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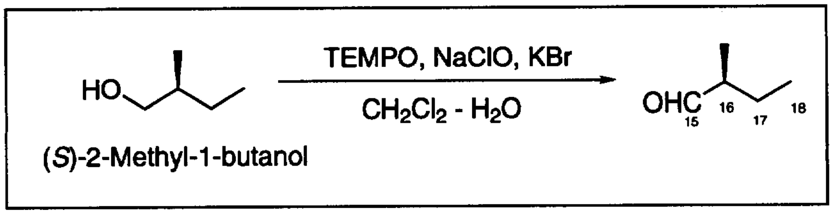
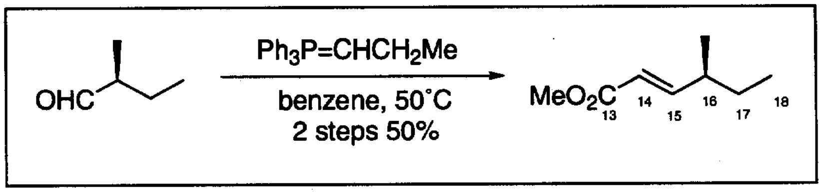
Total synthesis of nafuredin, a selective NADH-fumarate reductase inhibitor

Daisuke Takano, Tohru Nagamitsu, Hideaki Ui, Kazuro Shiomi, Yuuichi Yamaguchi, Rokuro Masuma, Isao Kuwajima and Satoshi Ōmura*

<Synthesis of side chain **4**>



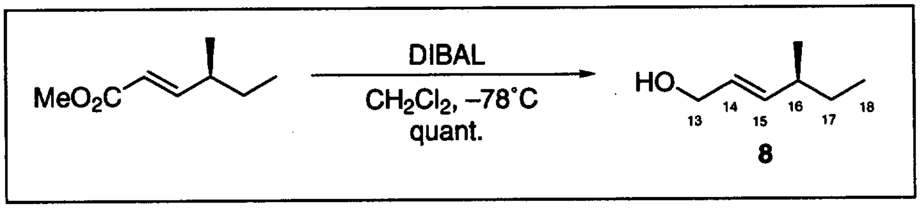
A aqueous solution of potassium bromide (0.62 g, 5.19 mmol) in water (2 mL) was added dropwise to a solution of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (0.081 g, 0.52 mmol) and (*S*)-(–)-2-methyl-1-butanol (4.57 g, 51.9 mmol) in dichloromethane (100 mL) at 0°C. After 10 min, sodium hypochloride (156 mL, 156 mmol, 1 M soln) adjusted to pH 9.5 using saturated $NaHCO_3$, was added dropwise to the reaction mixture over a period of 15 min. The reaction was allowed to warm to room temperature and stir for an additional 5 min. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with 20% HCl (50 ml) containing potassium iodide (0.16 g, 1.0 mmol), 10% $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate and concentrated in vacuo. The crude product (2.8 g) was subjected to next reaction without purification.



To a solution of aldehyde (2.8 g) in benzene (350 mL) was added methyl triphenylphosphoranylidene acetate (20.0 g, 59.9 mmol). The reaction was allowed to warm to 50°C, stirred for 12 h and poured into water. The reaction mixture was extracted with diethyl ether, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded methyl ester (3.7 g, 2 steps 50%) as a clear oil.

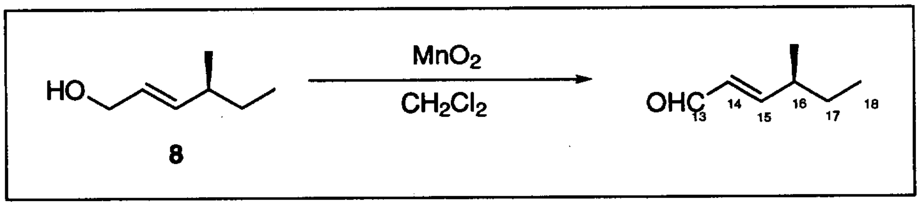
$[\alpha]_D^{27}$ = +24.8° (*c* = 0.58, $CHCl_3$); **IR (KBr)** 2964, 2931, 2854, 1727 (C=O) cm^{-1}; **^{1}H-**

NMR (270 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.42 Hz, H-18), 1.04 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.40 (m, 2H, H-17), 2.22 (m, 1H, H-16), 3.72 (s, 3H, CH_3OCO), 5.78 (d, 1H, *J* = 15.84 Hz, H-14), 8.87 (dd, 1H, *J* = 15.84, 7.59 Hz, H-15); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 167.2, 154.6, 119.2, 60.2, 38.2, 29.6, 20.9, 11.6.

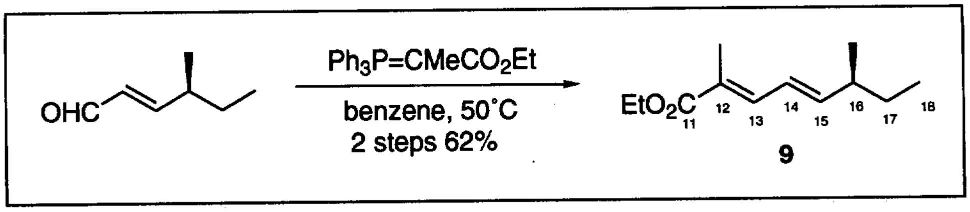


To a solution of methyl ester (3.7 g, 25.9 mmol) in dichloromethane (250 mL) was added diisopropylaluminium hydride (0.95 M solution in hexane, 68.1 mL, 64.7 mmol) at –78°C. The reaction was stirred for 30min, and quenched with MeOH. Celite (10 g) and $Na_2SO_4 \cdot 10H_2O$ (10 g) was added and the reaction mixture was warmed to room temperature. After stirred for 2 h, the suspension was filtered through a pad of celite and the filtrate was concentrated in vacuo. Purification on silica gel afforded alcohol **8** (2.9 g, 100%) as a clear oil.

$[\alpha]_D^{27}$ = +33.6° (*c* = 1.20, $CHCl_3$); **IR (KBr)** 3346 (OH), 2962, 2925, 2875 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, *J* = 7.42 Hz, H-18), 0.98 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.31 (m, 2H, H-17), 2.04 (m, 1H, H-16), 4.08 (d, 2H, *J* = 4.29 Hz, H-13), 5.58 (m, 2H, H-14 and H-15); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 139.0, 127.2, 63.6, 38.2, 29.5, 20.1, 11.7.

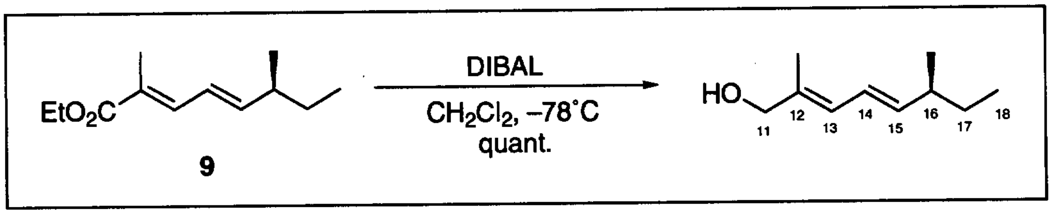


Alcohol **8** (2.9 g, 25.9 mmol) was dissolved in dichloromethane (250 mL) and manganese dioxide (67.5 g, 777 mmol) was added to the solution. The reaction mixture was stirred for 30 min, filtered through a pad of celite and concentrated in vacuo to afford aldehyde (3.0 g) as a yellow oil of sufficient purity for the use in the next reaction.



(1-Carboethoxyethylidene)triphenylphosphorane (11.2 g, 31.0 mnol) was added to a solution of aldehyde (3.0 g) in benzene (250 mL). The reaction mixture was warmed to 50°C and stirred for 12 h. The resultant solution was poured into water, extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded ester **9** (3.1 g, 2 steps 62%) as a clear oil.

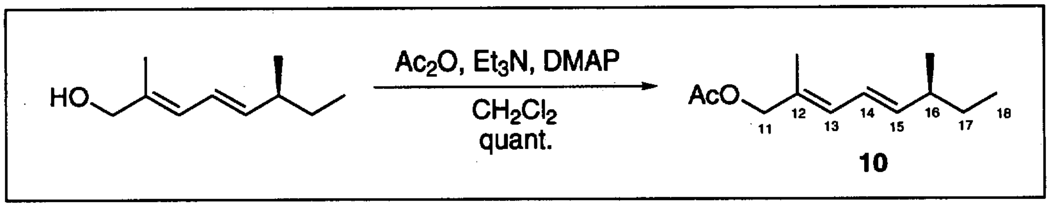
$[\alpha]_D^{27}$ = +38.5° (*c* = 0.28, $CHCl_3$); **IR (KBr)** 2962, 2929, 1706 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.87 (t, 3H, *J* = 7.42 Hz, H-18), 1.03 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.30 (t, 3H, *J* = 7.25 Hz, $C\underline{H}_3CH_2O$), 1.37 (m, 2H, H-17), 1.93 (s, 3H, 12-Me), 2.18 (m, 1H, H-16), 4.20 (q, 2H, J = 7.25 Hz, $CH_3C\underline{H}_2O$), 5.95 (dd, 1H, *J* = 14.84, 7.91Hz, H-15), 6.30 (dd, 1H, *J* = 14.84, 11.21 Hz, H-14), 7.16 (d, 1H, *J* = 11.21 Hz, H-13); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 168.6, 148.6, 138.7, 125.1, 124.2, 60.3, 39.0, 29.4, 19.7, 14.3, 12.5, 11.7; **HRMS (EI)** m/z M^+ 196.1471; Calcd for $C_{12}H_{20}O_2$: M 196.1463.



To a solution of ester **9** (3.1 g, 16.0 mmol) in dichloromethane (160 mL) was added diisopropylaluminium hydride (0.95 M solution in hexane, 42mL, 40.0 mmol) at –78°C. The reaction mixture was stirred for 30 min and quenched with methanol. Celite (10 g), $Na_2SO_4 \bullet 10H_2O$ (10 g) was added and the suspension was warmed to room temperature and stirred for 2 h. Filtration and concentration of the resulting mixture followed by flash chromatography provided alcohol (2.5 g, 100%) as a clear oil.

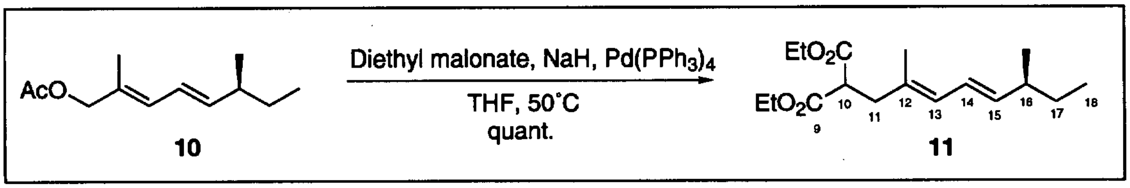
$[\alpha]_D^{27}$ = +30.2° (*c* = 0.92, $CHCl_3$); **IR (KBr)** 3349 (OH), 2962, 2925, 2873 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, *J* = 7.42 Hz, H-18), 1.00 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.33 (m, 2H, H-17), 1.78 (s, 3H, 12-Me), 2.10 (m, 1H, H-16), 4.04 (s, 2H, H-

11), 5.57 (dd, 1H, *J* = 14.84, 7.91 Hz, H-15), 6.02 (d, 1H, *J* = 10.88 Hz, H-13), 6.22 (dd, 1H, *J* = 14.84, 10.88 Hz, H-14); **^{13}C-NMR (67.5 MHz, CDCl$_3$)** δ 141.0, 134.6, 125.5, 124.0, 68.7, 38.7, 29.7, 20.1, 14.0, 11.7; **HRMS (EI)** m/z M$^+$ 154.1349; Calcd for $C_{10}H_{18}O$: M 154.1358.



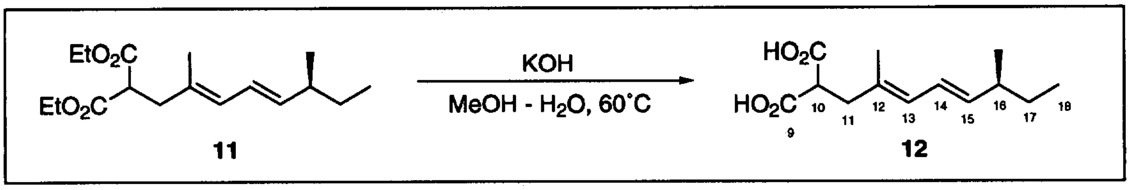
To a solution of alcohol (4.1 g, 26.4 mmol) in dichloromethane (260 mL) was added acetic anhydride (5.0 mL, 52.8 mmol), triethylamine (7.4 mL, 52.8 mmol), 4-dimethylaminopyridine (32.2 mg, 264 μmol) at room temperature. The reaction was stirred for 30 min and quenched with water. The reaction mixture was extracted with dichloromethane, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded acetate **10** (5.2 g, 100%) as a clear oil.

