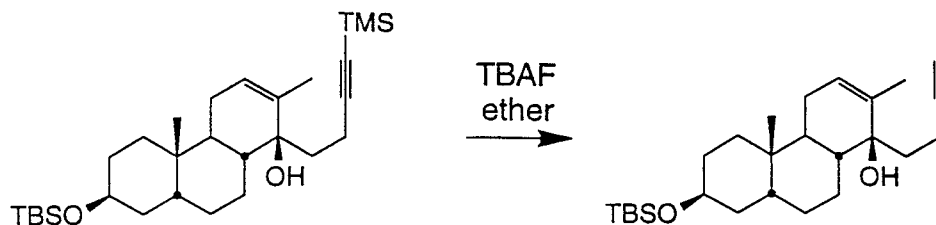
To a solution of enone (239.0 mg, 0.962 mmol) and imidazole (131 mg, 1.92 mmol) in DMF (1 mL), TBSCl (218 mg, 1.44 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature overnight. The mixture was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (50 mL \times 3). The combined organic layers were washed with brine (50 mL), and dried over MgSO_4 . The solvent was evaporated to give an oil which was purified by flash silica gel column chromatography (eluant: hexanes/ether 9/1) to give the expected TBS ether (354.1 mg, quant.).

$^1\text{H NMR}$ (CDCl_3) δ 6.72 (bs, 1H) 4.03 (bs, 1H) 2.3-1.8 (m, 8H) 1.76 (s, 3H) 1.8-1.2 (m, 5H) 0.97 (s, 3H) 0.89 (s, 9H) 0.02 (s, 6H)
 MS 362 M^+ , 305 M^+ -57 (*t*-Bu)
 IR (CHCl_3) 2929, 1658, 1059 cm^{-1}
 $[\alpha]_D^{26}$ +21.8 (c 1.09, CHCl_3)



Mg (298 mg, 12.42 mmol) was activated with dibromoethane in THF (1 mL). To the activated Mg, the butynyl bromide (850 mg, 4.14 mmol) in THF (5 mL) was added slowly from a dropping funnel at room temperature over 6 h. The solution of the above Grignard reagent was added to a solution of the enone (54.7 mg, 0.151 mmol) in THF (0.4 mL), at room temperature, until the enone had disappeared (TLC). The reaction mixture was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (30 mL \times 4). The combined layers were washed with brine (30 mL), and then dried over MgSO_4 . The solvent was evaporated, and the residue was chromatographed on a silica gel column (eluant: hexanes/ether 9/1 - 4/1) to give tertiary alcohol (55.4 mg, 75%).

$^1\text{H NMR}$ (CDCl_3) δ 5.46 (s, 1H) 4.06 (s, 1H) 2.26 (m, 2H) 2.0-1.2 (m, 17H) 1.74 (s, 3H,) 0.88 (s, 12H) 0.15 (s, 9H) 0.02 (s, 6H).
 IR (CHCl_3) 3386, 2930, 2174, 1060 cm^{-1} .
 MS 470 M^+ -18 (H_2O)
 $[\alpha]_D^{22}$ +28.7 (c 1.11, CHCl_3)

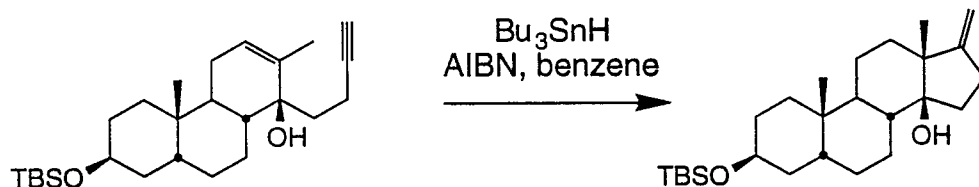


To a solution of TMS alkyne (9.5 mg, 0.0194 mmol) in ether (0.3 mL), TBAF (0.019 mL, 1 M solution in THF, 0.019 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature for 20 min. Saturated NH₄Cl solution (10 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (20 mL x 4). The combined layers were washed with brine (20 mL), and dried over MgSO₄. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluant: hexanes/ether/CH₂Cl₂ 9/1/1) to give the desired compound (7.3 mg, 89%) .

