Total Synthesis of (–)- and *ent*-(+)-Vindoline

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N-Methyl-6-methoxytryptamine (**6**). This material was prepared as previously detailed^{S1} from 6-methoxyindole^{S2} ((COCl)₂; NH₄OH (92% for 2 steps); LiAlH₄ (67%)) or by a improved route^{S3} detailed below.

POCl₃ (3.3 mL, 35.9 mmol) was added dropwise to DMF (35 mL, 450 mmol) at 0 °C. A solution of 6-methoxy-1-methylindole^{S2} (5.25 g, 32.6 mmol) in DMF (2 mL) was then added slowly with stirring at 0 °C. The mixture was kept at 35 °C for 45 min and then poured onto a crushed ice. The clear solution was treated with aqueous 1 N NaOH solution (150 mL, 150 mmol) at 20–30 °C. The last quarter was added all at once and the solution was quickly boiled for 10 min. The cooled mixture was diluted with CH₂Cl₂ (100 mL) and the organic layer was washed with water (4 x 50 mL), dried over MgSO₄ and evaporated under reduced pressure to afford 6.10 g (99%) of 6-methoxy-1-methylindole-3-carboxaldehyde as a light yellow oil: mp 124–125 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.91 (s, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 7.59 (s, 1H), 7.04 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H).

A solution of 6-methoxy-1-methylindole-3-carboxaldehyde (3.79 g, 20.0 mmol) in nitromethane (30 mL) was treated with ammonium acetate (1.70 g, 22.0 mmol). The mixture was warmed at reflux under Ar for 1 h. The reaction mixture was cooled and concentrated under reduced pressure. The residue was diluted with CH₂Cl₂ (100 mL), washed with water (2 x 50 mL) and saturated aqueous NaCl. The organic phase was dried over MgSO₄ and concentrated under reduced pressure to give a red solid, which was recrystallized (EtOAc–hexanes) to afford 4.60 g (99%) of 6-methoxy-1-methyl-3-(2-nitroethenyl)indole as red needles: mp 138–139 °C; ¹H NMR (600 MHz, CDCl₃) δ 8.20 (d, *J* = 13.2 Hz, 1H), 7.74 (d, *J* = 13.6 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.44 (s, 1H), 6.99 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.8, 139.8, 136.5, 133.6, 131.9, 121.6, 119.6, 111.9, 108.5, 94.5, 55.9, 33.7; HRMS (MALDI–FTMS) calcd for (C₁₁H₁₁N₂O₂) [M+H]⁺ 203.0742; found 203.0742.

A suspension of LiAlH₄ (2.39 g, 62.8 mmol) in anhydrous THF (60 mL) was treated dropwise with a solution of the 3-(2-nitroethenyl)indole (2.43 g, 10.5 mmol) in THF (10 mL) at 0 °C. The resulting mixture was warmed at a reflux for 2 h. The excess hydride was destroyed by dropwise addition of saturated aqueous Na₂SO₄ and the resulting mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to afford 2.04 g (96%) of **6**^{S1} as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 8.5 Hz, 1H), 6.74–6.79 (m, 3H), 3.88 (s, 3H), 3.69 (s, 3H), 2.97–3.01 (m, 2H), 2.83–2.87 (m, 2H), 1.62 (br s, 2H).

A solution of *N*-methyl-6-methoxytryptamine (**6**, 504 mg, 2.47 mmol, 1.0 equiv) dissolved in absolute EtOH (12.3 mL) was treated with diphenyl carbonate (528 mg, 2.47 mmol, 1.0 equiv) and the resulting mixture was stirred overnight at 25 °C. Hydrazine monohydrate (0.48 mL, 9.87 mmol, 4.0 equiv) was added and the reaction mixture was warmed at reflux for 5 h (monitored by TLC). After cooling to 25 °C, the mixture was concentrated in vacuo and absorbed onto Celite. Flash chromatography (SiO₂, 50% EtOAc–hexanes, 5–10% MeOH–CH₂Cl₂ gradient elution) afforded **7** as a tan solid. This solid was dissolved in minimal CH₂Cl₂ and Et₂O was added until a free floating white solid precipitated with stirring to provide pure **7** (369 mg, 64%): ¹H NMR (600 MHz, CDCl₃) δ 7.48 (d, *J* = 8.6 Hz, 1H), 6.74–6.80 (m, 3H), 6.08 (br s, 1H), 5.77 (br s, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H); ¹³C NMR (125 MHz, C₆D₆) δ 163.1, 160.1, 156.4, 137.7, 125.5, 122.4, 119.6, 112.0, 108.7, 92.8, 55.7, 40.2, 32.6, 26.0; IR (film) 3350, 2931, 1619, 1534, 1472, 1431, 1378, 1325, 1244, 1220, 1161, 1032, 791 cm⁻¹; HRMS (MALDI–FTMS) calcd for (C₁₃H₁₈N₄O₂) [M+H]⁺ 263.1502; found 263.1493.

N-Methyl-6-methoxytryptamine (**6**, 6.91 g, 34.2 mmol) in anhydrous CH₂Cl₂ (40 mL) was added dropwise to a solution of 1,1-carbonyldiimidazole (CDI, 11.08 g, 68.3 mmol) in anhydrous THF (40 mL) under Ar at 0 °C. The reaction mixture was allowed to warm to 25 °C overnight. Upon completion of the reaction as monitored by TLC, the reaction mixture was concentrated onto Celite in vacuo. Flash chromatography (SiO₂, 5% MeOH–CHCl₃) afforded **8** as a pale yellow foam (9.17 g, 90%): ¹H NMR (500 MHz, CDCl₃) δ 7.94 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.22 (s, 1H), 6.98 (s, 1H), 6.75–6.79 (m, 3H), 6.32 (br s, 1H), 3.87 (s, 3H), 3.66–3.72 (m, 5H), 3.03 (t, *J* = 6.6 Hz, 2H); ¹³C NMR (125 MHz, C₆D₆) δ 156.6, 148.8, 137.9, 135.7, 130.2, 125.8, 122.0, 119.2, 115.9, 110.8, 109.2, 93.0, 55.7, 41.6, 32.7, 25.0.

Conversion of 7 to 9. A solution of **7** (119 mg, 0.51 mmol, 1.0 equiv) and oxalic acid mono-methyl ester (80 mg, 0.77 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (3 mL) cooled to 0 °C was treated with EDCI (147 mg, 0.77 mmol, 1.5 equiv). After 5 min, DMAP (94 mg, 0.77 mmol, 1.5 equiv) was added and the resulting reaction mixture was stirred at 25 °C overnight. The mixture was concentrated in vacuo and absorbed onto Celite. Flash chromatography (SiO_2 , 1–5% $\text{MeOH}-\text{CHCl}_3$) afforded **9** as a yellow/tan colored solid (96 mg, 61%).

Conversion of 8 to 9. A solution of **8** (2.22 g, 7.44 mmol) and $\text{H}_2\text{NHNCOCO}_2\text{Me}$ (879 mg, 7.44 mmol) in THF (40 mL) at 35 °C was treated with glacial AcOH (2 mL) and the resulting mixture was stirred at 35 °C overnight. After approximately 19 h, the reaction mixture was concentrated onto Celite. Flash chromatography (SiO_2 , 5:70:25 $\text{MeOH}-\text{CHCl}_3$ -acetone) afforded **9** as a white solid (2.05 g, 79%): mp 162–163 °C; ^1H NMR (400 MHz, CDCl_3) δ 9.49 (br s, 1H), 7.88 (br s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 6.68–6.77 (m, 3H), 5.76 (br s, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.60 (s, 3H), 3.40–3.43 (m, 2H), 2.83 (t, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.2, 157.1, 156.3, 154.8, 137.7, 125.9, 122.1, 119.4, 111.2, 108.7, 92.8, 55.7, 53.6, 40.7, 32.5, 25.5; IR (film) 3348, 2938, 1721, 1648, 1560, 1482, 1439, 1212, 1118, 1070, 806 cm^{-1} ; HRMS (MALDI–FTMS) calcd for ($\text{C}_{16}\text{H}_{21}\text{N}_4\text{O}_5$) $[\text{M}+\text{H}]^+$ 349.1506; found 349.1491.

A solution of **9** (3.27 g, 9.38 mmol) in CH_2Cl_2 (3 mL) at 0 °C was treated with *p*-toluenesulfonyl chloride (1.79 g, 9.38 mmol) followed by Et_3N (3.25 mL, 23.45 mmol). The resulting reaction mixture was stirred overnight at 25 °C. After 16–20 h, the solvent was removed under reduced pressure and the material was absorbed onto Celite. Flash chromatography (SiO_2 , 50% EtOAc -hexanes) afforded **10** as a white solid (2.08 g, 67%): mp 156–157 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, J = 8.6 Hz, 1H), 6.75–6.81 (m, 3H), 5.28 (br s, 1H), 3.98 (s, 3H), 3.88 (s, 3H), 3.74 (dd, J = 6.3, 12.5 Hz, 2H), 3.70 (s, 3H), 3.07 (t, J = 6.5

Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 164.5, 156.6, 154.8, 150.9, 137.9, 126.0, 121.7, 119.3, 110.0, 109.1, 92.9, 55.7, 53.2, 43.5, 32.6, 25.1; IR (film) 3350, 2939, 1740, 1625, 1551, 1438, 1384, 1254, 1152, 814 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_4)$ $[\text{M}+\text{H}]^+$ 333.1557; found 333.1563.

