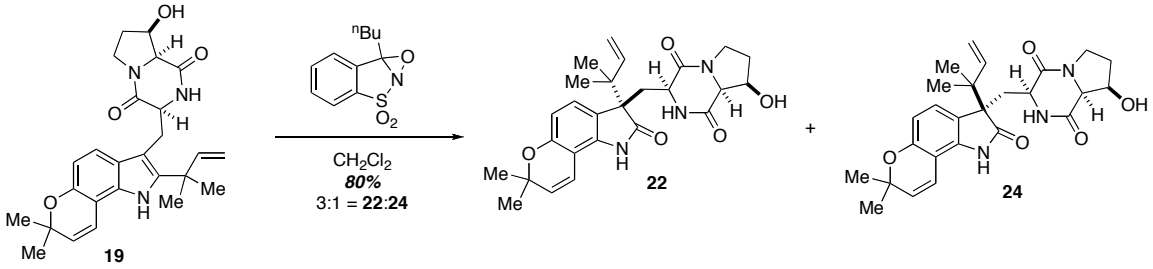
Asymmetric Total Syntheses of (+)- and (-)-Versicolamide B and Biosynthetic Implications

Kenneth A. Miller[1] and Robert M. Williams*[1,2]

[1]*Department of Chemistry, Colorado State University*
Fort Collins, Colorado 80523-1872
[2]*University of Colorado Cancer Center, Aurora, Colorado, 80045*

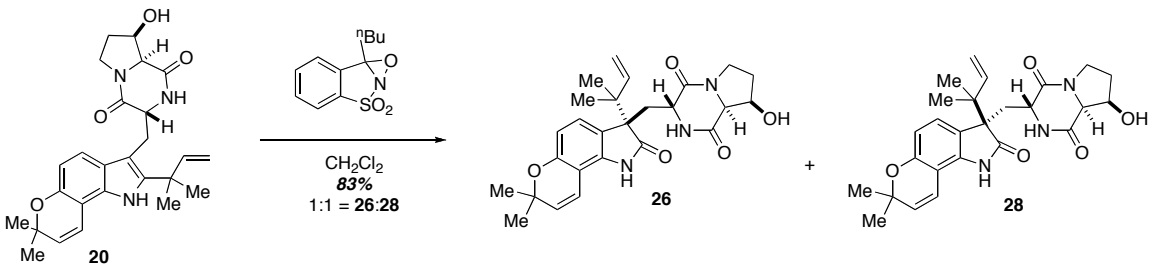
rmw@lamar.colostate.edu

SUPPORTING INFORMATION



(3*S*,8*R*,8a*S*)-3-(((*S*)-7,7-dimethyl-3-(2-methylbut-3-en-2-yl)-2-oxo-1,2,3,7-tetrahydropyrano[2,3-*g*]indol-3-yl)methyl)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (22) and **(3*S*,8*R*,8a*S*)-3-(((*R*)-7,7-dimethyl-3-(2-methylbut-3-en-2-yl)-2-oxo-1,2,3,7-tetrahydropyrano[2,3-*g*]indol-3-yl)methyl)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (24).** Davis oxaziridine (532 mg, 2.22 mmol) was added in one portion to a solution of *cis*-diketopiperazine **19** in CH_2Cl_2 (20 mL) at rt. The reaction was stirred at that temperature for 18 h at which time the entire contents were concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (97:3-95:5) to give 309 mg (60%) of the higher R_f compound **22** as a yellow film and 101 mg (20%) of the lower R_f compound **24** as a white film; data for major isomer **22**: $[\alpha]_D^{25}$ = -163.2 (c = 0.1, $CHCl_3$); ^{1}H NMR

