Mitomycin Synthetic Studies: Stereocontrolled and Convergent Synthesis of a Fully Elaborated Aziridinomitosane

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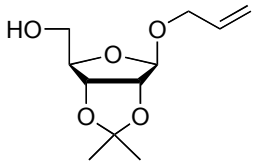
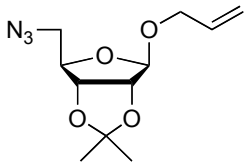
Supporting Information

Contents:

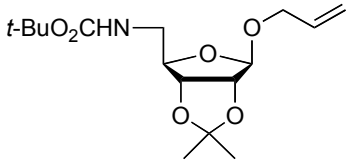
General Methods: Proton and carbon NMR spectra were recorded on 400 and 500 MHz spectrometers. Chemical shifts are reported in ppm relative to the chloroform peak at 7.24 ppm (^{1}H) or 77.0 ppm (^{13}C), or the acetone peak at 2.04 ppm (^{1}H) or 29.8 and 206.0 ppm (^{13}C). Assignments in the ^{1}H NMR spectra were made using ^{1}H COSY and ^{1}H/^{1}H decoupling experiments. Mass spectroscopy was performed by the Ohio State University Chemistry Mass Spectrometry Facility using electrospray (ESI) or electron impact (EI) ionization. Infrared (IR) spectra were recorded on an FT-IR spectrometer as neat samples on NaCl plates. Unless otherwise specified, all reactions were run under an inert atmosphere of nitrogen. Solvents were freshly distilled before use. Yields refer to isolated material determined to be pure by NMR spectroscopy and thin layer chromatography (TLC), unless specified otherwise in the text.



(6-Allyloxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (13). Concentrated H_2SO_4 (1.2 mL) was slowly added to a solution of D-ribose (15.0 g, 100 mmol) and allyl alcohol (68 mL) in acetone (60 mL) at 25 °C. The reaction mixture was stirred at reflux for 4 h. The reaction mixture was allowed to cool to 25 °C and Na_2CO_3 (15.0 g) was added. The mixture was filtered and the filtrate was evaporated in *vacuo*. The residue was diluted with CH_2Cl_2 (100 mL) and washed with water (70 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x). The collected organic extracts were dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by flash chromatography (silica, 20% EtOAc/hexane) to afford pure **13** (12.2 g, 53%) as a slightly yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.82 (m, 1H), 5.22 (dd, 1H, *J* = 17.2, 2.6 Hz), 5.18 (dd, 1H, *J* = 10.4, 2.4 Hz), 5.06 (s, 1H), 4.79 (d, 1H, *J* = 6.0 Hz), 4.57 (d, 1H, 5.9), 4.36 (s, 1H), 4.17 (dd, 1H, *J* = 5.4, 1.3 Hz), 4.02 (dd, 1H, *J* = 6.4, 1.2 Hz), 3.61 (m, 2H), 3.17 (dd, 1H, *J* = 10.1, 3.2 Hz), 1.43 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.0, 118.2, 112.2, 107.9, 88.3, 85.9, 81.4, 68.8, 63.9, 26.3, 24.6; IR (KBr) ν_{max} 3462, 3082, 2941 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{11}H_{18}O_5Na$: 253.1052; found: 253.1031.

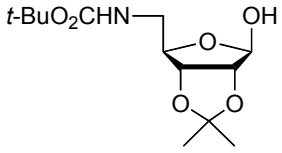


4-Allyloxy-6-azidomethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (14). Zinc azide bis-pyridine (32.4 g, 0.105 mol) was slowly added to a solution of **13** (24.2 g, 0.105 mol), Ph_3P (53.2 g, 0.211 mol), and diisopropyl azodicarboxylate (41.2 mL, 0.211 mol) in toluene (450 mL) at 0 °C. The reaction mixture was stirred overnight 16 h at 25 °C and was evaporated in *vacuo*. The residue was taken up in ether and triturated. The salts were filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (silica, 10% EtOAc/hexane) to afford pure **14** (25.2 g, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.93 (m, 1H), 5.26 (dd, 1H, *J* = 17.1 Hz, J = 1.2 Hz), 5.19 (dd, 1H, *J* = 10.4 Hz, J = 1.2 Hz), 5.12 (s, 1H, C1-H), 4.64 (d, 1H, *J* = 6.0 Hz), 4.59 (d, 1H, *J* = 6.3 Hz), 4.28 (t, 1H, *J* = 7.3 Hz), 4.21 (ddm, 1H, J = 12.9 Hz, J = 5.2 Hz), 4.04 (m, 1H), 3.45 (dd, 1H, *J* = 12.8, 6.1 Hz), 3.26 (dd, 1H, *J* = 12.8, J = 7.9 Hz), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.5, 117.7, 112.7, 107.66, 85.5, 85.2, 82.1, 68.4, 53.7, 26.4, 24.9; IR (KBr) ν_{max} 3082, 2940, 2103 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{11}H_{17}N_3O_4Na$: 278.1117; found: 278.1117.

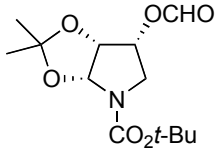


(6-Allyloxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ylmethyl) Carbamic Acid, *tert*-Butyl Ester (15). A slurry of Ph_3P (22.8 g, 87.0 mmol) was added to a solution of **14** (20.2 g, 79.13 mmol) in toluene (325 mL) at 25 °C. The reaction mixture was stirred for 1 h at 25 °C and water (68 mL) was added. The reaction mixture was stirred for 12 h at 25 °C and was evaporated in *vacuo*. The residue was dissolved in CH_2Cl_2 (325 mL). Triethylamine (80.4 mL, 0.58 mol) was added followed by the addition of di-*tert*-butyl dicarbonate (19.0 g, 87.1 mmol) at 0 °C. The reaction mixture was stirred for 4 h at 25 °C and saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were dried ($MgSO_4$), and evaporated in *vacuo*. The crude product was purified by flash chromatography (20% EtOAc/hexane) to afford **15** (30.4 g, 100%) as a colorless oil that solidified on standing: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.85 (m, 1H), 5.27 (app d,

1H, J = 17.1 Hz), 5.16 (app d, 1H, J = 10.4 Hz), 5.07 (br s, 2H), 4.61 (s, 2H), 4.26 (t, 1H, J = 5.5 Hz), 4.15 (m, 1H), 3.96 (m, 1H), 3.27 (br s, 2H), 1.44 (s, 3H), 1.41 (s, 9H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.8, 133.4, 117.4, 112.3, 107.8, 86.2, 85.6, 82.0, 79.5, 68.4, 43.6, 28.3, 26.4, 24.8; IR (KBr) ν_{max} 3342, 3058, 2938, 1694 cm^{-1}; HRMS (ESI), m/z calcd for $C_{16}H_{27}NO_6Na$: 352.1736; found: 352.1749.

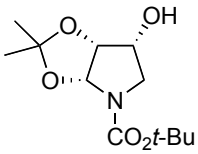


(6-Hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ylmethyl)carbamic Acid *tert*-Butyl Ester (16). A solution of Et_3Al (1.9 M in toluene, 49.8 mL) was slowly added to a solution of **15** (13.5 g, 41.41 mmol) and $NiCl_2$(dppp) (2.33 g, 4.14 mmol) in toluene (490 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and 4 h at 25 °C and water (50 mL) was added. The reaction mixture was stirred for 1 h at 25 °C, filtered, and evaporated in *vacuo*. The residue was purified by flash chromatography (35% EtOAc/hexane) to afford **16** (10.5 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.43 (s, 1H), 5.28 (br, 1H), 4.60 (m, 2H), 4.40 (s, 1H), 4.19 (s, 1H), 3.38 (br m, 1H), 3.20 (br m, 1H), 1.44 (s, 3H), 1.42 (s, 9H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.9, 112.5, 103.1, 86.6, 86.4, 82.2, 80.0, 44.3, 28.5, 26.6, 25.0; IR (KBr) ν_{max} 3342, 3058, 2938, 1694 cm^{-1}; HRMS (ESI), m/z calcd for $C_{13}H_{23}NO_6Na$: 312.1423; found: 312.1432.