Succinyl dichloride (4.6 mL, 41.6 mmol) in CH_2Cl_2 (200 mL) was cooled to $-40\text{ }^\circ\text{C}$ and ethylaluminum dichloride (50 mL, 50 mmol) was added at $-40\text{ }^\circ\text{C}$. The reaction mixture was stirred at $-40\text{ }^\circ\text{C}$ for 3.5 h and quenched with the addition of anhydrous MeOH (200 mL). The reaction mixture was concentrated to dryness and redissolved in CH_2Cl_2 (100 mL). The organic layer was washed with aqueous sodium potassium tartrate (2 x 50 mL), water (50 mL) and saturated aqueous NaCl (50 mL). The organic layer was dried over MgSO_4 , filtered and concentrated to provide pure methyl 4-ketohexanoate^{S4} (6.0 g, 99%): ^1H NMR (400 MHz, CDCl_3) δ 3.67 (s, 3H), 2.74 (t, J = 6.5 Hz, 2H), 2.60 (t, J = 6.5 Hz, 2H), 2.51 (q, J = 7.3 Hz, 2H), 1.09 (J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.4, 173.3, 51.7, 36.6, 35.9, 27.7, 7.7.

A suspension of (benzyloxymethyl)triphenylphosphonium bromide (83.8 g, 200 mmol) in anhydrous THF (120 mL) was cooled to $-78\text{ }^\circ\text{C}$ and treated dropwise with NaHMDS (100 mL, 200 mmol) in THF. Upon final addition of NaHMDS, the reaction mixture was warmed to $-40\text{ }^\circ\text{C}$ and was stirred for 30–40 min (mixture turns a deep red color). The mixture was recooled to $-78\text{ }^\circ\text{C}$ and a solution of methyl 4-ketohexanoate (12.6 g, 100 mmol) in THF (20 mL) was added slowly via a cannula. The resulting mixture was stirred overnight while slowly warming to $25\text{ }^\circ\text{C}$. The reaction mixture was quenched by addition of 1 N aqueous NaH_2PO_4 (100 mL), extracted with Et_2O (3 x 100 mL), and the combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude material (ca 1:1 mixture of isomers (23.6 g, 86%)) obtained was purified by flash chromatography (SiO_2 , 2–4% EtOAc–hexanes) to afford a clear oil. The (*Z*)-isomer eluted first off the column (10.3 g), followed by the (*E*)-isomer (11.0 g).

(*E*)-enol ether: ^1H NMR (600 MHz, CDCl_3) δ 7.30–7.35 (m, 5H), 5.90 (s, 1H), 4.73 (s, 2H), 3.61 (s, 3H), 2.36 (t, J = 7.9 Hz, 2H), 2.21 (t, J = 7.9 Hz, 2H), 2.12 (q, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 173.7, 140.7, 137.8, 128.3 (2C), 127.7, 127.2 (2C), 118.9, 73.4, 51.4, 33.3, 26.7, 20.0, 12.5; HRMS (MALDI–FTMS) calcd for ($\text{C}_{15}\text{H}_{20}\text{O}_3$) $[\text{M}+\text{Na}]^+$ 271.1305; found 271.1308.

(*Z*)-enol ether: ^1H NMR (500 MHz, CDCl_3) δ 7.27–7.38 (m, 5H), 5.92 (s, 1H), 4.74 (s, 2H), 3.64 (s, 3H), 2.36–2.47 (m, 4H), 1.90 (q, J = 7.4 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 174.1, 140.7, 137.8, 128.4 (2C), 127.7, 127.3 (2C), 118.8, 73.4, 51.4, 32.6, 24.8, 23.0, 13.1.

A solution of methyl (*Z*)-5-benzyloxy-4-ethylpent-4-enoate (3.0 g, 12 mmol) in a 3:1 mixture of THF (18 mL):MeOH (6 mL) was cooled to 0 °C and 1 N aqueous LiOH (36 mL, 36 mmol) was added. The mixture was stirred at 0–25 °C (ca 3 h) prior to dilution with H_2O , ethyl acetate and addition of 10% aqueous citric acid until the mixture reached pH 3–4. The cloudy solution was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4 , filtered, and concentrated in vacuo to afford (*Z*)-**11** as a clear oil (2.6 g, 93%). If necessary, this oil can be further purified by flash chromatography (SiO_2 , 25% EtOAc–hexanes): ^1H NMR (500 MHz, CDCl_3) δ 7.28–7.37 (m, 5H), 5.93 (s, 1H), 4.74 (s, 2H), 2.40–2.47 (m, 4H), 1.91 (dd, J = 7.4, 15.0 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 179.3, 140.9, 137.8, 128.4 (2C), 127.7, 127.3 (2C), 118.6, 73.5, 32.5, 24.8, 22.8, 13.1; HRMS (MALDI–FTMS) calcd for ($\text{C}_{14}\text{H}_{18}\text{O}_3$) $[\text{M}+\text{Na}]^+$ 257.1149; found 257.1149.

Similarly, hydrolysis of the (*E*)-enol ether afforded (*E*)-**11**: ^1H NMR (500 MHz, CDCl_3) δ 7.27–7.38 (m, 5H), 5.93 (s, 1H), 4.75 (s, 2H), 2.41 (t, J = 7.7 Hz, 2H), 2.23 (t, J = 7.7 Hz, 2H), 2.13 (dd, J = 7.7, 15.0 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 179.5, 140.8, 137.8, 128.4 (2C), 127.7, 127.3 (2C), 118.7, 73.5, 33.3, 26.4, 20.0, 12.5; HRMS (MALDI–FTMS) calcd for ($\text{C}_{14}\text{H}_{18}\text{O}_3$) $[\text{M}+\text{Na}]^+$ 257.1149; found 257.1149.

(*E*)- and (*Z*)-5-Benzyloxy-4-ethylpent-4-enoic acid: direct Wittig reaction. A solution of (benzyloxymethyl)triphenylphosphonium bromide (5.00 g, 11.9 mmol) in anhydrous THF (52 mL) was cooled to -78°C and treated dropwise with *t*-BuLi (5.9 mL, 10.0 mmol, 1.7 M solution in pentane). The reaction mixture was stirred for 5 min at -78°C before warming to -40°C where the solution was stirred for 30–40 min (mixture turns a deep red color), and then recooled to -78°C . A solution of 4-ketohexanoic acid (260 mg, 2.0 mmol) in THF (3 mL) was added slowly via a cannula and the resulting mixture was stirred overnight while slowly warming to 25°C . The reaction mixture was quenched by careful addition of 1 N aqueous NaH_2PO_4 (52 mL), extracted with Et_2O (3 x 75 mL), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude material (ca. 85:15 ratio of isomers by GC) thus obtained was purified by flash chromatography (SiO_2 , 10–100% EtOAc–hexanes gradient elution) to afford a yellow oil (262 mg, 56%) which was found to be almost exclusively one enol ether by GC and ^1H NMR (NOE) after chromatography. Continued purification can furnish >95% pure (*E*)- as well as >95% (*Z*)-enol ether as separate fractions, as determined by the respective GC traces of the individual fractions.

Oxadiazole **10** (345 mg, 1.04 mmol) was added to a solution of (*Z*)-**11** (>97% *Z*-enol ether by GC analysis, 1.30 g, 5.55 mmol) in anhydrous CH_2Cl_2 (150 mL) at 0°C under Ar. The mixture was cooled to 0°C and EDCI (854 mg, 4.45 mmol) was added. The resulting mixture was subsequently stirred for 2 min, before the addition of DMAP (550 mg, 4.50 mmol). The reaction mixture was stirred (16 h) while slowly warming to 25°C , at which time the solvent was removed under reduced pressure absorbing the mixture onto Celite. Flash chromatography (SiO_2 , 30% EtOAc–hexanes) afforded **4a** (550 mg, 96%) as a white solid: mp $86\text{--}87^{\circ}\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.54 (d, J = 8.3 Hz, 1H), 7.24–7.33 (m, 5H), 6.78 (dd, J = 2.2, 8.8 Hz,

