A Tandem Diels-Alder/ Fragmentation Approach to the Synthesis of Eleutherobin

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Supporting Information

(Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **6**, **10 - 12**, **15**, **16**, **18b** - **24**, **27**, **28**, and X-ray data for **18b** and **27**)

Allenic alcohol 10. To a solution of 4.40 mL of 1-bromobut-2-yne (50.3 mmol) in 150 mL of DMPU at room temperature were added 10.44 g of $SnCl_2$ (55.1 mmol) and 8.25 g of NaI (55.1 mmol). The resulting yellow slurry was stirred in the absence of light for 5 hours during which time complete dissolution of solids was observed. The mixture was cooled to 0 °C, and a solution of 8.34 g of aldehyde **9** (47.9 mmol) in 75 mL of DMPU was added dropwise over 30 minutes. The orange reaction mixture was allowed to warm to room temperature over 4 hours and stirred in the dark for an additional 20 hours. The reaction was diluted with Et_2O and quenched by addition of 100 mL of 30% aq. NH_4F. The phases were separated, and the aqueous phase was extracted with Et_2O (5x100 mL). The combined organic extracts were washed successively with H_2O and brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (3:2 to 1:1 pet. ether/Et_2O) provided 9.39 g (86%) of allenic alcohol **10** as a pale yellow oil. Data for **10** (as an inseparable 3.5:1 mixture of diastereomers): R_f 0.66 (EtOAc); **IR** (thin film) 3494, 2923, 2851, 1958, 1440, 1299, 1114 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.68 (bs, 1H, major), 5.66 (bs, 1H, minor), 4.88-4.79 (m, 2H), 4.35 (m, 1H, major), 4.28 (m, 1H, minor), 3.92 (d, *J*=10.3 Hz, 1H, major), 3.74 (s, 1H, major), 3.72 (m, 1H, minor), 3.64 (d, *J*=6.0 Hz, 1H, minor), 2.23-1.92 (m, 4H), 1.88 (d, *J*=0.8 Hz, 3H, minor), 1.85, (d, *J*=1.0 Hz, 3H, major), 1.77 (t, *J*=3.1 Hz, 3H, minor) 1.76 (t, *J*=3.2 Hz, 3H, major); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ204.6, 138.6 (major), 138.2 (minor), 117.0 (minor), 116.9 (major), 101.9 (minor), 100.7 (major), 77.7 (minor), 77.4 (major), 70.1 (major), 68.5 (minor), 64.6 (major), 63.8 (minor), 55.7 (minor), 55.6 (major), 33.3 (major), 33.1 (minor), 18.2 (major), 17.9 (minor), 15.0 (minor), 14.7 (major); **HRMS** calcd for $C_{11}H_{17}O_3S$ (MH^+) 229.0898, found 229.0895.

Allenic ketone 11. To a solution of 5.60 g of allenic alcohol **10** (24.7 mmol) in 300 mL of CH_2Cl_2 at 0 °C was added 8.30 g of $NaHCO_3$ (98.8 mmol) followed by 18.8 g of Dess-Martin periodinane (44.4 mmol). The slurry was stirred at 0 °C for 1 hour before the reaction was diluted with Et_2O and quenched with 100 mL of sat. $Na_2S_2O_3$. After stirring the biphasic mixture vigorously for 20 minutes, the layers were separated, and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic extracts were washed with sat. $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. The drying agent was removed by filtration, and the solvents were removed in vacuo. Purification by silica gel chomatography (2:1 pet. ether/EtOAc) provided 5.30 g (95%) of allenic ketone **11** as a white foam. Data for **11**: R_f 0.46 (1:1 pet. ether/EtOAc); **IR** (thin film) 2962, 2925, 1956, 1934, 1682, 1307, 1113 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.66 (br s, 1H), 5.25 (dq, *J*=14.3, 3.0 Hz, 1H), 5.20 (dq, *J*=14.3, 3.0 Hz, 1H), 4.18 (t, *J*=5.9 Hz, 1H), 3.80-3.66 (m, 2H), 3.31 (dd, *J*=18.4, 7.5 Hz, 1H), 2.97 (dd, *J*=18.1, 5.6 Hz, 1H), 1.83 (t, *J*=3.0 Hz, 3H), 1.78 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ196.2, 137.8, 117.2, 103.4, 79.7, 62.7, 55.9, 36.8, 17.9, 13.0, 1.0; **HRMS** calcd for $C_{11}H_{15}O_3S$ (MH^+) 227.0742, found 227.0740.