$[\alpha]_D^{27}$ = +25.7° (*c* = 0.38, CHCl$_3$); **IR (KBr)** 2962, 2925, 2873, 1741 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, CDCl$_3$)** δ 0.86 (t, 3H, *J* = 7.42 Hz, H-18), 0.99 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.33 (m, 2H, H-17), 1.77 (s, 3H, 12-Me), 2.07 (s, 3H, $\mathrm{COC\underline{H}_3}$), 2.10 (m, 1H, H-16), 4.50 (s, 2H, H-11), 5.61 (dd, 1H, *J* = 14.84, 7.91 Hz, H-15), 6.03 (d, 1H, *J* = 10.88 Hz, H-13), 6.20 (dd, 1H, *J* = 14.84, 10.88 Hz, H-14); **^{13}C-NMR (67.5 MHz, CDCl$_3$)** δ 170.9, 142.1, 129.4, 128.7, 123.8, 70.0, 38.7, 29.6, 20.9, 20.0, 14.4, 11.7; **HRMS (EI)** m/z M$^+$ 196.1471; Calcd for $C_{12}H_{20}O_2$: M 196.1463.

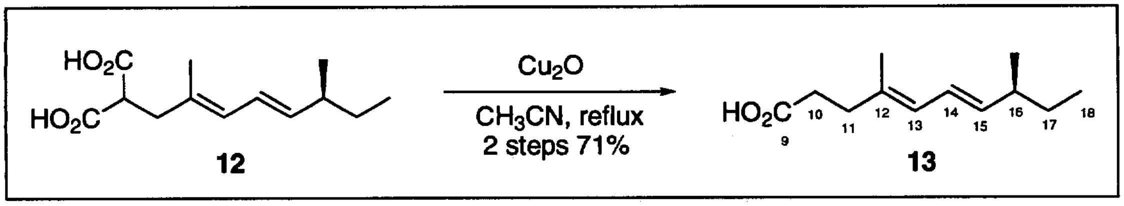


To a solution of acetate **10** (1.2 g, 5.95 mmol) in tetrahydrofuran (60 mL) was added tetrakis(triphenylphosphine)palladium (343 mg, 297 μmol), diethyl malonate (4.5 mL, 29.7 mmol) and sodium hydride (642 mg, 26.7 mmol). The resulting solution was warmed to 50°C, allowed to stir for 1 h and poured into brine. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded diester **11** (1.8 g, 100%) as a yellow oil.

$[\alpha]_D^{24}$ = +21.8° (*c* = 2.33, $CHCl_3$); **IR (KBr)** 2964, 2929, 2873, 1735(C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.84 (t, 3H, *J* = 7.42 Hz, H-18), 0.98 (d, 3H, *J* = 6.86 Hz, 16-Me), 1.24 (t, 6H, *J* = 7.25 Hz, 2x $CO_2CH_2C\underline{H}_3$), 1.30 (m, 2H, H-17), 1.74 (s, 3H, 12-Me), 2.06 (m, 1H, H-16), 2.63 (d, 2H, *J* = 7.91 Hz, H-11), 3.55 (t, 1H, *J* = 7.91 Hz, H-10), 4.18 (q, 4H, *J* = 7.25 Hz, 2x $CO_2C\underline{H}_2CH_3$), 5.47 (dd, 1H, *J* = 15.17, 7.91 Hz, H-15), 5.82 (d, 1H, *J* = 10.55 Hz, H-13), 6.13 (dd, 1H, *J* = 15.17, 10.55 Hz, H-14); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 169.1, 139.9, 131.0, 127.6, 124.3, 61.2, 50.1, 38.7, 38.6, 29.7, 20.1, 16.1, 14.0, 11.7; **HRMS (EI)** m/z M^+ 296.1979; Calcd for $C_{17}H_{28}O_4$: M 296.1988.

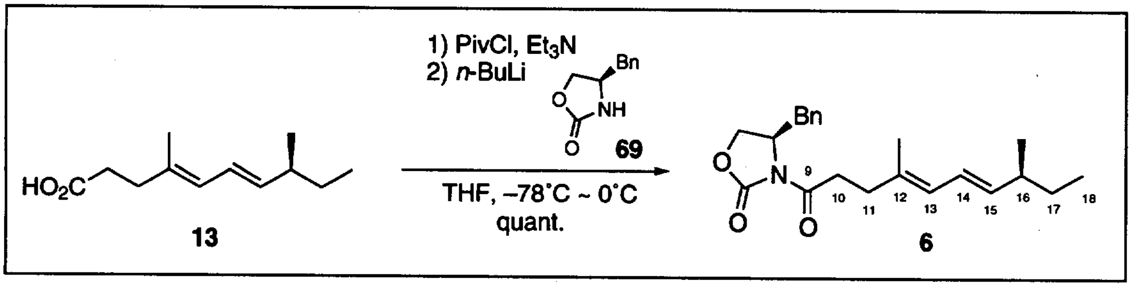


To a solution of diester **11** (1.8 g, 5.95 mmol) in MeOH (10 mL) was added aqueous potassium hydroxide solution (1 M in water, 50 mL). The solution was warmed to 60°C and stirred for 18 h. Methanol was concentrated in vacuo and the remaining aqueous solution was acidified with dil.HCl. The aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo to afford crude dicarboxylic acid **12** (1.6 g) which was subjected to the next reaction without purification.



To a solution of dicarboxylic acid **12** (1.6 g) in CH_3CN (45 mL) was added copper(I) oxide (644 mg, 4.50 mmol). The resulting solution was warmed to 80°C, stirred for 14 h, and concentrated in vacuo. The residue was subjected to flash chromatography to afford monocarboxylic acid **13** (828 mg, 2 steps 71%) as a yellow oil.

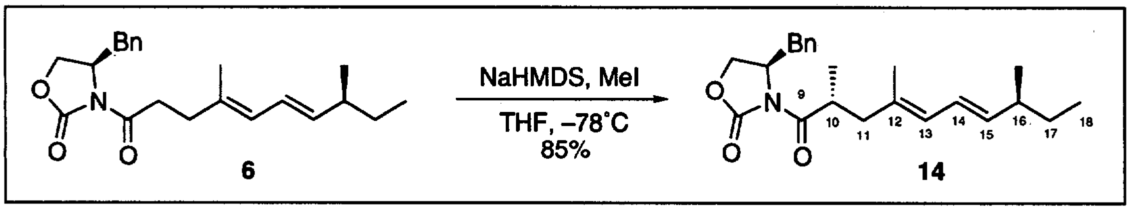
$[\alpha]_D^{27}$ = +23.3° (c = 2.19, $CHCl_3$); **IR (KBr)** 3348 (OH), 2962, 2927, 2873, 1712(C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.84 (t, 3H, J = 7.25 Hz, H-18), 0.97 (d, 3H, J = 6.59 Hz, 16-Me), 1.30 (m, 2H, H-17), 1.73 (s, 3H, 12-Me), 2.05 (m, 1H, H-16), 2.34 (t, 2H, J = 7.58 Hz, H-11), 2.46 (m, 2H, H-10), 5.47 (dd, 1H, J = 14.84, 7.91 Hz, H-15), 5.80 (d, 1H, J = 10.88 Hz, H-13), 6.16 (dd, 1H, J = 14.84, 10.88 Hz, H-14); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 179.9, 139.3, 133.5, 125.6, 124.4, 38.6, 34.2, 32.7, 29.7, 20.1, 16.3, 11.7; **HRMS (EI)** m/z M^+ 196.1443; Calcd for $C_{12}H_{20}O_2$: M 196.1463.



To a solution of monocarboxylic acid **13** (1.2 g, 6.22 mmol) in tetrahydrofuran (100 mL) was added triethylamine (1.2 mL, 8.08 mmol) and pivaloyl chloride (840 µL, 6.84 mmol) at –78°C. The resulting solution was stirred for 15 min at –78°C, allowed to warm up to room temperature, and stirred for a additional 1.5 h. This resulting mixture was added via cannula to a solution of (R)-4-benzyl-2-oxazolidinone (2.0 g, 11.1 mmol) treated with n-BuLi (1.6 M solution in hexane, 6.9 mL, 11.1 mmol) in tetrahydrofuran (20 mL) at –78°C. The resulting suspension was stirred for 15 min at –78°C and a additional 2 h at room temperature. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded oxazolidinone **6** (2.2 g, 100%) as a clear oil.

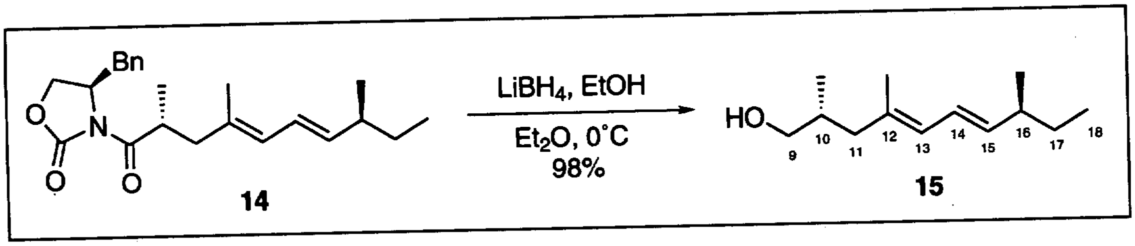
$[\alpha]_D^{27}$ = –27.8° (c = 2.58, $CHCl_3$); **IR (KBr)** 2960, 2919, 2852, 1783 (C=O), 1700 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.84 (t, 3H, J = 7.42 Hz, H-18), 0.98 (d, 3H, J = 6.92 Hz, 16-Me), 1.30 (m, 2H, H-17), 1.79 (s, 3H, 12-Me), 2.06 (m, 1H, H-16), 2.43 (t, 2H, J = 7.58 Hz, H-11), 2.75 (dd, 1H, J = 13.19, 9.56 Hz, 1/2 C$\underline{H}_2$Ph), 3.07 (m, 2H, H-10), 3.28 (dd, 1H, J = 13.19, 3.29 Hz, 1/2 C$\underline{H}_2$Ph), 4.17 (m, 2H, OC$\underline{H}_2$CHN), 4.66 (m, 1H, $OCH_2C\underline{H}N$), 5.49 (dd, 1H, J = 14.84, 7.91 Hz, H-15), 5.86 (d, 1H, J = 10.88 Hz, H-

13), 6.19 (dd, 1H, *J* = 14.84, 10.88 Hz, H-14), 7.29 (m, 5H, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 172.8, 153.3, 139.2, 135.2, 133.9, 129.3, 128.8, 127.2, 125.8, 124.5, 66.1, 55.1, 38.6, 37.8, 34.1, 34.0, 29.7, 20.2, 16.5, 11.7; **HRMS (FAB, *m*-NBA)** m/z M^+ 355.2151; Calcd for $C_{22}H_{29}NO_3$: M 355.2147.



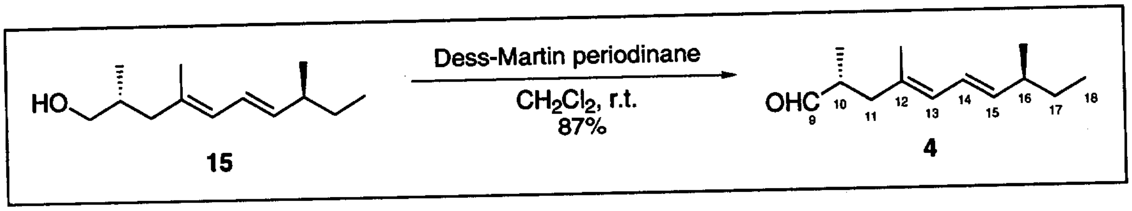
To a solution of sodium hexamethyldisilazide (1.0 M solution in THF, 8.7 mL, 8.71 mmol) in tetrahydrofuran (10 mL) was added dropwise a solution of **6** (2.2 g, 6.22 mmol) in tetrahydrofuran (20 mL) at –78°C. The reaction mixture was allowed to stir for 1 h at –78°C, treated with methyl iodide (1.2 mL, 18.6 mmol) and stirred for an additional for 2.5 h at –78°C. A solution of acetic acid (5 mL) in tetrahydrofuran (5 mL) was added dropwise to quench the reaction. The reaction mixture was warned to room temperature, extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded **14** (2.0 g, 85%) as a clear oil.

$[\alpha]_D^{27}$ = –36.5° (*c* = 1.82, $CHCl_3$); **IR (KBr)** 2964, 2927, 2873, 1781 (C=O), 1699 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.84 (t, 3H, *J* = 7.42 Hz, H-18), 0.97 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.19 (d, 3H, *J* = 6.59 Hz, 10-Me), 1.31 (m, 2H, H-17), 1.75 (s, 3H, 12-Me), 2.03 (m, 1H, H-16), 2.09, 2.67 (dd, 1H each, *J* = 13.52, 7.08 Hz, H-11), 2.77 (dd, 1H, *J* = 13.19, 9.56 Hz, 1/2 $PhC\underline{H}_2$), 3.26 (dd, 1H, *J* = 13.19, 3.30 Hz, 1/2 $PhC\underline{H}_2$), 3.99 (m, 1H, H-10), 4.14 (d, 2H, *J* = 4.94 Hz, $OC\underline{H}_2CHN$), 4.63 (m, 1H, $OCH_2C\underline{H}N$), 5.48 (dd, 1H, *J* = 14.84, 7.91 Hz, H-15), 5.80 (d, 1H, *J* = 10.88 Hz, H-13), 6.16 (dd, 1H, *J* = 14.84, 10.88 Hz, H-14), 7.19-7.35 (m, 5H, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 176.9, 153.0, 139.3, 135.3, 132.9, 129.4, 128.8, 127.3, 127.2, 124.5, 65.9, 55.4, 43.9, 38.5, 37.8, 35.9, 29.7, 20.1, 16.8, 16.4, 11.7; **HRMS (FAB, *m*-NBA)** m/z M^+ 369.2290; Calcd for $C_{23}H_{31}NO_3$: M 369.2304.