1H), 6.72 (s, 1H), 6.68 (d, $J = 6.9$ Hz, 1H), 5.90 (s, 1H), 4.70 (s, 2H), 4.17 (t, $J = 7.7$ Hz, 2H), 3.98 (s, 3H), 3.87 (s, 3H), 3.64 (s, 3H), 3.05 (t, $J = 7.7$ Hz, 2H), 2.91 (t, $J = 7.7$ Hz, 2H), 2.45 (t, $J = 7.7$ Hz, 2H), 1.89 (q, $J = 7.4$ Hz, 2H), 0.95 (t, $J = 7.4$ Hz, 3H); ^1H NMR (600 MHz, C_6D_6) δ 7.78 (d, $J = 8.6$ Hz, 1H), 7.12–7.20 (m, 3H), 7.00–7.04 (m, 2H), 6.58 (dd, $J = 1.7$ Hz, 1H), 6.25 (s, 1H), 5.79 (s, 1H), 4.42 (s, 2H), 4.10 (t, $J = 7.7$ Hz, 2H), 3.51 (s, 3H), 3.33 (s, 3H), 3.11 (t, $J = 7.7$ Hz, 2H), 3.03 (t, $J = 7.7$ Hz, 2H), 2.93 (s, 3H), 2.75 (t, $J = 7.7$ Hz, 2H), 1.89 (q, $J = 7.2$ Hz, 2H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 162.1, 156.4, 154.1, 153.1, 140.9, 137.7, 137.6, 128.4 (2C), 127.7, 127.3 (2C), 126.4, 121.7, 119.6, 118.5, 110.0, 109.0, 92.7, 73.4, 55.6, 53.5, 47.7, 34.6, 32.5, 24.9, 24.4, 23.0, 13.1; ^{13}C NMR (100 MHz, C_6D_6) δ 172.0, 162.3, 157.1, 154.4, 153.2, 141.4, 138.3, 128.6, 128.3 (2C), 128.1, 127.9, 127.5 (2C), 126.4, 122.6, 120.2, 118.7, 110.5, 109.3, 93.2, 73.5, 55.2, 52.5, 47.7, 35.4, 31.8, 25.4, 24.7, 23.6, 13.4; IR (film) 3446, 2943, 1749, 1703, 1626, 1564, 1441, 1262, 1226, 1154 cm^{-1} ; HRMS (MALDI–FTMS) calcd for ($\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_6$) $[\text{M}+\text{H}]^+$ 547.2551; found 547.2554.

A solution of **4a** (3 x 10.9 mg, 0.060 mmol) in triisopropylbenzene (3 x 200 mL, 0.1 mM) was purged with Ar for 30 min and was warmed at 230 °C for 90 h. The reaction mixture was cooled to room temperature, and loaded directly onto a silica gel chromatography column. The triisopropylbenzene was eluted with hexanes, and then the column was eluted with 50% EtOAc–hexanes to afford **5a** (15.4 mg, 50%) as a yellow foam. Alternatively, a solution of **4a** (2 x 4.3 mg, 0.016 mmol) in triisopropylbenzene (2 x 160 mL, 0.05 mM) was purged with Ar for 30 min and was warmed at 230 °C for 90 h. The reaction mixture was cooled to room temperature, and loaded directly onto a silica gel chromatography column. The triisopropylbenzene was eluted with hexanes, and then the column was eluted with 50% EtOAc–hexanes to afford **5a** (4.2 mg, 53%) as a yellow foam: mp 203–205 °C (EtOAc–hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.26 (d, $J = 7.3$ Hz, 2H), 7.07–7.18 (m, 3H), 6.51 (d, $J = 8.1$ Hz, 1H), 6.18 (dd, $J = 2.2, 8.1$ Hz, 1H), 6.10 (d, $J = 2.2$ Hz, 1H), 4.51 (d, $J = 11.0$ Hz, 1H), 4.33 (d, $J = 11.0$ Hz, 1H), 4.31 (s, 1H), 3.88–3.97 (m, 2H), 3.80 (s, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 2.87 (s, 3H), 2.60 (dd, $J = 5.9, 13.9$ Hz, 1H), 2.32 (dd, $J = 4.6, 18.5$ Hz, 1H), 2.07–2.19

(m, 2H), 1.69 (ddd, $J = 3.7, 5.5, 12.5$ Hz, 1H), 1.45 (dd, $J = 4.8, 14.3$ Hz, 1H), 0.89–0.98 (m, 1H), 0.68 (dq, $J = 7.3, 14.7$ Hz, 1H), 0.42 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.6, 169.6, 162.3, 155.1, 138.8, 129.0 (2C), 128.1 (2C), 124.5, 122.0, 105.0, 103.6, 95.1, 91.5, 87.6, 82.3, 77.9, 74.6, 64.5, 55.1, 51.8, 50.3, 47.4, 38.0, 35.6, 28.9, 22.9, 21.7, 10.1; IR (neat) 3444, 2953, 1734, 1664, 1620, 1493, 1400, 1247, 1097 cm^{-1} ; HRMS (MALDI-FTMS) calcd for ($\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_6$) $[\text{M}+\text{H}]^+$ 519.2490; found 519.2498. A sample of **5a** (CCDC 253429) for X-ray analysis was obtained by recrystallization from EtOAc–hexanes: mp 203–205 °C. The enantiomers of **5a** (40 mg/injection) were separated ($\alpha = 1.70$) on a semipreparative Chiralcel OD column (2 x 25 cm, 30% *i*-PrOH–hexanes, 10 mL/min flow rate) providing natural-(+)-**5a** ($t_{\text{R}} = 15.1$ min) and *ent*-(-)-**5a** ($t_{\text{R}} = 25.6$ min). For natural-(+)-**5a**: $[\alpha]_{\text{D}}^{23} +50$ (c 1.4, MeOH); for *ent*-(-)-**5a**: $[\alpha]_{\text{D}}^{23} -49$ (c 2.1, MeOH).

Data for lactone isolated upon premature workup of the cycloaddition of **4a**: ^1H NMR (500 MHz, C_6D_6) δ 7.50 (d, $J = 8.4$ Hz, 1H), 6.97–7.21 (m, 6H), 6.64 (d, $J = 1.8$ Hz, 1H), 6.34 (s, 1H), 4.67–4.72 (m, 1H), 4.49 (d, $J = 5.1$ Hz, 1H), 4.38 (d, $J = 11.7$ Hz, 1H), 4.25 (d, $J = 11.7$ Hz, 1H), 4.09 (d, $J = 4.8$ Hz, 1H), 3.55 (s, 3H), 3.44 (dt, $J = 2.6, 6.6$ Hz, 2H), 3.19 (s, 3H), 2.96 (s, 3H), 2.79 (t, $J = 7.0$ Hz, 2H), 2.28–2.48 (m, 3H), 2.12–2.19 (m, 1H), 1.21–1.51 (m, 2H), 0.69 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 176.8, 171.0, 169.5, 157.2, 138.3, 137.2, 129.0 (2C), 128.1 (2C), 125.5, 123.0, 119.9, 112.1, 109.1, 93.2, 81.7, 78.6, 72.4, 55.2, 52.0, 49.9, 40.2, 31.8, 31.4, 30.1, 27.6, 26.7, 25.7, 8.2; HRMS (MALDI-FTMS) calcd for ($\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_7$) $[\text{M}+\text{H}]^+$ 537.2523; found 537.2596.

A stirred solution of **5a** (27.3 mg, 0.053 mmol) in anhydrous THF (1 mL) under Ar at –40 °C was treated with bis(trimethylsilyl)peroxide (0.042 mL, 0.212 mmol), followed by a 1.65 M solution of lithium diisopropylamide (LDA, 0.064 mL in THF, 0.106 mmol). The reaction

mixture was stirred for 1 h at $-40\text{ }^{\circ}\text{C}$, followed by another three additions of bis(trimethylsilyl)peroxide (0.042 mL, 0.212 mmol) and LDA (0.064 mL, 0.106 mmol) every 1 h. The reaction mixture was treated with triisopropylsilyl trifluoromethanesulfonate (0.110 mL, 0.415 mmol) at $-40\text{ }^{\circ}\text{C}$, and the mixture was allowed to warm to room temperature over 2 h. The mixture was diluted with saturated aqueous NH_4Cl and was extracted with EtOAc (3 x 5 mL). The extract was washed with saturated aqueous NaCl, dried over MgSO_4 , and concentrated under reduced pressure. Flash chromatography (SiO_2 , 10% EtOAc–hexanes) gave 23.3 mg (64%) of **12** as a white foam: natural enantiomer $[\alpha]_{\text{D}}^{23} +53$ (c 1.6, MeOH), unnatural enantiomer $[\alpha]_{\text{D}}^{23} -50$ (c 1.15, MeOH); ^1H NMR (500 MHz, C_6D_6) δ 7.26 (d, $J = 7.3$ Hz, 2H), 7.07–7.18 (m, 3H), 6.42 (d, $J = 8.1$ Hz, 1H), 6.16 (dd, $J = 2.2, 8.1$ Hz, 1H), 6.08 (d, $J = 2.2$ Hz, 1H), 4.57 (d, $J = 11.4$ Hz, 1H), 4.53 (dd, $J = 5.5, 11.7$ Hz, 1H), 4.36 (d, $J = 11.4$ Hz, 1H), 4.26 (s, 1H), 3.82 (dd, $J = 10.6, 11.0$ Hz, 1H), 3.72–3.78 (m, 1H), 3.74 (s, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 3.08 (t, $J = 12.8$ Hz, 1H), 2.83 (s, 3H), 2.35 (dd, $J = 5.5, 13.9$ Hz, 1H), 2.08 (dt, $J = 10.3, 12.5$ Hz, 1H), 1.63 (m, 1H), 1.05–1.35 (m, 23H), 0.70 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.7, 170.4, 162.3, 155.1, 138.7, 129.0 (2C), 128.1 (2C), 124.4, 121.9, 104.8, 103.7, 95.1, 91.6, 88.1, 82.3, 74.8, 68.5, 64.3, 55.1, 51.9, 51.0, 47.1, 38.3, 35.5, 32.7, 30.4, 24.2, 18.7 (6C), 13.1 (3C), 10.5; IR (neat) 2940, 2865, 1732, 1683, 1620, 1500 cm^{-1} ; HRMS (MALDI–FTMS) calcd for $(\text{C}_{39}\text{H}_{55}\text{N}_2\text{O}_7\text{Si})$ $[\text{M}+\text{H}]^+$ 691.3773; found 691.3787.