Furan 12. To a solution of 6.33 g of allenic ketone **11** (28.0 mmol) in 150 mL of hexane and 30 mL of CH_2Cl_2 at room temperature was added 11.90 g of $AgNO_3$ on SiO_2 (10 wt. %, 7.0 mmol) in a single portion. The suspension was stirred at room temperature in the absence of light of 2 hours before it was diluted with Et_2O and filtered through a short pad of Celite. Solvents were removed in vacuo, and purification by silica gel chromatography (3:1 hexanes/EtOAc) gave 5.01 g (79%) of furan **12** as a pale yellow oil. Data for **12**: R_f 0.33 (3:1 hexanes/EtOAc); **IR** (thin film) 2922, 1510, 1443, 1306, 1248, 1210, 1150, 1116, 1090, 1044 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.24 (d, *J*=2.0 Hz, 1H), 6.15 (d, *J*=1.8 Hz, 1H), 5.65 (m, 1H), 3.82 (t, *J*=6.5 Hz, 1H), 3.64-3.67 (m, 2H), 3.23 (dd, *J*=15.5, 6.5 Hz, 1H), 2.92 (dd, *J*=15.5, 7.4 Hz, 1H), 1.97 (s, 3H), 1.69 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 145.1, 140.8, 139.0, 117.6, 116.6, 113.1, 65.2, 55.2, 24.9, 18.0, 9.8; **HRMS** calcd for $C_{11}H_{15}O_3S(MH^+)$ 227.0742, found 227.0741.

Bis-diene 6. To a solution of 5.88 g of sulfolene **12** (25.9 mmol) in 430 mL of $PhCH_3$ was added 6.30 g of $NaHCO_3$ (77.7 mmol), and the suspension was heated to reflux for 6 hours. After cooling to room temperature, the reaction mixture was filtered to remove $NaHCO_3$, and concentrated in vacuo. Purification by silica gel chromatography (20:1 pet. ether/Et_2O) provided 3.94 g (94%) of bis-diene **6** as a colorless oil. Data for **6**: R_f 0.40 (20:1 pet. ether/Et_2O); **IR** (thin film) 2924, 1606, 1510, 1444, 1261, 1150, 1087 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.20 (d, *J*=1.8 Hz, 1H), 6.36 (dd, *J*=17.4, 10.7 Hz, 1H), 6.14 (d, *J*=1.7 Hz, 1H), 5.58 (dt, *J*=6.8, 0.5 Hz, 1H), 5.13 (d, *J*=17.1 Hz, 1H), 4.96 (d, *J*=10.7 Hz, 1H),

3.41 (d, *J*=7.3 Hz, 2H), 1.96 (s, 3H), 1.83 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 149.1, 141.1, 140.1, 134.0, 128.0, 113.9, 112.9, 11.4, 25.4, 11.7, 9.7; **HRMS** calcd for $C_{11}H_{14}O(M^{=})$ 162.1045, found 162.1033.