¹HNMR (CDCl₃) δ 5.50 (bs, 1H) 4.06 (bs, 1H) 2.23 (m, 2H) 1.92 (t, 1H, *J* = 1.6Hz) 1.9-1.2 (m, 16H) 1.88 (s, 12H) 0.02 (s, 3H) 0.02 (s, 3H)

IR (CHCl₃) 3312, 2928, 1060 cm⁻¹

[α]_D²² +33.6 (c 0.85, CHCl₃)



The enyne (11.2 mg, 0.0269 mmol) was dissolved in benzene (1.3 mL), and Bu₃SnH (0.029 mL, 0.108 mmol) and AIBN (0.5 mg) were added. The mixture was refluxed for 5 h under Ar. The reaction mixture was then cooled to room temperature, and silica gel (0.5 g) was added. The mixture was stirred for 13 h at room temperature and filtered. The silica gel was washed with ethyl acetate (10 mL x 3), and the solvent was removed on a rotary evaporator. The crude residue was purified by flash silica gel column chromatography (eluant: hexanes/ether 5/1) to give the desired compound (4.3 mg, 40%), mp 134-136 °C.

¹HNMR (CDCl₃) δ 4.84 (s, 1H) 4.79 (s, 1H) 4.03 (brs, 1H) 2.50 (m, 2H) 2.04 (m, 1H) 1.2-1.9 (m, 18H) 1.06 (s, 3H) 0.92 (s, 3H) 0.87 (s, 9H) 0.00 (s, 6H)

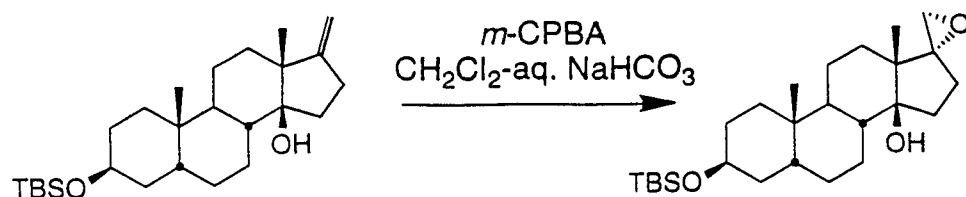
¹³CNMR (CDCl₃) δ 161.0, 104.4, 85.4, 67.2, 49.2, 40.9, 37.9, 36.1, 35.8, 35.3, 34.3, 30.4, 29.7, 28.7, 27.4, 26.7, 25.8, 23.9, 21.0, 18.0, 16.5, -4.8, -4.9

IR (CHCl₃)

3615, 2930, 2860, 1654, 1448, 1252, 1062 cm⁻¹

HRMS Calcd. for C₂₅H₄₆O₂SiNa: 441.3165; found 441.3160

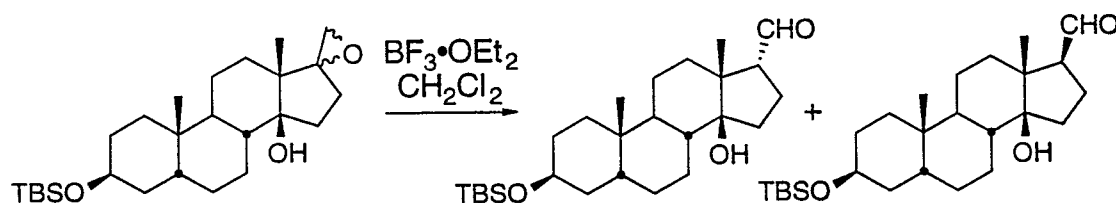
[α]_D²³ +4.3 (c 1.02, CHCl₃)



To a solution of olefin (48.5 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) and 0.5 M NaHCO_3 solution (1 mL), *m*-CPBA (40 mg, 0.23 mmol) was added at 0 °C in several portions. After stirring the reaction mixture at 0 °C for 2 h, the mixture was diluted with CH_2Cl_2 , washed with 10% sodium thiosulfate solution, and then with saturated NaHCO_3 solution. The organic layer was dried over MgSO_4 , and the solvent was removed. After purification by silica gel chromatography, the epoxide (45.7 mg, 90%, a 1:8 mixture) was obtained as a white solid.