To a solution of adduct **14** (2.0 g, 5.28 mmol) in diethyl ether (100 mL) was added ethanol (330 μL, 5.81 mmol) and lithium borohydride (2.0 M in THF, 2.9 mL, 5.81 mmol) at 0°C. The resulting mixture was stirred for 30min, and quenched with aqueous sodium hydroxide solution (1 M). The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded alcohol **15** (1.0 g, 98%) as a clear oil.

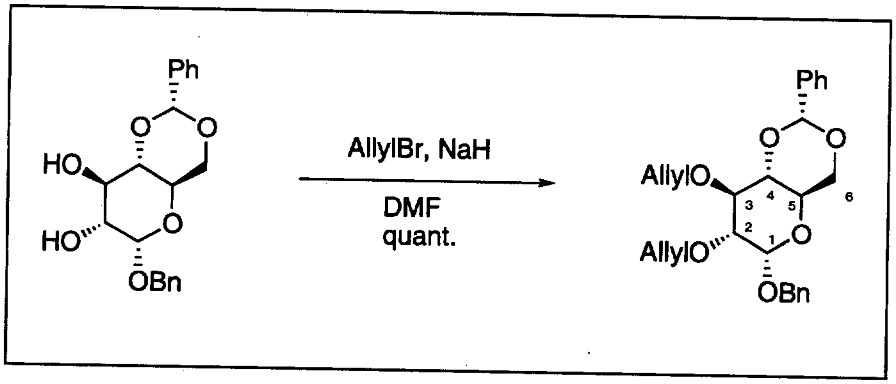
$[\alpha]_D^{27}$ = +40.1° (c = 1.17, $CHCl_3$); **IR (KBr)** 3376 (OH), 2962, 2923, 2873 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, J = 7.25 Hz, H-18), 0.89 (d, 3H, J = 6.59 Hz, 10-Me), 0.99 (d, 3H, J = 6.59 Hz, 16-Me), 1.32 (m, 2H, H-17), 1.74 (s, 3H, 12-Me), 1.85 (m, 1H, H-10), 1.88, 2.07 (m, 1H each, H-11), 2.12 (m, 1H, H-16), 3.46 (m, 2H, H-9), 5.46 (dd, 1H, J = 14.84, 7.91 Hz, H-15), 5.81 (d, 1H, J = 10.88 Hz, H-13), 6.19 (dd, 1H, J = 14.84, 10.88 Hz, H-14); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 138.7, 134.5, 126.6, 124.6, 68.3, 44.2, 38.6, 33.9, 29.8, 20.1, 16.7, 16.4, 11.7; **HRMS (FAB, *m*-NBA)** m/z M^+ 196.1818; Calcd for $C_{13}H_{24}O$: M 196.1827.



Dess-Martin periodinane (3.5 g, 8.40 mmol) was added to a solution of alcohol **15** (660 mg, 3.36 mmol) in dichloromethane (34 ml). The reaction mixture was stirred for 15 min. The reaction was quenched with saturated aqueous sodium thiosulfate solution and saturated aqueous sodium bicarbonate solution. The reaction mixture was extracted with dichloromethane, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded aldehyde **4** (561 mg, 87 %) as a yellow oil.

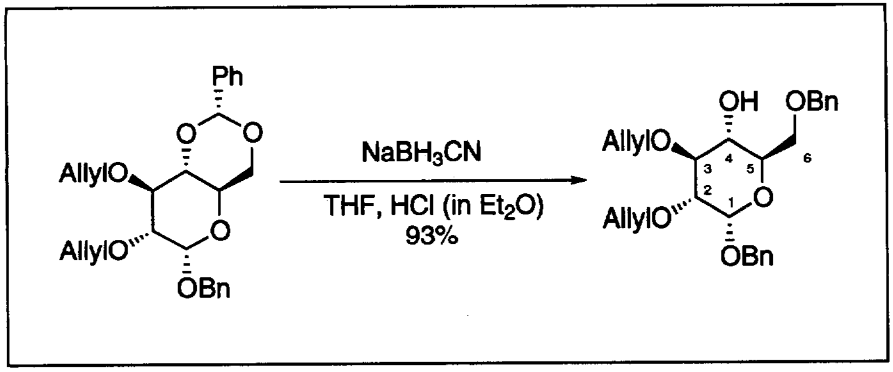
$[\alpha]_D^{24}$ = +31.4° (*c* = 3.01, $CHCl_3$); **IR (KBr)** 2962, 2929, 2873, 1727 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.83 (t, 3H, *J* = 7.25 Hz, H-18), 0.96 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.03 (d, 3H, *J* = 6.92 Hz, 10-Me), 1.32 (m, 2H, H-17), 1.70 (s, 3H, 12-Me), 2.00 (m, 1H, H-10), 2.04, 2.43 (m, 1H each, H-11), 2.50 (m, 1H, H-16), 5.46 (dd, 1H, *J* = 14.84, 7.91 Hz, H-15), 5.78 (d, 1H, *J* = 10.88 Hz, H-13), 6.13 (dd, 1H, *J* = 14.84, 10.88 Hz, H-14), 9.60 (d, 1H, *J* = 1.64 Hz, CHO); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 204.0, 139.5, 131.9, 127.6, 124.3, 44.4, 40.8, 38.6, 29.7, 20.0, 16.3, 13.2, 11.7.

<Synthesis of lactone moiety **3**>



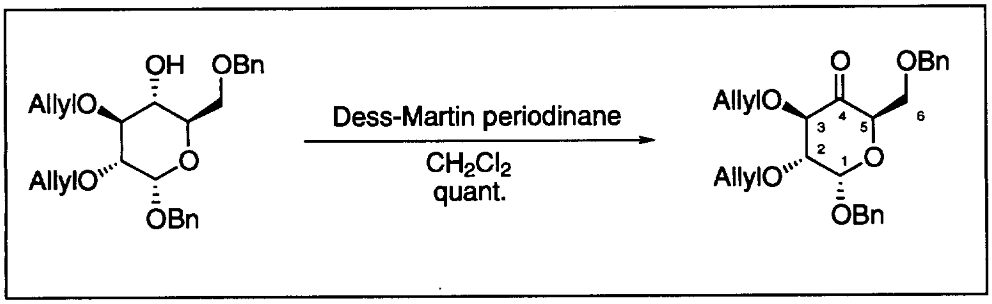
To a suspension of sodium hydride (60 % in oil, 2.8 g, 70.0 mmol), washed with hexane, in dimethylformamide (140 mL) was added slowly diol (5.0 g, 14.0 mmol). The resulting mixture was cooled to 0°C and treated with allyl bromide (6.1 mL, 70.0 mmol). The reaction mixture was warmed to room temperature and stirred for 30 min. The reaction was quenched with water at 0°C and the precipitated crude allyl ether was then filtrated. The crude allyl ether was recrystallized with methanol to provide allyl ether (6.1 g, 100%) as a white crystalline solid.

m.p. 129-130°C; $[\alpha]_D^{25}$ = +107.1° (c = 0.68, $CHCl_3$); **IR (KBr)** 3421, 2916, 2866, 1647 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 3.45 (dd, 1H, J = 9.2, 3.6 Hz, H-2), 3.56, 3.70 (t, 1H each, J = 9.8 Hz, H-6), 3.83-3.95 (m, 2H, H-3 and H-4), 4.07 (dd, 1H, J = 12.9, 6.3 Hz, 1/2 $C\underline{H}_2CH{=}CH_2$), 4.16-4.24 (m, 2H, 1/2 $C\underline{H}_2CH{=}CH_2$ and H-5), 4.29, 4.39 (dd, 1H each, J = 12.9, 5.6 Hz, $C\underline{H}_2CH{=}CH_2$), 4.64, 4.75 (d, 1H each, J = 12.4 Hz, $C\underline{H}_2Ph$), 4.94 (d, 1H, J = 3.6 Hz, H-1), 5.12-5.34 (m, 4H, 2x $CH_2CH{=}C\underline{H}_2$), 5.53 (s, 1H, $C\underline{H}Ph$), 5.79-6.03 (m, 2H, 2x $CH_2C\underline{H}{=}CH_2$), 7.21-7.53 (m, 10H, 2x Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 137.4, 137.0, 135.2, 134.8, 128.9, 128.4, 128.2, 128.1, 127.9, 126.0, 117.3, 116.6, 101.2, 96.6, 82.0, 79.1, 78.0, 74.0, 72.6, 69.3, 69.0, 62.5; **HRMS (FAB, *m*-NBA)** m/z $(M+H)^+$ 439.2151; Calcd for $C_{26}H_{31}O_6$: 439.2120.



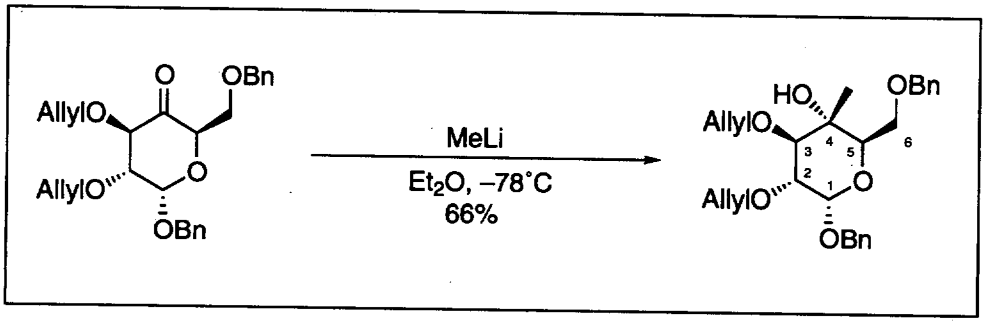
To a solution of allyl ether (8.0 g, 18.3 mmol) in THF (260 mL) was added sodium cyanoborohydride (13.8 g, 190 mmol) and molecular sieves 3Å. Hydrogen chloride in diethyl ether was added dropwise to the resulting suspension until the evolution of gas ceased. The reaction allowed to stir for 10 min and quenched with saturated aqueous sodium bicarbonate solution at 0°C. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. Purification on silica gel afforded alcohol (7.5 g, 93%) as a clear oil.

$[\alpha]_D^{25} = +88.5°$ (c = 1.48, $CHCl_3$); **IR (KBr)** 3444, 3437, 3030, 2920 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 3.34 (dd, 1H, J = 9.4, 3.7 Hz, H-2), 3.51-3.77 (m, 5H, H-3, H-4, H-5 and H-6), 3.89-4.05 (m, 2H, $C\underline{H}_2CH=CH_2$), 4.18, 4.38 (dd, 1H each, J = 12.5, 5.6 Hz, $C\underline{H}_2CH=CH_2$), 4.48, 4.54 (d, 1H each, J = 12.2 Hz, $C\underline{H}_2Ph$), 4.54, 4.68 (d, 1H each, J = 12.5 Hz, $C\underline{H}_2Ph$), 4.89 (d, 1H, J = 3.7 Hz, H-1), 5.04-5.28 (m, 4H, 2x $CH_2CH=C\underline{H}_2$), 5.70-6.04 (m, 2H, 2x $CH_2C\underline{H}=CH_2$), 7.19-7.44 (m, 10H, 2x Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 137.8, 136.9, 135.1, 134.5, 128.6, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 126.9, 117.5, 117.1, 95.2, 80.9, 79.2, 73.9, 73.3, 71.5, 70.3, 70.1, 69.2, 68.8; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 463.2127; Calcd for $C_{26}H_{32}O_6Na$: 463.2097.



Dess-Martin periodinane (6.5 g, 15.4 mmol) was added to a solution of alcohol (3.4 g, 7.68 mmol) in dichloromethane (77 mL) and stirred for 1 h. The reaction was quenched with saturated aqueous sodium thiosulfate solution and saturated aqueous sodium bicarbonate solution and the reaction mixture was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification on silica gel afforded ketone (3.4 g, 100%) as a clear oil.