Allenoate 15. To a solution of 2.01 g of propargyl bromide **13** (11.2 mmol) in 43 mL of DMPU at room temperature were added 2.47 g of $SnCl_2$ (12.8 mmol) and 1.97 g of NaI (12.8 mmol). The resulting yellow slurry was stirred in the absence of light for 4 hours. The mixture was cooled to 0 °C, and a solution of 1.19 g of aldehyde **14** (10.2 mmol) in 20 mL of DMPU was added dropwise over 15 minutes. The orange reaction mixture was allowed to warm to room temperature over 2 hours and stirred in the dark for an additional 16 hours. The reaction was cooled to 0°C, diluted with Et_2O, and quenched by addition of 50 mL of 30% aq. NH_4F followed by 30 mL H_2O. The phases were separated, and the aqueous phase was extracted with Et_2O (5x70 mL). The combined organic extracts were washed successively with H_2O and brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (3:2 Et_2O/hexanes) gave 1.43 g (72%) of allenoate **15** as a slightly yellow oil. Data for **15**: R_f 0.45 (3:2 Et_2O/hexanes); **IR** (thin film) 3431, 2957, 2869, 1964, 1716, 1464, 1437, 1383, 1363, 1261, 1080, 1010, 971 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.72 (ddd, *J*=7.8, 6.5, 1.1 Hz, 1H), 5.51 (ddd, *J*=7.8, 6.6, 1.3 Hz, 1H), 5.24 (d, *J*=2.0 Hz, 2H), 4.89 (d, *J*=4.5 Hz, 1H), 3.76, (s, 3H), 2.99 (s, 1H), 2.29 (sept, *J*=5.8 Hz, 1H), 0.97 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.1, 140.1, 126.1, 102.1, 80.8, 70.4, 70.2, 52.3, 30.6, 22.1, 22.0; **HRMS** calcd for $C_{11}H_{16}O_3(M^+)$ 196.1099, found 196.1077.

Diol 16. To a solution of 2.51 g of allenoate **15** (12.8 mmol) in 40 mL of CH_2Cl_2 at -78 °C was 40.0 mL of a 1.0M CH_2Cl_2 solution of DIBAL-H (40.0 mmol) dropwise over 1 hour. The reaction mixture was allowed to warm to 0 °C over 2 hours and stirred at this temperature for an additional 2 hours. The reaction was quenched by addition of 10 mL of MeOH and diluted with 50 mL of EtOAc. After warming to room temperature, 50 mL of sat. sodium potassium tartrate (Rochelle's salt) was added, and the mixture was stirred vigorously until two distinct phases were observed. The aqueous phase was extracted with EtOAc (6x50 mL), and the combined organic layers were dried over Na_2SO_4. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (3:1 EtOAc/pet. ether) provided 2.15 g (77%) of diol **16** as a pale yellow oil. Data for **16**: R_f 0.32 (3:1 EtOAc/pet. ether); **IR** (thin film) 3380, 2961, 1957, 1621, 1464, 1013 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.71 (dd, *J*=15.5, 6.5 Hz, 1H), 5.49 (ddd, *J*=15.4, 6.6, 0.8 Hz, 1H), 4.93 (d, *J*=2.1 Hz, 1H), 4.92 (d, *J*=2.1 Hz, 1H), 4.70 (d, *J*=6.6 Hz, 1H), 4.24 (d, *J*=12.2 Hz, 1H), 4.15 (d, *J*=12.2 Hz,

1H), 2.62 (s, 1H), 2.51 (s, 1H), 2.31 (m, 1H), 0.99 (d, *J*=6.7 Hz, 3H), 0.99 (d, *J*=6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 204.8, 140.0, 128.1, 106.0, 78.8, 72.0, 61.7, 30.6, 22.1 (2C); **HRMS** calcd for $C_{10}H_{16}O_2Na$ (MNa^+) 191.1048, found 191.1009.

Tetracycle 18b. To a solution of 803.1 mg of diol **16** (5.21 mmol) in 25 mL of CH_2Cl_2 at room temperature was added 2.67 g of $BaMnO_4$ (10.44 mmol). The slurry was heated to reflux for 3 hours after which time an additional 2.67 g of $BaMnO_4$ (10.44 mmol) was added, and heating was continued for 4 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filter cake was washed with Et_2O. Solvents were removed in vacuo, and the crude bis-dienophile **7** was used without purification.

