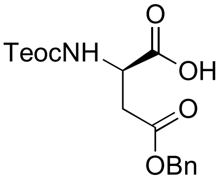
Supporting Information

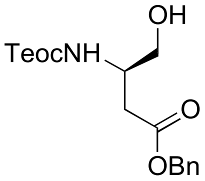
Asymmetric Total Synthesis of Vindoline

Daisuke Kato, Yoshikazu Sasaki, and Dale L. Boger*

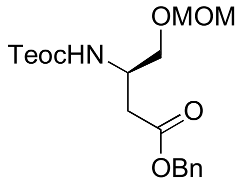
Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute,
10550 North Torrey Pines Road, La Jolla, California 92037



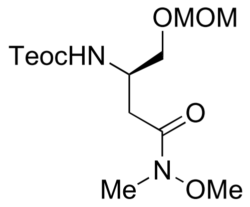
Compound 4. 1-[2-(Trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (Teoc-OSu, 9.22 g, 35.5 mmol) was added to a solution of D-aspartic acid β-benzyl ester (**3**, 7.19 g, 32.2 mmol) and Et_3N (11.6 mL, 83.7 mmol) in water (32 mL) and dioxane (32 mL). The reaction mixture was stirred at room temperature for 16 h, diluted with water (150 mL), and acidified with saturated aqueous $KHSO_4$ (300 mL). The mixture was extracted with Et_2O, washed with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 2% AcOH–30% EtOAc–hexanes) provided **4** (13.1 g, quantitative) as a colorless oil: ^1H NMR (600 MHz, C_6D_6) δ 7.12–7.07 (m, 4H), 7.06–7.03 (m, 1H), 5.91 (d, *J* = 8.3 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.81–4.73 (m, 1H), 4.19 (t, *J* = 8.0 Hz, 2H), 2.90 (dd, *J* = 17.1, 4.6 Hz, 1H), 2.74 (dd, *J* = 17.1, 4.2 Hz, 1H), 0.93–0.85 (m, 2H), –0.10 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 175.6, 171.1, 156.9, 136.0, 128.7, 128.5, 128.4, 66.9, 63.8, 50.7, 36.5, 17.8, –1.6; IR (neat) ν_{max} 2953, 1723, 1518, 1249 cm^{-1}; HRESI–TOF MS *m*/*z* 390.1332 ($C_{17}H_{25}NO_6Si + Na^+$ requires 390.1343). $[\alpha]_D^{23}$ –26 (*c* 1.0, $CHCl_3$).



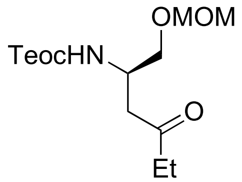
Compound 5. Isobutyl chloroformate (6.76 mL, 51.8 mmol) was added to a solution of **4** (19 g, 51.8 mmol) and *N*-methylmorpholine (5.69 mL, 51.8 mmol) in DME (52 mL) at –15 °C. After stirring the reaction mixture for 15 min, the precipitated *N*-methylmorpholine hydrochloride was removed by filtration, and washed with DME. A solution of $NaBH_4$ (2.94 g, 77.7 mmol) in water (25 mL) was carefully added to the combined filtrate solution cooled in an ice-salt bath (–20° C) followed by the addition of water (400 mL). After 5 min, the mixture was extracted with EtOAc, washed with water and saturated aqueous NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 20–50% EtOAc–hexanes gradient elution) provided **5** (16.7 g, 91%) as a colorless oil: ^1H NMR (400 MHz, C_6D_6) δ 7.19 (d, *J* = 7.4 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 5.13–5.06 (m, 1H), 4.90 (s, 2H), 4.24–4.18 (m, 2H), 4.06–3.99 (m, 1H), 3.35 (s, 2H), 2.38 (d, *J* = 5.9 Hz, 2H), 0.95–0.89 (m, 2H), –0.09 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 171.6, 156.9, 136.4, 128.7, 128.5, 128.3, 66.5, 64.3, 63.2, 50.4, 36.1, 17.9, –1.5; IR (neat) ν_{max} 3329, 2953, 1782, 1694, 1528, 1250 cm^{-1}; HRESI–TOF MS *m*/*z* 376.1542 ($C_{17}H_{27}NO_5Si + Na^+$ requires 376.1551). $[\alpha]_D^{23}$ +11 (*c* 1.2, $CHCl_3$).



Compound 6. MOMCl (21 mL, 276 mmol) was added to a solution of **5** (19.5 g, 55.2 mmol) in CH_2Cl_2 (110 mL) and *i*-Pr_2NEt (45.5 mL, 276 mmol) at 0 °C. The reaction mixture was stirred and allowed to warm to room temperature in the course of 2 h. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 15–30% EtOAc–hexanes gradient elution) provided **6** (18.5 g, 84%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 7.19–7.14 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 2H), 7.05–7.02 (m, 1H), 5.28 (s, 1H), 4.94 (s, 2H), 4.41 (s, 1H), 4.28–4.22 (m, 4H), 3.50 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.39 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.02 (s, 3H), 2.55 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.46 (dd, *J* = 15.6, 6.0 Hz, 1H), 0.96–0.91 (m, 2H), –0.09 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 171.0, 156.1, 136.5, 128.7, 128.6, 128.3, 96.6, 68.9, 66.4, 63.0, 55.0, 48.3, 36.3, 18.0, –1.6; IR (neat) ν_{max} 3339, 2951, 2892, 1718, 1512, 1248 cm^{-1}; HRESI–TOF MS *m/z* 398.1992 ($C_{19}H_{31}NO_6Si + H^+$ requires 398.1993). $[\alpha]_D^{23}$ –3.7 (*c* 1.1, $CHCl_3$).

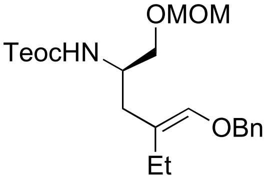


Compound 7. A solution of **6** (6.19 g, 15.6 mmol) in THF (80 mL) was stirred under H_2 (1 atm) in the presence of 10% Pd/C (619 mg) for 30 min at room temperature. The reaction mixture was filtered through Celite, and concentrated under reduced pressure. *i*-Pr_2NEt (3.08 mL, 18.7 mmol), *N,O*-dimethylhydroxylamine hydrochloride (1.82 g, 18.7 mmol), EDCI (3.15 g, 16.4 mmol), and DMAP (95.2 mg, 0.78 mmol) were added successively to a solution of the resulting crude carboxylic acid in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, allowed to warm up, and stirred at room temperature for 14 h. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50–100% EtOAc–hexanes gradient elution) provided **7** (5.14 g, 94%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 5.90 (d, *J* = 7.4 Hz, 1H), 4.51 (s, 1H), 4.38 (s, 2H), 4.26 (dd, *J* = 9.1, 7.6 Hz, 2H), 3.80 (dd, *J* = 9.2, 4.6 Hz, 1H), 3.68–3.63 (m, 1H), 3.10 (s, 3H), 3.00 (s, 3H), 2.88 (d, *J* = 13.1 Hz, 1H), 2.78 (s, 3H), 2.66–2.58 (m, 1H), 0.96–0.92 (m, 2H), –0.09 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 172.4, 156.3, 96.7, 69.1, 62.8, 60.6, 55.0, 48.3, 33.1, 31.7, 18.0, –1.6; IR (neat) ν_{max} 3336, 2950, 1714, 1657, 1506, 1248 cm^{-1}; HRESI–TOF MS *m/z* 351.1947 ($C_{14}H_{30}N_2O_6Si + H^+$ requires 351.1946). $[\alpha]_D^{23}$ –4.4 (*c* 0.99, $CHCl_3$).