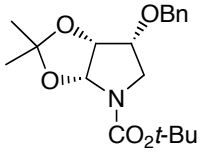


6-Formyloxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*b*]pyrrole-4-carboxylic Acid *tert*-Butyl Ester (17). Freshly prepared PhIO (14.9 g, 67.8 mmol) was slowly added to a solution of **16** (7.84 g, 27.1 mmol) and I_2 (6.89 g, 27.1 mmol) in CH_2Cl_2 (1600 mL) at 25 °C. The reaction mixture was stirred for 24 h at 25 °C and a saturated aqueous $Na_2S_2O_3$ solution (300 mL) was added. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated in *vacuo*. The residue was purified by flash chromatography (20% EtOAc/hexane) to afford pure **17** (7.79 g, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 60 °C) δ 8.04 (s, 1H), 5.85 (s br, 1H), 4.95 (m, 1H), 4.76 (t, 1H, J = 9.2 Hz), 3.97 (br m, 1H),

3.38 (t, 1H, J = 10.4 Hz), 1.49 (s, 3H), 1.44 (s, 9H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7, 153.5, 113.0, 81.0, 69.8, 60.2, 46.0, 28.4, 26.8, 26.3; IR (KBr) ν_{max} 2982, 2937, 2891, 1731, 1708 cm^{-1}; HRMS (ESI), m/z calcd for $C_{13}H_{21}NO_6Na$ (M + Na): 310.1267; found: 310.1264.

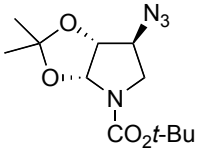


6-Hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*b*]pyrrole-4-carboxylic Acid *tert*-Butyl Ester (18). A solution of **17** (3.50 g, 12.2 mmol) in MeOH (55 mL) and H_2O (5 mL) at room temperature was treated with K_2CO_3 (5.05 g, 36.6 mmol) for 4 h. The solvent was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (50 mL). The organic phase was washed with water and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash chromatography (50% EtOAc/hexane) to afford **18** (3.10 g, 97%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 500 MHz, 60 °C) δ 5.85 (s br, 1H), 4.54 (t, 1H, J = 4.9 Hz), 4.05 (s br, 1H), 3.85-3.89 (m, 1H), 3.10 (dd, 1H, J = 9.2, 10.6 Hz), 2.41 (s br, 1H), 1.50 (s, 3H), 1.46 (s, 9H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0, 112.8, 89.0, 81.0, 78.8, 69.9, 49.7, 28.6, 27.0, 26.6; IR (KBr) ν_{max} 3442, 2980, 2935, 1704 cm^{-1}; HRMS (ESI), m/z calcd for $C_{12}H_{21}NO_5Na$: 282.1317; found: 282.1324.

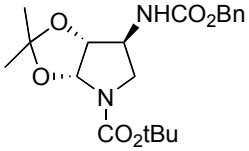


6-Benzyloxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*b*]pyrrole-4-carboxylic Acid *tert*-Butyl Ester (19). A slurry of NaH (19.2 mg, 0.80 mmol) was added in one portion to a solution of **22** (102 mg, 0.40 mmol) and n-Bu_4NI (15.0 mg, 0.04 mmol) in THF (4 mL) and DMF (0.4 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and benzyl bromide (0.070 mL, 0.60 mmol) was added. The mixture was stirred for 1 h at 0 °C and saturated aqueous $NaHCO_3$ (4 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were washed with saturated aqueous NaCl (4 mL), dried (Na_2SO_4), filtered, and the filtrated was evaporated in *vacuo*. The residue was purified by flash

chromatography (silica, 15% EtOAc/hexane) to afford pure **24** (84.3 mg, 89%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.25 (br, 5H), 5.80-5.75, 5.67-5.61(2 parts, br, 1H), 4.71-4.54 (br m, 3H), 3.85-3.71 (br m, 1H), 3.70-3.63 (br t, 1H), 3.23 (br t, 1H), 1.51 (br d, 3H), 1.43 (s, 9H), 1.34 (br s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.91 (153.68, rotamer), 137.52 (137.47), 128.5, 128.07 (128.00), 112.71 (112.58), 88.2 (88.05), 80.6, 78.3, 75.38 (74.85), 72.1, 46.75 (45.94), 28. 3, 27.1, 26.37 (26.10); HRMS (ESI), *m/z* calcd for $C_{19}H_{27}NO_5Na$: 372.1787; found: 372.1798.

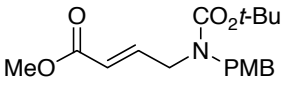


6-Azido-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*b*]pyrrole-4-carboxylic Acid *tert*-Butyl Ester (22). Diphenylphosphoryl azide (0.73 mL, 3.37 mmol) was slowly added to a solution of alcohol **18** (437 mg, 1.69 mmol), Ph_3P (884 mg, 3.37 mmol) and diisopropyl azodicarboxylate (0.66 mL, 3.37 mmol) in THF (6 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed and the residue was dissolved in ether. The resulting white precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/toluene) to afford azide **22** (479 mg, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 60 °C) δ 5.97 (s br, 1H), 4.53 (d, 1H, J = 4.6 Hz), 3.95 (d, 1H, J = 4.1 Hz), 3.79 (s br, 1H), 3.64 (dd, 1H, J = 4.2, 12.3 Hz), 1.53 (s, 9H), 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, 60 °C) δ 153.7, 112.1, 89.0, 83.1, 81.1, 63.2, 48.6, 28.5, 27.1, 26.2; IR (KBr) ν_{max} 2978, 2109, 1710 cm^{-1}; HRMS (ESI), *m/z* calcd for $C_{12}H_{20}N_4O_4Na$: 307.1377; found: 307.1390.

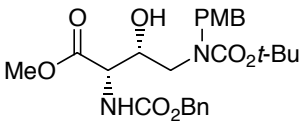


6-Carbobenzyloxyamino-2,2-dimethyltetrahydro-[1,3]dioxolo [4,5-*b*] pyrrole-4-carboxylic Acid *tert*-Butyl Ester (23). Azide **22** (1 g, 3.52 mmol) in CH_3CN (15 mL) was added to a solution of $SnCl_2$ (1.07 g, 5.63 mmol), thiophenol (1.73 mL, 16.9 mmol) and Et_3N (2.35 mL, 16.9 mmol) in CH_3CN (30 mL) at room temperature. The resulting mixture was stirred for 1 h and then, diluted with CH_2Cl_2 and washed twice with 2N NaOH solution. The aqueous phase was extracted with CH_2Cl_2 (3 ×). The collected organic extracts were dried

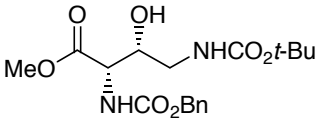
($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude amine. The residue was dissolved in CH_2Cl_2 (70 mL) and treated by Et_3N (2.45 mL, 17.6 mmol) and benzyl chloroformate (2.00 mL, 14.08 mmol) at 0 °C. After being stirred during 2 h, the solution was washed with saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted three times with CH_2Cl_2. The collected organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica, 25% EtOAc/hexane) afforded **23** (1.20 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 50 °C) δ 7.30-7.37 (m, 5H), 5.85 (s br, 1H), 5.12 (s, 2H), 4.75 (s br, 1H), 4.52 (s br, 1H), 4.11-4.17 (m, 1H), 3.66 (dd, 1H, J = 4.7 , 11.9 Hz), 3.53 (d, 1H, J = 11.9 Hz), 1.48 (s, 9H), 1.45 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, 50 °C) δ 155.7, 154.1, 136.4, 128.6, 128.3, 128.3, 111.8, 88.5, 85.5, 80.9, 67.2, 54.7, 49.4, 28.5, 27.1, 26.1; IR (KBr) ν_{max} 3315, 2979, 2930, 1697 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{20}H_{28}N_2O_6Na$: 415.1840; found: 415.1842.