A solution of **12** (10.0 mg, 0.015 mmol) in THF (3 mL) was treated with a 1.0 M solution of Bu_4NF (0.025 mL, 0.025 mmol) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was concentrated under reduced pressure to give a yellow oil. A solution of *p*-bromobenzoyl chloride (10 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) was treated with Et_3N (15 mg, 0.14 mmol), DMAP (1.7 mg, 0.015 mmol) and a solution of the above mixture in CH_2Cl_2 (1 mL), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure. Flash chromatography (SiO_2 , 25% EtOAc–hexanes) gave 8.7 mg (81%, two steps) of **12a** as a white solid. A sample of **12a** (CCDC 255976) for X-ray analysis was obtained as block shaped crystals by recrystallization from EtOAc–hexanes: mp

223–224 °C; ^1H NMR (500 MHz, C_6D_6) δ 7.67 (d, J = 8.4 Hz, 2H), 7.11–7.17 (m, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.02–7.05 (m, 2H), 6.97–7.01 (m, 1H), 6.38 (d, J = 8.1 Hz, 1H), 6.21 (dd, J = 2.2, 8.1 Hz, 1H), 6.07 (d, J = 1.8 Hz, 1H), 5.97 (dd, J = 5.9, 12.8 Hz, 1H), 4.44 (d, J = 11.0 Hz, 1H), 4.30 (s, 1H), 4.29 (d, J = 11.0 Hz, 1H), 3.94 (t, J = 11.0 Hz, 1H), 3.77 (s, 1H), 3.68–3.75 (m, 1H), 3.39 (s, 6H), 3.16 (t, J = 13.1 Hz, 1H), 2.81 (s, 3H), 2.30 (dd, J = 5.9, 13.6 Hz, 1H), 2.08 (dt, J = 10.5, 12.5 Hz, 1H), 1.68 (dd, J = 7.9, 12.5 Hz, 1H), 0.85–1.02 (m, 2H), 0.61–0.69 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.3, 166.9, 165.5, 162.4, 155.0, 138.3, 132.1 (2C), 132.0 (2C), 129.4, 129.3, 128.9 (2C), 128.7 (2C), 124.7, 121.4, 104.7, 103.9, 95.1, 91.8, 87.9, 82.4, 75.0, 68.4, 64.4, 55.1, 51.9, 51.3, 47.1, 38.4, 35.6, 30.4, 28.5, 24.2, 10.3; HRMS (MALDI–FTMS) calcd for $(\text{C}_{37}\text{H}_{38}\text{BrN}_2\text{O}_8)$ $[\text{M}+\text{H}]^+$ 717.1733; found 717.1733.

A solution of **12** (52 mg, 0.075 mmol) in toluene (4 mL) was treated with Lawesson's reagent (61 mg, 0.151 mmol) at room temperature, and the heterogeneous mixture was warmed at 110 °C for 3 h. Upon completion, the now homogeneous yellow solution was cooled to room temperature, and concentrated under reduced pressure. Flash chromatography (SiO_2 , 25% EtOAc–hexanes) followed by PTLC (25% EtOAc–hexanes) gave **13** (37.3 mg, 70%) and its C7 epimer (5.3 mg, 10%) as yellow solids.

For **13**: natural enantiomer $[\alpha]_{\text{D}}^{23} +96$ (c 0.68, CHCl_3), unnatural enantiomer $[\alpha]_{\text{D}}^{23} -94$ (c 2.8, CHCl_3); ^1H NMR (500 MHz, C_6D_6) δ 7.28 (d, J = 7.3 Hz, 2H), 7.07–7.21 (m, 3H), 6.48 (d, J = 8.1 Hz, 1H), 6.12 (dd, J = 2.2, 8.1 Hz, 1H), 6.09 (d, J = 2.2 Hz, 1H), 4.73 (dd, J = 5.5, 11.4 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 11.0 Hz, 1H), 4.31 (s, 1H), 4.21 (ddd, J = 8.1, 10.6, 13.9 Hz, 1H), 4.13 (dd, J = 9.5, 13.9 Hz, 1H), 3.73 (s, 1H), 3.37 (s, 3H), 3.31 (s, 3H), 2.99 (dd, J = 12.8, 12.8 Hz, 1H), 2.83 (s, 3H), 2.38 (dd, J = 5.5, 13.9 Hz, 1H), 2.10 (dt, J = 10.6, 12.5 Hz, 1H), 1.68 (dd, J = 7.0, 12.5 Hz, 1H), 1.20–1.37 (m, 21H), 1.03 (dq, J = 7.3, 14.7 Hz, 1H), 0.78 (dq, J = 7.3, 14.7 Hz, 1H), 0.63 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.2, 170.1, 162.2, 154.9, 138.3, 129.0 (2C), 128.5, 128.1 (2C), 124.1, 121.1, 103.5, 102.0, 95.0, 91.7, 87.5, 81.9, 74.5, 73.6, 64.7, 54.8, 54.5, 51.6, 51.0, 37.6, 35.2, 32.3, 23.8, 18.7

(3C), 18.6 (3C), 13.2 (3C), 10.2; IR (neat) 2942, 2865, 1765, 1732, 1621, 1591, 1500, 1422, 1356, 1246, 1202, 1102 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{39}\text{H}_{55}\text{N}_2\text{O}_6\text{SSi})$ $[\text{M}+\text{H}]^+$ 707.3544; found 707.3519.

For the C7 epimer of **13**: natural enantiomer $[\alpha]_{\text{D}}^{23} +106$ (c 0.28, CHCl_3), unnatural enantiomer $[\alpha]_{\text{D}}^{23} -114$ (c 0.42, CHCl_3); ^1H NMR (500 MHz, C_6D_6) δ 7.28 (d, $J = 7.4$ Hz, 2H), 7.10–7.21 (m, 3H), 6.62 (d, $J = 7.7$ Hz, 1H), 6.14 (s, 1H), 6.12 (dd, $J = 2.2, 7.7$ Hz, 1H), 4.91 (dd, $J = 2.9, 6.2$ Hz, 1H), 4.55 (d, $J = 11.0$ Hz, 1H), 4.39 (d, $J = 11.0$ Hz, 1H), 4.37 (s, 1H), 4.30–4.40 (m, 1H), 4.23 (ddd, $J = 7.7, 11.0, 13.6$ Hz, 1H), 3.73 (s, 1H), 3.40 (s, 3H), 3.33 (s, 3H), 2.95 (dd, $J = 6.4, 14.9$ Hz, 1H), 2.83 (s, 3H), 2.08–2.17 (m, 2H), 1.72 (dd, $J = 7.3, 12.5$ Hz, 1H), 1.51 (dq, $J = 6.6, 13.7$ Hz, 1H), 1.12–1.41 (m, 21H), 0.91–0.96 (m, 1H), 0.71 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.4, 169.9, 162.1, 155.0, 138.3, 128.4 (2C), 127.6, 127.0 (2C), 124.1, 121.3, 103.4, 102.5, 95.2, 91.4, 87.8, 82.1, 74.3, 74.2, 65.4, 54.9, 54.8, 51.6, 50.6, 37.7, 35.4, 31.2, 25.2, 18.7 (6C), 13.5 (3C), 11.0; IR (neat) 2941, 2864, 1762, 1734, 1618, 1499, 1437, 1362, 1244, 1087 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{39}\text{H}_{55}\text{N}_2\text{O}_6\text{SSi})$ $[\text{M}+\text{H}]^+$ 707.3544; found 707.3539.

A solution of excess Raney-Ni (pretreated with successive washes with H_2O (5x), and THF (5x)) in THF (3 mL) was treated with a solution of **13** (11 mg, 0.016 mmol) in THF (1 mL), and the mixture was stirred for 15 h at room temperature under an atmosphere of H_2 . The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give 8.3 mg (91%) of **14** as a yellow oil: natural enantiomer $[\alpha]_{\text{D}}^{23} +73$ (c 1.5, CHCl_3), unnatural enantiomer $[\alpha]_{\text{D}}^{23} -72$ (c 0.52, CHCl_3); ^1H NMR (500 MHz, C_6D_6) δ 6.90 (d, $J = 8.1$ Hz, 1H), 6.30 (dd, $J = 2.2, 8.1$ Hz, 1H), 6.16 (d, $J = 2.2$ Hz, 1H), 4.50 (d, $J = 7.5$ Hz, 1H), 4.28–4.32 (m, 1H), 3.92 (s, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 3.17–3.25 (m, 2H), 2.95–3.04 (m, 2H), 2.81 (s, 3H), 2.35 (dd, $J = 12.3, 12.3$ Hz, 1H), 2.10–2.18 (m, 2H), 1.96–2.05 (m, 1H), 1.90–1.94 (m, 1H), 1.21–1.38 (m, 2H), 0.96–1.06 (m, 21H), 0.82 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.2, 161.9, 154.5, 128.2, 125.1, 124.5, 102.9, 94.4, 89.5, 84.5, 79.7, 66.2, 62.5, 55.1, 54.8, 51.4, 51.3 49.4, 41.2, 35.3, 32.8, 24.9, 18.4 (6C), 12.6 (3C), 10.1; IR (neat)

3498, 2938, 2856, 1729, 1609, 1506, 1470, 1345, 1268, 1247 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{32}\text{H}_{51}\text{N}_2\text{O}_6\text{Si}) [\text{M}+\text{H}]^+$ 587.3511 found 587.3504.