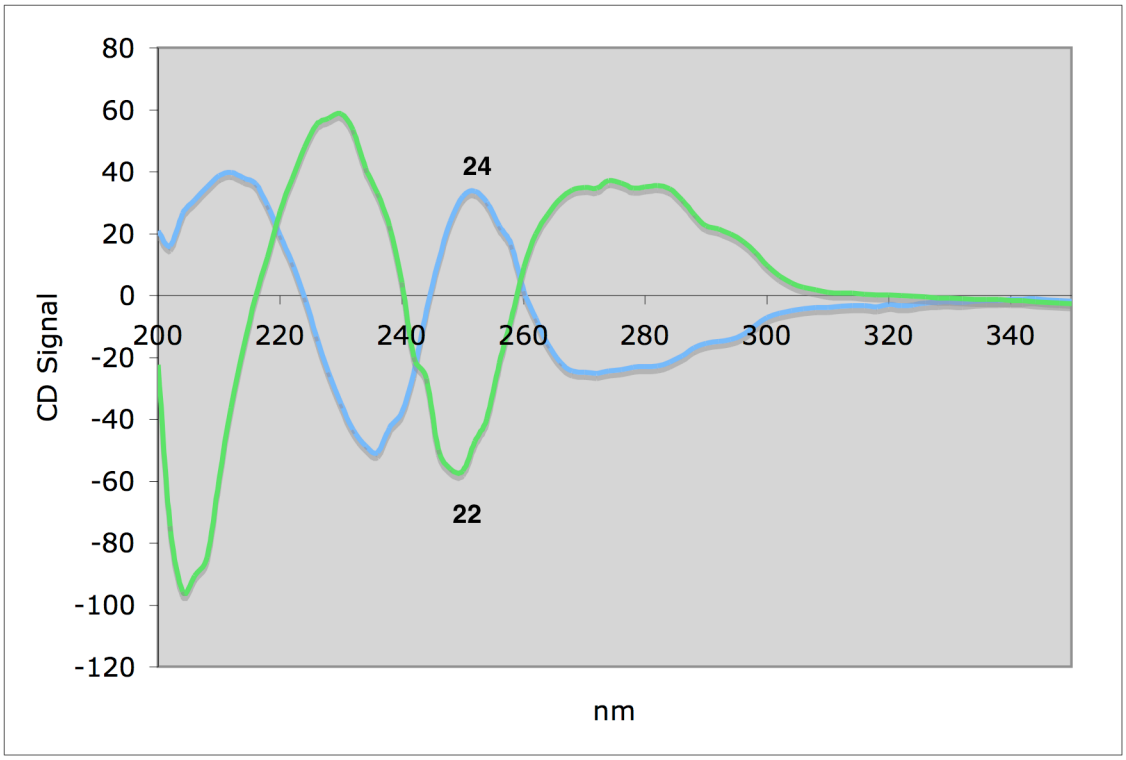
(300 MHz, CD_3Cl) δ 10.03 (s, 1H), 7.09 (s, 1H), 6.97 (d, *J* = 8.1 Hz, 1 H), 6.44 (d, *J* = 8.6 Hz, 1 H), 6.05 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.71 (d, *J* = 9.9 Hz, 1 H), 5.10 (d, *J* = 10.8 Hz, 1 H), 5.02 (d, *J* = 17.4 Hz, 1 H), 4.57 (bs, 1 H), 3.96 (bs, 1 H), 3.71-3.55 (comp, 2 H), 3.23 (d, *J* = 9.4 Hz, 1 H), 3.19 (d, *J* = 5.0 Hz, 1 H), 2.24 (dd, J = 15.2, 8.6 Hz, 1 H), 2.08 (dd, *J* = 13.7, 7.1 Hz, 1 H), 1.89 (m, 1 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (100 MHz, CD_3Cl) δ 183.6, 169.0, 165.3, 153.2, 142.7, 137.8, 131.2, 126.4, 121.1, 116.5, 114.5, 110.1, 105.5, 76.5, 70.8, 64.2, 58.1, 52.8, 44.3, 42.6, 31.3, 30.4, 28.3, 27.8, 22.6, 21.7; IR (neat) 3321, 1671, 1450, 1120, 732 cm^{-1}; HRMS (TOF+) calcd for $C_{26}H_{32}N_3O_5$ (M+H) 466.2336, found 466.2333; data for minor isomer **24**: $[\alpha]_D^{25}$ = -11.2 (c = 0.1, $CHCl_3$); ^1H NMR (300 MHz, CD_3Cl) δ 9.98 (bs, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 6.48 (d, *J* = 8.2 Hz, 1 H), 6.40 (d, *J* = 9.9 Hz, H), 6.13-6.03 (comp, 2 H), 5.70 (d, *J* = 9.9 Hz, 1 H), 5.12 (d, *J* = 10.9 Hz, 1 H), 5.03 (d, *J* = 17.4 Hz, 1 H), 4.52 (bs, 1 H), 3.97 (bs, 1 H), 3.95 (s, 1 H), 3.58-3.52 (comp, 2 H), 3.02 (dd, *J* = 14.9, 3.5 Hz, 1 H), 2.84 (s, 1 H), 2.41 (dd, *J* = 14.9, 6.9 Hz, 1 H), 2.02-1.85 (comp, 2 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.15 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (100 MHz, CD_3Cl) δ 182.5, 167.8, 164.9, 153.5, 142.9, 137.8, 131.3, 126.8, 120.8, 116.5, 114.5, 109.7, 105.9, 76.5, 70.7, 64.0, 56.6, 54.0, 44.2, 43.0, 31.7, 30.2, 28.1, 27.8, 22.5, 21.7; IR (neat) 3360, 1671, 1456, 1120, 731 cm^{-1}; HRMS (TOF+) calcd for $C_{26}H_{32}N_3O_5$ (M+H) 466.2336, found 466.2336.