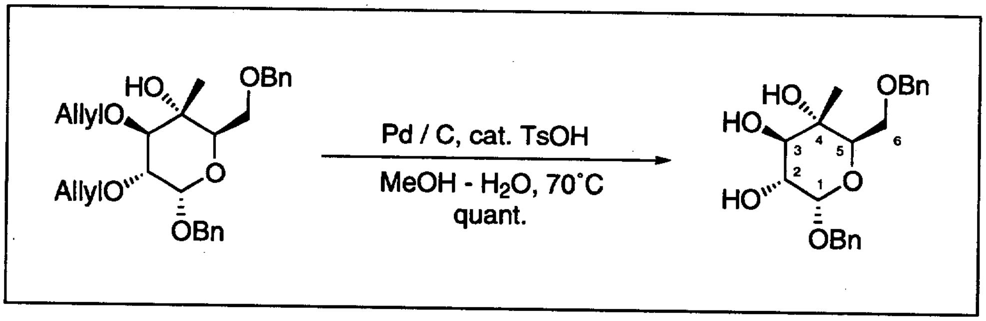
$[\alpha]_D^{25}$ = +147.0° (c = 1.14, $CHCl_3$); **IR (KBr)** 3467, 3032, 2920, 2872, 1736 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 3.63 (m, 2H, H-2 and 1/2 H-6), 3.80 (dd, 1H, J = 10.7, 3.5 Hz, 1/2 H-6), 3.96-4.32 (m, 4H, 2x $C\underline{H}_2CH=CH_2$), 4.24-4.29 (m, 2H, H-3 and H-5), 4.48, 4.55 (d, 1H each, J = 12.2 Hz, $C\underline{H}_2Ph$), 4.63, 4.75 (d, 1H each, J = 12.2 Hz, $C\underline{H}_2Ph$), 5.05-5.30 (m, 5H, H-1 and 2x $CH_2CH=C\underline{H}_2$), 5.69-5.97 (m, 2H, 2x $CH_2C\underline{H}=CH_2$), 7.13-7.39 (m, 10H, 2x Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 199.9, 135.9, 134.8, 132.3, 132.2, 126.9, 126.8, 126.7, 126.4, 126.3, 126.2, 126.1, 125.9, 115.5, 94.0, 80.3, 78.0, 71.6, 71.3, 71.0, 70.6, 67.8, 65.5; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 461.1948; Calcd for $C_{26}H_{30}O_6Na$: 461.1940.



A solution of ketone (3.4 g, 7.67 mmol) in diethyl ether (77 mL) was cooled to –78°C and methyl lithium (1.1 M solution in diethyl ether, 10.5 mL, 11.5 mmol) was added dropwise. The reaction was stirred for 30 min, quenched with saturated aqueous ammonium chloride solution. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. Purification on silica gel afforded tertiary alcohol (2.3 g, 66%) as a clear oil, along with C4 epimer (0.63 g, 18%).

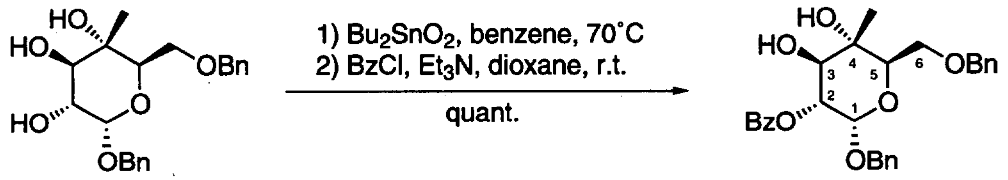
$[\alpha]_D^{25}$ = +96.7° (c = 2.55, $CHCl_3$); **IR (KBr)** 3487, 3481, 2920, 2873 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 1.11 (s, 3H, 4-Me), 2.66 (bs, 1H, 4-O$\underline{H}$), 3.24 (dd, 1H, J = 9.9, 4.0 Hz, H-2), 3.48, 3.67 (dd, 1H each, J = 9.7, 7.1 Hz, H-6), 3.63 (d, 1H, 9.9 Hz, H-3), 3.65

(m, 1H, H-5), 3.89-4.06 (m, 2H, $C\underline{H}_2CH=CH_2$), 4.19, 4.34 (dd, 1H each, J = 12.9, 5.4 Hz, $C\underline{H}_2CH=CH_2$), 4.46, 4.52 (d, 1H each, J = 11.7 Hz, $C\underline{H}_2Ph$), 4.56, 4.71 (d, 1H each, J = 12.2 Hz, $C\underline{H}_2Ph$), 4.83 (d, 1H, J = 4.0 Hz, H-1), 5.01-5.27 (m, 4H, 2x $CH_2CH=C\underline{H}_2$), 5.69-6.01 (m, 2H, 2x $CH_2C\underline{H}=CH_2$), 7.19-7.44 (m, 10H, 2x Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 138.2, 137.5, 135.9, 135.1, 129.6, 129.3, 129.2, 128.8, 128.4, 128.1, 127.8, 127.6, 127.5, 127.3, 117.7, 116.7, 95.1, 83.5, 78.7, 75.2, 74.8, 74.2, 72.3, 71.5, 69.3, 69.0, 16.4; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 477.2261; Calcd for $C_{27}H_{34}O_6Na$: 477.2253.



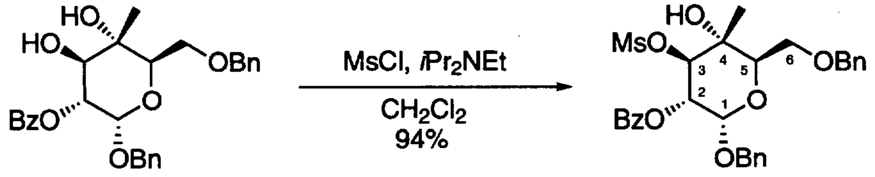
To a solution of palladium on carbon (240 mg, 20% w/w) and alcohol (1.2 g, 2.65 mmol) in methanol (20 mL) and water (4 mL) was added *p*-toluenesulfonic acid monohydrate (240 mg, 20% w/w). The reaction mixture was warmed to 70°C and allowed to stir for 12 h. The resulting suspension was filtered through a pad of celite, washed with methanol, and concentrated in vacuo. Purification on silica gel afforded triol (0.8 g, 100%) as a white solid.

m.p. 104-105°C; $[\alpha]_D^{25}$ = +99.9° (c = 0.11, $CHCl_3$); **IR (KBr)** 3454 , 3248, 2914 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 1.18 (s, 3H, 4-Me), 2.35 (bd, 1H, J = 9.6 Hz, 2-O$\underline{H}$), 2.94, 3.09 (bs, 1H each, 2x O$\underline{H}$), 3.48 (m, 1H, H-2), 3.59 (dd, 1H, J = 9.6, 6.6 Hz, 1/2 H-6), 3.73-3.84 (m, 2H, H-3 and 1/2 H-6), 3.96 (t, 1H, J = 6.6 Hz, H-5), 4.55, 4.61 (d, 1H each, J = 11.9 Hz, $C\underline{H}_2Ph$), 4.55, 4.79 (d, 1H each, J = 11.6 Hz, $C\underline{H}_2Ph$), 4.99 (d, 1H, J = 4.0 Hz, H-1), 7.28-7.44 (m, 10H, 2x Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 137.6, 136.9, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 97.0, 76.5, 73.6, 73.4, 71.2, 71.1, 69.6, 68.8, 14.6; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 397.1651; Calcd for $C_{21}H_{26}O_6Na$: 397.1627.



To a solution of triol (1.3 g, 3.44 mmol) in benzene (34 mL) and methanol (34 mL) was added dibuthyltin oxide (942 mg, 3.78 mmol). The reaction mixture was warmed to 70°C and stirred for 12 h. The resulting solution was concentrated in vacuo and the residue was then dissolved in dioxane (34 mL) and triethylamine (500 µL, 3.61 mmol). To this solution was added dropwise benzoyl chloride (420 µL, 3.61 mmol) at 0°C. The reaction mixture was stirred for 30 min at room temperature and quenched with water. The product was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded benzoate (1.6 g, 100%) as a clear oil.

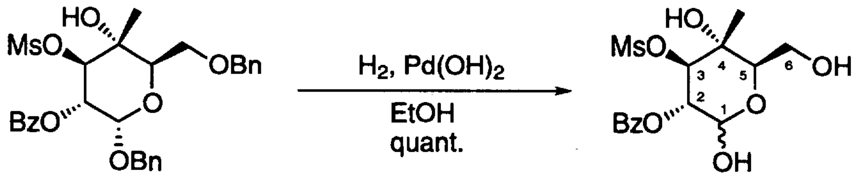
m.p. 108-110°C; $[\alpha]_D^{25}$ = +98.3° (*c* = 1.08, $CHCl_3$); **IR (KBr)** 3547, 3423 1752 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 1.19 (s, 3H, 4-Me), 2.36, 2.97 (bs, 1H each, 2x O$\underline{H}$), 3.53, 3.68 (dd, 1H each, *J* = 9.6, 6.6 Hz, H-6), 3.98 (t, 1H, *J* = 6.6 Hz, H-5), 4.15 (d, 1H, *J* = 10.6 Hz, H-3), 4.41, 4.65 (d, 1H each, *J* = 12.2 Hz, C$\underline{H}_2$Ph), 4.46, 4.52 (d, 1H each, *J* = 11.5 Hz, C$\underline{H}_2$Ph), 4.79 (dd, 1H, *J* = 10.6, 4.0 Hz, H-2), 5.10 (d, 1H, *J* = 4.0 Hz, H-1), 7.06-7.55 (m, 13H, Ph), 7.96 (d, 2H, *J* = 6.9 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 167.3, 138.4, 138.1, 134.2, 131.0, 130.8, 130.6, 130.5, 129.8, 129.4, 129.3, 129.2, 129.0, 128.9, 128.7, 128.6, 96.1, 75.1, 74.9, 74.4, 73.6, 71.6, 70.4, 69.8, 15.8; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 501.1923; Calcd for $C_{28}H_{30}O_7Na$: 501.1889.



7

To a solution of benzoate (340 mg, 710 μmol) in dichloromethane (14 mL) was added *N*-ethyl-diisopropylamine (370 μL, 2.13 mmol) and methanesulfonyl chloride (170 μL, 2.13 mmol). The reaction was stirred for 30 min and quenched with water. The reaction mixture was extracted with dichloromethane, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded mesylate **7** (373 mg, 94%) as a white amorphous solid.

m.p. 120-121°C; $[\alpha]_D^{25}$ = +67.4° (*c* = 1.92, $CHCl_3$); **IR (KBr)** 3527, 1716 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 1.39 (s, 3H, 4-Me), 3.17 (s, 3H, $C\underline{H}_3SO_2$), 3.61 (bs, 1H, $O\underline{H}$), 3.68, 3.83 (dd, 1H each, *J* = 9.4, 6.8 Hz, H-6), 4.18 (t, 1H, *J* = 6.8 Hz, H-5), 4.61, 4.66 (d, 1H each, *J* = 11.9 Hz, $C\underline{H}_2Ph$), 4.61, 4.80 (d, 1H each, *J* = 12.2 Hz, $C\underline{H}_2Ph$), 5.01 (dd, 1H, *J* = 10.6, 4.0 Hz, H-2), 5.29 (d, 1H, *J* = 10.6 Hz, H-3), 5.34 (d, 1H, *J* = 4.0 Hz, H-1), 7.16-7.69 (m, 13H, Ph), 8.19 (d, 2H, *J* = 6.9 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 165.7, 137.2, 136.7, 133.4, 129.8, 129.3, 129.2, 129.0, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 94.8, 82.7, 76.5, 76.1, 74.1, 73.6, 70.2, 69.8, 69.4, 68.6, 38.7, 14.6; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 579.1667; Calcd for $C_{29}H_{32}O_9SNa$: 579.1665.

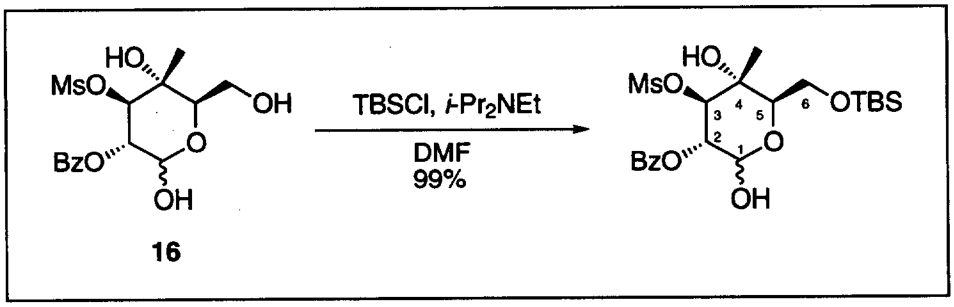


7 **16**

Palladium hydroxide (3.2 g, 50% w/w) and mesylate **7** (6.3 g, 11.4 mmol) were dissolved in ethanol (110 mL) and the resulting suspension was stirred under 1 atm of hydrogen gas for 24 hr at room temperature. Palladium was removed by filtration with celite and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography provided triol **16** (4.3 g, 100%) as a white amorphous solid.