major epoxide (amorphous), "mp" 185-190 °C

$^1\text{H NMR}$ (CDCl_3) δ 4.04 (brs, 1H) 2.88 (d, 1H, $J = 5.3$ Hz) 2.56 (d, 1H, $J = 5.3$ Hz) 2.26 (m, 1H) 2.03 (m, 1H) 1.1-1.9 (m, 19H) 0.92 (s, 3H) 0.86 (s, 9H) 0.72 (s, 3H) 0.00 (s, 6H).



A few drops of $\text{BF}_3 \cdot \text{OEt}_2$ were added to a solution of epoxide (15.7 mg, 0.0361 mmol) in CH_2Cl_2 (1 mL) at -78 °C. After 3 min, the reaction mixture was quenched with saturated NaHCO_3 solution, and the mixture was allowed to come to room temperature. The aqueous phase was extracted with CH_2Cl_2 , and the organic layer was dried over MgSO_4 . After evaporation, the residue was purified by column chromatography on silica gel (eluant: hexane/ethyl acetate 9/1). The aldehyde (11.2 mg, 72%) was obtained as a white solid. $^1\text{H NMR}$ spectrum showed that the aldehyde was a 10:1 mixture of α and β isomers.

α -aldehyde

$^1\text{H NMR}$ (CDCl_3) δ 9.80 (d, 1H, $J = 1.9$ Hz) 4.03 (brs, 1H) 2.99 (dt, 1H, $J = 9.0, 1.7$ Hz) 2.1-2.2 (m, 2H) 1.21-1.91 (m, 19H) 1.23 (s, 3H) 0.92 (s, 3H) 0.87 (s, 9H) 0.00 (s, 6H)

$^{13}\text{C NMR}$ (CDCl_3) δ 205.7, 86.3, 67.1, 61.6, 49.1, 41.3, 36.0, 35.7, 35.2, 34.2, 31.6, 31.5, 29.6, 25.8, 23.8, 21.2, 20.1, 18.7, 18.2, 18.0, -4.9

IR (CHCl_3) 3600, 2932, 1713, 1064 cm^{-1}

HRMS: Calcd. for $\text{C}_{26}\text{H}_{46}\text{O}_3\text{Si Na}$: 457.3114; found 457.3111

$[\alpha]_D^{31}$ -27.1 (c 0.65, CHCl_3)

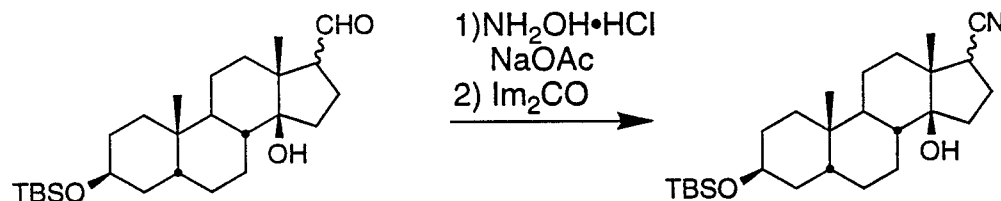
β -aldehyde, mp 137-138 °C

$^1\text{H NMR}$ (CDCl_3) δ 9.73 (d, 1H, $J = 3.9$ Hz) 4.05 (brs, 1H) 2.32 (m, 1H) 1.20-2.23 (m, 21H) 1.04 (s, 3H) 0.94 (s, 3H) 0.89 (s, 9H) 0.02 (s, 6H)

$^{13}\text{C NMR}$ (CDCl_3) δ 206.8, 85.7, 67.2, 61.9, 50.5, 41.2, 38.2, 36.1, 35.7, 35.3, 34.3, 33.0, 29.8, 28.7, 26.7, 25.8, 23.8, 21.5, 20.3, 20.2, 18.1, 15.0, -4.8

IR (CHCl_3) 3603, 2932, 2860, 1708, 1061 cm^{-1}

$[\alpha]^{31}_{\text{D}} -14.8$ (c 1.81, CHCl_3)