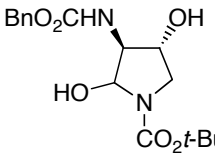
4-[*tert*-Butoxycarbonyl-(4-methoxybenzyl)amino]but-2-enoic acid methyl ester (25). *p*-Methoxybenzylamine (1.43 mL, 11.0 mmol) was slowly added to a solution of methyl 4-bromocrotonate (1.40 mL, 10.0 mmol) and EtN(*i*-Pr)$_2$ (6.64 mL, 33.0 mmol) in THF (50 mL) at 25 °C. The reaction mixture was stirred for 12 h at 25 °C and saturated aqueous $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) at 25 °C and Et_3N (3.34 mL, 24.0 mmol) and (*t*-BuOCO)$_2$O (2.76 mL, 12.0 mmol) were added. The reaction mixture was stirred for 3 h at 25 °C and saturated aqueous $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 10% EtOAc/hexane) to afford pure **25** (2.35 g, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 60°C) δ 7.12 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.5 Hz), 6.79 (m, 1H), 5.82 (d, 1H, *J* = 15.9 Hz), 4.35 (br, 2H), 3.88 (br, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 1.47 (s, 9H); HRMS (ESI), *m/z* calcd for $C_{18}H_{25}NO_5Na$: 358.1631; found: 358.1617.



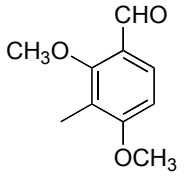
2-Benzyloxycarbonylamino-4-*tert*-butoxycarbonyl-(4-methoxy benzyl) amino-3-hydroxy butyric acid methyl ester (26). A slurry of benzyl carbamate (234 mg, 1.55 mmol) was added in one portion to a solution of NaOH (60.0 mg, 1.50 mmol) in H_2O (3.8 mL) and *n*-PrOH (2.3 mL) at 25 °C. After the solution was completely clear, *t*-BuOCl (0.17 mL, 1.50 mmol) was added to the reaction mixture and the solution was stirred in the dark for 5 min at 25 °C. The reaction mixture was cooled to 0 °C in the dark and a solution of $(DHQD)_2AQN$ (21 mg, 0.025 mmol) in *n*-PrOH (2.0 mL) was added followed by the addition of **31** (167 mg, 0.50 mmol) and $K_2OsO_4 \cdot 2H_2O$ (7.4 mg, 0.020 mmol). The reaction mixture was stirred for 6 h at 0 °C in the dark and saturated aqueous $Na_2S_2O_3$ (5 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 5% acetone/CH_2Cl_2) to afford **26** (168.2 mg, 67%) as a colorless oil, with slight contamination of benzyl carbamate that was used without further purification.



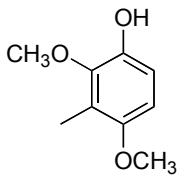
2-Benzyloxycarbonylamino-4-*tert*-butoxycarbonylamino-3-hydroxy butyric acid methyl ester. A solution of $(NH_4)_3Ce(NO_3)_6$ (605 mg, 1.1 mmol) in H_2O (2 mL) was added to a solution of crude **26** (168.2 mg, 0.34 mmol) in CH_3CN (6 mL) at 25 °C. The reaction mixture was stirred for 5 min at 25 °C and EtOAc (5 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 20% EtOAc/hexane) to afford the pure carbamate (112.0 mg, 56% for 2 steps) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (m, 5H), 5.80 (br, 1H), 5.28 (br, 1H), 5.10 (br s, 2H), 4.44 (br, 1H), 4.20 (br, 1H), 3.76 (br, 1H), 3.73 (s, 3H), 3.35 (br, 1H), 3.00 (br, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 159.3, 156.1, 136.2, 128.4, 128.1, 127.9, 80.0, 71.6, 67.2, 56.5, 44.0, 28.3; HRMS (ESI), *m/z* calcd for $C_{18}H_{26}N_2O_7Na$: 405.1638; found: 405.1609.



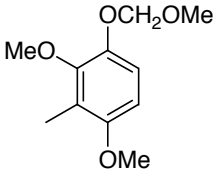
3-Benzyloxycarbonylamino-2,4-dihydroxypyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (27). A solution of *i*-Bu_2AlH (1.0 M in THF, 1.21 mL) was slowly added to a solution of the above carbamate (84.8 mg, 0.22 mmol) in THF (2 mL) at –78 °C. The reaction mixture was stirred for 14 h at –78 °C and aqueous K_2HPO_4/KH_2PO_4 buffer (1.0 M, pH 7, 5 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 25% EtOAc/hexane) to afford pure **27** (61.5 mg, 67%) as an unstable pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 60 °C) δ 7.33 (m, 5H), 5.60-5.20 (br, 2H), 5.12 (br, 2H), 4.40-4.15 (br, 1H), 3.97 (br, 1H), 3.83-3.43 (br, 2H), 3.15 (m, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 154.8, 135.9, 128.6, 128.3, 128.2, 81.1, 79.1, 74.8, 67.4, 59.5, 50.3, 28.3; HRMS (ESI), *m/z* calcd for $C_{17}H_{24}N_2O_6Na$: 375.1532; found: 375.1558.



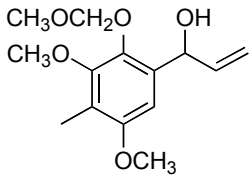
2,4-Dimethoxy-3-methylbenzaldehyde (29). A solution of $SnCl_4$ (1.0 M in CH_2Cl_2, 95 mL, 95 mmol) was added dropwise to a solution of 2,6-dimethoxytoluene **28** (11.11 g, 73.09 mmol) in CH_2Cl_2 (220 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and Cl_2CHOCH_3 [CAUTION: HIGHLY TOXIC; LACHRYMATOR] (7.94 mL, 87.7 mmol) was slowly added. The reaction mixture was stirred for 1 h at 0 °C and was allowed to warm to 25 °C. The reaction mixture was poured onto crushed ice (40 mL) and was stirred for 1 h at 25 °C. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and the filtrate was evaporated *in vacuo*. Recrystallization of the residue from hexane afforded **29** as colorless, needle-like crystals (12.36 g, 94%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.20 (s, 1H), 7.71 (d, 1H, *J* = 8.8 Hz), 6.71 (d, 1H, *J* = 8.7 Hz), 3.88 (s, 3H), 3.83 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.2, 164.1, 162.7, 128.0, 122.9, 120.2, 106.6, 63.2, 56.0, 8.6; HRMS (ESI), *m*/*z* calcd for $C_{10}H_{12}O_3Na$: 203.0679; found: 203.0693.



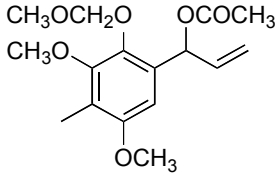
2,4-Dimethoxy-3-methylphenol (30). *m*-Chloroperbenzoic acid (33.8 g, 0.137 mol) was added in one portion to a solution of **29** (12.4 g, 68.7 mmol) in CH_2Cl_2 (185 mL) at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. The reaction mixture was washed with saturated aqueous K_2CO_3 (3 ×) and the solvent was evaporated in *vacuo*. The residue was dissolved in MeOH (120 mL) at 0 °C and KOH (5.77 g, 0.103 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C and the solvent evaporated in *vacuo*. The residue was dissolved in ether (300 mL) and acidified with aqueous 3N HCl. The organic layer was washed with water (2 x), saturated aqueous NaCl, dried ($MgSO_4$), and evaporated in *vacuo*. Purification of the residue by flash chromatography (silica, 20% EtOAc-hexane) afforded pure **30** (10.1 g, 87%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.76 (d, 1H, J = 8.8 Hz), 6.54 (d, 1H, J = 8.8 Hz), 5.48 (s, 1H), 3.78 (s, 6H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 146.1, 143.0, 120.1, 111.8, 106.9, 60.9, 56.1, 9.4; IR (KBr) ν_{max} 3425, 2942 cm^{-1}.