To a 15 mL flask containing the crude bis(dienophile) was added 408.1 mg of bis-diene **6** (2.51 mmol), and the neat mixture was heated to 50 °C for 16 hours) at which time TLC analysis indicated completion of the reaction. Due to the instability of the unprotected tetracycle **18a**, it was used without purification in the next step.

The crude unprotected tetracycle **18a** was dissolved in 10 mL of CH_2Cl_2, and the solution was cooled to 0 °C before addition of 1.20 mL of 2,6-lutidine (10.4 mmol). TBSOTf (1.20 mL, 5.2 mmol) was added dropwise, and the orange solution was allowed to stir at 0 °C for 1 hour. The reaction was quenched by addition of 10 mL of sat. $NaHCO_3$ and diluted with 20 mL of Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O (4x20 ml). The combined organic layers were washed sequentially with water and brine and dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (20:1 hexanes/Et_2O) provided 565.8 mg (51% overall) of protected tetracycle **18b** as a white solid. Crystals of **18b** suitable for X-ray analysis were obtained by recrystallization from hexane. Data for **18b**: R_f 0.29 (20:1 hexanes/Et_2O); mp=113-115 °C; **IR** (thin film) 2962, 2935, 2853, 2359, 2322, 1699, 1252, 1092 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.08 (dd, *J*=3.6,1.8 Hz, 1H), 5.32 (bs,1H), 5.03 (s, 1H), 5.00 (s, 1H), 4.89 (s, 1H), 4.23 (d, 1H, *J*=9.9 Hz, 1H), 3.32 (m,1H), 3.11 (d, *J*=9.9 Hz, 1H), 2.88 (m, 1H), 2.55 (dd, *J*=14, 8.4 Hz, 1H), 2.27 (dd, *J*=14, 10.6 Hz, 1H), 2.21 (m,1H), 1.98-1.88 (m, 5H), 1.70 (s, 3H), 1.59 (m, 1H), 0.91 (m, 6H), 0.85 (s, 9H), 0.02 (s, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 211.8, 148.6, 147.8, 135.2, 129.7, 121.1, 106.7, 92.8. 81.9, 68.8, 61.9, 46.4, 37.6, 33.6, 28.4, 27.5, 26.3, 26.2, 24.2, 21.8, 21.6, 20.8, 18.4, 13.1, -5.4, -5.5; **HRMS** calcd for $C_{27}H_{43}O_3Si$ (MH^+) 443.2881, found 443.3001.

Alcohol 19. To a solution of 315.5 mg of ketone **18b** (0.713 mmol) in 30 mL of CH_2Cl_2 at -78 °C was added 3.0 mL of a 1.0M CH_2Cl_2 solution of DIBAL-H (3.0 mmol) over 10 minutes. The pale yellow reaction mixture was stirred at -78 °C for 2 hours. The reaction was quenched by the addition of 5 ml of

EtOAc and allowed to warm to room temperature before 30 mL of sat. sodium potassium tartrate (Rochelle's salt) was added. The mixture was stirred vigorously until two distinct layers were observed . The layers were separated, and the aqueous phase was extracted with Et_2O (4x25 ml). The combined organic layers were washed sequentially with water and brine and dried over $MgSO_4$. The drying agent was removed by filtration, and the solvents were removed in vacuo. Purification by silica gel chromatography (7:2 hexanes/Et_2O) provided 305.5 mg (96%) of alcohol **19** as an off-white foam. Data for **19**: R_f 0.35 (7:2 hexanes/Et_2O); **IR** (thin film) 2574-3327, 2951, 2916, 2869, 2363, 1464, 1253, 1083, 838 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.12 (s, 1H), 5.46 (s, 1H), 5.35 (s, 1H), 5.09 (s, 1H), 4.89 (s, 1H), 4.45 (bs, 1H), 4.23 (d, *J*=9.2 Hz, 1H), 4.10 (dd, *J*=7.6, 4.3 Hz, 1H), 3.36 (d, *J*= 9.4 Hz, 1H), 2.57 (bs, 1H), 2.33 (m, 2H), 1.75-2.38 (m, 5H), 1.80 (s, 3H), 1.71 (s, 3H), 0.98 (m, 6H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 151.7, 146.6, 136.8, 130.7, 122.0, 106.7, 91.8, 83.2, 81.0, 69.5, 51.4, 43.6, 38.7, 28.1, 27.7, 26.1, 25.8, 22.7, 22.0, 18.4, 16.3, 14.0, -5.4, -5.5; **HRMS** calcd for $C_{27}H_{45}O_3Si$ (MH^+) 445.3138, found 445.3122.