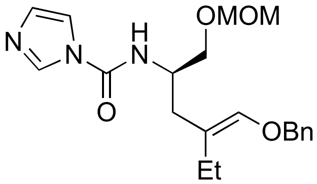


Compound 8. $CeCl_3$ heptahydrate (26.6 g, 71.2 mmol) was heated at 140 °C in vacuo for 19 h to be thoroughly dehydrated, cooled and suspended quickly in anhydrous THF (100 mL) at 0 °C with vigorous stirring. A solution of **7** (8.31 g, 23.7 mmol) in THF (58 mL) was added to this suspension, and the mixture was stirred for 1 h at 0 °C under Ar followed by the addition of 1 M solution of ethylmagnesium bromide (71.2 mL, 71.2 mmol) in THF. After stirring at 0 °C for another 1 h, 5% aqueous AcOH was added to the reaction mixture until the suspension was completely dissolved. The mixture was extracted

with EtOAc, washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 20–40% EtOAc–hexanes gradient elution) provided **8** (7.56 g, quantitative) as a colorless oil: ^1H NMR (600 MHz, C_6D_6) δ 5.31 (s, 1H), 4.40–4.29 (m, 3H), 4.28–4.23 (m, 2H), 3.50 (ddd, *J* = 14.8, 9.4, 5.1 Hz, 2H), 3.06 (s, 3H), 2.50–2.28 (m, 2H), 1.96–1.88 (m, 2H), 0.95 (dd, *J* = 10.3, 6.4 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H), –0.09 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 208.5, 156.2, 96.7, 69.2, 62.9, 55.0, 47.9, 43.3, 36.1, 18.0, 7.7, –1.6; IR (neat) ν_{max} 3334, 2950, 1710, 1525, 1248 cm^{-1}; HRESI–TOF MS *m/z* 320.1882 ($C_{14}H_{29}NO_5Si + H^+$ requires 320.1888). $[\alpha]_D^{23}$ –1.4 (*c* 0.98, $CHCl_3$).

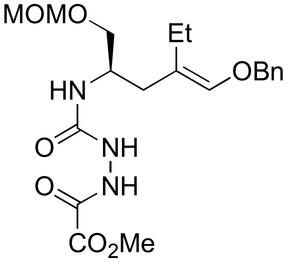


Compound (*E*)-9. A 0.5 M solution of KHMDS in toluene (37.6 mL, 18.8 mmol) was added to a suspension of (benzyloxymethyl)triphenylphosphonium chloride (8.71 g, 18.8 mmol) in anhydrous THF (35 mL) at –78 °C. Upon final addition of KHMDS, the reaction mixture was warmed to –40 °C, and stirred for 30 min until it turned a deep red color. The reaction mixture was recooled to –78 °C, and a solution of **8** (3.00 g, 9.40 mmol) in THF (10 mL) was slowly added. The reaction mixture was stirred at –40 °C for 16 h before being quenched with the addition of saturated aqueous NH_4Cl at 0 °C. The mixture was extracted with EtOAc, washed with water and saturated aqueous NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) provided (*E*)- and (*Z*)-**9** (ca. 1 : 1 mixture of isomers, 3.56 g, 89%) as a colorless oil. The (*Z*)-isomer eluted first off the column, followed by the (*E*)-isomer. For (*E*)-**9:** ^1H NMR (600 MHz, C_6D_6) δ 7.19–7.11 (m, 4H), 7.06 (t, *J* = 7.3 Hz, 1H), 5.80 (s, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.50–4.41 (m, 2H), 4.35 (q, *J* = 6.4 Hz, 2H), 4.30–4.25 (m, 2H), 4.07 (s, 1H), 3.45 (s, 2H), 3.10 (s, 3H), 2.40–2.28 (m, 2H), 2.19–2.10 (m, 2H), 1.10 (t, *J* = 7.6 Hz, 3H), 0.96 (dd, *J* = 15.2, 6.9 Hz, 2H), –0.09 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 156.2, 142.6, 138.5, 128.6, 128.3, 127.5, 117.1, 96.8, 73.5, 69.2, 62.8, 55.0, 49.4, 34.1, 20.6, 18.0, 12.8, –1.5; IR (neat) ν_{max} 2953, 1701, 1507, 1249, 1210, 1037 cm^{-1}; HRESI–TOF MS *m/z* 446.2337 ($C_{22}H_{37}NO_5Si + Na^+$ requires 446.2333). $[\alpha]_D^{23}$ –5.8 (*c* 0.2, C_6H_6).

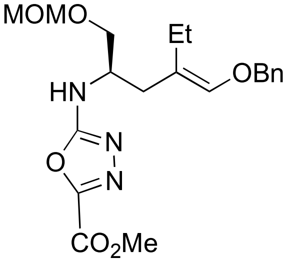


Compound 10. Bu_4NF (1.0 M in THF, 13.6 mmol) was added to a solution of (*E*)-**9** (1.92 g, 4.53 mmol) in THF (58.5 mL) at room temperature. The reaction mixture was stirred at 44 °C for 3 h before being quenched with the addition of 0.1 M aqueous NaOH. The mixture was extracted with EtOAc, and the extract was washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude amine in CH_2Cl_2 (10 mL) was treated with CDI (2.20 g, 13.6 mmol) and DMAP (55.3 mg, 0.453 mmol) at room temperature. The reaction mixture was stirred for 10 h, and concentrated under reduced pressure. Flash chromatography (SiO_2, 67% EtOAc–hexanes) provided **10** (1.45 g, 86%) as an oil: ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.33–7.23 (m, 5H), 7.02 (s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.89 (s, 1H), 4.72 (s, 2H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.13–4.06 (m, 1H), 3.71 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.57 (dd, *J* = 10.5, 3.4 Hz, 1H), 3.33 (s, 3H), 2.24–2.19 (m, 2H), 2.19–2.10 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.3, 142.3, 137.5, 135.9, 130.1, 128.4, 127.8, 127.1, 116.1,

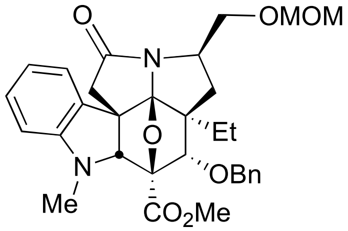
115.8, 97.2, 73.4, 69.4, 55.5, 49.1, 33.0, 19.9, 12.4; IR (film) ν_{max} 2930, 1717, 1543, 1478, 1368, 1285, 1141, 1104, 1033, 912, 828, 734 cm^{-1}; HRESI–TOF MS *m/z* 374.2090 ($C_{20}H_{27}N_3O_4$ + H^+ requires 374.2074). $[\alpha]_D^{26}$ +2.2 (*c* 1.1, $CHCl_3$).