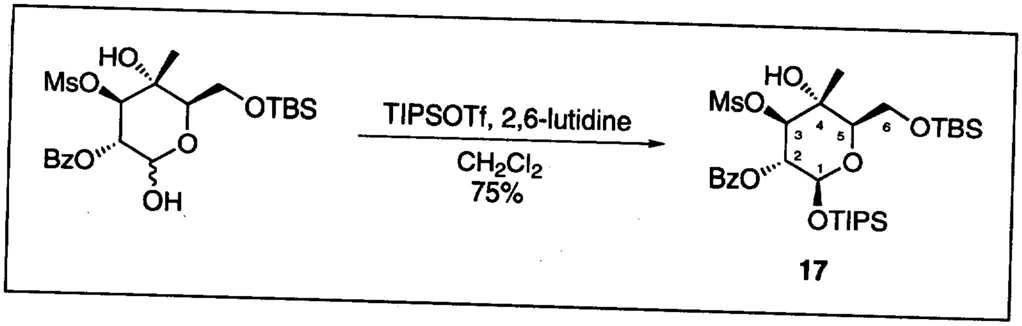
m.p. 85-86°C; $[\alpha]_D^{25}$ = +116.9° (*c* = 0.46, $CHCl_3$); **IR (KBr)** 3463 (OH), 2940, 2360, 2337, 1722 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 1.41 (s, 3H, 4-Me), 3.24 (s, 3H,

$C\underline{H}_3SO_2$), 3.83 (dd, 1H, *J* = 11.54, 7.91 Hz, 1/2 H-6), 4.07 (dd, 1H, *J* = 11.54, 2.30 Hz, 1/2 H-6), 4.24 (m, 1H, H-5), 5.10 (dd, 1H, *J* = 10.55, 3.62 Hz, H-2), 5.28 (d, 1H, *J* = 10.55 Hz, H-3), 5.69 (d, 1H, *J* = 3.62 Hz, H-1), 7..58-7.78 (m, 3H, Ph), 8.29 (d, 2H, *J* = 7.91 Hz, Ph); **^{13}C-NMR (67.5 MHz, CDCl$_3$)** δ 167.2, 134.4, 130.9, 130.5, 129.4, 90.9, 84.5, 75.1, 73.9, 72.7, 61.0, 39.2, 15.4; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 399.0746; Calcd for $C_{15}H_{20}O_9SNa$: M+Na 399.0726.



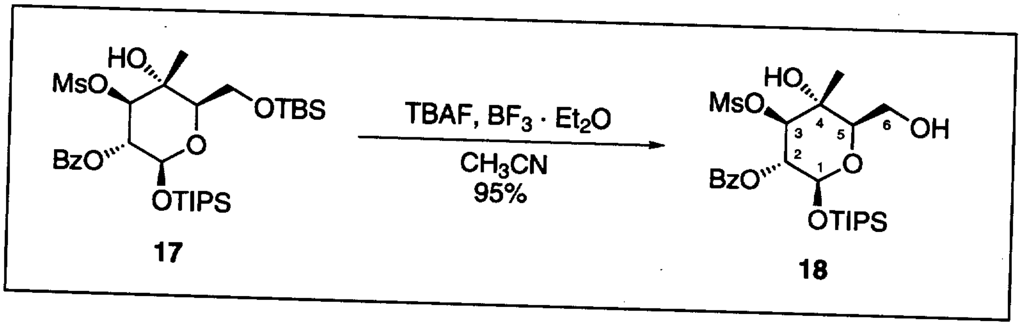
A solution of triol **16** (4.3 g, 11.4 mmol) in dimethylformamide (230 mL) at 0°C was treated with *N*-ethyldiisopropylamine (2.3 mL, 13.6 mmol) and TBSCl (2.0g, 13.6 mmol). The reaction was stirred for 45 min at room temperature and quenched with water. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded diol (5.5 g, 99%) as a clear oil.

$[\alpha]_D^{27}$ = +97.6° (*c* = 1.04, CHCl$_3$); **IR (KBr)** 3467 (OH), 2952, 2931, 2886, 2858, 1726 (C=O) cm^{-1}; major compound of anomeric mixture **^{1}H-NMR (270 MHz, CDCl$_3$)** δ 0.00 (s, 6H, 2x $SiC\underline{H}_3$), 0.78 (s, 9H, *t*-Bu), 1.22 (s, 3H, 4-Me), 2.99 (s, 3H, $C\underline{H}_3SO_2$), 3.71 (d, 2H, *J* = 7.25 Hz, H-6), 4.03 (t, 1H, *J* = 7.25 Hz, H-5), 4.78 (dd, 1H, *J* = 10.55, 3.62 Hz, H-2), 5.07 (d, 1H, *J* = 10.55 Hz, H-3), 5.46 (d, 1H, *J* = 3.62 Hz, H-1), 7.27-7.44 (m, 3H, Ph), 7.98 (d, 2H, *J* = 7.26 Hz, Ph); **^{13}C-NMR (67.5 MHz, CDCl$_3$)** δ 166.0, 133.4, 130.0, 129.7, 128.4, 90.1, 82.5, 74.0, 70.6, 70.0, 62.5, 38.7, 25.7, 18.0, 15.3, -5.6; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 513.1591; Calcd for $C_{21}H_{34}O_9SSiNa$: M+Na 513.1590.



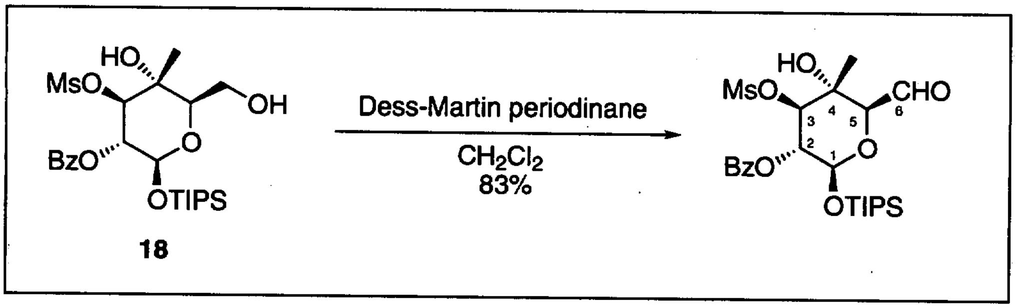
To a solution of diol (5.5 g, 11.2 mmol) in dichloromethane (220 mL) was added 2,6-lutidine (5.1 mL, 44.8 mmol) and TIPSOTf (9.1 mL, 33.7 mmol) at 0°C, and the reaction was allowed to warm to room temperature. After 24 hr, the reaction was quenched with saturated aqueous ammonium chloride solution and extracted with chloroform. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded tertiary alcohol **17** (5.4 g, 75%) as a clear oil.

$[\alpha]_D^{27}$ = +5.60° (c = 1.64, CHCl$_3$); **IR (KBr)** 3519 (OH), 2946, 2867, 1737 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, CDCl$_3$)** δ 0.00 (s, 6H, 2x SiC$\underline{H}_3$), 0.78-0.83 (m, 30H, 3x *i*-Pr, *t*-Bu), 1.28 (s, 3H, 4-Me), 2.91 (s, 3H, C$\underline{H}_3$SO$_2$), 3.42 (dd, 1H, J = 5.93, 7.91 Hz, 1/2 H-6), 3.68-3.80 (m, 2H, H-5 and 1/2 H-6), 4.69 (d, 1H, J = 10.55 Hz, H-3), 4.80 (d, 1H, J = 7.58 Hz, H-1), 5.03 (dd, 1H, J = 10.55, 7.58 Hz, H-2), 7.26-7.43 (m, 3H, Ph), 7.89 (d, 2H, J = 9.23 Hz, Ph); **^{13}C-NMR (67.5 MHz, CDCl$_3$)** δ 165.1, 133.0, 129.7, 129.1, 128.2, 96.3, 85.1, 75.0, 73.7, 72.4, 62.1, 38.8, 25.7, 17.5, 17.4, 16.0, 11.8, -5.8; **HRMS [FAB, *m*-NBA + NaI]** m/z (M+Na)$^+$ 669.2905; Calcd for C$_{30}$H$_{54}$O$_9$SSi$_2$Na: M+Na 669.2924.



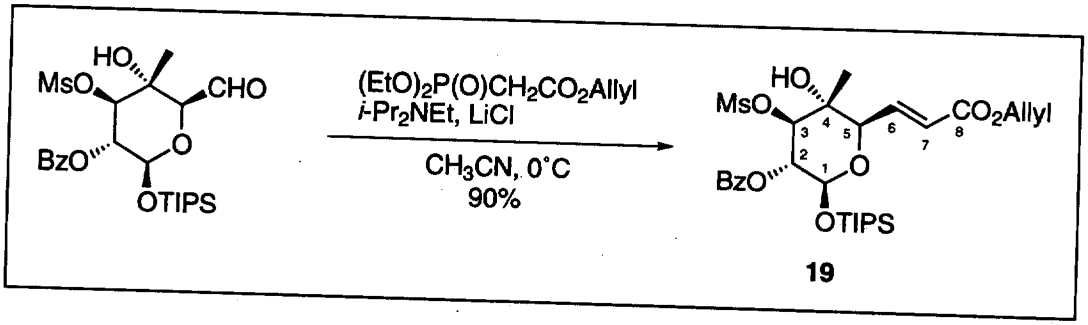
To a solution of tertiary alcohol **17** (5.0 g, 7.73 mmol) in CH$_3$CN (150 mL) was added TBAF (1.0 M solution in THF, 38.7 mL, 38.7 mmol) and boron trifluoride diethyl ether complex (4.9 mL, 38.7 mmol) at 0°C. The resulting solution was warmed to room temperature and stirred for 1 hr. Saturated aqueous sodium bicarbonate was added to quench the reaction. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded diol **18** (3.9 g, 95%) as a clear oil.

$[\alpha]_D^{27}$ = +22.0° (*c* = 0.49, $CHCl_3$); **IR (KBr)** 3504 (OH), 2944, 2867, 2364, 1735 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.93-1.08 (m, 21H, 3x *i*-Pr), 1.40 (s, 3H, 4-Me), 2.96 (s, 3H, $C\underline{H}_3SO_2$), 3.57 (t, 1H, *J* = 6.04 Hz, H-5), 3.84 (dd, 1H, *J* = 11.21, 6.04 Hz, 1/2 H-6), 3.95 (dd, 1H, *J* = 11.21, 6.04 Hz, 1/2 H-6), 4.83 (d, 1H, *J* = 10.55 Hz, H-3), 4.98 (d, 1H, *J* = 7.58 Hz, H-1), 5.18 (dd, 1H, *J* = 10.55, 7.58 Hz, H-2), 7.11-7.59 (m, 3H, Ph), 8.05 (d, 2H, *J* = 7.68 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 165.1, 133.2, 129.7, 129.3, 128.4, 96.3, 84.9, 76.7, 73.2, 72.7, 61.0, 38.5, 17.5, 16.0, 11.9; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 555.2067; Calcd for $C_{24}H_{40}O_9SSiNa$: M+Na 555.2060.



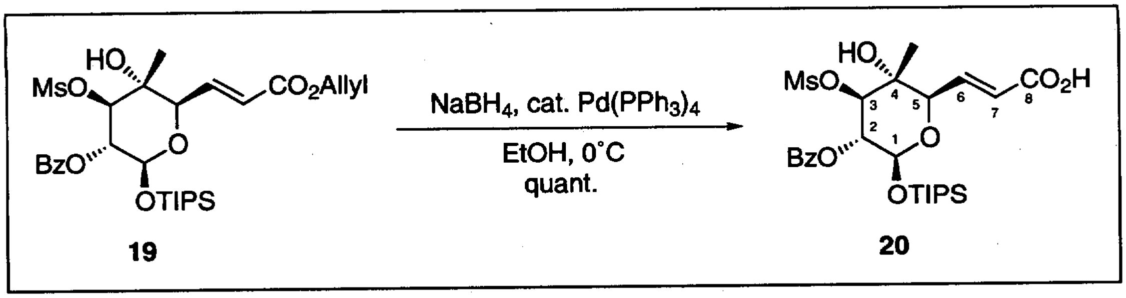
Diol **18** (79.5 mg, 149 μmol) was dissolved in dichloromethane (1.5 mL) and Dess-Martin periodinane (190 mg, 448 μmol) was added to the solution. After 2 hr, the reaction was quenched with saturated aqueous sodium thiosulfate solution and saturated aqueous sodium bicarbonate solution. The reaction mixture was extracted with chloroform, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded aldehyde (65.5 mg, 83 %) as a clear oil.

$[\alpha]_D^{27}$ = +7.0° (*c* = 2.12, $CHCl_3$); **IR (KBr)** 3455 (OH), 2944, 2867, 1737 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.95-1.10 (m, 21H, 3x *i*-Pr), 1.42 (s, 3H, 4-Me), 3.01 (s, 3H, $C\underline{H}_3SO_2$), 3.86 (s, 1H, H-5), 4.86 (d, 1H, *J* = 10.22 Hz, H-3), 5.04 (d, 1H, *J* = 7.25 Hz, H-1), 5.25 (dd, 1H, *J* = 10.22, 7.25 Hz, H-2), 7.40-7.59 (m, 3H, Ph), 8.05 (d, 2H, *J* = 7.35 Hz, Ph), 9.74 (s, 1H, $C\underline{H}O$); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 199.9, 164.9, 133.2, 129.7, 129.2, 128.3, 96.5, 83.6, 79.9, 73.7, 72.2, 38.7, 17.4, 17.0, 11.8; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 553.1897; Calcd for $C_{24}H_{38}O_9SSiNa$: M+Na 553.1903.