Epoxide 20. To a solution of 303.1 mg of homoallylic alcohol **19** (0.68 mmol) in 15 ml of CH_2Cl_2 at 0 °C were added 1.50 g of crushed 4Å molecular sieves, 27.3 mg of $VO(acac)_2$ (0.10 mmol), and 600 µL of a 5.0M decanes solution of *t*-butyl hydroperoxide (3.0 mmol) sequentially. The deep red mixture was allowed to warm to room temperature over 30 minutes and stirred at this temperature for an additional 2 hours. The reaction was quenched by addition of sat. sodium sulfite solution, and the bipahsic mixture was stirred vigorously for 20 minutes. The layers were separated, and the aqueous phase was extracted with EtOAc (5x25 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (7:3 hexanes/Et_2O) provided 241.0 mg (77%) of epoxide **20** as a white solid. Data for **20**: R_f 0.42 (7:3 hexanes/Et_2O); mp=149-152 °C; **IR** (thin film) 3522, 2947, 2915, 2873, 1463, 1437, 1383, 1362, 1304, 1256, 1085, 1022 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.00 (s, 1H), 5.46 (s, 1H), 4.57 (bs, 1H), 4.25 (s, 1H), 4.10 (d, *J*=11.0 Hz, 1H), 3.75 (d, *J*=11.0 Hz, 1H), 3.07 (bs, 1H), 2.95 (s, 1H), 2.89 (d, *J*=3.5 Hz, 1H), 2.33 (m, 2H), 1.79-2.25 (m, 5H), 1.81 (s, 3H), 1.72 (s, 3H), 0.98 (m, 6H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.6, 136.4, 127.2, 122.0, 91.8, 83.1, 77.9, 58.4, 50.3, 49.1, 41.9, 39.1, 38.4, 28.2, 27.6, 26.2, 26.1, 25.8, 25.4, 22.2, 22.0, 18.4, 16.2, 14.7, -5.4, -5.5; **HRMS** calcd for $C_{27}H_{44}O_4Si$ (M^+) 460.3009, found 460.2988.

Ketodiol 21. To a solution of 170.7 mg of epoxide **20** (0.369 mol) in 15 mL of 1,4-dioxane at room temperature was added 8 mL of 2M NaOH. The mixture was heated to 85 °C for 3 hours with vigorous stirring before being cooled to room temperature. The reaction was diluted with 15 mL of brine and

extracted with EtOAc (5x15 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. Drying agent was removed by filtration, and the solvents were removed in vacuo to provide the crude tetraol which was used without purification in the following step.