Compound 11. A solution of **10** (718 mg, 1.93 mmol) in THF (9.6 mL) was treated with methyl oxalylhydrazide (250 mg, 2.12 mmol) and AcOH (110 μL, 1.93 mmol) at room temperature. After being stirred at room temperature for 12 h, the reaction mixture was concentrated under reduced pressure. Flash chromatography (SiO_2, 2% MeOH–$CHCl_3$) provided **11** (631 mg, 78%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.47–9.19 (br, 1H), 8.04 (br, 1H), 7.34–7.15 (m, 5H), 5.84 (s, 1H), 5.68–5.55 (br, 1H), 4.73 (d, *J* = 12.6 Hz, 1H), 4.68 (d, *J* = 12.6 Hz, 1H), 4.52 (d, *J* = 6.6 Hz, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.46 (m, 2H), 3.26 (s, 3H), 2.09 (q, *J* = 7.2 Hz, 2H), 2.09 (m, 1H), 2.01 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 156.2, 153.5, 142.2, 137.8, 128.4, 127.7, 127.2, 116.6, 96.8, 73.4, 69.5, 55.3, 53.6, 48.4, 33.5, 20.0, 12.5; IR (film) ν_{max} 3324, 2958, 1722, 1670, 1549, 1235, 1146, 1039, 916, 738, 699 cm^{-1}; HRESI–TOF MS *m/z* 446.1889 ($C_{20}H_{29}N_3O_7$ + Na^+ requires 446.1898). $[\alpha]_D^{26}$ +1.2 (*c* 0.81, $CHCl_3$).

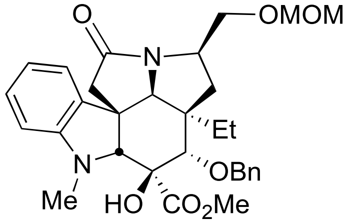


Compound 12. TsCl (1.05 g, 5.53 mmol) and Et_3N (1.75 mL, 12.6 mmol) were added to a solution of **11** (2.13 g, 5.03 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h before being quenched with the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 60–67% EtOAc–hexanes gradient) provided **12** (1.92 g, 94%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 5.90 (s, 1H), 5.72 (d, *J* = 8.3 Hz, 1H), 4.72 (d, *J* = 12.6 Hz, 1H), 4.69 (d, *J* = 12.6 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 1H), 4.52 (d, *J* = 6.6 Hz, 1H), 3.95 (s, 3H), 3.93 (m, 1H), 3.62 (dd, *J* = 3.6, 10.2 Hz, 1H), 3.58 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.28 (s, 3H), 2.22 (m, 2H), 2.12 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 154.8, 150.8, 142.7, 137.6, 128.4, 127.8, 127.2, 115.8, 96.7, 73.4, 68.3, 55.4, 53.2, 51.9, 33.4, 19.9, 12.4; IR (film) ν_{max} 3289, 2957, 1741, 1617, 1441, 1150, 1038, 737 cm^{-1}; HRESI–TOF MS *m/z* 406.1965 ($C_{20}H_{27}N_3O_6$ + H^+ requires 406.1973). $[\alpha]_D^{26}$ –17 (*c* 0.81, $CHCl_3$).



Compound 14. Method A: A solution of **13** (10.0 mg, 0.0173 mmol) in xylenes (17.3 mL) was purged with Ar for 0.5 h, and warmed at 150 °C for 10 h. The reaction mixture was cooled, and concentrated under reduced pressure. PTLC (SiO_2, 3% Et_3N–40% EtOAc–hexanes) provided **14** (6.8 mg, 72%) as a white solid.

Method B: A solution of **13** (10.0 mg, 0.0173 mmol) in xylenes (17.3 mL) was purged with Ar for 0.5 h, and warmed at 180 °C for 10 h. The reaction mixture was cooled, and concentrated under reduced pressure. PTLC (SiO_2, 3% Et_3N–40% EtOAc–hexanes) provided **14** (6.7 mg, 70%): ^{1}H NMR (400 MHz, C_6D_6) δ 7.22–7.13 (m, 5H), 7.12–7.07 (m, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.55 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.14 (d, *J* = 7.9 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.46 (s, 2H), 4.42 (s, 1H), 4.35 (dd, *J* = 9.6, 3.8 Hz, 1H), 4.23 (s, 1H), 4.22 (d, *J* = 11.7 Hz, 1H), 4.06–3.97 (m, 1H), 3.82 (dd, *J* = 9.6, 8.0 Hz, 1H), 3.31 (s, 3H), 3.26 (d, *J* = 16.2 Hz, 1H), 3.15 (s, 3H), 2.68 (s, 1H), 2.67 (d, *J* = 16.2 Hz, 1H), 2.43–2.38 (m, 2H), 1.05–0.96 (m, 1H), 0.79–0.69 (m, 1H), 0.51 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 171.5, 170.4, 152.8, 138.5, 129.8, 128.4, 128.3, 127.9, 127.2, 123.9, 118.2, 116.5, 105.7, 97.0, 89.6, 86.6, 81.9, 73.8, 68.6, 56.4, 56.0, 55.0, 52.5, 52.0, 50.6, 44.1, 33.3, 20.8, 10.0; HRESI–TOF MS *m/z* 549.2592 ($C_{31}H_{36}N_2O_7 + H^+$ requires 549.2595). $[\alpha]_D^{23}$ +56 (*c* 0.52, $CHCl_3$).

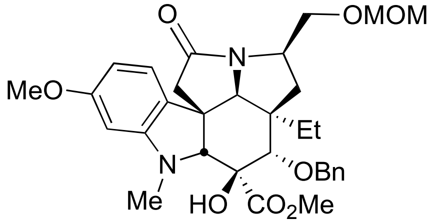


Compound 15. From **13**: A solution of **13** (225 mg, 0.390 mmol) in xylenes (260 mL) was purged with Ar for 0.5 h, and warmed at 150 °C for 10 h. The reaction mixture was cooled, and concentrated under reduced pressure. The resulting crude product in MeOH (10 mL) was treated with $NaCNBH_3$ (165 mg, 0.779 mmol) and AcOH (650 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and then at room temperature for 1 h before being quenched with the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 33% EtOAc–hexanes) provided **15** (122 mg, 57%) as a white foam.

Alternatively, a solution of **13** (437 mg, 0.758 mmol) in xylenes (486 mL) was purged with Ar for 0.5 h, and warmed at 180 °C for 10 h. The reaction mixture was cooled, and concentrated under reduced pressure. The resulting crude product in MeOH (20 mL) was treated with $NaCNBH_3$ (330 mg, 1.56 mmol) and AcOH (1.3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and then at room temperature for 1 h before being quenched with the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 33% EtOAc–hexanes) provided **15** (277 mg, 67%).

Additionally, a solution of **13** (57.7 mg, 0.100 mmol) in xylenes (100 mL) was purged with Ar for 0.5 h, and warmed at 140 °C for 8 h and at 175 °C for 8 h. The reaction mixture was cooled, and concentrated under reduced pressure. The resulting crude product in *i*-PrOH (2 mL) was treated with NaCNBH$_3$ (12.6 mg, 0.200 mmol) and AcOH (0.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and then at room temperature for 1 h before being quenched with the addition of saturated aqueous NaHCO$_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous NaHCO$_3$ and saturated aqueous NaCl, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Flash chromatography (SiO$_2$, 50% EtOAc–hexanes) provided **15** (38.4 mg, 70%).