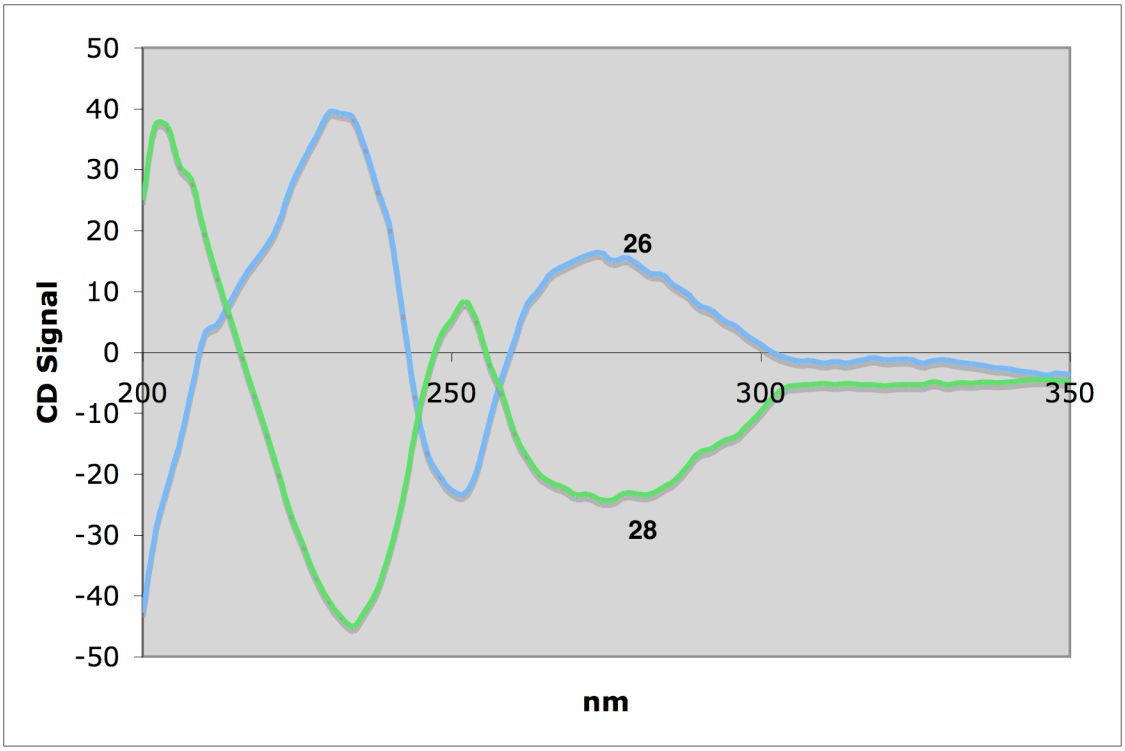
(3*R*,8*R*,8a*S*)-3-(((*S*)-7,7-dimethyl-3-(2-methylbut-3-en-2-yl)-2-oxo-1,2,3,7-tetrahydropyrano[2,3-*g*]indol-3-yl)methyl)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (26) and **(3*R*,8*R*,8a*S*)-3-(((*R*)-7,7-dimethyl-3-(2-methylbut-3-en-2-yl)-2-oxo-1,2,3,7-tetrahydropyrano[2,3-*g*]indol-3-yl)methyl)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (28).** Davis oxaziridine (532 mg, 2.22 mmol) was added in one portion to a solution of *trans*-diketopiperazine **20** in CH_2Cl_2 (20 mL) at rt. The reaction was stirred at that temperature for 18 h at which time the entire contents were concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (97:3-95:5-90:10) to give 218 mg (42%) of the higher R_f compound **26** as a white film and 211 mg (41%) of the lower R_f compound **28** as a yellow film; data for higher R_f isomer **26**: $[\alpha]_D^{25}$ = -107.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3Cl) δ 11.25 (s, 1 H), 8.77 (s, 1 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 6.60 (d, *J* = 9.9 Hz, 1 H), 6.46 (d, *J* = 8.1 Hz, 1 H), 6.03 (dd, *J* = 17.4, 10.7 Hz, 1 H), 5.65 (d, *J* = 9.9 Hz, 1 H), 5.11 (d, *J* = 10.7 Hz, 1 H), 5.01 (d, *J* = 17.4 Hz, 1 H), 4.52 (bs, 1 H), 4.05 (s, 1 H), 3.67-3.43 (comp, 2 H), 2.76 (s, 1 H), 2.40-1.88 (comp, 3 H), 1.49 (s, 3 H), 1.42 (s, 3 H), 1.14 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (100 MHz, CD_3Cl) δ 184.2, 169.9, 167.1, 153.2, 142.8, 138.4, 129.8, 126.3, 119.3, 118.1, 114.5, 109.7, 106.6, 76.0, 70.7, 63.6, 56.3, 55.6, 44.3, 42.6, 34.4, 29.7, 28.8, 27.4, 22.0, 21.9; IR (neat) 3183, 1703, 1668, 1454, 912, 732 cm^{-1}; HRMS (TOF+) calcd for $C_{26}H_{32}N_3O_5$ (M+H) 466.2336,