To a suspension of aldehyde (78 mg, 0.179 mmol) in EtOH (3 mL), were added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (27 mg, 0.394 mmol) and $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (56 mg, 0.411 mmol). After stirring for 1 h, the EtOH was removed *in vacuo*. The residue was diluted with water, and the aqueous layer was extracted with CH_2Cl_2 . The organic solution was dried over MgSO_4 . After evaporation of the solvent, the oxime was suspended in CH_2Cl_2 . Upon addition of 1,1'-carbonyldiimidazole (87 mg, 0.537 mmol), the oxime dissolved and the mixture was stirred overnight. After dilution of the reaction mixture with CH_2Cl_2 , the organic layer was washed with water and dried over MgSO_4 . After concentration, the residue was purified by silica gel chromatography (eluant: hexanes/ethyl acetate 5/1) to give the nitrile mixture (73 mg, 95%; α : β ratio = 10:1).

α -nitrile, mp 236-240 °C.

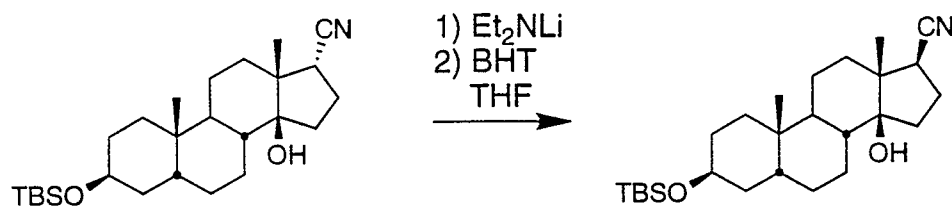
$^1\text{H NMR}$ (CDCl_3) δ 4.03 (brs, 1H) 3.05 (t, 1H, $J = 9.2$ Hz) 1.2-2.3 (m, 21H) 1.08 (s, 3H) 0.93 (s, 3H) 0.87 (s, 9H) 0.00 (s, 6H)

$^{13}\text{C NMR}$ (CDCl_3) δ 121.4, 84.7, 67.0, 48.2, 41.6, 39.0, 35.9, 35.8, 35.2, 34.2, 31.7, 313.5, 29.6, 28.6, 26.5, 25.8, 24.1, 23.8, 21.0, 20.1, 18.0, 16.8, -4.9

IR (CCl_4) 3610, 2930, 2885, 2862, 2238, 1471, 1381, 1253, 1064 cm^{-1}

HRMS: Calcd. for $\text{C}_{26}\text{H}_{45}\text{N O}_2$ Si Na: 454.3118; found 454.3112

$[\alpha]^{23}_{\text{D}} -8.9$ (c 0.70, CHCl_3)



BuLi (0.14 mL, 2.5 M solution in hexanes, 0.347 mmol) was added at 0 °C to a solution of Et₂NH (0.036 mL, 0.347 mmol) in THF (0.5 mL). To the solution of the Et₂NLi, the α-nitrile (15 mg, 0.0347 mmol) in THF (0.3 mL) was slowly added, via cannula. After 30 min at 0 °C, the mixture was cooled to -78 °C, and 2,6-di-tert-butyl-4-methylphenol (77 mg, 0.347 mmol) in THF (0.3 mL) was added via cannula. After 40 min, saturated NH₄Cl solution was added, and the aqueous layer was extracted with ethyl acetate (20 mL x 4). The combined layers were washed with brine (20 mL), and dried over MgSO₄. The solvent was removed to give crude material which showed (NMR) the ratio of α-nitrile:β-nitrile to be ~1:5. The crude material was chromatographed on a silica gel column (eluant: hexanes/ethyl acetate 5/1) to give pure β-nitrile (11 mg, 73%).