From **14**: AcOH (1.2 mL) was added to a solution of **14** (129 mg, 0.235 mmol) and NaBH$_3$CN (29.5 mg, 0.469 mmol) in *i*-PrOH (4.7 mL) at 0 °C. After being stirred at room temperature for 0.5 h, the reaction mixture was quenched by the addition of saturated aqueous NaHCO$_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous NaHCO$_3$ and saturated aqueous NaCl, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Flash chromatography (SiO$_2$, 50% EtOAc–hexanes) provided **15** (121 mg, 94%) as a white foam: ^{1}H NMR (600 MHz, C$_6$D$_6$) δ 7.34–7.29 (m, 3H), 7.28–7.23 (m, 2H), 7.05 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.64 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.24 (d, *J* = 7.8 Hz, 1H), 5.06 (d, *J* = 11.9 Hz, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.75 (d, *J* = 6.4 Hz, 1H), 4.72 (d, *J* = 6.4 Hz, 1H), 4.54 (s, 1H), 4.35 (dd, *J* = 10.1, 10.2 Hz, 1H), 4.33 (s, 1H), 4.09 (s, 1H), 3.93 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.86 (br, 1H), 3.74 (s, 1H), 3.38 (s, 3H), 3.12 (s, 3H), 2.95 (s, 3H), 2.79 (d, *J* = 16.8 Hz, 1H), 2.60 (d, *J* = 16.8 Hz, 1H), 2.48–2.35 (m, 2H), 1.70–1.61 (m, 1H), 1.61–1.50 (m, 1H), 0.90 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, C$_6$D$_6$) δ 172.8, 168.7, 150.8, 139.1, 132.1, 128.3, 128.1, 127.3, 126.8, 119.8, 116.8, 104.6, 96.8, 84.8, 82.5, 77.6, 76.7, 67.9, 65.9, 55.6, 54.6, 51.8, 51.6, 49.3, 45.3, 43.1, 33.6, 23.4, 9.9; HRESI–TOF MS *m/z* 551.2749 (C$_{31}$H$_{36}$N$_2$O$_7$ + H$^+$ requires 551.2752). $[\alpha]_D^{23}$ −103 (*c* 0.39, CHCl$_3$). A single crystal X-ray structure determination confirmed the structure and stereochemistry of **15** (CCDC 758511).

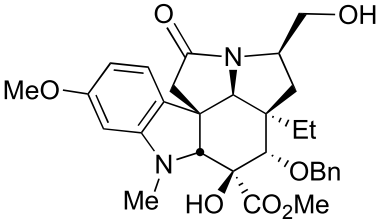


Compound 18. A solution of **16** (12.1 mg, 0.020 mmol) in toluene (20 mL) was purged with Ar for 0.5 h, and warmed at 150 °C for 10 h. The reaction mixture was cooled, and concentrated under reduced pressure. Typically crude **17** was subjected reductive oxido bridge cleavage prior to purification. However and in initial studies, a sample of pure **17** was isolated by PTLC (SiO$_2$, 0.3% Et$_3$N–33% EtOAc–hexanes) and characterized: ^{1}H NMR (600 MHz, C$_6$D$_6$) δ 7.26–7.10 (m, 4H), 7.07 (t, *J* = 6.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.14 (d, *J* = 8.1 Hz, 1H), 5.93 (s, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.46 (s, 2H), 4.44 (s, 1H), 4.38 (dd, *J* = 9.5, 3.6 Hz, 1H), 4.24 (s, 1H), 4.23 (d, *J* = 11.8 Hz, 1H), 4.07–4.00 (m, 1H), 3.83 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.38 (s, 3H), 3.30 (s, 3H), 3.29 (d, *J* = 16.2 Hz, 1H), 3.14 (s, 3H), 2.70 (d, *J* = 16.2 Hz, 1H), 2.65 (s, 3H), 2.46–2.38 (m, 2H), 1.13 (dd, *J* = 14.4, 7.3 Hz, 1H), 0.86 (dd, *J* = 14.4, 7.3 Hz, 1H), 0.55 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, C$_6$D$_6$) δ 172.1, 171.1, 163.2, 154.7, 139.2, 129.1, 129.0, 127.8, 124.8, 120.3, 118.9, 101.8, 97.6, 93.3, 90.2, 87.2, 83.0, 74.5, 69.2, 56.7, 56.5, 55.7, 55.4, 53.1, 52.6, 51.2, 44.8, 33.8, 21.6, 10.7; HRESI–TOF MS *m/z* 579.2690 (C$_{32}$H$_{38}$N$_2$O$_8$ + H$^+$ requires 579.2701). $[\alpha]_D^{23}$ +52 (*c* 0.081, CHCl$_3$).

The resulting crude product containing **17** from the reaction above was placed in *i*-PrOH (200 μL) and toluene (50 μL) was treated with NaCNBH$_3$ (2.5 mg, 0.040 mmol) and AcOH (32 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and then at room temperature for 1 h before being quenched with the addition of saturated aqueous NaHCO$_3$, and extracted with EtOAc. The extract was washed with saturated aqueous NaHCO$_3$ and saturated aqueous NaCl, dried over Na$_2$SO$_4$, and was concentrated under reduced pressure. Flash chromatography (SiO$_2$, 50% EtOAc–hexanes) provided **18** (5.9 mg, 51%) as a white foam.

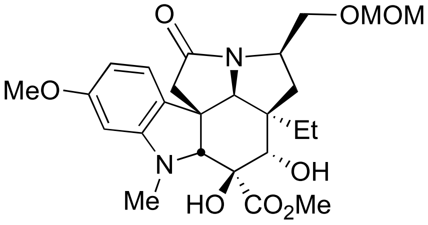
Alternatively, a solution of **16** (60.3 mg, 0.0995 mmol) in xylenes (100 mL) was purged with Ar for 0.5 h, and warmed at 130 °C for 10 h and at 175 °C for 8 h. The reaction mixture was cooled, and concentrated under reduced pressure. The resulting crude product containing **17** from the reaction above was placed in *i*-PrOH (2 mL) and treated with $NaBH_3CN$ (12.5 mg, 0.20 mmol) and AcOH (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h before being quenched with the addition of saturated aqueous $NaHCO_3$, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and was concentrated under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) provided **18** (31.8 mg, 55%).