1,3-Dimethoxy-4-methoxymethoxy-2-methylbenzene (31). A slurry of NaH (3.26 g, 136 mmol) was added in one portion to a solution of **30** (11.4 g, 68.0 mmol) in THF (340 mL) and DMF (34 mL) at 0 °C. The reaction mixture was stirred 1 h at 25 °C and chloromethyl methyl ether [CAUTION: HIGHLY TOXIC; LACHRYMATOR] (5.68 mL, 74.8 mmol) was slowly added. The reaction mixture was stirred 1 h at 25 °C and ether (500 mL) was added. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was distilled under vacuum to afford **31** as a colorless oil (11.72 g, 89%, 64 °C/0.2 mm Hg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.90 (d, 1H, J = 9.2 Hz), 6.51 (d, 1H, J = 9.2 Hz), 5.12 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.50(s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 149.3, 144.4, 129.9, 114.5, 105.5, 96.1, 60.5, 56.1, 55.9, 9.0; HRMS (ESI), *m/z* calcd for $C_{11}H_{16}O_4Na$: 235.0947; found: 235.0933.

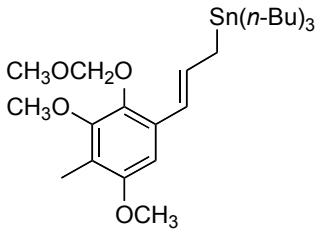


1-(3,5-Dimethoxy-2-methoxymethoxy-4-methylphenyl)prop-2-en-1-ol (32). A solution of *n*-BuLi (2.32 M in hexane, 37.0 mL, 86.0 mmol) was slowly added to a solution of **31** (11.4 g, 53.8 mmol) in THF (200 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and freshly distilled acrolein (4.82 mL, 71.5 mmol) was added. The reaction mixture was allowed to warm to 25 °C and saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 25% EtOAc-hexane) to afford pure **32** (12.4 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.60 (s, 1H), 6.07-6.12 (m, 1H), 5.53-5.55 (m, 1H), 5.43 (dd, 1H, *J* = 17.2 Hz, J = 1.5 Hz), 5.24 (dd, 1H, *J* = 10.5 Hz, J = 1.5 Hz), 5.06 (dd, 1H, *J* = 5.8, 16.1 Hz), 3.78 (s, 3H), 3.76 (s, 3H), 3.56 (s, 3H), 3.26 (br s, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 151.4, 142.1, 139.2, 134.2, 120.8, 114.8, 104.3, 99.8, 69.2, 60.3, 57.6, 55.8, 9.0; IR (KBr) ν_{max} 3453, 3087, 2938, 1641 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{14}H_{20}O_5Na$: 291.1203; found: 291.1180.

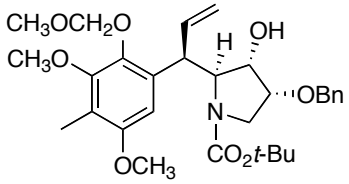


Acetic acid 1-(3,5-dimethoxy-2-methoxymethoxy-4-methyl phenyl)allyl ester (33). Acetic anhydride (8.70 mL, 92.3 mmol) was slowly added to a solution of **32** (12.37 g, 46.16 mmol), Et_3N (19.3 mL, 0.138 mol) and 4-(*N*,*N*-dimethylamino)pyridine (catalytic) in CH_2Cl_2 (190 mL) at 25 °C. The reaction mixture was stirred for 3 h at 25 °C and saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 25% EtOAc-hexane) to afford pure **33** (12.7 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.70 (dt, 1H, *J* = 5.1, 1.5 Hz), 6.59 (s, 1H), 6.04 (ddd, 1H, *J* = 5.12, 10.5, 17.2 Hz), 5.20-5.29 (m, 2H), 5.08 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.61 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 154.8, 151.7, 141.6, 136.3, 130.0, 121.4, 116.1, 104.4, 99.6, 70.8, 60.4, 57.8, 55.9, 21.3,

9.1; IR (KBr) ν_{max} 2937, 1743, 1643 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{16}H_{22}O_6Na$: 333.1314; found: 333.1309.

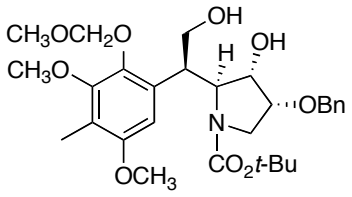


Tri-*n*-butyl-[3-(3,5-dimethoxy-2-(methoxy) methoxy-4-methylphenyl)allyl]stannane (34). A solution of SmI_2 (0.1 M in THF, 95 mL) was added over 2 h to a solution of **33** (1.18 g, 3.81 mmol), $Pd(PPh_3)_4$ (220 mg, 0.19 mmol), and *n*-Bu_3SnCl (1.54 mL, 5.71 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 12 h at 25 °C and was quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 5% Et_3N/hexane) to afford pure **34** (1.59 g, 77%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.64 (s, 1H), 6.52 (d, 1H, *J* = 15.7 Hz), 6.31-6.40 (m, 1H), 5.01 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.59 (s, 3H), 2.11 (s, 3H), 2.00 (d, 2H, *J* = 8.7 Hz), 1.49-1.55 (m, 6H), 1.29-1.34 (m, 6H), 0.88-0.94 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 152.1, 140.5, 131.6, 130.4, 119.6, 118.7, 102.0, 99.4, 60.4, 57.7, 55.7, 29.3, 27.5, 16.6, 13.7, 9.7, 9.0; IR (KBr) ν_{max} 2924, 1683, 1631 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{27}H_{50}O_5SnNa$ (M + Na + CH_3OH): 597.2572; found: 597.2544.

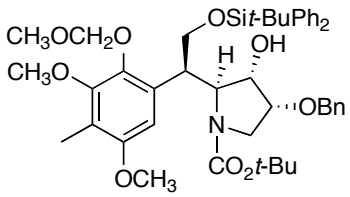


4-Benzyloxy-2-[1-(3,5-dimethoxy-2-methoxymethoxy-4-methylphenyl) allyl]-3-hydroxypyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (36). Boron trifluoride etherate (0.38 mL, 3.0 mmol) was added over 30 min to a solution of **19** (797.2 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and stannane **34** (2.15 g, 3.98 mmol) was added. The reaction mixture was stirred for 30 min at −78 °C and aqueous K_2HPO_4/KH_2PO_4 buffer (1.0 M, pH 7, 15 mL) was added. The aqueous

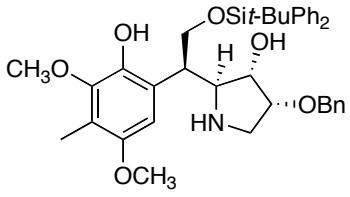
layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 15% EtOAc/hexane) to afford pure **36** (1.22 g, 75%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56-6.45 (br, 1H), 6.19-6.03 (m, 1H), 5.05-4.87 (m, 4H), 4.54-4.44 (m, 2H), 4.27-3.36 (br, 16H), 2.59-2.37 (br, 1H), 2.08 (br, 3H), 1.49-1.40 (br, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 154.8, 151.6, 142.0, 138.8, 137.2, 132.1, 128.5, 128.1, 127.8, 119.6, 115.8, 104.7, 99.6, 79.3, 71.9, 70.7, 67.8, 60.2, 57.6, 55.8, 48.5, 44.8, 29.7, 28.4, 8.8; HRMS (ESI), *m/z* calcd for $C_{30}H_{41}NO_8Na$: 566.2724; found: 566.2680.