A mixture of **14** (9.0 mg, 0.015 mmol) and NaOAc (6.3 mg, 0.075 mmol) was treated with acetic anhydride (0.5 mL), and the mixture was stirred for 17 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NaHCO_3 . The aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic mixture was washed with saturated aqueous NaCl, dried over MgSO_4 , and concentrated under reduced pressure. Flash chromatography (SiO_2 , 50% EtOAc-hexanes) provided 9.1 mg (97%) of **15** as a yellow oil: natural enantiomer $[\alpha]_{\text{D}}^{23} +41$ (*c* 1.2, CHCl_3), $[\alpha]_{\text{D}}^{25} +50$ (*c* 0.36, CHCl_3), unnatural enantiomer $[\alpha]_{\text{D}}^{23} -40$ (*c* 1.3, CHCl_3); ^1H NMR (500 MHz, C_6D_6) δ 6.89 (d, *J* = 8.1 Hz, 2H), 6.33 (dd, *J* = 2.2, 8.1 Hz, 1H), 6.07 (d, *J* = 2.2 Hz, 1H), 6.07 (s, 1H), 4.21–4.32 (m, 1H), 3.99 (s, 1H), 3.40 (s, 6H), 3.19–3.27 (m, 2H), 3.01 (t, *J* = 9.7 Hz, 1H), 2.97–3.01 (m, 1H), 2.90 (s, 3H), 2.50 (dd, *J* = 12.3, 12.3 Hz, 1H), 2.18 (ddd, *J* = 4.4, 10.6, 13.0 Hz, 1H), 2.04–2.10 (m, 1H), 2.02 (dd, *J* = 2.9, 13.2 Hz, 1H), 1.63 (s, 3H), 1.31–1.45 (m, 1H), 1.00–1.15 (m, 22H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.3, 169.3, 162.5, 154.8, 125.3, 124.1, 110.2, 103.7, 94.5, 89.0, 84.7, 80.4, 66.4, 63.0, 55.4, 55.2, 51.7, 49.9, 45.8, 41.0, 35.2, 34.3, 25.2, 20.6, 18.7 (6C), 13.1 (3C), 10.6; IR (neat) 2944, 2866, 1753, 1731, 1612, 1501 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{34}\text{H}_{53}\text{N}_2\text{O}_7\text{Si}) [\text{M}+\text{H}]^+$ 629.3616; found 629.3605.

A solution of **15** (25 mg, 0.040 mmol) in MeOH (2.5 mL) and EtOAc (2.5 mL) was sonicated to give a homogeneous solution. This mixture was treated with PtO_2 (5.0 mg) in one portion, and the mixture was stirred under 40–45 psi of H_2 for 3 h. The resulting mixture was filtered through a pad of Celite (EtOAc eluent) to remove the catalyst. The filtrate was concentrated under reduced pressure to give 24.6 mg (98%) of **16** as a yellow oil: natural

enantiomer $[\alpha]_D^{23} -28$ (c 1.15, CHCl_3), unnatural enantiomer $[\alpha]_D^{23} +32$ (c 0.66, CHCl_3); ^1H NMR (500 MHz, C_6D_6) δ 8.05–8.09 (m, 1H), 6.61 (d, $J = 8.2$ Hz, 1H), 6.41 (dd, $J = 2.2, 8.2$ Hz, 1H), 5.98 (d, $J = 2.2$ Hz, 1H), 5.91 (s, 1H), 4.18–4.23 (m, 1H), 3.73 (s, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 2.96 (dd, $J = 5.8, 11.1$ Hz, 1H), 2.86–2.91 (m, 1H), 2.81 (dd, $J = 11.8, 13.7$ Hz, 1H), 2.50 (s, 3H), 2.43–2.48 (m, 1H), 2.37 (s, 1H), 1.91–2.02 (m, 3H), 1.84 (s, 3H), 1.64–1.67 (m, 1H), 1.41 (dq, $J = 7.5, 14.9$ Hz, 1H), 1.05–1.09 (m, 21H), 1.03–1.05 (m, 1H), 0.65 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.7, 169.8, 161.7, 154.3, 125.8, 123.0, 105.4, 95.9, 83.9, 80.4, 73.7, 71.3, 65.8, 60.9, 54.8, 52.9, 52.7, 51.2, 46.2, 40.6, 38.4, 38.3, 33.8, 20.8, 18.2 (6C), 12.6 (3C), 8.6; HRMS (MALDI–FTMS) calcd for $(\text{C}_{34}\text{H}_{54}\text{N}_2\text{O}_7\text{Si})$ $[\text{M}+\text{H}]^+$ 631.3773; found 631.3777.

A solution of **16** (16.0 mg, 0.025 mmol) in THF (2 mL) was treated with a 1.0 M solution of Bu_4NF (0.05 mL in THF, 0.05 mmol) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was concentrated under reduced pressure. Flash chromatography (SiO_2 , 5% Et_3N – EtOAc) provided 10.6 mg (89%) of **17** as a yellow oil: natural enantiomer $[\alpha]_D^{23} +24$ (c 0.71, CHCl_3), unnatural enantiomer $[\alpha]_D^{23} -24$ (c 0.75, CHCl_3); ^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), 4.21–4.32 (m, 1H), 3.99 (s, 1H), 3.73–3.79 (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), 1.94–2.00 (m, 1H), 1.89 (s, 3H), 1.76–1.88 (m, 3H), 1.68 (d, $J = 16.1$ Hz, 1H), 1.61 (dd, $J = 2.2, 11.4$ Hz, 1H), 1.29–1.38 (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) 3549, 2952, 1746, 1615, 1504, 1435, 1225 cm^{-1} ; HRMS (MALDI–FTMS) calcd for $(\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_7)$ $[\text{M}+\text{H}]^+$ 475.2439; found 475.2443.

Vindoline (3). DEAD (4.7 μ L, 0.029 mmol) was added to a solution of **17** (4.6 mg, 0.0097 mmol) and Ph_3P (7.7 mg, 0.029 mmol) in anhydrous THF (100 μ L) at room temperature under Ar. The reaction mixture was stirred for 24 h at room temperature in the dark, before the solvent was removed under reduced pressure. PTLC (SiO_2 , 75% EtOAc–hexanes) afforded vindoline (**3**) as a white amorphous solid (3.3 mg, 75%) identical in all respects with authentic material. For synthetic natural vindoline (**3**): $[\alpha]_{\text{D}}^{20} -45$ (c 0.14, MeOH), -17 (c 0.40, CHCl_3); for *ent*-vindoline (**3**): $[\alpha]_{\text{D}}^{25} +46$ (c 0.19, MeOH); for authentic natural vindoline: $[\alpha]_{\text{D}}^{20} -48$ (c 0.19, MeOH), -19 (c 0.30, CHCl_3), lit⁵⁵ $[\alpha]_{\text{D}}^{20} -18$ (c 0.20, CHCl_3); ^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), 2.88–2.94 (m, 1H), 2.86 (dt, $J = 2.2, 9.2$ Hz, 1H), 2.41 (s, 3H), 2.20–2.28 (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), 1.85–1.89 (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, 125.0–128.0 (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) 2962, 1740, 1616, 1501, 1371, 1242, 1032, 735 cm^{-1} ; HRMS (MALDI–FTMS) calcd for ($\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_6$) $[\text{M}+\text{H}]^+$ 457.2333; found 457.2337.

Oxadiazole **10** (330 mg, 1.00 mmol) was added in one portion to a solution of (*E*)-**11** (584 mg, 2.50 mmol) in anhydrous CH_2Cl_2 (53 mL) at 25 $^\circ\text{C}$ under Ar. The mixture was cooled to 0 $^\circ\text{C}$ and EDCI (479 mg, 2.50 mmol) was added. The resulting mixture was stirred for 5 min, before the addition of DMAP (305 mg, 2.50 mmol). The reaction mixture was stirred at room

temperature overnight, before the solvent was removed under reduced pressure absorbing the mixture onto Celite. Flash chromatography (SiO₂, 30% EtOAc–hexanes) afforded **4b** as a white solid (480 mg, 88%): mp 69–70 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.53 (d, *J* = 9.1 Hz, 1H), 7.25–7.36 (m, 5H), 6.78 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.72 (s, 1H), 6.68 (d, *J* = 1.7 Hz, 1H), 5.93 (s, 1H), 4.73 (s, 2H), 4.18 (t, *J* = 7.5 Hz, 2H), 3.99 (s, 3H), 3.87 (s, 3H), 3.65 (s, 3H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 2.09 (q, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.1, 162.0, 156.4, 154.0, 153.2, 141.0, 137.8, 137.7, 128.4 (2C), 127.7, 127.3 (2C), 126.5, 121.7, 119.6, 118.7, 109.9, 109.0, 92.7, 73.5, 55.6, 53.6, 47.7, 35.5, 32.6, 26.7, 24.4, 20.1, 12.6; IR (neat) 2961, 1748, 1703, 1624, 1564, 1493, 1441, 1409, 1333, 1257, 1228, 1154, 1069, 1035, 813, 729 cm⁻¹; HRMS (MALDI–FTMS) calcd for (C₃₀H₃₄N₄O₆) [M+H]⁺ 547.2551; found 547.2554.