Similarly, a solution of **16** (303 mg, 0.500 mmol) in xylenes (500 mL) was purged with Ar for 0.5 h, and warmed at 130 °C for 10 h and at 175 °C for 8 h. The reaction mixture was cooled, and concentrated under reduced pressure. The resulting crude product containing **17** from the reaction above was placed in *i*-PrOH (10 mL) was treated with $NaBH_3CN$ (62.8 mg, 1.0 mmol) and AcOH (2.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h before being quenched with the addition of saturated aqueous $NaHCO_3$, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and was concentrated under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) provided **18** (136 mg, 47%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.28–7.23 (m, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.14 (dd, *J* = 1.8, 7.8 Hz, 1H), 5.83 (d, *J* = 2.4 Hz, 1H), 5.05 (d, *J* = 11.9 Hz, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.75 (d, *J* = 6.4 Hz, 1H), 4.72 (d, *J* = 6.4 Hz, 1H), 4.48 (s, 1H), 4.34 (dd, *J* = 10.1, 5.1 Hz, 1H), 4.31 (s, 1H), 4.10 (s, 1H), 3.93 (dd, *J* = 10.1, 2.8 Hz, 1H), 3.87–3.82 (m, 1H), 3.75 (s, 3H), 3.37 (s, 3H), 3.21 (s, 3H), 2.92 (s, 3H), 2.76 (d, *J* = 16.8 Hz, 1H), 2.57 (dd, *J* = 16.8, 1.2 Hz, 1H), 2.44 (dd, *J* = 14.2, 4.0 Hz, 1H), 2.37 (dd, *J* = 14.2, 10.6 Hz, 1H), 1.72 (s, 1H), 1.66 (qd, *J* = 15.1, 7.6 Hz, 1H), 1.56 (qd, *J* = 15.1, 7.6 Hz, 1H), 0.90 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 168.8, 160.8, 152.2, 139.0, 128.2, 127.3, 126.8, 124.8, 120.0, 100.1, 96.8, 92.4, 84.8, 82.5, 77.6, 77.3, 68.0, 65.9, 55.6, 55.3, 54.8, 51.79, 51.76, 48.6, 45.2, 43.0, 33.3, 23.4, 9.9; IR (film) ν_{max} 2948, 2885, 1726, 1689, 1620, 1500, 1439, 1252, 1110, 1095, 1037 cm^{-1}; HRESI–TOF MS *m/z* 581.2855 ($C_{32}H_{40}N_2O_8 + H^+$ requires 581.2857). $[\alpha]_D^{26}$ –94 (*c* 0.98, $CHCl_3$).

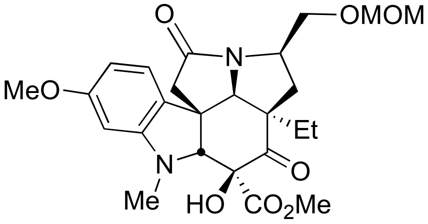


Compound S1. A solution of 12 N HCl (60 μL) was added to a solution of **18** (4.3 mg, 0.0074 mmol) in MeOH (165 μL) and H_2O (17.5 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h before being diluted with saturated aqueous NaCl at 0 °C, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 100% EtOAc) provided **S1** (2.6 mg, 66%) as a white solid. A sample of **S1** was recrystallized from EtOAc–hexanes: mp 170–174 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.2 Hz, 2H), 7.32–7.29 (m, 1H), 7.28 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.16 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.87 (d, *J* = 1.2 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 4.97 (d, *J* = 11.9 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.51 (s, 1H), 4.17 (s, 1H), 3.76 (s, 3H), 3.76 (m, 1H), 3.75–3.72 (m, 1H), 3.69 (m, 1H), 3.57 (s, 1H), 3.43 (m, 1H), 3.26 (s, 3H), 2.93 (s, 3H), 2.81 (d, *J* = 16.7 Hz, 1H), 2.67 (d, *J* = 16.7 Hz, 1H), 2.27 (dd, *J* = 14.4, 10.7 Hz, 1H), 1.67 (dd, *J* = 14.4, 4.7 Hz, 1H), 1.61 (m, 1H), 1.54 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 170.3, 161.0, 152.2, 138.0, 128.4, 127.90, 127.89, 124.0, 120.3, 100.5, 92.8, 84.9, 82.5, 77.4, 77.3, 68.9, 66.1, 56.7, 55.4, 54.4, 52.0, 49.6, 45.0, 42.4, 33.7, 23.3, 9.8; IR (film) ν_{max} 2950, 1729, 1621, 1501, 1453, 1255, 1096, 800 cm^{-1}; HRESI–TOF MS *m/z* 537.2585 ($C_{30}H_{36}N_2O_7 + H^+$ requires

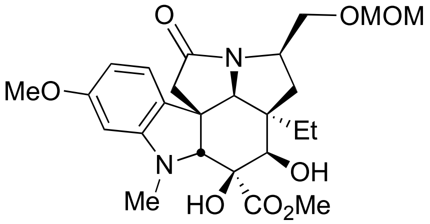
537.2595). $[\alpha]_D^{26}$ –126 (*c* 0.25, $CHCl_3$). A single crystal X-ray structure determination confirmed the structure and stereochemistry of **S1** (CCDC 758510).



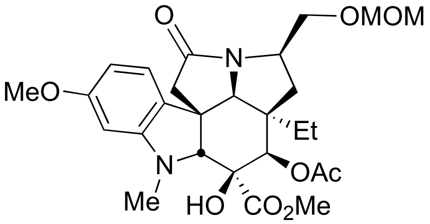
Compound 19. Compound **18** (179 mg, 0.308 mmol) in THF (6.2 mL) was stirred with $Pd(OH)_2$ (716 mg) under a balloon of H_2 for 10 min. The reaction mixture was filtered through Celite and concentrated. Flash chromatography (SiO_2, 75–100% EtOAc–hexanes gradient elution) provided **19** (138 mg, 91%) as an colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (t, *J* = 7.9 Hz, 1H), 6.26 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.96 (d, *J* = 2.0 Hz, 1H), 4.67 (s, 2H), 4.26 (dd, *J* = 9.7, 3.7 Hz, 1H), 4.19 (s, 1H), 4.13 (s, 1H), 4.01 (s, 1H), 4.01–3.97 (m, 1H), 3.75 (s, 3H), 3.75–3.71 (m, 1H), 3.59 (s, 3H), 3.58 (s, 1H), 3.45 (s, 1H), 3.38 (s, 3H), 2.82 (s, 3H) 2.82 (d, *J* = 16.2 Hz, 1H), 2.69 (d, *J* = 16.2 Hz, 1H), 2.47 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.25 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.60 (qd, *J* = 14.6, 7.3 Hz, 1H), 1.35 (qd, *J* = 14.6, 7.3 Hz, 1H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 168.9, 160.8, 152.7, 125.4, 121.1, 102.8, 96.8, 94.9, 78.9, 78.3, 73.9, 71.5, 66.6, 56.1, 55.4, 55.3, 53.1, 52.5, 49.3, 43.7, 42.7, 36.5, 28.1, 9.4; IR (film) ν_{max} 2950, 2886, 1728, 1620, 1502, 1440, 1251, 1095, 1039 cm^{-1}; HRESI–TOF MS *m/z* 491.2389 ($C_{25}H_{34}N_2O_8$ + H^+ requires 491.2388). $[\alpha]_D^{26}$ –21 (*c* 0.98, $CHCl_3$).