4-Benzyloxy-2-[1-(3,5-dimethoxy-2-methoxymethoxy-4-methylphenyl)-2-hydroxyethyl]-3-hydroxypyrrolidine-1-car-boxylic Acid *tert*-Butyl Ester (39). A stream of O_3 in O_2 was slowly bubbled into a solution of **36** (164 mg, 0.30 mmol) in MeOH (7 mL) at −78 °C. The progress of the reaction was carefully monitored by TLC and N_2 was bubbled into the reaction mixture for 30 min immediately after the reaction was judged complete. The reaction mixture was warmed to 0 °C and $NaBH_4$ (330 mg, 8.0 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C and was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 20% EtOAc/hexane) to afford pure **39** (92.5 mg, 62%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33-7.25 (m, 5H), 6.98 (s, 1H), 4.95-4.90 (app q, 2H), 4.58-4.52 (br, 1H), 4.52-4.43 (app q, 2H), 4.36-4.31 (m, 1H), 4.31-4.26 (br, 1H), 3.87-3.80 (br, 1H), 3.79 (br, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.65-3.58 (m, 1H), 3.58-3.51 (br, 1H), 3.48-3.42 (br, 1H), 3.36 (s, 3H), 2.97-2.91 (br d, 1H), 2.58-2.40 (br, 1H), 2.12 (s, 1H), 2.09 (s, 3H), 1.54-1.44 (br, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.1, 154.7, 151.0, 141.8, 137.1, 132.0, 128.5, 128.1, 127.8, 119.3, 105.7, 99.7, 80.7, 72.0, 71.5, 64.6, 62.8, 60.1, 57.4, 55.7, 48.6, 41.2, 28.3, 8.8; HRMS (ESI), *m/z* calcd for $C_{29}H_{41}NO_9Na$: 570.2674; found: 570.2668.

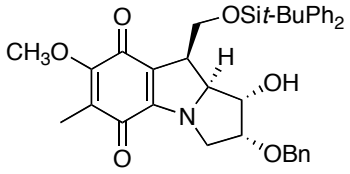


4-Benzyloxy-2-[2-(*tert*-butyldiphenylsilanyloxy)-1-(3,5-dimethoxy-2-methoxymethoxy-4-methylphenyl)ethyl]-3-hydroxy-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (40). *tert*-Butyldiphenylsilyl chloride (0.063 mL, 0.24 mmol) was added to a solution of **39** (102 mg, 0.19 mmol), Et_3N (0.034 mL, 0.24 mmol), and 4-(dimethylamino)pyridine (10 mg) in CH_2Cl_2 (1 mL) at 25 °C. The reaction mixture was stirred for 3 h at 25 °C and saturated aqueous $NaHCO_3$ (1 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 10% EtOAc/hexane) to afford pure **40** (149 mg, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60-7.50 (m, 2H), 7.41-7.20 (m, 13H), 6.58-6.38 (br, 1H), 5.10-4.90 (m, 2H), 4.54-4.44 (m, 2H), 4.27-4.18 (br, 1H), 4.14-3.98 (br, 2H), 3.97-3.82 (br, 2H), 3.74 (s, 3H), 3.69-3.64 (br, 3H), 3.57-3.48 (br, 4H), 3.45-3.32 (br, 1H), 2.52-3.38 (br, 1H), 2.20-2.12 (br, 3H), 1.44-1.18 (br, 9H), 1.00-0.86 (br, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.4, 155.2, 154.7, 151.7, 151.6, 143.1, 142.8, 137.3, 135.6, 135.5, 133.8, 133.6, 133.5, 133.4, 131.9, 129.6, 129.5, 129.3, 128.5, 128.1, 127.7, 127.6, 127.4, 127.3, 119.4, 119.1, 104.2, 99.7, 99.6, 79.8, 79.4, 72.1, 71.1, 66.2, 65.8, 60.2, 57.3, 55.6, 55.5, 48.4, 48.1, 28.3, 28.1, 26.8, 26.7, 19.1, 8.9 (many are rotamers); HRMS (ESI), *m/z* calcd for $C_{45}H_{59}O_9NSiNa$: 808.3851; found: 808.3880.

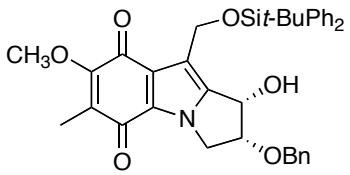


4-Benzyloxy-2-[2-(*tert*-butyldiphenylsilanyloxy)-1-(2-hydroxy-3,5-dimethoxy-4-methylphenyl)ethyl]pyrrolidin-3-ol (41). Trifluoroacetic acid (1 mL) was added to a solution of **40** (149 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) at 25 °C. The reaction mixture was stirred for 10 min at 25 °C, cooled to –40 °C and aqueous K_2HPO_4/KH_2PO_4 buffer (1.0 M, pH 7, 5 mL) was added followed by the addition of NaOH (520 mg). The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica,

50% EtOAc/hexane) to afford pure the pyrrolidine/phenol **41** (97.1 mg, 79%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (m, 3H), 7.44-7.23 (m, 12H), 6.19 (s, 1H), 4.53 (s, 2H), 4.15 (m, 1H), 3.94 (m, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.49 (m, 1H), 3.25 (m, 1H), 2.98 (dd, 1H, *J* = 9.8, 4.9 Hz), 2.70 (d, 1H, *J* = 4.9 Hz), 2.49 (dd, 1H, *J* = 9.8, 4.9 Hz), 2.09 (s, 3H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 150.9, 143.7, 137.4, 135.6, 134.7, 133.6, 133.2, 129.7, 129.5, 128.5, 128.1, 127.7, 127.7, 127.5, 124.4, 119.5, 105.8, 79.1, 72.8, 72.1, 65.3, 64.1, 60.9, 56.3, 53.8, 47.7, 30.3, 26.8, 19.1, 8.9; HRMS (ESI), *m/z* calcd for $C_{38}H_{47}NO_6Si$ + H: 642.3245; found: 642.3195.

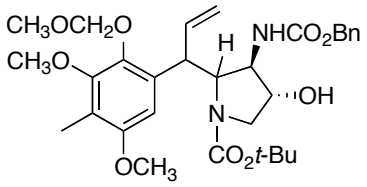


2-Benzyloxy-8-(*tert*-butyldiphenylsilanyloxymethyl)-1-hydroxy-6-methoxy-5-methyl-2,3,8,8a-tetrahydro-1H-3a-azacyclopenta[*a*]-indene-4,7-dione (42). A solution of $(NH_4)_3Ce(NO_3)_6$ (11.0 mg, 8.7 μmol) in H_2O (0.08 mL) was added to a solution of the above pyrrolidine/phenol (5.6 mg, 8.7 μmol) in CH_3CN (0.2 mL) at 25 °C. The reaction mixture was stirred for 5 min at 25 °C, cooled to 0 °C and saturated aqueous $NaHCO_3$ (0.2 mL) and EtOAc (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 5% EtOAc/hexane) to afford pure **48** (1.1 mg, 21%) as a pink oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (m, 3H), 7.49-7.34 (m, 12H), 5.14 (m, 1H), 5.04 (d, 2H, *J* = 3.7 Hz), 4.84 (d, 1H, *J* = 11.6 Hz), 4.70 (d, 1H, *J* = 12.2 Hz), 4.47 (dd, 1H, *J* = 12.2, 7.3 Hz), 4.31 (dd, 1H, *J* = 12.2, 7.3 Hz), 4.04 (dd, 1H, *J* = 12.2, 7.3 Hz), 4.01 (s, 3H), 3.42 (dd, 1H, *J* = 14.6, 7.3Hz), 3.35 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.77 (d, 1H, *J* = 1.8 Hz), 2.13 (s, 1H), 2.00 (s, 3H), 1.15 (s, 9H); HRMS (ESI), *m/z* calcd for $C_{37}H_{41}NO_6SiNa$: 646.2601; found: 646.2655.

