Supporting Information

Catharanthine C16 Substituent Effects on the Biomimetic Coupling with Vindoline: Preparation and Evaluation of a Key Series of Vinblastine Analogues

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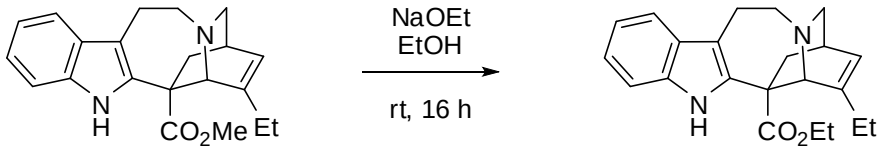
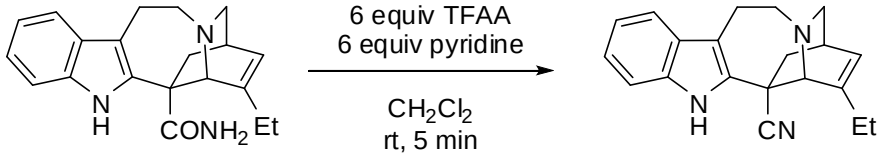


4 **5**

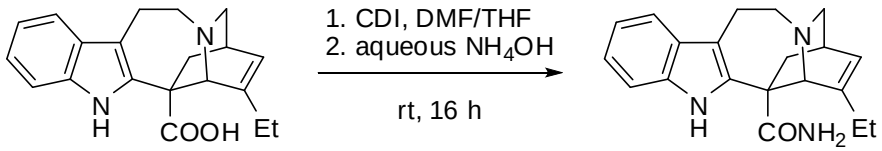
Compound 5. Catharanthine **4** (14.8 mg, 0.044 mmol) was dissolved in a solution of 1 M NaOEt (2 mL) and stirred for 16 h at room temperature. EtOAc (5 mL) was added and the resulting mixture was washed with saturated aqueous NaCl (5 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 50% EtOAc−CH_2Cl_2) provided **5** (7.6 mg, 49% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br s, NH, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.1 Hz, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 5.94 (d, *J* = 4.9 Hz, 1H), 4.23−4.16 (m, 2H), 3.60−3.56 (m, 1H), 3.41−3.38 (m, 1H), 3.33−3.27 (m, 1H), 2.94−2.92 (m, 1H), 2.87−2.85 (m, 3H), 2.74−2.71 (m, 2H), 2.37−2.32 (m, 1H), 2.19−2.14 (m, 1H), 1.78 (d, *J* = 11.1 Hz, 1H), 1.27 (t, *J* = 8.8 Hz, 3H), 1.07 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 173.7, 136.5, 134.9, 129.0, 123.6, 121.8, 119.4, 118.2, 110.5, 110.4, 61.8, 55.2, 53.0, 49.1, 38.7, 30.7, 29.7, 26.5, 21.3, 14.1, 10.6; IR (film) ν_{max} 3232, 2969, 2360, 1736, 1459, 1235, 1085, 746 cm^{-1}; HRMS ESI–TOF *m/z* 351.2054 ($C_{22}H_{26}N_2O_2$ + H^+, required 351.2067); $[\alpha]^{23}_D$ +36 (*c* 0.14, $CHCl_3$).



7 **6**

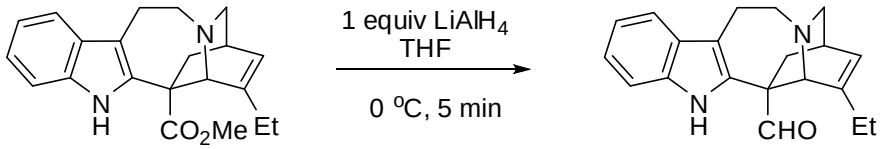
Compound 6. Compound **7** (62 mg, 0.19 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and pyridine (94 µL, 1.16 mmol) was added, followed by dropwise addition of trifluoroacetic anhydride (161 µL, 1.16 mmol). The reaction mixture was stirred for 5 min, then diluted with EtOAc (5 mL) and washed with saturated sodium bicarbonate (5 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 25% EtOAc−hexanes) provided **6** (27 mg, 46% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br s, NH, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.05 (d, *J* = 5.3 Hz, 1H), 3.88 (s, 1H), 3.46−3.38 (m, 3H), 3.08 (d, *J* = 8.2 Hz, 1H),

2.88−2.86 (m, 2H), 2.78−2.74 (m, 1H), 2.45−2.38 (m, 3H), 2.10 (d, *J* = 13.4 Hz, 1H), 1.18 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 134.2, 132.3, 129.3, 122.34, 122.30, 121.9, 119.9, 118.2, 110.8 (2C), 64.0, 52.6, 47.5, 44.2, 41.1, 29.6, 27.1, 20.4, 10.4; IR (film) ν_{max} 3347, 2849, 2231, 1457, 1123, 906, 727 cm^{-1}; HRMS ESI–TOF *m/z* 304.1819 ($C_{20}H_{21}N_3$ + H^+, required 304.1808); $[\alpha]^{23}_D$ −0.11 (*c* 0.46, $CHCl_3$).