A solution of **4b** (21.8 mg, 0.04 mmol) in triisopropylbenzene (40 mL, 1 mM) was purged with Ar for 30 min and was warmed at 230 °C for 20 h. The mixture was cooled at room temperature, and loaded directly onto silica gel chromatography column. The triisopropylbenzene was eluted with hexanes, and then the column was eluted with 50% EtOAc–hexanes to afford **5b** (20.4 mg, 99%) as a pale yellow solid.

In earlier preparative studies, the following procedure was used. A solution of **4b** (720 mg, 1.32 mmol) in 1,2-dichlorobenzene (253 mL, 0.0052 M, passed through a column of basic alumina, degassed with Ar for 1 h while protected from the light) was warmed at a gentle reflux in the absence of light for 18 h. The reaction mixture was cooled to 25 °C, and loaded directly onto SiO₂ equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with hexanes, and then the column was eluted with 30–60% EtOAc–hexanes (gradient eluent) to afford **5b** (510 mg, 75%, 72–84%) as a white solid: mp 173–174 °C; ¹H NMR (600 MHz, C₆D₆) δ 7.07–7.13 (m, 4H), 7.03–7.06 (m, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 6.12 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.83 (d, *J* = 1.9 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.25 (s, 1H), 4.17 (d, *J* = 11.7 Hz, 1H), 3.81–3.93 (m, 3H), 3.77 (s, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.58 (s, 3H), 2.22 (dd, *J* = 4.8, 17.8 Hz, 1H),

1.99–2.17 (m, 3H), 1.76 (dd, $J = 7.6, 12.3$ Hz, 1H), 1.43 (dd, $J = 4.9, 12.9$ Hz, 1H), 1.09–1.15 (m, 1H), 0.70–0.76 (m, 1H), 0.36 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.6, 170.3, 161.7, 153.9, 137.9, 128.1 (2C), 127.4, 126.8, 123.7 (2C), 120.3, 107.4, 100.9, 92.3, 87.5, 85.8, 81.6, 74.2, 63.9, 55.3, 52.9, 46.7, 46.0, 38.0, 33.0, 29.3, 29.0, 18.6, 9.6; ^{13}C NMR (150 MHz, C_6D_6) δ 172.6, 171.5, 162.3, 154.3, 138.5, 128.4 (2C), 127.6 (2C), 127.0, 124.1, 120.7, 108.0, 101.5, 92.6, 87.8, 86.1, 82.3, 74.2, 66.3, 63.8, 54.7, 52.0, 46.9, 45.9, 38.9, 37.2, 32.9, 19.9, 9.7; IR (film) 2954, 1735, 1667, 1621, 1589, 1503, 1453, 1398, 1376, 1332, 1254, 1208, 1120, 1059, 1021, 908, 868, 811, 733 cm^{-1} ; HRMS (MALDI–FTMS) calcd for $(\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_6)$ $[\text{M}+\text{H}]^+$ 519.2490; found 519.2482. The relative stereochemistry was confirmed upon X-ray (CCDC 253430) analysis enlisting white crystals grown from EtOAc–hexanes. The enantiomers of **5b** (10 mg/injection) were separated ($\alpha = 1.19$) on a semipreparative Chiralcel OD column (2 x 25 cm, 20% *i*-PrOH–hexanes, 10 mL/min flow rate) providing (–)-**5b** ($t_{\text{R}} = 27.6$ min) and (+)-**5b** ($t_{\text{R}} = 32.8$ min). For (–)-**5b**: $[\alpha]_{\text{D}}^{23} -21$ (c 0.44, MeOH); for (+)-**5b**: $[\alpha]_{\text{D}}^{23} +23$ (c 0.20, MeOH).

A stirred solution of **5b** (28.0 mg, 0.054 mmol) in anhydrous THF (1 mL) under Ar at -40 °C was treated with bis(trimethylsilyl)peroxide (0.043 mL, 0.216 mmol), followed by a 1.65 M solution of lithium diisopropylamide (0.065 mL in THF, 0.108 mmol). The reaction mixture was stirred for 1 h at -40 °C, followed by another three additions of bis(trimethylsilyl)peroxide (0.043 mL, 0.216 mmol) and lithium diisopropylamide (0.065 mL, 0.108 mmol) every 1 h. The reaction mixture was treated with triisopropylsilyl trifluoromethanesulfonate (0.118 mL, 0.440 mmol) at -40 °C, and the mixture was allowed to warm to room temperature over 2 h. The mixture was diluted with saturated aqueous NH_4Cl and was extracted with EtOAc (3 x 5 mL). The extract was washed with saturated aqueous NaCl, dried over MgSO_4 , and concentrated under reduced pressure. Chromatography (SiO_2 , 10% EtOAc–hexanes) gave 27.9 mg (75%) of **18** as a white foam: ^1H NMR (600 MHz, C_6D_6) δ 7.14–7.18 (m, 4H), 7.05–7.09 (m, 1H), 6.42 (d, $J = 7.9$ Hz, 1H), 6.13 (dd, $J = 2.2, 7.9$ Hz, 1H), 5.86 (d, $J = 2.2$ Hz, 1H), 4.71 (d, $J = 11.9$ Hz, 1H), 4.53 (dd, $J = 5.7, 11.9$ Hz, 1H), 4.27 (d, $J = 0.9$ Hz, 1H), 4.18 (d, $J = 11.8$ Hz, 1H), 3.94

(d, $J = 1.3$ Hz, 1H), 3.74–3.81 (m, 2H), 3.40 (s, 3H), 3.36 (s, 3H), 2.70 (t, $J = 12.3$ Hz, 1H), 2.59 (s, 3H), 2.38 (dd, $J = 6.1, 13.1$ Hz, 1H), 2.05–2.11 (m, 1H), 1.75 (ddd, $J = 2.6, 7.4, 12.7$ Hz, 1H), 1.29–1.38 (m, 3H), 1.27 (d, $J = 7.5$ Hz, 9H), 1.23 (d, $J = 7.5$ Hz, 9H), 0.70 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 171.7, 170.2, 162.2, 154.3, 138.5, 128.4 (2C), 127.6, 127.0 (2C), 124.2, 120.9, 107.9, 101.5, 92.7, 88.0, 86.0, 82.1, 74.2, 68.2, 63.9, 54.7, 52.1, 47.0, 46.6, 40.1, 38.8, 33.0, 20.3, 18.5 (3C), 18.4 (3C), 12.6 (3C), 10.1; IR (film) 2943, 2860, 1731, 1684, 1613, 1502, 1455, 1378, 1343, 1102, 1026, 908, 879 cm^{-1} ; HRMS (MALDI-FTMS) calcd for ($\text{C}_{39}\text{H}_{54}\text{N}_2\text{O}_7\text{Si}$) $[\text{M}+\text{H}]^+$ 691.3773; found 691.3767.

The corresponding intermediate alcohol could also be isolated and characterized: ^1H NMR (600 MHz, C_6D_6) δ 7.10–7.23 (m, 4H), 7.07 (t, $J = 6.8$ Hz, 1H), 6.41 (d, $J = 7.9$ Hz, 1H), 6.18 (d, $J = 7.9$ Hz, 1H), 5.84 (s, 1H), 4.61 (d, $J = 11.8$ Hz, 1H), 4.26 (s, 1H), 4.11 (d, $J = 11.9$ Hz, 1H), 4.03 (dd, $J = 5.5, 12.1$ Hz, 1H), 3.80–3.86 (m, 1H), 3.81 (s, 1H), 3.64–3.70 (m, 1H), 3.55 (s, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.58 (s, 3H), 2.40–2.46 (m, 1H), 2.27 (dd, $J = 5.5, 12.9$ Hz, 1H), 2.04–2.09 (m, 1H), 1.75–1.80 (m, 1H), 1.17–1.23 (m, 1H), 0.68–0.73 (m, 1H), 0.47 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.3, 171.3, 161.8, 153.9, 137.7, 128.2, 127.5, 126.9, 123.6, 120.1, 107.5, 100.9, 92.3, 87.5, 86.1, 81.8, 74.4, 66.0, 63.6, 55.3, 52.9, 46.6, 45.8, 38.5, 36.3, 33.0, 19.5, 9.7; ^{13}C NMR (150 MHz, C_6D_6) δ 172.6, 171.5, 162.3, 154.3, 138.5, 128.4 (2C), 127.6 (2C), 127.0, 124.1, 120.7, 108.0, 101.5, 92.6, 87.8, 86.1, 82.3, 74.2, 66.3, 63.8, 54.7, 52.0, 46.9, 45.9, 38.9, 37.2, 32.9, 19.4, 9.7; IR (film) 3404 (br), 2956, 1728, 1672, 1621, 1454, 1377, 1285, 1125 cm^{-1} ; HRMS (MALDI-FTMS) calcd for ($\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_7$) $[\text{M}+\text{H}]^+$ 535.2439; found 535.2438. The relative stereochemistry was confirmed upon X-ray (CCDC 253428) analysis of a crystal grown from EtOAc–hexanes.