β-nitrile

¹HNMR (CDCl₃): δ 4.02 (brs, 1H) 2.57 (m, 1H) 2.21 (m, 2H) 2.06 (m, 1H) 1.2-1.9 (m, 18H) 1.24 (s, 3H) 0.92 (s, 3H) 0.86 (s, 9H) 0.00 (s, 6H)

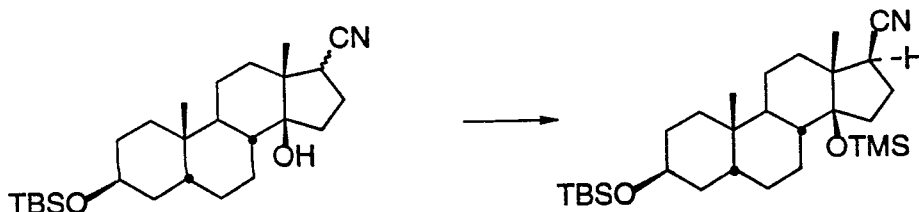
¹³CNMR (CDCl₃) δ 122.9, 85.5, 67.0, 48.3, 41.3, 39.9, 36.8, 35.9, 35.6, 35.2, 34.2, 32.3, 29.7, 28.6, 26.6, 25.8, 25.4, 23.8, 21.3, 20.9, 18.1, 16.2, -4.9

IR(CHCl₃) 3603, 2931, 2859, 2237, 1065 cm⁻¹

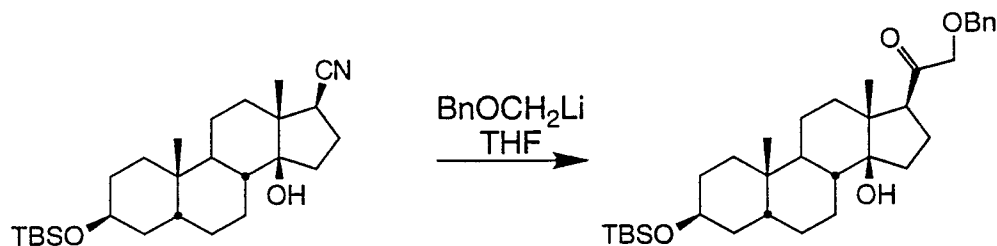
HRMS: Calcd. for C₂₆H₄₅N O₂ Si N: 454.3118; found 454.3104

[α]_D²⁷ +8.5 (c 1.37, CHCl₃)

The alternative epimerization via the TMS derivative of the 14 hydroxyl is described below. It is preferable because the separation of the epimers is much easier.



TMS triflate (93ml) was added at 0 °C to a solution of 70.3 mg of the 14 β -hydroxy-17-cyano compound (mainly the 17 α epimer) and 78 ml of triethylamine in 3 ml of CH₂Cl₂. The epimerization of the resulting TMS derivative of the 14-hydroxyl was carried out with LiNEt₂ as previously described, and the TMS group was then cleaved with TBAF. at 0° C for 5 h, to give the pure 14 β -hydroxy-17 β -cyano compound, mp 193-195 °C, after recrystallization from hexane-ethyl acetate.



Butyllithium (0.6 mL, 2.5 M solution in hexanes, 1.50 mmol) was added dropwise to a solution of benzyloxymethyltributylstannane (Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481) (629.6 mg, 1.53 mmol) in THF (5 mL) at -78 °C. The resulting yellow solution of benzyloxymethyl lithium was stirred for 5 min, and the nitrile (86.0 mg, 0.20 mmol) was added as a solution in THF (2 mL) at -78 °C. After stirring the mixture for 3 h, it was quenched with water. The mixture was diluted with saturated NaHCO₃ solution and the aqueous layer was extracted with CH₂Cl₂. The organic layer was dried over MgSO₄, the solvent was removed on a rotary evaporator. Purification and concomitant imine hydrolysis were achieved by silica gel chromatography (eluant: hexanes/ethyl acetate 9/1). The benzyloxymethyl ketone (98.6 mg, 89%) was obtained as a white solid, mp 109-110 °C.