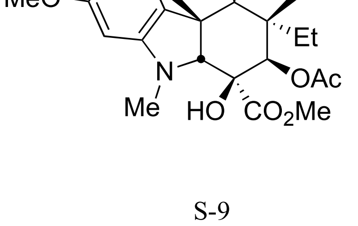
Compound 20. Dess–Martin periodinane (74.7 mg, 0.176 mmol) in CH_2Cl_2 (2.0 mL) was added to a solution of **19** (72.0 mg, 0.147 mmol) in CH_2Cl_2 (940 μL) and pyridine (734 μL) at 0 °C under Ar. The reaction mixture was stirred for 3 h before being quenched with the addition of saturated aqueous $Na_2S_2O_3$ at 0 °C. The organic layer was extracted with EtOAc, washed with saturated aqueous $NaHCO_3$, 1 N HCl and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 90% EtOAc–hexanes) provided **20** (54.3 mg, 76%) as a white foam and recovered starting material **19** (8.8 mg, 12%). For **20**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.1 Hz, 1H), 6.24 (dd, *J* = 8.1, 2.2 Hz, 1H), 5.96 (d, *J* = 2.2 Hz, 1H), 4.59 (d, *J* = 6.3 Hz, 1H), 4.57 (d, *J* = 6.3 Hz, 1H), 4.53 (s, 1H), 4.30 (s, 1H), 3.99 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.85 (s, 1H), 3.84 (s, 1H), 3.77 (s, 3H), 3.61 (dd, *J* = 9.6, 2.1 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.99 (dd, *J* = 13.8, 1.5 Hz, 1H), 2.89 (s, 3H), 2.91–2.78 (m, 2H), 2.27 (dd, *J* = 13.8, 9.9 Hz, 1H), 2.04 (qd, *J* = 14.9, 7.5 Hz, 1H), 1.47 (qd, *J* = 14.9, 7.5 Hz, 1H), 0.70 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.6, 169.6, 169.3, 161.1, 152.4, 123.7, 120.7, 101.8, 96.4, 93.9, 81.1, 79.0, 72.8, 65.2, 55.5, 55.4, 53.1, 53.0, 52.3, 52.1, 48.0, 43.7, 34.4, 31.6, 9.0; IR (film) ν_{max} 2945, 1748, 1689, 1620, 1501, 1437, 1250, 1038 cm^{-1}; HRESI–TOF MS *m/z* 489.2231 ($C_{25}H_{32}N_2O_8$ + H^+ requires 489.2231). $[\alpha]_D^{25}$ –92 (*c* 0.78, $CHCl_3$).



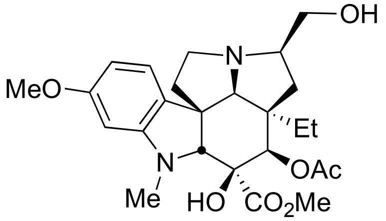
Compound 21. A suspension of LiAlH(O*t*-Bu)$_3$ (56.5 mg, 0.222 mmol) in THF (0.80 mL) was added to a solution of **20** (54.3 mg, 0.111 mmol) in THF (0.83 mL) at 0 °C under Ar. The reaction mixture was stirred at 0 °C for 10 h before being quenched with the addition of 1 N HCl followed by the extraction with EtOAc. The extract was washed with saturated aqueous NaCl, dried over Na$_2$SO$_4$, and concentrated in vacuo. PTLC (SiO$_2$, 100% EtOAc) provided **21** (47.6 mg, 87%) as a white foam and **19** (1.6 mg, 3%) as a white foam. For **21**: ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.99 (d, *J* = 8.3 Hz, 1H), 6.37 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 4.68 (s, 2H), 4.45–4.41 (m, 1H), 4.28 (d, *J* = 5.8 Hz, 1H), 4.02–3.98 (m, 1H), 3.90 (s, 3H), 3.86 (s, 1H), 3.77 (s, 3H), 3.64 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.46 (s, 1H), 3.38 (s, 3H), 3.16 (dd, *J* = 17.1, 1.4 Hz, 1H), 2.82 (dd, *J* = 13.5, 9.4 Hz, 1H), 2.71 (d, *J* = 17.2 Hz, 1H), 2.63 (s, 3H), 1.74 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.45 (dd, *J* = 13.9, 7.4 Hz, 1H), 1.38–1.32 (m, 1H), 0.57 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 175.1, 161.1, 153.8, 137.9, 129.0, 128.2, 125.3, 122.8, 104.9, 96.9, 96.4, 83.4, 79.6, 68.5, 55.6, 55.5, 55.4, 54.7, 53.1, 48.2, 44.3, 39.0, 34.1, 21.5, 8.4; IR (neat) ν_{max} 3426, 2957, 1726, 1672, 1616, 1502, 1461, 1230 cm^{-1}; HRESI–TOF MS *m/z* 491.2397 ($C_{25}H_{34}N_2O_8 + H^+$ requires 491.2388). $[\alpha]_D^{23}$ –5.4 (*c* 0.62, CHCl$_3$).



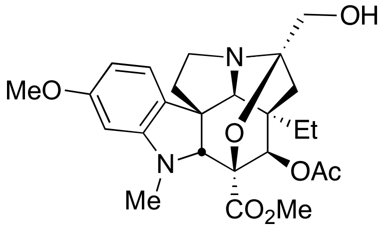
Compound 22. Acetic anhydride (516 μL) was added to a solution of alcohol **21** (25.3 mg, 0.0516 mmol) and DMAP (0.63 mg, 0.00516 mmol) in pyridine (516 μL) under Ar. The reaction mixture was stirred at room temperature for 1 h, and diluted with EtOAc followed by the addition of saturated aqueous NH$_4$Cl at 0 °C. The mixture was extracted with EtOAc, washed sequentially with water, saturated aqueous NaHCO$_3$ and saturated aqueous NaCl, dried over MgSO$_4$, and concentrated under reduced pressure. Flash chromatography (SiO$_2$, 100% EtOAc) provided **22** (26.2 mg, 95%) as a pale yellow oil: ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.01 (d, *J* = 8.3 Hz, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 6.12 (s, 1H), 5.71 (s, 1H), 4.73–4.65 (m, 3H), 3.88–3.81 (m, 5H), 3.79 (s, 3H), 3.64–3.58 (m, 1H), 3.39 (s, 3H), 3.38 (s, 1H), 3.22 (d, *J* = 17.2 Hz, 1H), 2.89 (dd, *J* = 12.7, 10.9 Hz, 1H), 2.72 (d, *J* = 17.2 Hz, 1H), 2.61 (s, 3H), 2.04 (s, 3H), 1.59 (dd, *J* = 13.0, 7.0 Hz, 1H), 1.35 (dd, *J* = 14.2, 7.2 Hz, 1H), 1.24 (dd, *J* = 14.3, 7.3 Hz, 1H), 0.44 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 174.6, 169.8, 169.7, 161.1, 154.0, 125.1, 122.8, 105.5, 96.9, 96.5, 84.8, 78.8, 77.3, 69.3, 67.6, 55.8, 55.38, 55.35, 55.0, 53.2, 48.8, 45.2, 43.0, 39.8, 32.9, 20.8, 7.7; IR (neat) ν_{max} 3367, 2954, 1743, 1685, 1616, 1108 cm^{-1}; HRESI–TOF MS *m/z* 533.2489 ($C_{27}H_{36}N_2O_9 + H^+$ requires 533.2493). $[\alpha]_D^{23}$ –22 (*c* 2.2, CHCl$_3$).