A solution of **18** (304 mg, 0.044 mmol) in MeOH (22 mL) was stirred under H_2 (1 atm) in the presence of 10% Pd/C (152 mg) for 17 h at 25 $^\circ\text{C}$. The reaction mixture was filtered through Celite and concentrated in vacuo. Flash chromatography (SiO_2 , 25% EtOAc–hexanes) afforded **19** as a white solid (238 mg, 90%): ^1H NMR (600 MHz, C_6D_6) δ 6.40 (d, $J = 8.3$ Hz,

1H), 6.29 (d, J = 10.5 Hz, 1H), 6.25 (dd, J = 2.2, 8.3 Hz, 1H), 5.95 (d, J = 2.2 Hz, 1H), 4.54 (dd, J = 5.3, 11.9 Hz, 1H), 4.41 (dd, J = 1.3, 10.5 Hz, 1H), 4.06 (d, J = 1.3 Hz, 1H), 3.74 (dd, J = 4.4, 10.1 Hz, 2H), 3.35 (s, 3H), 3.27 (s, 3H), 2.64–2.69 (m, 1H), 2.59 (s, 3H), 2.46 (dd, J = 5.7, 13.2 Hz, 1H), 1.99–2.05 (m, 1H), 1.57–1.61 (m, 1H), 1.28–1.35 (m, 3H), 1.26 (d, J = 7.4 Hz, 9H), 1.22 (d, J = 7.4 Hz, 9H), 1.02–1.07 (m, 1H), 0.86–0.96 (m, 5H); ^{13}C NMR (150 MHz, C_6D_6) δ 170.6, 170.2, 161.8, 154.5, 124.3, 123.6, 107.9, 107.1, 98.1, 84.4 (2C), 82.7, 68.3, 63.9, 54.9, 52.1, 46.1, 46.0, 39.4, 38.4, 37.4, 20.2, 18.4 (3C), 18.3 (3C), 12.9 (3C), 10.0; IR (film) 3307 (br), 2943, 2907, 2860, 1737, 1690, 1584, 1461, 1443, 1378, 1343, 1273, 1161, 1096, 1061, 1032, 885, 797 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{32}\text{H}_{48}\text{N}_2\text{O}_7\text{Si})$ $[\text{M}+\text{H}]^+$ 623.3132; found 623.3123.

TPAP (2.8 mg, 0.008 mmol) was added a solution of **19** (97 mg, 0.16 mmol), NMO (28 mg, 0.24 mmol), and powered activated 4 Å molecular sieves in anhydrous CH_2Cl_2 (3 mL) at 0 °C under Ar. The mixture was stirred at 0 °C for 10 min, before warming to 25 °C. Upon disappearance of the starting material (ca. 7 h), the mixture was filtered through a short pad of SiO_2 eluting with EtOAc. The filtrate was concentrated in vacuo and flash chromatography (SiO_2 , 25% EtOAc–hexanes) afforded **20** as a white solid (67 mg, 69%; 60–81%): ^1H NMR (500 MHz, C_6D_6) δ 6.39 (d, J = 8.0 Hz, 1H), 6.14 (dd, J = 2.0, 8.2 Hz, 1H), 5.87 (d, J = 2.2 Hz, 1H), 4.54 (dd, J = 5.8, 11.3 Hz, 1H), 4.14 (s, 1H), 3.87–3.92 (m, 1H), 3.72–3.78 (m, 1H), 3.32 (s, 3H), 3.29 (s, 3H), 2.96–3.01 (m, 1H), 2.74 (s, 3H), 2.51 (dd, J = 5.7, 13.4 Hz, 1H), 2.00–2.07 (m, 1H), 1.62–1.67 (m, 1H), 1.14–1.27 (m, 22H), 0.98–1.07 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 204.3, 169.8, 166.8, 162.5, 154.9, 123.9, 120.4, 105.5, 103.5, 94.4, 93.9, 80.7, 67.8, 64.2, 54.8, 52.4, 51.7, 47.3, 36.4, 34.2, 34.0, 20.9, 18.3 (3C), 18.2 (3C), 12.9 (3C), 9.2; ^{13}C NMR (150 MHz, CDCl_3) δ 203.5, 170.3, 166.2, 162.0, 154.6, 123.6, 119.9, 104.9, 103.0, 94.6, 93.4, 80.8, 67.1, 64.0, 55.4, 53.2, 51.3, 47.1, 36.4, 34.4 (2C), 20.2, 18.0 (3C), 17.9 (3C), 12.4 (3C), 9.0; IR (film) 2949, 2855, 1775, 1740, 1693, 1622, 1499, 1458, 1399,

1381, 1349, 1234, 1199, 1152, 1135, 1097, 1036, 1007, 883, 734, 682 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{32}\text{H}_{46}\text{N}_2\text{O}_7\text{Si})$ $[\text{M}+\text{H}]^+$ 621.2966; found 621.2945.

Lawesson's reagent (28 mg, 0.71 mmol) was added to a toluene solution (1.8 mL) of **20** (35 mg, 0.059 mmol) at 25 °C under Ar. The heterogeneous mixture was warmed to 110 °C and stirred for 4 h. Upon completion, the now homogeneous yellow solution was cooled to 25 °C and concentrated onto Celite. Flash chromatography (SiO_2 , 20% EtOAc–hexanes) afforded **21** as a pale yellow solid (25 mg, 69%, 50–81%): ^1H NMR (600 MHz, C_6D_6) δ 6.42 (d, J = 8.4 Hz, 1H), 6.09 (dd, J = 1.4, 8.0 Hz, 1H), 5.87 (d, J = 1.4 Hz, 1H), 4.74 (dd, J = 5.5, 10.6 Hz, 1H), 4.16–4.21 (m, 2H), 4.12 (s, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 2.93 (t, J = 12.1 Hz, 1H), 2.72 (s, 3H), 2.56 (dd, J = 5.5, 13.2 Hz, 1H), 2.01–2.09 (m, 1H), 1.66–1.71 (m, 1H), 1.25–1.34 (m, 3H), 1.20 (d, J = 7.7 Hz, 9H), 1.15 (d, J = 7.7 Hz, 9H), 0.86–0.93 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.9, 203.8, 166.5, 162.6, 155.0, 123.9, 119.9, 103.6, 102.5, 94.6, 94.1, 80.7, 73.0, 64.9, 54.9, 54.8, 52.5, 52.0, 36.0, 34.1, 34.0, 20.9, 18.6 (3C), 18.5 (3C), 13.2 (3C), 9.2; IR (film) 2940, 2865, 1774, 1742, 1621, 1500, 1420, 1360, 1321, 1236, 1205, 1135, 1106, 1006, 881, 850 cm^{-1} ; HRMS (MALDI-FTMS) calcd for $(\text{C}_{32}\text{H}_{46}\text{N}_2\text{O}_6\text{SSi})$ $[\text{M}+\text{H}]^+$ 615.2918; found 615.2920.

A solution of **21** (31 mg, 0.051 mmol) in anhydrous THF (2.5 mL) was added to excess Ra–Ni (pretreated with successive washes in H_2O (3x), MeOH (3x), THF (3x)) under Ar. The mixture was stirred at 25 °C for 2 h before being filtered through a pad of Celite, and concentrated under reduced pressure. The residue was taken up in EtOAc and passed through a short plug of SiO_2 to provide **22** as a pale yellow oil (18 mg, 61%; 54–78%): ^1H NMR (600

MHz, C₆D₆) δ 6.83 (d, J = 8.3 Hz, 1H), 6.27 (dd, J = 2.2, 8.3 Hz, 1H), 5.95 (d, J = 2.2 Hz, 1H), 4.34 (s, 1H), 4.22–4.27 (m, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 3.21–3.25 (m, 2H), 2.96–3.01 (m, 2H), 2.87 (s, 3H), 2.39–2.44 (m, 1H), 2.30 (dd, J = 4.0, 12.7 Hz, 1H), 2.12–2.18 (m, 1H), 1.99–2.04 (m, 1H), 0.85–1.20 (m, 26H); ¹³C NMR (150 MHz, C₆D₆) δ 207.3, 168.2, 162.3, 154.7, 124.6, 123.0, 110.9, 103.1, 93.9, 92.6, 82.9, 65.3, 62.5, 54.9, 54.8, 52.2, 51.6, 51.1, 38.8, 35.3, 34.0, 21.9, 18.2 (6C), 12.5 (3C), 10.0; IR (film) 2943, 2865, 1770, 1621, 1500, 1462, 1328, 1252, 1097, 1026, 882, 881, 737, 683 cm⁻¹; HRMS (MALDI-FTMS) calcd for (C₃₂H₄₈N₂O₆Si) [M+H]⁺ 585.3354; found 585.3385.