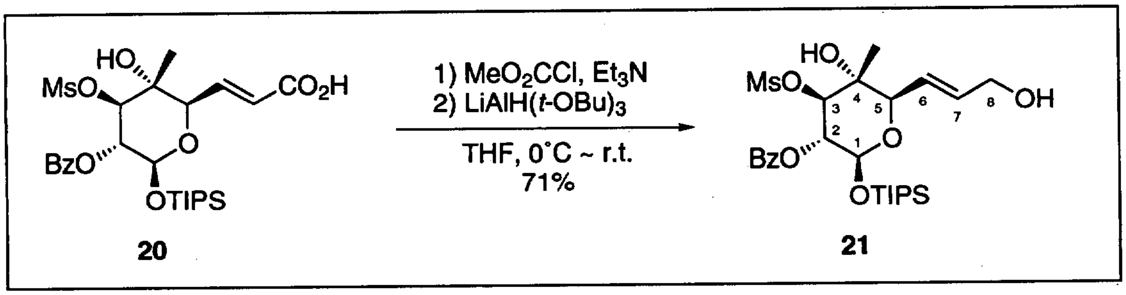
To a solution of aldehyde (179 mg, 337 μmol), allyl diethylphosphonoacetate (140 μL, 675 μmol) and *N*-ethyldiisopropylamine (170 μL, 1.01 mmol) in 3.5 mL of CH_3CN was added lithium chloride (57.2 mg, 1.35 mmol) at 0°C. After stirred for 1 hr, the reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded ester **19** (186 mg, 90 %) as a white solid.

m.p. 163-164°C; $[\alpha]_D^{27} = +20.4°$ (c = 1.30, $CHCl_3$); **IR (KBr)** 3467(OH), 2944, 2867, 1723 (C=O), 1712 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.94-1.11 (m, 21H, 3x *i*-Pr), 1.30 (s, 3H, 4-Me), 2.93 (s, 3H, $C\underline{H}_3SO_2$), 4.13 (m, 1H, H-5), 4.68 (d, 2H, J = 5.60 Hz, $C\underline{H}_2CH=CH_2$), 4.89 (d, 1H, J = 10.22 Hz, H-3), 5.01 (d, 1H, J = 7.58 Hz, H-1), 5.21 (dd, 1H, J = 10.22, 7.58 Hz, H-2), 5.26 (d, 1H, J = 10.55 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.35 (d, 1H, J = 17.15 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.97 (m, 1H, $CH_2C\underline{H}=CH_2$), 6.23 (dd, 1H, J = 15.83, 1.98 Hz, H-6), 7.09 (dd, 1H, J = 15.83, 3.30 Hz, H-7), 7.41-7.61 (m, 3H, Ph), 8.05 (d, 2H, J = 6.92 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 165.6, 165.0, 141.1, 133.4, 132.0, 129.7, 129.3, 128.4, 122.9, 118.1, 96.3, 84.7, 77.1, 73.5, 72.6, 65.2, 38.5, 17.5, 16.9, 11.9; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 635.2314; Calcd for $C_{29}H_{44}O_{10}SSiNa$: M+Na 635.2322.



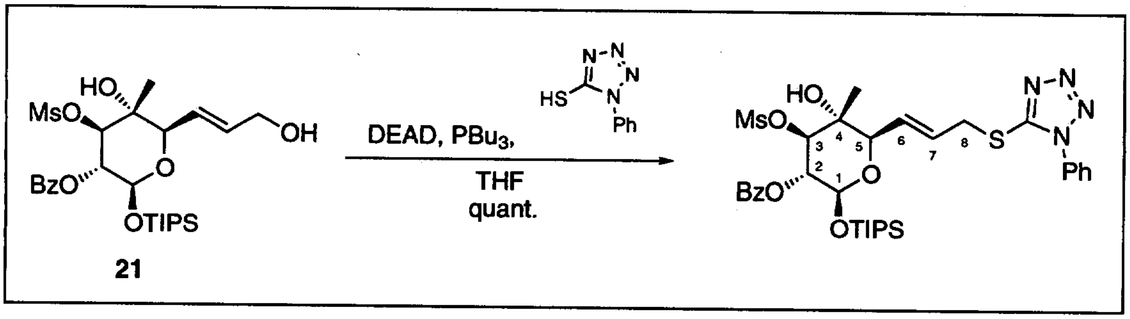
To a mixture of ester **19** (186 mg, 304 µmol) and tetrakistriphenylphosphine palladium (3.50 mg, 3.03 µmol) in ethanol (3.0 mL) was added sodium borohydride (17.2 mg, 456 µmol) at 0°C. The solution was warmed to room temperature, stirred for 30 min, and poured into water. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded acid **20** (183 mg, 100 %) as a white solid.

m.p. 178-179°C; $[\alpha]_D^{27} = +20.9°$ (*c* = 4.43, $CHCl_3$); **IR (KBr)** 3415 (OH), 2944, 2867, 2362, 1727 (C=O), 1712 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.82-1.11 (m, 21H, 3x *i*-Pr), 1.31 (s, 3H, 4-Me), 2.93 (s, 3H, $C\underline{H}_3SO_2$), 4.17 (m, 1H, H-5), 4.91 (d, 1H, *J* = 10.22 Hz, H-3), 5.03 (d, 1H, *J* = 7.58 Hz, H-1), 5.22 (dd, 1H, *J* = 10.22, 7.58 Hz, H-2), 6.22 (d, 1H, *J* = 15.83 Hz, H-7), 7.18 (dd, 1H, *J* = 15.83, 2.97 Hz, H-6), 7.41-7.61 (m, 3H, Ph), 8.05 (d, 2H, *J* = 6.92 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 165.5, 165.0, 142.6, 133.4, 130.7, 129.7, 129.2, 128.5, 124.7, 96.3, 84.7, 76.3, 73.5, 72.7, 38.6, 17.5, 16.8, 11.9; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 595.2017; Calcd for $C_{26}H_{40}O_{10}SSiNa$: M+Na 595.2009.



Methyl chloroformate (20 µL, 235 µmol) was added at 0°C to the solution of acid **20** (89.9 mg, 157 µmol) and triethylamine (35 µL, 235 µmol) in tetrahydrofurane (1.5 mL). After stirred for 1 hr, the resulting mixture was added via cannula to a suspension of lithium tri-*t*-butoxyaluminohydride (159 mg, 628 μmol) and MS4Å (89.9 mg) in tetrahydrofurane (1.5 mL), and the reaction was stirred 1hr at room temperature. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution, extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded diol **21** (62.3 mg, 71 %) as a white solid.

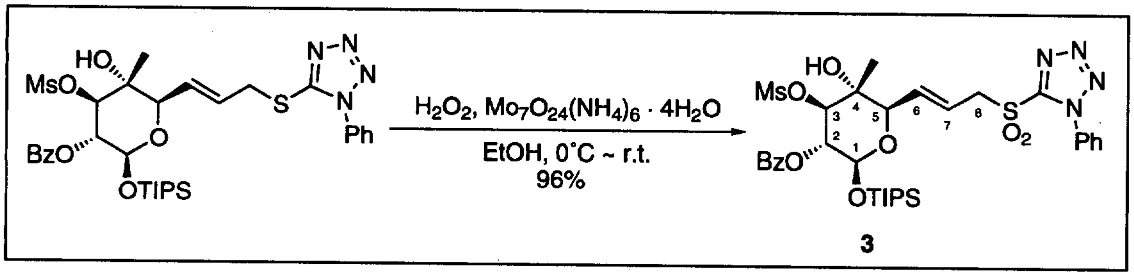
m.p. 61-63°C; $[\alpha]_D^{27}$ = +18.4° (*c* = 0.80, $CHCl_3$); **IR (KBr)** 3513 (OH), 2944, 2867, 2360, 1735 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.85-1.10 (m, 21H, 3x *i*-Pr), 1.32 (s, 3H, 4-Me), 2.93 (s, 3H, $C\underline{H}_3SO_2$), 3.95 (d, 1H, *J* = 4.61 Hz, H-5), 4.23 (d, 2H, *J* = 4.94 Hz, H-8), 4.85 (d, 1H, *J* = 10.22 Hz, H-3), 4.98 (d, 1H, *J* = 7.25 Hz, H-1), 5.22 (dd, 1H, *J* = 10.22, 7.25 Hz, H-2), 5.84 (dd, 1H, *J* = 15.50, 4.61 Hz, H-6), 6.04 (dt, 1H, *J* = 15.50, 4.94 Hz, H-7), 7.41-7.60 (m, 3H, Ph), 8.08 (d, 2H, *J* = 7.91 Hz, Ph); **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 581.2214; Calcd for $C_{26}H_{42}O_9SSiNa$: M+Na 581.2216.



A solution of diol **21** (280 mg, 501 μmol) and 1-phenyl-1*H*-tetrazole-5-thiol (172 mg, 1.00 mmol) in tetrahydrofuran (10 mL) was cooled to 0°C and DEAD (200 μL, 1.25 mmol) and tri-*n*-butylphosphine (310 mL, 1.25 μmol) were added to the solution. After 30min, water was added to quench the reaction. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded sulfide (361 mg, 100 %) as a white solid.

m.p. 55-56°C; $[\alpha]_D^{27}$ = +27.2° (*c* = 4.44, $CHCl_3$); **IR (KBr)** 3418 (OH), 2942, 2865, 1735 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, CDCl3)** δ 0.78-1.07 (m, 21H, 3x i-Pr), 1.27 (s, 3H, 4-Me), 2.97 (s, 3H, CH_3SO_2), 3.93 (d, 1H, J = 3.63 Hz, H-5), 4.02-4.05 (m, 2H, H-8), 4.84 (d, 1H, J = 10.22 Hz, H-3), 4.95 (d, 1H, J = 7.58 Hz, H-1), 5.20 (dd, 1H, J =

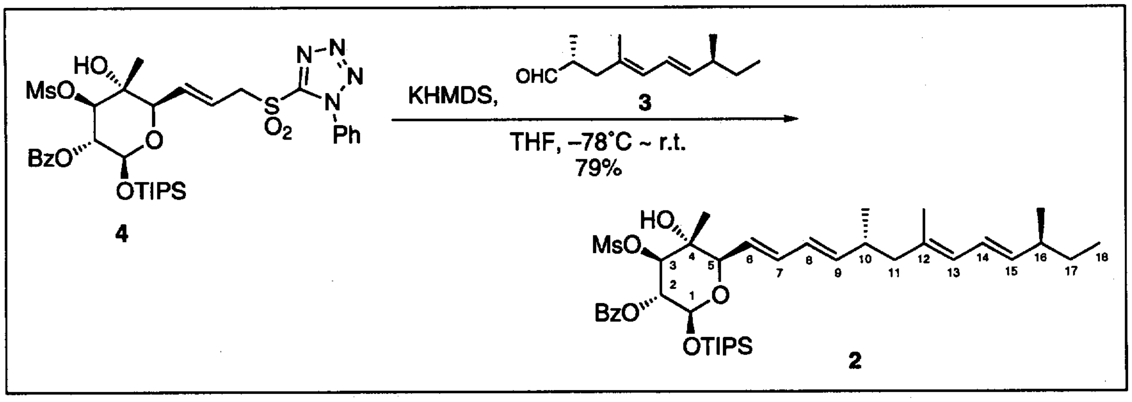
10.22, 7.58 Hz, H-2), 5.93-6.09 (m, 2H, H-6 and H-7), 7.39-7.62 (m, 8H, Ph), 8.05 (d, 2H, J = 7.25 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 165.0, 153.4, 133.4, 133.1, 130.2, 129.8, 129.7, 129.4, 128.8, 128.3, 127.1, 123.9, 96.2, 84.8, 77.1, 73.6, 72.8, 38.6, 34.9, 17.4, 16.3, 11.8; **HRMS [FAB, m-NBA + NaI)]** m/z $(M+Na)^+$ 741.2460; Calcd for $C_{33}H_{46}N_4O_8S_2SiNa$: M+Na 741.2424.



To a solution of sulfide (361 mg, 503 μmol) and ammonium heptamolybdate tetrahydrate (186 mg, 151 μmol) in ethanol (10 mL) was added H_2O_2 (30% solution in water, 570 μL, 5.02 mmol) at 0°C. The solution was warmed to room temperature, and stirred for 8 hr, poured into saturated aqueous sodium thiosulfate solution. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded sulfone **3** (355 mg, 96 %) as a white solid.

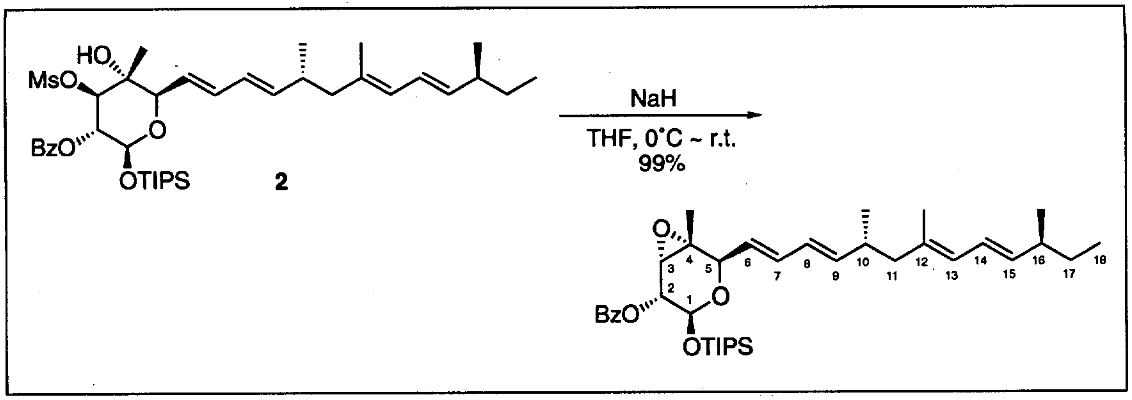
m.p. 70-72°C; $[\alpha]_D^{27} = +18.4°$ (*c* = 2.15, $CHCl_3$); **IR (KBr)** 3519 (OH), 2944, 2867, 1733 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.90-1.06 (m, 21H, 3x *i*-Pr), 1.20 (s, 3H, 4-Me), 2.92 (s, 3H, $C\underline{H}_3SO_2$), 4.00 (d, 1H, *J* = 3.95 Hz, H-5), 4.50 (m, 2H, H-8), 4.84 (d, 1H, *J* = 10.22 Hz, H-3), 4.97 (d, 1H, *J* = 7.58 Hz, H-1), 5.17 (dd, 1H, *J* = 10.22, 7.58 Hz, H-2), 5.95 (m, 1H, H-7), 6.18 (dd, 1H, *J* = 15.83, 3.95 Hz, H-6), 7.41-7.62 (m, 8H, Ph), 8.05 (d, 2H, *J* = 7.91 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 164.9, 136.7, 133.3, 132.8, 131.5, 129.7, 129.3, 128.4, 125.0, 116.4, 96.2, 84.6, 76.6, 73.5, 72.7, 59.3, 38.5, 17.4, 16.4, 11.8; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 773.2321; Calcd for $C_{33}H_{46}N_4O_{10}S_2SiNa$: M+Na 773.2322.