Compound 23. Methyl trifluoromethanesulfonate (21.8 μL, 0.194 mmol) was added in portions to a solution of **22** (34.4 mg, 0.0645 mmol) and 2,6-di-*tert*-butylpyridine (22.9 μL) in CH_2Cl_2 (645 μL). The reaction mixture was stirred at room temperature for 2 h, and concentrated under positive flow of N_2. The residue was dissolved in MeOH (645 μL), and treated with $NaBH_4$ (7.32 mg, 0.194 mmol). The reaction mixture was stirred at room temperature for 5 min, diluted with EtOAc, and treated sequentially with saturated aqueous NH_4Cl and NH_4OH. The mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 1% Et_3N–10% MeOH–EtOAc) provided **23** (29.5 mg, 96%) as a pale yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 6.64 (d, *J* = 8.1 Hz, 1H), 6.43 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.16 (s, 1H), 6.01 (d, *J* = 1.9 Hz, 1H), 4.38 (q, *J* = 6.4 Hz, 2H), 3.79 (s, 1H), 3.45–3.42 (m, 2H), 3.40 (s, 3H), 3.36 (s, 3H), 3.15 (s, 3H), 3.06 (t, *J* = 8.3 Hz, 1H), 3.00 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.54–2.48 (m, 2H), 2.42 (s, 3H), 2.34 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.15 (dd, *J* = 17.8, 8.8 Hz, 1H), 1.83 (s, 3H), 1.61 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.43 (dd, *J* = 13.2, 6.1 Hz, 1H), 1.20 (dd, *J* = 14.4, 7.2 Hz, 1H), 0.58 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 169.9, 161.6, 154.9, 126.4, 123.1, 105.6, 96.6, 96.1, 85.7, 84.1, 80.8, 70.8, 69.3, 57.8, 55.0, 54.9, 51.8, 51.3, 48.7, 46.5, 43.1, 42.8, 39.1, 33.6, 20.9, 8.4; IR (neat) ν_{max} 2947, 1743, 1614, 1503, 1461, 1237 cm^{-1}; HRESI–TOF MS *m/z* 519.2714 ($C_{27}H_{38}N_2O_8 + H^+$ requires 519.2701). $[\alpha]_D^{23}$ –2.8 (*c* 0.31, $CHCl_3$).

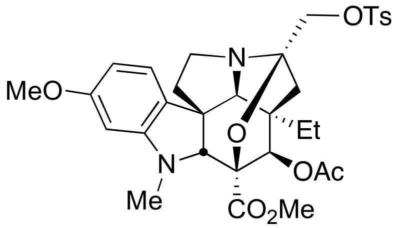


Compound 24. A solution of 12 N HCl (285 μL) was added to a solution of **23** (22.2 mg, 0.0428 mg) in MeOH (855 μL). The reaction mixture was stirred at room temperature for 16 h, diluted with EtOAc, and quenched with the addition of 28–30% aqueous NH_4OH at 0 °C. The mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 1% Et_3N–10% MeOH–EtOAc) provided **24** (18 mg, 89%) as a colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (d, *J* = 7.8 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 6.08 (s, 1H), 5.68 (s, 1H), 3.80 (s, 3H), 3.79–3.78 (m, 1H), 3.77 (s, 3H), 3.73–3.67 (m, 2H), 3.40–3.32 (m, 1H), 2.85–2.79 (m, 1H), 2.70–2.65 (m, 2H), 2.63 (s, 1H), 2.06 (s, 1H), 2.05 (s, 3H), 1.61 (dd, *J* = 13.3, 6.1 Hz, 1H), 1.38–1.30 (m, 1H), 1.29–1.23 (m, 2H), 0.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 161.0, 154.2, 125.3, 122.9, 105.0, 96.0, 85.1, 82.8, 80.4, 70.7, 63.6, 59.9, 55.4, 52.4, 51.2, 48.8, 46.0, 42.79, 42.78, 41.0, 39.4, 32.8, 29.7, 21.1, 7.9; IR (neat) ν_{max} 3425, 2925, 1742, 1615, 1502, 1458, 1232 cm^{-1}; HRESI–TOF MS *m/z* 475.2444 ($C_{25}H_{34}N_2O_7 + H^+$ requires 475.2439). $[\alpha]_D^{23}$ –9.2 (*c* 0.1, CH_2Cl_2).

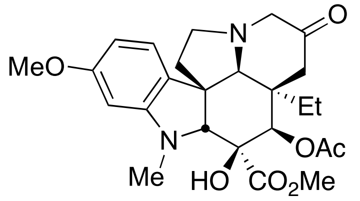


Compound 25. A solution of the complex SO_3-pyridine (15.1 mg, 0.0947 mmol) in anhydrous DMSO (105 μL) was added to a solution of **24** (15.0 mg, 0.0316 mmol) in CH_2Cl_2 (527 μL) and Et_3N (13.2 μL, 0.0947 mmol) under Ar at room temperature. The reaction mixture was stirred at room temperature for 30 min before the addition of H_2O. The mixture was extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was removed under reduced pressure. PTLC (SiO_2, 1% Et_3N–EtOAc) provided **25** (12.7 mg, 85%)

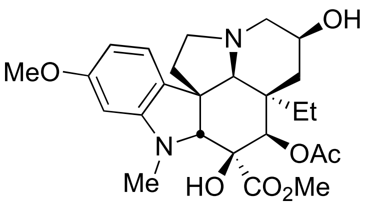
as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.1 Hz, 1H), 6.17 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.03 (d, *J* = 2.4, 1H), 5.30 (s, 1H), 3.69 (s, 3H), 3.68 (s, 3H) 3.61 (d, *J* = 11.4 Hz, 1H), 3.57 (s, 1H), 3.46 (d, *J* = 11.4 Hz, 1H), 3.21 (s, 1H), 3.05 (dd, *J* = 10.6, 8.3 Hz, 1H), 2.81 (dd, *J* = 10.6, 8.3 Hz, 1H), 2.60 (s, 3H), 2.23 (d, *J* = 11.5 Hz, 1H), 2.13–2.06 (m, 1H), 1.92 (s, 3H), 1.90–1.86 (m, 1H), 1.77 (d, *J* = 11.6 Hz, 1H), 1.23–1.12 (m, 2H), 0.55 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.6, 161.1, 154.3, 128.3, 122.6, 120.8, 104.0, 96.1, 96.0, 82.5, 79.8, 73.8, 68.0, 63.4, 55.3, 53.7, 52.3, 47.3, 43.6, 40.1, 38.5, 27.6, 21.1, 8.4; IR (neat) ν_{max} 2924, 1745, 1504, 1235 cm^{-1}; HRESI–TOF MS *m/z* 473.2287 ($C_{25}H_{32}N_2O_7 + H^+$ requires 473.2282). $[\alpha]_D^{23}$ –6.6 (*c* 0.15, $CHCl_3$).



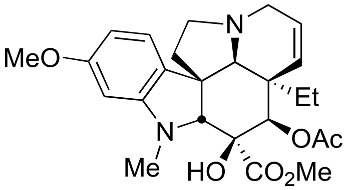
Compound 26. TsCl (3.63 mg, 0.0190 mmol) was added to a solution of **25** (3.0 mg, 0.00634 mmol), DMAP (0.0773 mg, 0.634 μmol) and Et_3N (4.41 μL, 0.0317 mmol) in CH_2Cl_2 (200 μL). The reaction mixture was stirred at room temperature for 16 h, and concentrated under reduced pressure. PTLC (SiO_2, 1% Et_3N–EtOAc) provided **26** (3.7 mg, 93%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.16 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.00 (d, *J* = 2.2 Hz, 1H), 5.26 (s, 1H), 3.96 (d, *J* = 10.3 Hz, 1H), 3.87 (d, *J* = 10.3 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.54 (s, 1H), 3.16 (s, 1H), 2.92–2.86 (m, 1H), 2.73–2.69 (m, 1H), 2.57 (s, 3H), 2.35 (s, 3H), 2.12 (d, *J* = 11.4 Hz, 1H), 2.09–2.03 (m, 1H), 1.91 (s, 3H), 1.82 (dd, *J* = 12.5, 6.7 Hz, 1H), 1.77 (d, *J* = 11.4 Hz, 1H), 1.15 (td, *J* = 14.6, 7.1 Hz, 2H), 0.50 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.2, 161.1, 154.3, 144.9, 132.7, 129.8, 128.3, 128.1, 122.7, 104.1, 96.1, 93.6, 82.6, 79.6, 73.5, 68.6, 67.6, 55.3, 53.8, 52.3, 47.2, 43.4, 40.1, 39.9, 38.5, 27.6, 21.7, 21.1, 8.5; IR (neat) ν_{max} 2924, 1745, 1615, 1502, 1364, 1233, 1176 cm^{-1}; HRESI–TOF MS *m/z* 627.2364 ($C_{32}H_{38}N_2O_9S + H^+$ requires 627.2371). $[\alpha]_D^{23}$ –8.1 (*c* 0.12, $CHCl_3$).