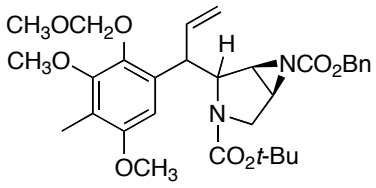


2-Benzyloxy-8-(*tert*-butyldiphenylsilanyloxy-methyl)-1-hydroxy-6-methoxy-5-methyl-2,3-dihydro-1H-3a-azacyclopenta[*a*]in-dene-4,7-dione (43). A solution

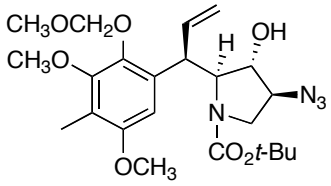
of $MeSO_2Cl$ (2.8 μl, 0.036 mmol) in CH_2Cl_2 (0.1 mL) was slowly added to a solution of **42** (7.4 mg, 0.012 mmol) and Et_3N (8.4 μl, 0.060 mmol) in CH_2Cl_2 (0.1 mL) at −20 °C. The reaction mixture was stirred for 3 h at 25 °C and aqueous K_2HPO_4/KH_2PO_4 buffer (1.0 M, pH 7, 0.2 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 5% EtOAc/hexane) to afford **43** with some contamination of **42** (3.9 mg, 56%) as a pink oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 3H), 7.43-7.26 (m, 12H), 5.21 (s, 1H), 5.07 (d, 1H, *J* = 15.3 Hz), 4.95 (d, 1H, *J* = 15.0 Hz), 4.75 (d, 1H, *J* = 11.9 Hz), 4.61 (d, 1H, *J* = 11.9 Hz), 4.54 (m, 1H), 4.44 (dd, 1H, *J* = 13.1, 6.7 Hz), 4.42 (dd, 1H, *J* = 13.1, 4.0 Hz), 3.97 (s, 3H), 3.35 (d, 1H, *J* = 1.2 Hz), 1.94 (s, 3H), 1.11 (s, 9H); HRMS (ESI), *m/z* calcd for $C_{37}H_{39}NO_6SiNa$: 644.2445; found: 644.2418.



3-Benzyloxycarbonylamino-2-[1-(3,5-dimethoxy-2-methoxymethoxy-4-methylphenyl)allyl]-4-hydroxy-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (46). Boron trifluoride etherate (0.42 mL, 3.00 mmol) was slowly added to a solution of **37** (898.6 mg, 2.55 mmol) and **34** (1.79 g, 3.32 mmol) in CH_2Cl_2 (12 mL) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C and aqueous K_2HPO_4/KH_2PO_4 buffer (1.0 M, pH 7, 15 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 25% EtOAc/hexane) to afford pure **46** (838.0 mg, 56%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (m, 5H), 6.54-6.50 (br, 1H), 6.17 (m, 1H), 5.24 (m, 2H), 5.29-4.96 (br, 6 H), 4.69-3.16 (br, 15 H), 2.10-2.03 (br, 3H), 1.44 (br, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.3, 151.8, 151.6, 141.7, 135.9, 135.8, 128.53, 128.5, 128.2, 128.0, 127.8, 119.8, 119.4, 105.7, 99.6, 99.6, 80.3, 79.8, 71.8, 67.3, 67.1, 66.9, 65.9, 60.4, 60.2, 57.6, 55.7, 52.7, 52.1, 51.7, 28.3, 8.9, 8.7 (mixture of diastereomers; some peaks belong to rotamers); HRMS (ESI), *m/z* calcd for $C_{31}H_{42}N_2O_9Na$: 609.2783; found: 609.2766.

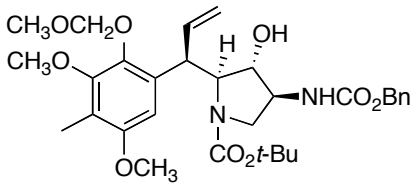


2-[1-(3,5-Dimethoxy-2-methoxymethoxy-4-methyl phenyl)allyl]-3,6-diazabicyclo[3.1.0]hexane-3,6-dicarboxylic Acid 6-Benzyl Ester 3-*tert*-Butyl Ester (47). Diisopropyl azodicarboxylate (0.039 mL, 0.20 mmol) was slowly added to a solution of **46** (118.2 mg, 0.20 mmol) and PPh_3 (104.8 mg, 0.40 mmol) in THF (10 mL) at 25 °C. The reaction mixture was stirred for 1 h at 25 °C and aqueous K_2HPO_4/KH_2PO_4 buffer (1.0 M, pH 7, 5 mL) was added. The aqueous layer was extracted with EtOAc (3 ×) and the combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by flash chromatography (silica, 10% EtOAc/hexane) to afford pure **47** (89.7 mg, 79%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (m, 5H), 6.57-6.46 (br, 1H), 6.23 (br, 1H), 5.28-4.94 (br, 8 H), 4.42-3.31 (br, 13 H), 3.15-2.63 (br, 2H), 2.08-2.00 (br, 3H), 1.47 (br, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.7, 152.3, 152.0, 141.9, 136.2, 136.0, 129.6, 129.2, 128.5, 128.0, 127.7, 119.4, 119.0, 106.4, 98.7, 98.6, 80.9, 80.7, 67.0, 66.9, 66.5, 66.4, 65.9, 61.4, 61.3, 58.3, 54.6, 52.0, 51.9, 51.7, 45.0, 44. 6, 39.4, 39.4, 38.8, 28.8, 8.7, 8.5 (mixture of diastereomers; some peaks belong to rotamers); HRMS (ESI), *m/z* calcd for $C_{31}H_{40}N_2O_8Na$: 591.2683; found: 591.2697.



Azidoalcohol 49. Borontrifluoride etherate (0.58 mL, 4.58 mmol) was added to a solution of azide **22** (1.00 g, 3.52 mmol) and stannane **34** (2.48 g, 4.58 mmol) in CH_2Cl_2 (15 mL) at –40 °C and the reaction mixture was stirred for 2 h at this temperature. The reaction was quenched by the addition of saturated aqueous Na_2CO_3 and was extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in *vacuo*. The residue was purified by a short-column flash chromatography (silica, 35% EtOAc/hexane) to give azidoalcohol **49** (1.26 g, 73%) as a colorless oil, and the recovered azide **22** (120 mg, 12%). Crude NMR showed two diastereoisomers in a 7:3 ratio, inseparable by flash chromatography. The mixture was characterized: ^{1}H NMR ($CDCl_3$, 500 MHz, 60 °C) δ 5.88-5.70 (br, 1H), 4.50

(br t, 1H), 4.02 (br, 1H), 3.87-3.73 (br, 1H), 3.07 (br t, 1H), 2.45-2.37 (br, 1H), 1.46 (s, 3H), 1.43 (s, 9H), 1.33 (s, 3H); IR (KBr) ν_{max} 3408, 3078, 2937, 2104, 1674, 1605, 1584 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{23}H_{34}N_4O_7Na$: 501.1825; found: 501.2268.

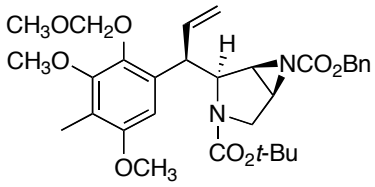


Carbamate Alcohol 50. A solution of azidoalcohol **49** (1.41 g, 2.94 mmol) in CH_3CN (20 mL) was added to a solution of $SnCl_2$ (937 mg, 4.71 mmol), thiophenol (1.45 mL, 14.2 mmol) and Et_3N (1.97 mL, 14.2 mmol) in CH_3CN (20 mL) at 0 °C. The reaction mixture was stirred for 1 h and additional thiophenol (0.30 mL, 2.94 mmol) was added. After an additional 1 h, the mixture was diluted with CH_2Cl_2 (100 mL) and washed with 2N NaOH solution (2 x). The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow oil was diluted with CH_2Cl_2 (50 mL) and was treated with Et_3N (0.82 mL, 5.90 mmol) and benzyl chloroformate (0.42 mL, 2.94 mmol) at 0 °C. The reaction mixture was stirred 3 h at room temperature and was quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 ×) and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 30% Et_2O/toluene) to give the major diastereoisomer **50** (933 mg, 54%) and the minor diastereoisomer **50** (363 mg, 21%): IR (KBr) ν_{max} 3356, 2929, 1694, 1607, 1589 cm^{-1}.