<Completion of total synthesis>



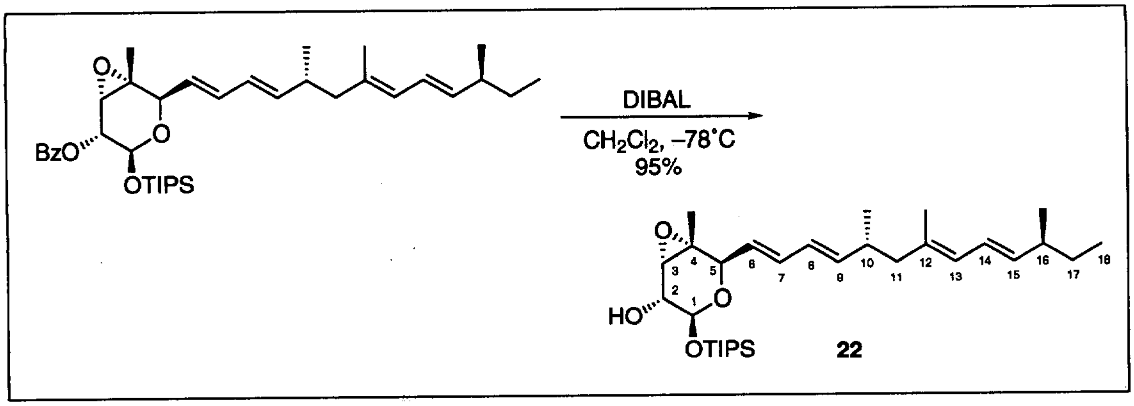
To a solution of sulfone **3** (209 mg, 279 μmol) in tetrahydrofuran (4.5 mL) was added dropwise potassium hexamethyldisilazide (0.5 M solution in THF, 1.2 mL, 595 μmol) at -78°C. The mixture was then stirred for 30 min before addition of the solution of aldehyde **4** (57.7 mg, 298 μmol) in tetrahydrofuran (1.5 mL). After stirring for a further 3h at -78°C, the reaction mixture was allowed to warm to room temperature. After 2hr, the resultant mixture was poured into brine. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded adduct **2** (157 mg, 79 %) as a clear oil.

$[\alpha]_D^{27}$ = +41.2° (c = 2.83, $CHCl_3$); **IR (KBr)** 3521 (OH), 2960, 2867, 2358, 1737 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, J = 7.42 Hz, H-18), 0.93-1.10 (m, 27H, 3x i-Pr, 10-Me and 16-Me), 1.31 (m, 2H, H-17), 1.71 (s, 3H, 12-Me), 1.95 (m, 2H, H-11), 2.03 (s, 3H, 4-Me), 2.07 (m, 1H, H-16), 2.41 (m, 1H, H-10), 2.94 (s, 3H, $C\underline{H}_3SO_2$), 3.92 (d, 1H, J = 5.27 Hz, H-5), 4.84 (d, 1H, J = 10.22 Hz, H-3), 4.96 (d, 1H, J = 7.25 Hz, H-1), 5.21 (dd, 1H, J = 10.22, 7.25 Hz, H-2), 5.46 (dd, 1H, J = 14.84, 7.91 Hz, H-15), 5.62 (dd, 1H, J = 14.84, 5.27 Hz, H-6), 5.67 (dd, 1H, J = 14.84, 6.92 Hz, H-9), 5.77 (d, 1H, J = 10.88 Hz, H-13), 6.06 (dd, 1H, J = 14.84, 10.88 Hz, H-8), 6.18 (dd, 1H, J = 14.84, 10.88 Hz, H-14), 6.35 (dd, 1H, J = 14.84, 10.88 Hz, H-7), 7.40-7.58 (m, 3H, Ph), 8.05 (d, 2H, J = 7.25 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 171.1, 165.0, 141.7, 138.5, 134.0, 133.2, 129.7, 129.5, 128.3, 127.1, 126.8, 124.6, 123.1, 96.2, 85.0, 77.9, 73.8, 73.0, 47.4, 38.6 x2, 34.6, 29.8, 20.1, 19.4, 17.5, 16.6, 16.4, 11.9, 11.7; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 741.3840; Calcd for $C_{39}H_{62}O_8SSiNa$: M+Na 741.3832.



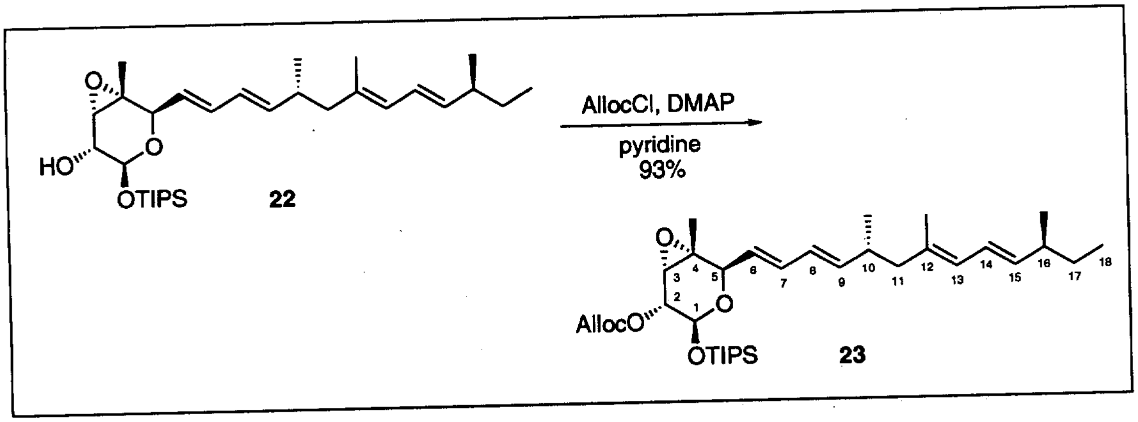
Adduct **2** (61.9 mg, 86.2 μmol) was dissolved in tetrahydrofuran (8.6 mL) and the solution was cooled to 0°C. Sodium hydride (51.7 mg, 1.29 μmol) was added and resulting suspension was stirred for 30 min. The reaction mixture was quenched with acetic acid and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification on silica gel afforded epoxide (53.0 mg, 99 %) as a clear oil.

$[\alpha]_D^{27}$ = –42.8° (*c* = 1.53, $CHCl_3$); **IR (KBr)** 2962, 2927, 2867, 1726 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, *J* = 7.25 Hz, H-18), 0.95-1.11 (m, 27H, 3x *i*-Pr, 10-Me and 16-Me), 1.28 (m, 2H, H-17), 1.58 (s, 3H, 4-Me), 1.72 (s, 3H, 12-Me), 1.93-2.19 (m, 3H, H-10 and H-11), 2.42 (m, 1H, H-16), 3.44 (s, 1H, H-3), 4.41 (d, 1H, *J* = 7.91 Hz, H-5), 5.12 (d, 1H, *J* = 6.92 Hz, H-1), 5.24 (d, 1H, *J* = 6.92 Hz, H-2), 5.47 (dd, 1H, *J* = 14.84, 7.91 Hz, H-15), 5.62 (dd, 1H, *J* = 14.84, 7.91 Hz, H-6), 5.70 (dd, 1H, *J* = 7.58, 15.17 Hz, H-9), 5.78 (d, 1H, *J* = 10.55 Hz, H-13), 6.04 (dd, 1H, *J* = 15.17, 10.55 Hz, H-8), 6.19 (dd, 1H, *J* = 14.84, 10.55 Hz, H-14), 6.30 (dd, 1H, *J* = 14.84, 10.55 Hz, H-7), 7.40-7.59 (m, 3H, Ph), 8.08 (d, 2H, *J* = 7.91 Hz, Ph); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 166.0, 142.0, 138.6, 134.1, 133.9, 133.1, 130.8, 129.8, 128.2, 127.0, 126.8, 126.2, 124.7, 92.3, 78.1, 73.4, 63.8, 61.0, 47.4, 38.7, 34.7, 29.8, 20.3, 20.1, 19.5, 17.6, 16.5, 11.9, 11.7; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 645.3959; Calcd for $C_{38}H_{58}O_5SiNa$: M+Na 645.3951.



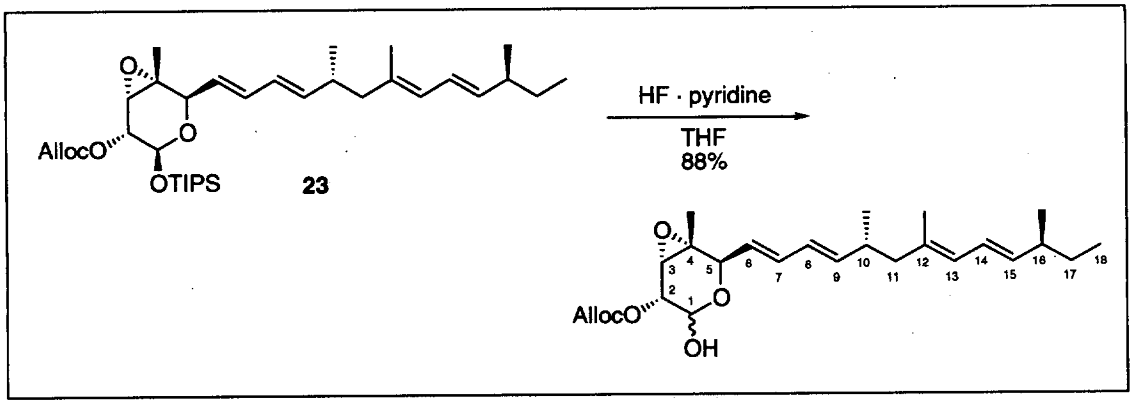
To a -78°C solution of epoxide (53.9 mg, 86.6 μmol) in dichloromethane (1.7 mL) was added diisobutylaluminium hydride (1.02 M solution in hexane, 210 μL, 216 μmol), and the reaction was allowed to stir for 30min at –78°C. MeOH was added to quench the reaction, the resulting solution was warmed to room temperature, celite (1 g), $Na_2SO_4 \bullet 10H_2O$ (1 g) was added, and the mixture was stirred vigorously for 2hr. Filtration and concentration of the resulting mixture followed by flash chromatography afforded alcohol **22** (43.0 g, 95%) as a clear oil.

$[\alpha]_D^{27}$ = +20.9° (*c* = 4.23, $CHCl_3$); **IR (KBr)** 3465 (OH), 2962, 2927, 2867 cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, *J* = 7.42 Hz, H-18), 0.97 (d, 3H, *J* = 6.59 Hz, 10-Me), 0.99 (d, 3H, *J* = 6.59 Hz, 16-Me), 1.03-1.17 (m, 21H, 3x *i*-Pr), 1.26 (s, 3H, 4-Me), 1.28-1.37 (m, 2H, H-17), 1.71 (s, 3H, 12-Me), 1.92-2.17 (m, 3H, H-11 and H-16), 2.38-2.43 (m, 1H, H-10), 3.30 (s, 1H, H-3), 3.75 (d, 1H, *J* = 5.94 Hz, H-2), 4.33 (d, 1H, *J* = 7.91 Hz, 5-H), 4.89 (d, 1H, *J* = 5.94 Hz, H-1), 5.45 (dd, 1H, *J* = 15.18, 7.59 Hz, H-15), 5.61 (dd, 1H, *J* = 15.18, 7.91 Hz, H-6), 5.63 (dd, 1H, *J* = 15.51, 7.25 Hz, H-9), 5.77 (d, 1H, *J* = 10.88 Hz, H-13), 6.01 (dd, 1H, *J* = 15.51, 10.22 Hz, H-8), 6.18 (dd, 1H, *J* = 15.18, 10.88 Hz, H-14), 6.24 (dd, 1H, *J* = 15.18, 10.22 Hz, H-7); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 141.8, 138.5, 134.0, 133.8, 127.0, 126.9, 126.8, 124.7, 94.4, 77.8, 71.1, 63.0, 62.0, 47.4, 38.6, 34.7, 29.8, 20.5, 20.1, 19.5, 17.7, 16.5, 12.0, 11.7; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 541.3688; Calcd for $C_{31}H_{54}O_4SiNa$: M+Na 541.3689.