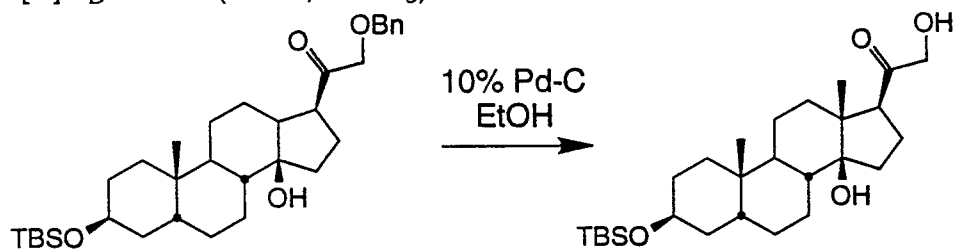
¹HNMR (CDCl₃) δ 7.3-7.4 (m, 5H) 4.59 (dd, 2H, *J* = 15.9, 12.0 Hz) 4.25 (s, 1H, OH) 4.10 (dd, 2H, *J* = 21.8, 18.2 Hz) 4.02 (brs, 1H) 2.88 (dd, 1H, *J* = 9.5, 4.5 Hz) 1.1-2.2 (m, 21H) 0.91 (s, 6H) 0.87 (s, 9H) 0.00 (s, 6H).

¹³CNMR (CDCl₃) δ 216.1, 136.9, 128.5, 128.0, 127.9, 85.0, 76.1, 73.2, 67.2, 57.0, 49.6, 40.0, 39.2, 36.1, 35.3, 35.1, 34.3, 34.0, 29.8, 28.7, 26.7, 25.8, 24.8, 23.9, 21.7, 20.9, 18.0, 15.2, -4.9

IR (CHCl₃) 3435, 2931, 1712, 1065 cm⁻¹.

HRMS Calcd. for C₃₄H₅₄O₄ Si Na: 577.3689; found 577.3681

[α]_D²⁷ +31.5 (c 1.06, CHCl₃)



A solution of the benzyl ether (62.7 mg, 0.11 mmol) in EtOH (5 mL) containing a spatula tip of 10 % Pd-C was stirred under a hydrogen atmosphere for 24 h. After filtration (celite), the catalyst was washed with EtOH (10 mL x 2). The solvent was removed under vacuum, and the residue was purified by flash silica gel

chromatography (eluant: hexanes/ethyl acetate 5/1). The hydroxy ketone (50.3 mg, 96%) was obtained as a crystalline white solid, mp 169-171 °C.

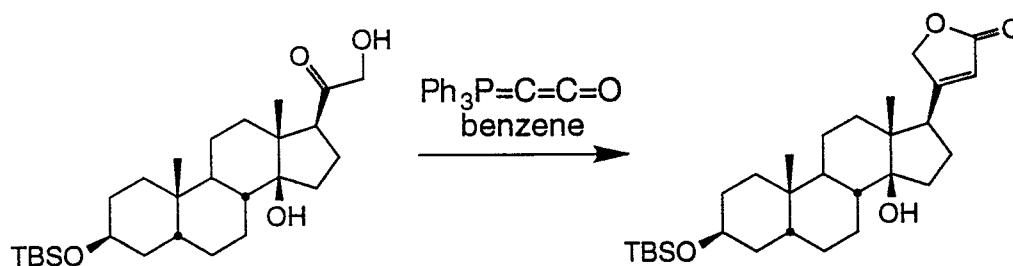
$^1\text{H NMR}$ (CDCl_3) δ 4.27 (dd, 2H, $J = 27.6, 20.1$ Hz) 4.06 (s, 1H, OH) 4.02 (bs, 1H) 3.06 (bs, 1H, OH) 2.70 (dd, 1H, $J = 9.7, 4.2$ Hz) 1.2-2.2 (m, 21H) 0.92 (s, 3H) 0.90 (s, 3H) 0.87 (9H, s) 0.00 (s, 6H)

$^{13}\text{C NMR}$ (CDCl_3) δ 217.2, 70.2, 67.2, 57.9, 49.9, 40.2, 39.4, 36.1, 35.3, 35.2, 34.3, 34.0, 29.8, 28.7, 26.8, 25.8, 24.9, 23.9, 21.7, 20.9, 18.1, 15.3, -4.8, -4.9

IR (CHCl_3) 3683, 3468, 2931, 1702, 1063 cm^{-1}

HRMS Calcd. for $\text{C}_{24}\text{H}_{48}\text{O}_4$ Si Na: 487.3220; found 487.3231