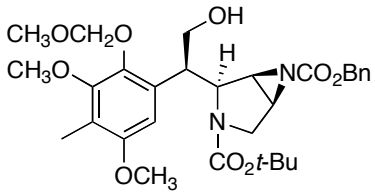
The major isomer of **50** was characterized: ^1H NMR ($CDCl_3$, 500 MHz, 60 °C) δ 7.28-7.37 (m, 5H), 6.56 (s, 1H), 6.11-6.19 (m, 1H), 5.74 (br s, 1H), 4.99-5.13 (m, 6H), 4.18-4.26 (m, 2H), 3.99-4.02 (m, 1H), 3.93 (app t, 1H, *J* = 9.1 Hz), 3.80 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.44 (s, 3H), 3.06-3.10 (m, 1H), 2.51 (s, 1H), 2.11 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, 60 °C) δ 156.4, 155.4, 155.0, 152.1, 141.8, 138.9, 136.7, 132.1, 128.6, 128.3, 128.2, 120.2, 116.2, 105.5, 100.1, 80.0, 79.5, 69.3, 67.1, 60.3, 58.5, 57.8, 56.0, 51.8, 45.6, 28.6, 8.9; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{42}N_2O_9Na$: 609.2783; found: 609.2749.

The minor isomer of **50** was characterized: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.36 (m, 5H), 6.55 (s, 1H), 6.10-6.19 (m, 1H), 5.63 (br s, 1H), 4.95-5.22 (m, 6H), 3.98-4.23 (m, 5H), 3.78-3.81

(m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), (m, 1H), 3.05 (br s, 1H), 2.08 (s, 3H), 1.26 (s, 9H); HRMS (ESI), *m*/*z* calcd for $C_{31}H_{42}N_2O_9Na$: 609.2783; found: 609.2769.

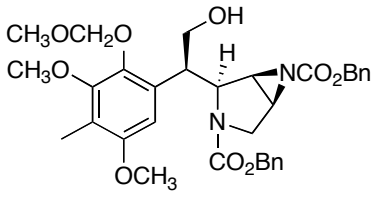


Aziridine 51. Diisopropyl azodicarboxylate (0.29 mL, 1.45 mmol) was added to a solution of compound **50** (426 mg, 0.727 mmol) and Ph_3P (381 mg, 1.45 mmol) in THF (15 mL) at 0 °C. The mixture was stirred for 2 h at room temperature and the volatiles were removed under reduced pressure. The residue was taken up in ether and the white precipitate in filtered. The filtrate was concentrated in *vacuo*, and the residue was purified by flash chromatography (silica, 30% EtOAc/hexane) to give aziridine **51** (336 mg, 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.40 (m, 5H), 6.73 (s, 1H), 6.19-6.28 (m, 1H), 5.16 (d, 1H, J = 12.3 Hz), 4.96-5.05 (m, 5H), 4.63 (app d, 1H, J = 9.5 Hz), 4.21 (m, 1H), 3.82 (s, 3H), 3.77-3.82 (m, 1H), 3.77 (s, 3H), 3.61-3.65 (m, 1H), 3.61 (s, 3H), 3.31 (s, 2H), 2.17 (s, 3H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 60 °C) δ 161.9, 155.2, 154.2, 151.9, 142.0, 140.3, 135.7, 131.9, 128.4, 128.2, 127.9, 119.0, 114.6, 105.7, 99.0, 79.9, 67.9, 61.4, 60.0, 57.3, 55.6, 50.1, 46.9, 44.3, 28.2, 8.8; IR (KBr) ν_{max} 2934, 1728, 1698 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{40}N_2O_8Na$: 591.2677; found: 591.2718.



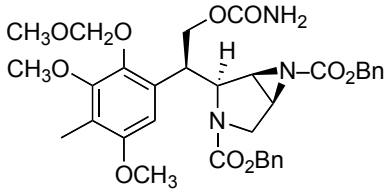
Aziridinoalcohol 52. A stream of O_3 in O_2 was slowly bubbled into a solution of **51** (390 mg, 0.687 mmol) in MeOH (60 mL) and CH_2Cl_2 (18 mL) at −78 °C. The progress of the reaction was carefully monitored by TLC and N_2 was bubbled into the reaction mixture for 30 min immediately after the reaction was judged complete. The reaction mixture was warmed to 0 °C and $NaBH_4$ (261 mg, 6.87 mmol) was added. The reaction mixture was stirred for 4 h at 0 °C and was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 ×), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 30% EtOAc/hexane) to afford **52** (247 mg, 63%) as a colorless

oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.34 (m, 3H), 7.12 (s, 2H), 6.78 (s, 1H), 5.08 (d, 1H, J = 12.4 Hz), 4.96-4.99 (m, 2H), 4.85 (d, 1H, J = 12.4 Hz), 4.65-4.68 (m, 1H), 4.27 (s br, 1H), 3.85 (s, 3H), 3.80-3.86 (m, 1H), 3.71 (s, 3H), 3.65-3.71 (m, 1H), 3.60 (d, 1H, J = 12.6 Hz), 3.55 (s, 3H), 3.28-3.31 (m, 2H), 2.13 (s, 3H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, 60 °C) δ 161.9, 157.1, 154.3, 151.7, 142.2, 135.7, 131.8, 128.5, 128.2, 127.8, 119.2, 105.9, 99.2, 81.2, 68.0, 63.9, 60.1, 58.5, 57.2, 55.8, 50.5, 47.4, 44.1, 42.5, 28.4, 9.0; IR (KBr) ν_{max} 3446, 3064, 2937, 1729, 1677 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{40}N_2O_9Na$: 595.2632; found: 595.2628.

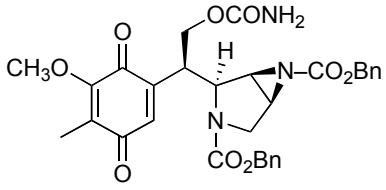


Bis-benzylcarbamate 53. Trimethylsilyl trifluoromethanesulfonate (84 μL, 0.47 mmol) was added to a solution of 2,6-di-*tert*-butylpyridine (122 μL, 0.544 mmol) and carbamate **52** (89.0 mg, 0.156 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h when a buffered solution of pyridinium fluoride (1 mL HF/3 mL pyridine, 1.55 mmol) was added and the mixture was stirred for 15 min at 0 °C. The mixture was washed with aqueous 3 N NaOH and the aqueous phase was extracted CH_2Cl_2 (3 ×). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo.* The residue was dissolved in CH_2Cl_2 (4 mL) at 0 °C and treated sequentially with Et_3N (32.0 μL, 0.233 mmol) and benzyl chloroformate (24.0 μL, 0.171 mmol). The reaction mixture was allowed to warm to room temperature, and was stirred 3 h at this temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (3 x). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (silica, 40% EtOAc/hexane) to afford pure **53** (56.5 mg, 60%): ^{1}H NMR ($CDCl_3$, 500 MHz, 60 °C) δ 7.27-7.39 (m, 8H), 7.06 (s br, 2H), 6.37 (s, 1H), 5.47 (s br, 1H), 5.14-5.20 (m, 2H), 4.91 (d, 2H, J = 12.2 Hz), 4.72 (s br, 1H), 4.69-4.70 (m, 2H), 4.38 (s br, 1H), 4.23 (s br, 2H), 4.15 (t, 1H, J = 8.2 Hz), 3.81-3.84 (m, 2H), 3.73 (s br, 6H), 3.54 (s br, 3H), 3.04 (t, 1H, J = 10.4 Hz), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, 60 °C) δ 156.1, 154.7, 152.0, 143.4, 136.7, 136.5, 128.7, 128.5, 128.3, 128.3, 128.1, 128.1, 127.3, 120.2, 105.4, 100.0, 83.1, 82.4, 74.0, 67.2, 64.7, 60.2, 57.4,

56.1, 53.7, 51.7, 43.9, 9.0; IR (KBr) ν_{max} 3430, 3334, 2941, 1710 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{33}H_{38}N_2O_9Na$: 629.2470; found: 629.2477.