The crude tetraol was dissolved in 28 mL of MeOH and 14 mL of water. The mixture was cooled to 0 °C, and 99.0 mg of sodium periodate (0.461 mmol) was added. The reaction mixture was stirred at 4 °C for 4 hours after which time MeOH was removed on the rotary evaporator. The aqueous residue was diluted with 10 mL of brine and 30 mL of EtOAc and transferred to a separatory funnel. The layers were separated, and the aqueous phase was extracted with EtOAc (5x20mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (2:1 hexanes/EtOAc) gave 80.9 mg (66% for two steps) of ketodiol **21** as a white foam. Data for **21**: R_f 0.15 (2:1 hexanes/EtOAc); **IR** (thin film) 3645-3209, 2958, 2918, 2867, 2363, 2324, 1739, 1435, 1098, 1012 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.15 (dd, *J*=3.7,1.8 Hz, 1H), 5.49 (s, 1H), 4.63 (s, 1H), 4.43 (d, *J*=4.5 Hz, 1H), 4.23 (bs, 1H), 3.72 (d, *J*=11.7 Hz, 1H), 2.89 (bs, 1H), 2.40-2.52 (m, 2H), 2.30 (m, 1H), 1.80-2.20 (m, 5H), 1.92 (s, 3H), 1.74 (s, 3H), 0.94 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 211.5, 154.3, 135.90, 125.5, 122.4, 92.1, 83.0, 77.6, 63.5, 51.4, 41.8, 38.5, 37.9, 28.4, 27.9, 25.5, 22.3, 21.9, 16.5; **HRMS** calcd for $C_{20}H_{28}O_4Na$ (MNa^+) 355.1885, found 355.1902.

Triol 22. To a solution of 60.6 mg of ketone **21** (0.18 mmol) in 9 mL of THF at room temperature was added 150.0 mg of samarium powder (1.0 mmol). The slurry was cooled to -20 °C and 3.0 mL of a freshly prepared 0.1M THF solution of SmI_2 (0.30 mmol) was added dropwise. To the deep blue reaction mixture was added 15.1 mg of NiI_2 (0.048 mmol) which caused the blue color to dissipate slowly. Additional 1.5 mL portions of 0.1M SmI_2 in THF were added until the deep blue color persisted. The reaction mixture was stirred for 30 minutes at -20 °C after which time it was quenched by addition of sat. sodium potassium tartrate (Rochelle's salt). After warming to room temperature, the mixture was diluted with EtOAc and transferred to a separatory funnel. The layers were separated, and the aqueous phase was extracted with EtOAc (4x30 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (4:1 hexanes/EtOAc) provided 43.5 mg (72%) of triol **22** as a colorless oil. Data for **22**: R_f 0.15 (4:1 hexanes/EtOAc); **IR** (thin film) 3600-3130, 2954, 2919, 1713, 1443, 1196, 1067 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.81 (m, 1H), 5.53 (m, 1H), 4.99 (m, 1H), 4.31 (d, *J*=11.7 Hz, 1H), 4.06 (m, 1H), 3.64 (d, *J*=11.4 Hz, 1H), 3.60 (d, *J*=4.2 Hz, 1H), 3.25 (dq, *J*= 4.2, 2.2 Hz, 1H), 3.00 (dq, *J*=4.8, 2.3 Hz, 1H), 2.52 (bd, *J*=11.4 Hz, 1H), 2.48 (m, 1H), 2.37 (m, 1H), 2.04-1.78 (m, 4H), 1.82 (s, 3H), 1.71 (s, 3H), 1.35 (m, 2H), 0.97 (d, *J*=7.0 Hz, 3H),

0.93 (d, *J*=6.6 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 212.6, 138.9, 135.8, 124.4, 123.1, 76.9, 75.1, 65.7, 62.1, 41.5, 39.1, 39.0, 37.5, 33.4, 29.4, 25.4, 22.5, 22.0, 18.6, 16.7; **HRMS** calcd for $C_{20}H_{30}O_4Na$ (MNa^+) 357.2042, found 357.2035.