Compound 27. A solution of 2 N aqueous sodium acetate (360 μL) was added to a solution of **26** (6.8 mg, 0.0108 mmol) in dioxane (1.1 mL). The reaction mixture was stirred at 70 °C for 48 h, cooled to room temperature, and diluted with EtOAc followed by the addition of H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure. PTLC (1% Et_3N–EtOAc) provided **27** (3.1 mg, 61%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.2 Hz, 1H), 6.20 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.98 (d, *J* = 2.2 Hz, 1H), 5.28 (s, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.63 (s, 1H), 3.57 (d, *J* = 17.6 Hz, 1H), 3.38–3.34 (m, 1H), 3.04 (d, *J* = 16.1 Hz, 1H), 2.80 (d, *J* = 17.6 Hz, 1H), 2.75 (s, 1H), 2.61 (s, 3H), 2.49–2.43 (m, 1H), 2.25–2.21 (m, 2H), 1.97 (d, *J* = 16.1 Hz, 1H), 1.92 (s, 3H), 1.33 (dd, *J* = 14.5, 7.4 Hz, 1H), 1.07 (dd, *J* = 14.5, 7.4 Hz, 1H), 0.51 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8, 171.2, 170.1, 161.4, 153.4, 123.6, 122.7, 104.7, 95.8, 82.4, 80.0, 73.8, 69.8, 63.2, 55.4, 52.5, 52.4, 51.5, 45.6, 45.3, 41.2, 38.0, 32.9, 20.9, 7.4; IR (neat) ν_{max} 2922, 2852, 1741, 1614, 1502, 1460, 1227 cm^{-1}; HRESI–TOF MS *m/z* 473.2289 ($C_{25}H_{32}N_2O_7 + H^+$ requires 473.2282). $[\alpha]_D^{23}$ –22 (*c* 0.14, $CHCl_3$).



Compound 28. A solution of 1 M L-selectride in THF (6.34 µL, 6.34 µmol) was added to a solution of **27** (2.4 mg, 4.23 µmol) in anhydrous THF (211 µL) under Ar at –78 °C. The reaction mixture was stirred for 30 min at –78 °C before the reaction was quenched with the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, washed with saturated aqueous NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure. PTLC (SiO_2, 5% Et_3N–EtOAc) provided **28** as a colorless oil (2.2 mg, 91%): ^1H NMR (500 MHz, C_6D_6) δ 6.58 (d, *J* = 8.1 Hz, 1H), 6.35 (dd, *J* = 2.2, 8.1 Hz, 1H), 6.03 (d, *J* = 2.2 Hz, 1H), 5.98 (s, 1H), 4.32–4.21 (m, 1H), 3.99 (s, 1H), 3.79–3.73 (m, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 2.99 (d, *J* = 11.7 Hz, 1H), 2.67 (t, *J* = 8.6 Hz, 1H), 2.35 (s, 3H), 2.20 (ddd, *J* = 9.2, 10.3, 13.6 Hz, 1H), 2.00–1.94 (m, 1H), 1.89 (s, 3H), 1.88–1.76 (m, 3H), 1.68 (d, *J* = 16.1 Hz, 1H), 1.61 (dd, *J* = 2.2, 11.4 Hz, 1H), 1.38–1.29 (m, 1H), 1.25 (dq, *J* = 7.2, 14.7 Hz, 1H), 1.14 (dd, *J* = 4.2, 15.4 Hz, 1H), 0.49 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.8, 169.4, 162.1, 155.0, 127.4, 123.7, 105.6, 96.7, 84.0, 79.8, 76.5, 73.6, 65.1, 59.8, 55.3, 53.7, 53.2, 51.9, 44.1, 41.1, 37.9, 35.8, 34.6, 21.1, 8.5; IR (neat) ν_{max} 3549, 2952, 1746, 1615, 1504, 1435, 1225 cm^{-1}; HRMALDIFTMS (DHB) *m/z* 475.2443 ($C_{25}H_{35}N_2O_7 + H^+$ requires 475.2439). $[\alpha]_D^{23}$ +24 (*c* 0.71, $CHCl_3$).



Vindoline (1). DEAD (4.7 µL, 0.029 mmol) was added to a solution of **29** (4.6 mg, 0.0097 mmol) and Ph_3P (7.7 mg, 0.029 mmol) in anhydrous THF (100 µL) at 23 °C under Ar. The reaction mixture was stirred for 24 h at 23 °C in the dark before the solvent was removed under reduced pressure. PTLC (SiO_2, 75% EtOAc–hexanes) afforded vindoline (**1**) as a white amorphous solid (3.3 mg, 75%) identical in all respects with authentic material: ^1H NMR (500 MHz, C_6D_6) δ 8.52 (s, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.37 (dd, *J* = 2.2, 8.1 Hz, 1H), 6.05 (d, *J* = 2.2 Hz, 1H), 5.97 (s, 1H), 5.47 (ddd, *J* = 1.4, 4.7, 10.2 Hz, 1H), 5.27 (d, *J* = 10.2 Hz, 1H), 3.83 (s, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.94–2.88 (m, 1H), 2.86 (dt, *J* = 2.2, 9.2 Hz, 1H), 2.41 (s, 3H), 2.28–2.20 (m, 2H), 2.13 (dq, *J* = 7.3, 14.7 Hz, 1H), 2.02 (ddd, *J* = 2.2, 9.5, 13.5 Hz, 1H), 1.90 (s, 3H), 1.89–1.85 (m, 1H), 1.55 (dq, *J* = 7.3, 14.7 Hz, 1H), 0.47 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 172.5, 170.5, 131.3, 128.0–125.0 (3C, overlapped C_6D_6), 124.1, 123.1, 105.2, 96.2, 83.7, 79.4, 76.6, 68.7, 54.9, 53.2, 52.6, 51.6, 51.5, 44.0, 43.8, 37.6, 31.6, 20.9, 8.3; IR (neat) ν_{max} 2962, 1740, 1616, 1501, 1371, 1242, 1032, 735 cm^{-1}; HRMALDIFTMS (DHB) *m/z* 457.2337 ($C_{25}H_{33}N_2O_6 + H^+$ requires 457.2333). For synthetic natural vindoline (**1**): $[\alpha]_D^{20}$ –45 (*c* 0.14, MeOH); for authentic natural vindoline: $[\alpha]_D^{20}$ –48 (*c* 0.19, MeOH) and –19 (*c* 0.30, $CHCl_3$), lit $[\alpha]_D^{20}$ –18 (*c* 0.20, $CHCl_3$).