PtO₂ (1–2 mg) and a drop of conc. HCl was added to a solution of **22** (8.8 mg, 0.015 mmol) in MeOH (0.7 mL) at 25 °C. The mixture was stirred under 40–45 psi of H₂ for 2 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst, diluted with EtOAc and washed with a saturated aqueous NaHCO₃. The aqueous layer was extracted with EtOAc (2x), the combined organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (SiO₂, 25% EtOAc–hexanes) afforded **23** as a white solid (7.2 mg, 82%): ¹H NMR (600 MHz, C₆D₆) δ 7.76 (s, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.43 (dd, J = 2.0, 8.1 Hz, 1H), 6.10 (d, J = 1.8 Hz, 1H), 3.86 (s, 3H), 3.81–3.83 (m, 1H), 3.49 (s, 3H), 3.37 (s, 3H), 2.92 (d, J = 11.4 Hz, 1H), 2.82 (t, J = 8.8 Hz, 1H), 2.68 (d, J = 14.0 Hz, 1H), 2.45 (s, 3H), 2.29 (td, J = 10.1, 13.6 Hz, 1H), 2.04–2.08 (m, 2H), 1.93–1.99 (m, 1H), 1.66 (d, J = 11.4 Hz, 1H), 1.53–1.58 (m, 1H), 1.29–1.35 (m, 1H), 1.08–1.20 (m, 21H), 0.87 (dd, J = 3.3, 13.8 Hz, 1H), 0.49 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 200.8, 170.1, 161.6, 155.5, 128.3, 123.1, 105.7, 96.8, 86.2, 80.2, 77.1, 65.9, 59.6, 54.9, 54.2, 51.6 (2C), 47.3, 45.3, 40.3, 36.9, 28.2, 18.4 (6C), 12.5 (3C), 7.5; IR (film) 2944, 2861, 1749, 1718, 1610, 1595, 1497, 1456, 1246, 1226, 1164, 1092, 1072, 1020, 882, 728, 677 cm⁻¹; HRMS (MALDI-FTMS) calcd for (C₃₂H₅₀N₂O₆Si) [M+H]⁺ 587.3511; found 587.3521.

Bu₄NF (15 μ L, 0.015 mmol, 1.0 M in THF) was added dropwise to a THF (1 mL) solution of **23** (5.8 mg, 0.010 mmol) at 0 °C under Ar. The reaction mixture was stirred for 3 h at 0 °C and then slowly warmed to 25 °C until the starting material was consumed. The mixture was diluted with EtOAc and washed with a saturated aqueous NH₄Cl. The aqueous layer was extracted with EtOAc (2x), and the combined organic layers were dried with Na₂SO₄, filtered, and concentrated in vacuo. PTLC (SiO₂, 5% MeOH–CH₂Cl₂) afforded **24** as a white amorphous solid (4.1 mg, 98%): ¹H NMR (600 MHz, C₆D₆) δ 8.46 (br s, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.37 (dd, *J* = 1.6, 8.1 Hz, 1H), 6.13 (d, *J* = 1.7 Hz, 1H), 4.05–4.08 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H), 3.30–3.35 (m, 1H), 3.26 (d, *J* = 11.8 Hz, 1H), 2.67 (s, 3H), 2.64 (d, *J* = 14.9 Hz, 1H), 2.43–2.52 (m, 3H), 2.40 (s, 1H), 2.17 (d, *J* = 11.8 Hz, 1H), 1.74 (br s, 1H), 1.36–1.44 (m, 1H), 1.36 (dd, *J* = 3.3, 14.7 Hz, 1H), 1.21–1.29 (m, 1H), 0.50 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 205.9, 169.9, 161.1, 154.6, 127.0, 123.0, 105.3, 96.8, 85.1, 79.5, 76.6, 65.2, 58.0, 55.4, 53.7, 52.6, 51.5, 48.2, 44.6, 40.1, 36.3, 26.8, 7.2; IR (film) 3367 (br), 2934, 2864, 1743, 1712, 1617, 1499, 1456, 1432, 1255, 1224, 1165, 1082, 1070, 1039 cm⁻¹; HRMS (MALDI–FTMS) calcd for (C₂₃H₃₀N₂O₆) [M+H]⁺ 431.2177; found 431.2181.

A solution of **24** (3.0 mg, 0.007 mmol) and Ph₃P (3.7 mg, 0.014 mmol) in anhydrous CH₃CN (60 μ L) was warmed to 70 °C. After 10–15 min at this temperature, anhydrous CCl₄ (40 μ L) was added dropwise via syringe and the mixture was stirred for an additional 1 h at 70 °C, before cooling to 25 °C. The solution is diluted with CH₂Cl₂ and washed with dilute aqueous NH₄OH. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo. PTLC (SiO₂, 5% MeOH–CH₂Cl₂) afforded **25** as a white amorphous solid (1.75 mg, 62%) identical in all respects

to material previously reported (*J. Org. Chem.* **1985**, *50*, 961): ^1H NMR (500 MHz, CDCl_3) δ 6.99 (d, J = 8.4 Hz, 1H), 6.35 (dd, J = 2.2, 8.1 Hz, 1H), 6.11 (d, J = 1.8 Hz, 1H), 5.79 (dd, J = 4.4, 9.9 Hz, 1H), 5.69 (d, J = 9.9 Hz, 1H), 3.93 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.44–3.58 (m, 2H), 2.87 (d, J = 16.1 Hz, 1H), 2.71 (s, 1H), 2.69 (s, 3H), 2.49–2.59 (m, 3H), 1.49–1.57 (m, 1H), 1.28–1.33 (m, 1H), 0.45 (t, J = 7.3 Hz, 3H); HRMS (MALDI–FTMS) calcd for ($\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_5$) $[\text{M}+\text{H}]^+$ 413.2085; found 413.2085.

A solution of **25** (1.4 mg, 0.0034 mmol) in anhydrous THF (38 μL) at -30 to -25 $^\circ\text{C}$ was treated with AlCl_3 (5.4 mg, 0.04 mmol). The mixture was stirred and sodium bis(2-methoxyethoxy)aluminium hydride (86 μL of a 0.0512 M solution in THF) was added dropwise. The temperature was slowly raised to -20 $^\circ\text{C}$. Upon completion of the reaction based on TLC, the solution was diluted with EtOAc, and washed with H_2O . The aqueous layer was extracted with EtOAc (3x), dried over Na_2SO_4 , filtered, and concentrated in vacuo. PTLC (SiO_2 , 5% $\text{MeOH}-\text{CH}_2\text{Cl}_2$) afforded **26** as a film (0.6 mg, 43%; 43–50%) identical in all respects to material previously reported (*Collect. Czech. Chem. Commun.* **2000**, *65*, 789) and identical to authentic material prepared from naturally occurring vindoline: ^1H NMR (600 MHz, CDCl_3) δ 9.24 (s, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.28 (dd, J = 2.2, 7.9 Hz, 1H), 6.06 (d, J = 2.2 Hz, 1H), 5.87 (dd, J = 3.5, 10.5 Hz, 1H), 5.74 (d, J = 10.1 Hz, 1H), 4.08 (d, J = 7.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.72 (s, 1H), 3.36–3.50 (m, 2H), 2.83–2.89 (m, 1H), 2.72 (s, 3H), 2.66 (s, 1H), 2.49–2.62 (m, 2H), 2.19–2.28 (m, 2H), 1.44–1.51 (m, 1H), 0.98–1.04 (m, 1H), 0.67 (t, J = 7.4 Hz, 3H); HRMS (MALDI–FTMS) calcd for ($\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5$) $[\text{M}+\text{H}]^+$ 415.2227; found 415.2222.

A solution of deacetylvindoline (**26**, 1.2 mg, 0.0029 mmol) in Ac₂O (80 µL) at 25 °C was treated with NaOAc (1.2 mg, 0.014 mmol). The reaction mixture was stirred at 25 °C for 2 h, before being diluted with CH₂Cl₂. The pH was adjusted to 10 with addition of saturated aqueous NaHCO₃, the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. PTLC (SiO₂, EtOAc) afforded vindoline (**3**) as a white amorphous solid (1.1 mg, 83%) identical in all respects with authentic material: ¹H NMR (600 MHz, CDCl₃) δ 9.55 (s, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.29 (dd, *J* = 1.8, 7.9 Hz, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 5.85 (dd, *J* = 4.6, 10.3 Hz, 1H), 5.46 (s, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.37–3.55 (m, 2H), 2.77–2.87 (m, 1H), 2.67 (s, 3H), 2.46–2.59 (m, 1H), 2.25–2.41 (m, 2H), 2.07 (s, 3H), 2.04 (s, 1H), 1.60–1.71 (m, 1H), 1.06–1.19 (m, 1H), 0.48 (t, *J* = 7.2 Hz, 3H); HRMS (MALDI–FTMS) calcd for (C₂₅H₃₂N₂O₆) [M+H]⁺ 457.2333; found 457.2313.

References

- (S1) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.
- (S2) Feldman, P. L. Rapoport, H. *Synthesis* **1986**, 735.
- (S3) He, F.; Bo, Y.; Altom, J. D. Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.
- (S4) Other synthetic routes to methyl 4-ketohexanoate: (a) Mori, K.; Takikawa, H.; Nishimura, Y. ; Horikiri, H. *Liebigs. Ann. Chem.* **1997**, 327. (b) Banwell, M. G.; Edward, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296.
- (S5) (a) Moza, B., K.; Trojanek, J. *Chem. Industry* **1962**, *4*, 1425-1427. (b) Norbert N. *Bull. Chim. Soc. France* **1963**, 1509