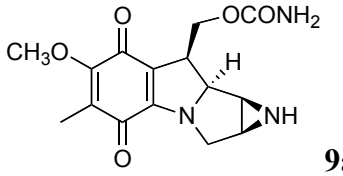


Carbamate 54. A solution of alcohol **53** (70.1 mg, 0.116 mmol) in CH_2Cl_2 (1 mL) was added trichloroacetyl isocyanate (83 μL, 0.693 mmol). The resulting mixture was stirred for 12 h at 65 °C in a sealed tube. After cooling to room temperature, another portion of trichloroacetyl isocyanate (83 μL, 0.693 mmol) was added and the solution was stirred for 24 h at 65 °C. Then, the mixture was carefully deposited on a short column of neutral alumina that was pre-wetted with CH_2Cl_2. After 30 min on standing, the mixture was mixture was eluted with EtOAc. The crude was purified by flash chromatography (silica, 60% EtOAc/hexane) to afford pure **54** (64.5 mg, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 50 °C) δ 7.33-7.41 (m, 5H), 7.22 (s br, 3H), 6.95 (s br, 2H), 6.19 (s, 1H), 5.31 (d, 1H, *J* = 11.9 Hz), 5.22 (s, 1H), 5.21 (d, 1H, *J* = 11.9 Hz), 4.81 (m, 4H), 4.61 (s br, 1H), 4.10-4.20 (m, 4H), 3.93 (m, 1H), 3.46-3.79 (m, 10H), 2.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, 50 °C) δ 156.3, 155.5, 154.6, 154.4, 151.7, 142.9, 136.2, 134.7, 129.0, 128.9, 128.3, 128.0, 127.9, 127.0, 119.8, 105.5, 99.6, 83.0, 73.7, 69.3, 67.0, 63.7, 60.1, 57.5, 57.2, 56.1, 53.4, 48.1, 43.3, 8.9. IR (KBr) ν_{max} 3430, 3337, 2954, 1720, 1698 cm^{-1}; HRMS (ESI), *m*/*e* calcd for $C_{34}H_{39}N_3O_{10}Na$: 672.2528; found: 672.2520.

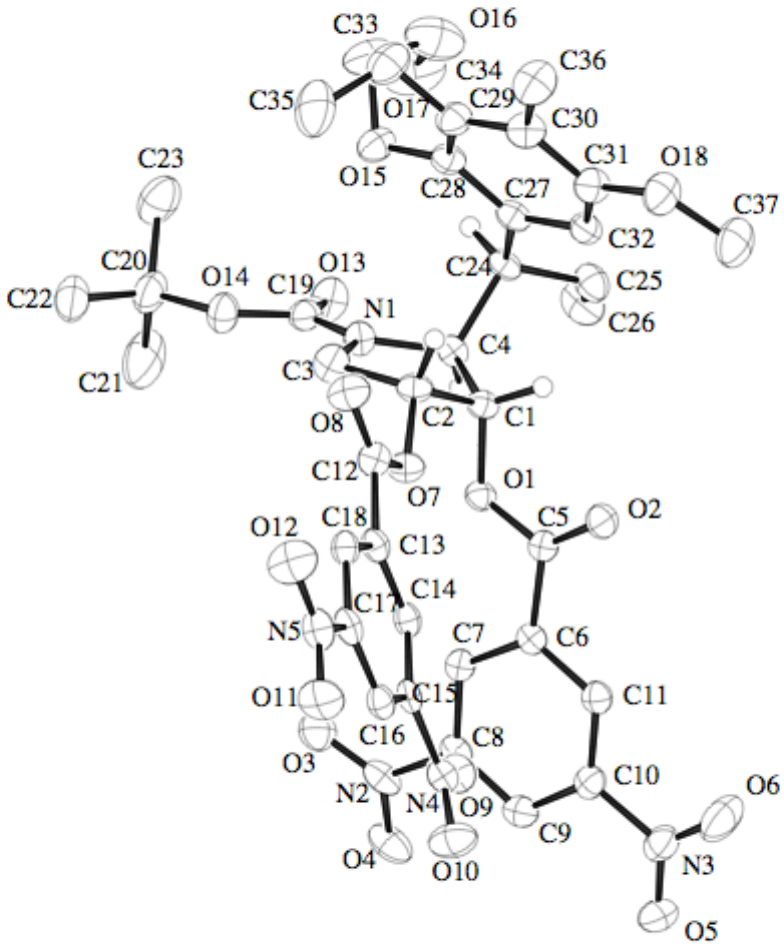


Quinone 55. A solution of ceric ammonium nitrate (128 mg, 0.234 mmol) in H_2O (0.6 mL) was added to a room temperature solution of compound **54** (38 mg, 0.059 mmol) in CH_3CN (2.5 mL). The mixture was stirred 10 min at this temperature and was diluted with CH_2Cl_2 and washed with water. The aqueous phase was extracted with CH_2Cl_2 (3 ×), and the organic phase was dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (60% EtOAc/hexane) to give **55** (32.7 mg, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.45 (m, 5H), 7.26-7.30 (m, 3H), 7.14 (br s, 2H), 5.76 (s,

1H), 5.24 (m, 2H), 4.99 (d, 1H, *J* = 12.4 Hz), 4.86-4.89 (m, 1H), 4.82 (d, 1H, *J* = 12.4 Hz), 4.75 (t, 1H, *J* = 5.2 Hz), 4.56 (t, 1H, *J* = 5.4 Hz), 4.05 (s, 3H), 3.91-4.00 (m, 2H), 3.65-3.67 (m, 2H), 3.38 (m, 1H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.7, 181.6, 157.6, 156.1, 155.3, 154.9, 142.4, 136.5, 134.3, 130.3, 129.6, 129.2, 129.1, 128.7, 128.2, 127.5, 126.9, 82.1, 69.7, 69.2, 67.1, 63.5, 60.6, 56.5, 47.7, 43.6, 8.4; IR (KBr) ν_{max} 3437, 3331, 2921, 1726, 1695, 1654, 1610 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{31}N_3O_9Na$: 612.1953; found: 612.1950.



9a-Desmethoxy Mitomycin A (1). A solution of carbamate **55** (15 mg, 0.027 mmol) in MeOH (2 mL) was stirred with Pd/C (catalytic) under an atmosphere of H_2 (balloon) at room temperature for 3 h. Following filtration of the catalyst first through Celite then through a 45 micron filter, the solution was vigorously stirred open to the air for 4 h. The volatiles were removed under reduced pressure and the residue was purified by preparative TLC (10% MeOH/CH_2Cl_2) to afford the title compound **1** as a purple oil (6.0 mg, 74%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.13 (m, 1H), 4.62 (dd, 1H, *J* = 4.5, 8.9 Hz), 4.53-4.58 (m, 1H), 4.35 (app t, 1H, *J* = 5.0 Hz), 4.28 (br s, 2H), 4.05 (app d, 1H, *J* = 9.2 Hz), 4.00 (s, 3H), 3.82 (dd, 1H, *J* = 6.0, 9.3 Hz), 3.70-3.74 (m, 2H), 3.50 (dd, 1H, *J* = 5.5, 12.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.3, 178.5, 157.2, 156.8, 153.9, 124.6, 120.7, 82.9, 74.6, 74.1, 60.7, 56.4, 45.1, 31.5, 29.3, 28.9, 22.3, 13.4, 7.5; IR (KBr) ν_{max} 3450, 3354, 3205, 2915, 1647, 1609 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{15}H_{17}N_3O_9Na$: 342.1060; found: 342.1057.



ORTEP Structure of **37**