$[\alpha]^{24}_{\text{D}} +38.5$ (c 0.53, CHCl_3)



To a mixture of the hydroxy ketone (72.4 mg, 0.16 mmol), triethylamine (0.07 mL, 0.50 mmol), and benzene (3 mL), was added triphenylphosphoranylidene ketene (62.7 mg, 0.21 mmol) at room temperature, and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (eluant: hexanes/ethyl acetate 7/3) to give the 3-*tert*butyldimethylsilyl ether of digitoxigenin (56.0 mg, 74%), mp 233-235 °C, identical in all respects (^1H and ^{13}C NMR, high and low resolution mass spectra, and rotation) with an authentic sample prepared from digitoxigenin.

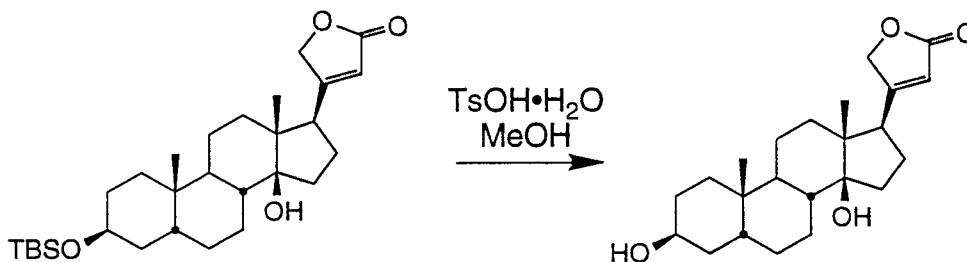
$^1\text{H NMR}$ (CDCl_3) δ 5.85 (d, 1H, $J = 1.4$ Hz) 4.98 (dd, 1H, $J = 17.9, 1.3$ Hz) 4.79 (dd, 1H, $J = 18.1, 1.7$ Hz) 4.03 (brs, 1H) 2.77 (m, 1H) 2.12 (m, 2H) 1.2-1.9 (m, 9H) 0.91 (s, 3H) 0.87 (s, 9H) 0.85 (s, 3H) 0.00 (s, 6H).

$^{13}\text{C NMR}$ (CDCl_3) δ 174.7, 174.5, 117.6, 85.6, 73.4, 67.1, 50.9, 49.6, 41.9, 40.0, 35.9, 35.6, 35.2, 34.2, 33.1, 29.7, 28.6, 26.9, 26.7, 25.8, 23.8, 21.5, 21.2, 18.1, 15.7, -4.9.

IR (CHCl_3) 3604, 2932, 1784, 1745, 1621, 1254, 1064 cm^{-1} .

HRMS Calcd. for $\text{C}_{29}\text{H}_{48}\text{O}_4\text{SiNa}$: 511.3220; found 511.3242

$[\alpha]^{27}_{\text{D}} +20.0$ (c 1.69, CHCl_3).



The silyl ether (101.2 mg, 0.20 mmol) was suspended in methanol (5 mL), and a few crystals of p-toluenesulfonic acid were added at room temperature. The mixture was stirred for 24 h at room temperature, the solvent was removed, and the residue was purified directly by flash chromatography (eluant: ether-ethyl acetate) to give digitoxigenin (75.6 mg, 97%), mp 249-250 °C.

^1H NMR (CDCl_3) δ 5.85 (s, 1H) 4.98 (dd, 1H, $J = 18.2, 1.6$ Hz) 4.79 (dd, 1H, $J = 18.2, 1.6$ Hz) 4.11 (brs, 1H) 2.76 (m, 1H) 1.2-2.2 (m, 21H) 0.93 (s, 3H) 0.85 (s, 3H)

^{13}C NMR (CDCl_3) δ 174.7, 174.6, 117.6, 85.5, 73.4, 66.7, 50.9, 49.6, 41.7, 39.9, 35.9, 35.4, 35.3, 33.2, 33.1, 29.6, 27.8, 26.8, 26.4, 23.7, 22.3, 21.1, 15.7

$[\alpha]_D^{25} +17.8$ (c 1.64, MeOH).

$[\alpha]_D^{25} +17.8$ (c 1.64, MeOH).