found 466.2340; data for lower R_f isomer **28**: $[\alpha]_D^{25}$ = -316.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3Cl) δ 11.45 (s, 1 H), 8.72 (s, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.48 (d, *J* = 9.9 Hz, 1 H), 6.35 (d, *J* = 8.2 Hz, 1 H), 6.00 (dd, *J* = 17.3, 10.8 Hz, 1 H), 5.67 (d, *J* = 9.9 Hz, 1 H), 5.06 (d, *J* = 10.8 Hz, 1 H), 4.95 (d, *J* = 17.3 Hz, 1 H), 4.27 (s, 1 H), 4.12 (s, 1 H), 3.71-2.63 (comp, 5 H), 2.07 (s, 1 H), 1.76 (comp, 2 H), 1.41 (s, 6 H), 1.07 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (100 MHz, CD_3Cl) δ 184.0, 166.5, 165.5, 153.2, 142.8, 139.6, 130.8, 128.2, 120.0, 116.7, 114.3, 108.2, 105.7, 76.3, 71.1, 62.5, 56.0, 55.3, 43.2, 42.8, 33.4, 29.6, 28.4, 27.6, 22.0, 21.7; IR (neat) 3203, 1704, 1642, 1459, 913, 731 cm^{-1}; HRMS (TOF+) calcd for $C_{26}H_{32}N_3O_5$ (M+H) 466.2336, found 466.2332.

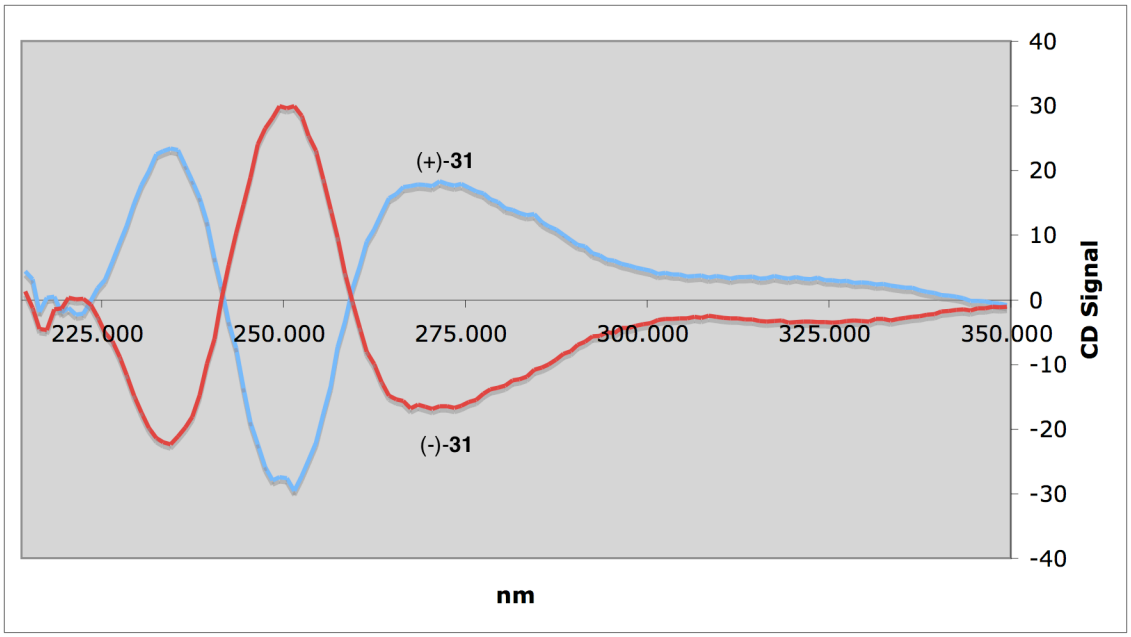
CD Spectra of **22** and **24**



CD Spectra of **26** and **28**



CD Spectra of (+)-**31** and (-)-**31**



CD Spectra of (+)-versicolamide B and (-) versicolamide B