Carbonate 23. To a solution of 28.0 mg of triol **22** (0.084 mmol) in 2 mL of CH_2Cl_2 at 0 ºC was added 50 µL of pyridine (0.62 mmol) followed by 96 µL of a 2.0M toluene solution of phosgene (0.19 mmol), and the solution was stirred for 15 minutes. The volatiles were evaporated by a stream of argon to provide a white solid. Purification by silica gel chromatography (1:1 pet. ether/EtOAc) provided 24.0 mg (79%) of carbonate **23** as a clear oil. Data for **23**: R_f 0.38 (1:1 pet. ether/EtOAc); **IR** (thin film) 3511-3153, 2962, 2958, 1731, 1484, 1442, 1388, 1221, 1185, 1110 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.90 (m, 1H), 5.56 (s, 1H), 5.37 (d, *J*=5.9 Hz, 1H), 4.42 (m, 2H), 3.20 (m, 2H), 2.59 (m, 2H), 2.21 (m, 1H), 2.04 (m, 1H), 1.96-1.80 (m, 3H),1.88 (dd, *J*=3.7 and 1.9 Hz, 3H), 1.74 (s, 3H), 1.58 (m, 2H), 0.96 (d, *J*= 6.5 Hz, 3H), 0.90 (d, *J*=6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 203.6, 148.7, 138.8, 135.6, 125.4, 123.1, 80.0, 75.5, 69.1, 53.9, 39.3, 38.9, 38.3, 34.6, 32.3, 31.1, 24.7, 22.3, 22.0, 18.5, 17.1; **HRMS** calcd for $C_{21}H_{28}O_5Na$ (MNa^+) 383.1834, found 383.1830.

Enone 24. To a solution of 71.8 mg of carbonate **23** (0.20 mmol) in 72 mL of CH_2Cl_2 at 0 ºC were added 400 mg of crushed 4Å molecular sieves, 14.0 mg of $VO(acac)_2$ (0.052 mmol), and 80 µL of a 5.0M decanes solution of *t*-butyl hydroperoxide (0.40 mmol) sequentially. The resulting deep red slurry was allowed to warm to room temperature over 30 minutes and stirred at this temperature for 2 hours. The reaction was quenched by addition of sat. sodium sulfite solution, and the biphasic mixture was stirred vigorously for 20 minutes. The layers were separated, and the aqueous phase was extracted with EtOAc (5x15 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo to provide the crude epoxide as a yellow oil that was used without purification in the next step.

The crude epoxide was dissolved in 6 mL of CH_2Cl_2 at room temperature, and 40 µL of Et_3N and 100 mg of silica gel were added. The slurry was stirred for 5 minutes after which time it was filtered to remove silica gel. The solvent was removed in vacuo, and purification by silica gel chromatography (3:1 EtOAc/pet. ether) gave 70.1 mg (93%) of enone **24** as a white foam. Data for **24**: R_f 0.24 (3:1 EtOAc/pet. ether); **IR** (thin film) 33301, 2921, 2901, 1691, 1460, 1442, 1299, 1211, 1145, 1003 cm^{-1}; **^{1}H NMR** (CD_3CN, 500 MHz) δ 6.46 (d, *J*=10.5 Hz, 1H), 6.07 (d, *J*=10.3 Hz, 1H), 5.57 (s, 1H), 5.31 (dd, *J*=6.2, 2.7 Hz, 1H), 4.65 (d, *J*=10.8 Hz, 1H), 4.55 (dd, *J*= 10.8, 2.7 Hz, 1H), 3.00 (s, 1H), 2.58 (m, 2H), 2.51 (s, 1H), 2.11 (m, 1H), 1.95 (m, 1H), 1.89-1.78 (m, 3H), 1.70 (s, 3H), 1.60 (m, 2H), 1.44 (s, 3H), 0.96 (d, *J*=7 Hz, 1H), 0.91 (d, *J*=6.6 Hz, 1H); **^{13}C NMR** (CD_3CN, 125 MHz) δ 198.6, 149.8, 148.1,

136.9, 125.3, 123.0, 81.4, 79.3, 72.8, 70.8, 52.9, 41.0, 38.6, 35.9, 31.2, 29.4, 24.7, 23.2, 22.2, 21.8, 16.1; **HRMS** calcd for $C_{21}H_{28}O_6Na$ (MNa^+) 399.1779, found 399.1779.