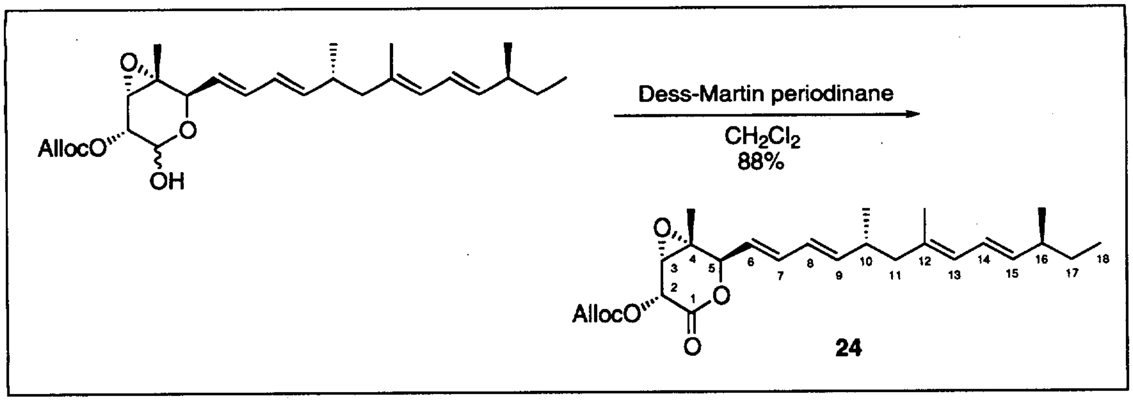
To a solution of alcohol **22** (43.0 mg, 83.0 μmol) in pyridine (1.4 mL) was added allyl choloroformate (1.0 mL, 9.42 μmol) and DMAP (10.0 mg, 83.0 μmol). After 24 hr, water was added to the solution. The reaction mixture was extracted with EtOAc, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded allyl carbonate **23** (46.3 mg, 93 %) as a clear oil.

$[\alpha]_D^{24} = -18.2°$ (c = 2.02, $CHCl_3$); **IR (KBr)** 3021, 2925, 2894, 2335, 1751 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.84 (t, 3H, J = 7.42 Hz, H-18), 0.95 (d, 3H, J = 6.60 Hz, 16-Me), 0.97 (d, 3H, J = 6.60 Hz, 10-Me), 0.99-1.03 (m, 21H, 3x *i*-Pr), 1.24 (s, 3H, 4-Me), 1.30 (m, 2H, H-17), 1.68 (s, 3H, 12-Me), 1.97 (m, 1H, H-16), 2.05 (m, 2H, H-11), 2.39 (m, 1H, H-10), 3.33 (d, 1H, J = 1.65 Hz, H-3), 4.32 (d, 1H, J = 7.59 Hz, H-5), 4.61 (d, 2H, J = 6.60 Hz, $C\underline{H}_2CH=CH_2$), 4.81 (dd, 1H, J = 6.93, 1.65 Hz, H-2), 4.92 (d, 1H, J = 6.93 Hz, H-1), 5.23 (dd, 1H, J = 10.55, 1.32 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.33 (dd, 1H, J = 17.16, 1.32 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.46 (dd, 1H, J = 15.18, 7.92 Hz, H-6), 5.57 (dd, 1H, J = 15.17, 7.92 Hz, H-15), 5.69 (dd, 1H, J = 14.84, 7.59 Hz, H-9), 5.75 (d, 1H, J= 10.56 Hz, H-13), 5.91 (m, 1H, $CH_2C\underline{H}=CH_2$), 6.00 (dd, 1H, J = 14.84, 10.56 Hz, H-8), 6.15 (dd, 1H, J = 15.17, 10.56 Hz, H-14), 6.24 (dd, 1H, J = 15.18, 10.56 Hz, H-7); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 154.6, 142.0, 138.6, 134.0 x2, 131.4, 127.0, 126.8, 126.0, 124.7, 118.7, 92.0, 78.0, 76.4, 68.5, 64.0, 60.6, 47.4, 38.6, 34.7, 29.8, 20.3, 20.1, 19.4, 17.6, 16.5, 11.9, 11.7; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 625.3918; Calcd for $C_{35}H_{58}O_6SiNa$: M+Na 625.3900.



To a solution of allyl carbonate **23** (40.3 mg, 76.9 μmol) in 1.5 mL of THF was added HF · pyridine (200 μL) at room temperature. The reaction was stirred for 24 hr, then filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue was followed by flash chromatography to afford lactol (26.1 mg, 88 %) as a clear oil.

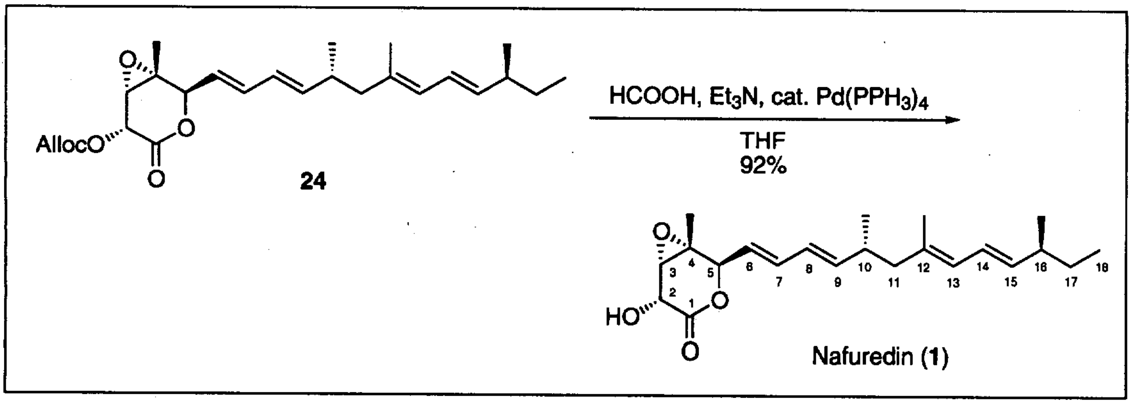
$[\alpha]_D^{23}$ = +36.6° (*c* = 1.26, $CHCl_3$); **IR (KBr)** 3463(OH), 2962, 2925, 2871, 1749 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** major compound: δ 0.83 (t, 3H, *J* = 7.25 Hz, H-18), 0.94 (d, 3H, *J* = 6.60 Hz, 16-Me), 0.97 (d, 3H, *J* = 6.60 Hz, 10-Me), 1.27 (s, 3H, 4-Me), 1.29 (m, 2H, H-17), 1.67 (s, 3H, 12-Me), 1.97 (m, 1H, H-16), 2.04 (m, 2H, H-11), 2.36 (m, 1H, H-10), 3.93 (d, 1H, *J* = 1.65 Hz, H-3), 4.41 (d, 1H, *J* = 8.25 Hz, H-5), 4.65 (d, 2H, *J* = 5.60 Hz, $C\underline{H}_2CH=CH_2$), 4.79 (dd, 1H, *J* = 6.92, 1.65 Hz, H-2), 4.94 (d, 1H, *J* = 6.92 Hz, H-1), 5.26 (dd, 1H, *J* = 10.22, 1.32 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.36 (dd, 1H, *J* = 15.84, 1.32 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.43 (dd, 1H, *J* = 15.18, 7.92 Hz, H-15), 5.54 (dd, 1H, *J* = 15.18, 8.25 Hz, H-6), 5.68 (dd, 1H, *J* = 15.18, 7.26 Hz, H-9), 5.73 (d, 1H, *J* = 10.56 Hz, H-13), 5.92 (m, 1H, $CH_2C\underline{H}=CH_2$), 5.99 (dd, 1H, *J* = 15.18, 10.22 Hz, H-8), 6.14 (dd, 1H, *J* = 15.18, 10.56 Hz, H-14), 6.29 (dd, 1H, *J* = 15.18, 10.22 Hz, H-7); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 154.8, 142.8, 138.6, 135.2, 134.0, 131.1, 126.8, 126.7, 125.5, 124.6, 119.2, 91.6, 78.4, 75.4, 69.0, 63.5, 60.1, 47.4, 38.6, 34.8, 29.8, 20.2, 20.1, 19.6, 16.5, 11.8; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 469.2588; Calcd for $C_{26}H_{38}O_6Na$: M+Na 469.2566.



24

Dess-Martin periodinane (140 mg, 329 μmol) was added to the solution of lactol (14.7 mg, 33.0 μmol) in dichloromethane (700 μL). After 15 min, saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate solution was added to quench the reaction. The reaction mixture was extracted with chloroform, dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel afforded lactone **24** (12.9 mg, 88 %) as a clear oil.

$[\alpha]_D^{27} = +16.9^\circ$ (c = 0.33, $CHCl_3$); **IR (KBr)** 2960, 2927, 2854, 1758 (C=O) cm^{-1}; **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, J = 7.41 Hz, H-18), 0.98 (d, 3H, J = 6.59 Hz, 10-Me), 0.99 (d, 3H, J = 6.92 Hz, 16-Me), 1.31 (m, 2H, H-17), 1.49 (s, 3H, 4-Me), 1.71 (s, 3H, 12-Me), 1.98 (m, 1H, H-16), 2.07 (m, 2H, H-11), 2.44 (m, 1H, H-10), 3.50 (s, 1H, H-3), 4.72 (d, 2H, J = 5.61 Hz, $C\underline{H}_2CH=CH_2$), 4.93 (d, 1H, J = 7.91 Hz, H-5), 5.31 (d, 1H, J = 10.23 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.42 (d, 1H, J = 17.49 Hz, 1/2 $CH_2CH=C\underline{H}_2$), 5.46 (dd, 1H, J = 15.18, 5.94 Hz, H-15), 5.50 (dd, 1H, J = 14.84, 7.91 Hz, H-6), 5.51 (s, 1H, H-2), 5.77 (d, 1H, J = 10.89 Hz, H-13), 5.82 (dd, 1H, J = 14.84, 6.92 Hz, H-9), 5.94 (m, 1H, $CH_2C\underline{H}=CH_2$), 6.02 (dd, 1H, J = 14.84, 10.22 Hz, H-8), 6.18 (dd, 1H, J = 15.18, 10.89 Hz, H-14), 6.39 (dd, 1H, J = 14.84, 10.22 Hz, H-7); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 163.7, 154.1, 145.3, 138.8, 138.0, 133.7, 130.8, 127.0, 126.0, 124.6, 122.0, 119.4, 79.5, 71.2, 69.4, 58.3, 56.6, 47.2, 38.6, 34.8, 29.8, 20.1, 19.3, 17.7, 16.5, 11.8; **HRMS [FAB, *m*-NBA + NaI]** m/z $(M+Na)^+$ 467.2411; Calcd for $C_{26}H_{36}O_6Na$: M+Na 467.2410.



To a solution of lactone **24** (11.9 mg, 26.8 μmol), and tetrakis(triphenylphosphine)-palladium (1.60 mg, 1.45 μmol) in tetrahydrofuran (1.0 mL) was added formic acid (3 μL, 58.1 μmol), and triethylamine (8 μL, 58.1 μmol). The reaction was stirred for 5 min, then concentrated in vacuo and subjected to flash chromatography to afford nafuredin **1** (8.90 mg, 92%) as a white solid.

m.p. 102-103°C; $[\alpha]_D^{27} = +99.9°$ ($c = 0.10$, $CHCl_3$); **IR (KBr)** 3444 (OH), 2962, 2923, 2854, 1735 (C=O); **^{1}H-NMR (270 MHz, $CDCl_3$)** δ 0.86 (t, 3H, $J = 7.42$ Hz, H-18), 0.98 (d, 3H, $J = 6.92$ Hz, 10-Me), 0.99 (d, 3H, $J = 6.92$ Hz, 16-Me), 1.32 (m, 2H, H-17), 1.47 (s, 3H, 4-Me), 1.70 (s, 3H, 12-Me), 2.01 (m, 2H, H-11), 2.08 (m, 1H, H-16), 2.43 (m, 1H, H-10), 3.52 (s, 1H, H-3), 4.57 (s, 1H, H-2), 4.94 (d, 1H, $J = 7.91$ Hz, H-5), 5.47 (dd, 1H, $J = 15.18$, 7.92 Hz, H-15), 5.50 (dd, 1H, $J = 15.18$, 7.91 Hz, H-6), 5.76 (d, 1H, $J = 10.55$ Hz, H-13), 5.80 (dd, 1H, $J = 15.18$, 6.92 Hz, H-9), 6.02 (dd, 1H, $J = 15.18$, 10.56 Hz, H-8), 6.17 (dd, 1H, $J = 15.18$, 10.55 Hz, H-14), 6.38 (dd, 1H, $J = 15.18$, 10.56 Hz, H-7); **^{13}C-NMR (67.5 MHz, $CDCl_3$)** δ 170.5, 145.2, 138.9, 137.9, 133.7, 127.0, 126.1, 124.6, 122.0, 80.2, 68.1, 58.6, 58.2, 47.2, 38.6, 34.8, 29.8, 20.2, 19.5, 17.8, 16.5, 11.8; **HRMS [FAB, *m*-NBA]** m/z $(M+H)^+$ 361.2370; Calcd for $C_{22}H_{33}O_4$: M+H 361.2379.