Bis-hemiketal 27. To a solution of 25.1 mg of carbonate **24** (0.066 mmol) in 5 mL of DMF were added 260 mg of crushed 4Å molecular sieves and 150.0 mg of anhydrous K_2CO_3 (1.014 mmol), and the resulting slurry was heated to 75 °C for 15 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through Celite. Solvents were removed in vacuo, and purification by silica gel chromatography (5:2 pet. ether/ EtOAc) gave 15.0 mg (68%) of bis-hemiketal **27** as a white solid. Crystals of **27** suitable for X-ray analysis were obtained by recrystallization from pentane and EtOAc. Data for **27**: R_f 0.41 (5:2 pet. ether/EtOAc); mp=131 °C; **IR** (thin film) 3577-3130, 2954, 2919, 2848, 1437, 1367, 1266, 1131, 1072 1025, 914 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.16 (d, *J*=5.7 Hz, 1H), 6.00 (d, *J*=5.6 Hz, 1H), 5.42 (s, 1H), 5.39 (s, 1H), 5.12 (s, 1H), 4.96 (s, 1H), 3.16 (m, 1H), 2.81 (s, 1H), 2.57 (dd, *J*=14.1, 4.5 Hz, 1H), 2.16-2.20 (m, 1H), 1.78-2.06 (m, 3H), 1.72 (s, 3H), 1.42 (s, 3H), 1.30 (m, 2H), 0.95 (d, *J*=6.85 Hz, 3H), 0.82 (d, *J*=6.85 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 155.3, 136.9, 136.1, 134.7, 121.2, 110.1, 108.6, 99.2, 93.6, 76.6, 43.5, 35.6, 34.6 (2C), 26.7, 24.6, 21.7 (2C), 20.7, 15.1; **HRMS** calcd for $C_{20}H_{28}O_4$ (M^+) 332.1988, found 332.1988.

Monomethyl ketal 28. To a solution of the 14.1 mg of bis-hemiketal **27** (0.042 mmol) in MeI (12 ml) at room temperature were added 800 mg of freshly pulverized anhydrous $CaCO_3$ and 22.0 mg of Ag_2O (0.095 mmol). The resulting slurry was stirred in the dark at room temperature for 24 hours before being diluted with EtOAc and filtered through Celite. After removal of the solvents in vacuo, purification by silica gel chromatography (8:1 hexanes/EtOAc) provided 2.9 mg (21% recovery) of bis-hemiketal **27** and 11.2 mg (76%, 95% BORSM) of monomethyl ketal **28** as a colorless oil. Data for **28**: R_f 0.22 (8:1 hexanes/EtOAc); **IR** (thin film) 3577-3177, 2995, 2932, 1431, 1365, 1338, 1160, 1124, 1108, 1086, 1061, 1034 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.18 (d, *J*=5.7 Hz, 1H), 5.90 (d, *J*=5.9 Hz, 1H), 5.37 (s, 2H), 5.09 (s, 1H), 4.94 (s, 1H), 3.35 (s, 3H), 3.16 (m, 1H), 2.55 (dd, *J*=14.1, 4.5 Hz, 1H), 2.18-2.12 (m, 1H), 2.06-1.75 (m, 4H), 1.72 (s, 3H), 1.62 (s, 3H), 1.30 (m, 2H), 0.99 (d, *J*=6.8 Hz, 3H); 0.87 (d, *J*=6.9 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 154.4, 136.8, 136.3, 133.1, 121.0, 112.0, 110.2, 99.4, 92.8, 76.8, 50.3, 43.1, 35.4, 34.4 (2C), 26.6, 24.4, 21.6, 21.5, 20.0, 15.0; **HRMS** calcd for $C_{21}H_{30}O_4Na$ (MNa^+) 369.2042, found 369.20467.