9 **7**

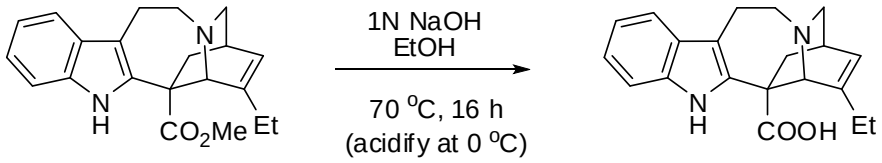
Compound 7. Compound **9** (81 mg, 0.25 mmol) was dissolved in anhydrous DMF (500 µL) and anhydrous THF (2.5 mL). 1,1'-Carbonyldiimidazole (203 mg, 1.25 mmol) was added and the resulting mixture was stirred for 45 min at room temperature. The solution was cooled to 0 °C before the addition of NH_4OH (3 mL). The resulting mixture was warmed to room temperature and stirred for 16 h. Water was added (5 mL) and the mixture was extracted with EtOAc (3×10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 5:47:47 MeOH/EtOAc/CH_2Cl_2) provided **7** (52 mg, 65% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, NH, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 6.9 Hz, 1H), 5.96 (d, *J* = 5.5 Hz, 1H), 5.60 (br s, 2H), 3.95 (s, 1H), 3.62−3.56 (m, 1H), 3.40−3.35 (m, 1H), 3.32−3.28 (m, 1H), 3.02−2.96 (m, 1H), 2.85−2.81 (m, 2H), 2.76−2.74 (m, 1H), 2.38−2.24 (m, 1H), 2.24 (d, *J* = 5.5 Hz, 1H), 2.04−1.99 (m, 2H), 1.62 (d, *J* = 12.67 Hz, 1H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 148.0, 137.1, 135.4, 128.5, 123.2, 122.1, 119.3, 118.2, 111.2, 110.4, 63.8, 55.5, 53.1, 49.4, 36.5, 30.39, 26.93, 21.5, 10.5; IR (film) ν_{max} 3291, 2962, 1676, 1460, 1363, 1105, 745 cm^{-1}; HRMS ESI–TOF *m/z* 322.1924 ($C_{20}H_{23}N_3O$ + H^+, required 322.1914); $[\alpha]^{23}_D$ +0.48 (*c* 0.17, $CHCl_3$).



4 **8**

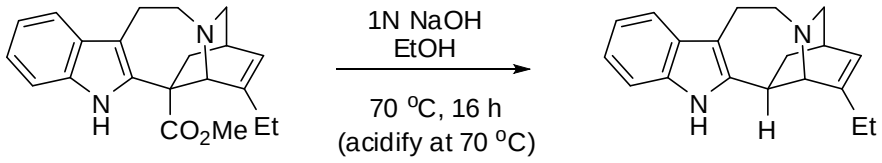
Compound 8. Catharanthine **4** (84 mg, 0.25 mmol) was dissolved in anhydrous THF (4 mL) and cooled to 0 °C. $LiAlH_4$ (9.2 mg, 0.25 mmol) was added portion-wise to the solution and the resulting suspension was stirred for 5 min. The reaction was carefully quenched by addition of a solution of saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 10% MeOH−EtOAc) provided **8** (28 mg, 37% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.83 (br s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 6.9 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 5.99 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 1H), 3.57−3.52 (m, 1H), 3.45−3.35 (m, 2H), 3.00 (d, *J* = 8.6 Hz, 1H), 2.94−2.88 (m, 2H), 2.80−2.79 (m, 1H), 2.56 (dt, *J* = 13.0, 3.0 Hz, 1H), 2.37−2.32 (m, 1H), 2.11−2.05 (m, 1H), 1.77 (dd, *J* = 13.0, 2.1 Hz, 1H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 148.2, 135.2, 134.0, 129.0, 124.3, 123.0,

119.5, 118.1, 112.7, 110.6, 62.1, 59.4, 53.2, 49.4, 35.3, 30.5, 26.8, 21.1, 10.6; IR (film) ν_{max} 3383, 3051, 2843, 1708, 1458, 740 cm^{-1}; HRMS ESI–TOF *m/z* 307.1798 ($C_{20}H_{22}N_2O$ + H^+, required 307.1805); $[\alpha]^{23}_D$ +0.52 (*c* 0.48, $CHCl_3$).



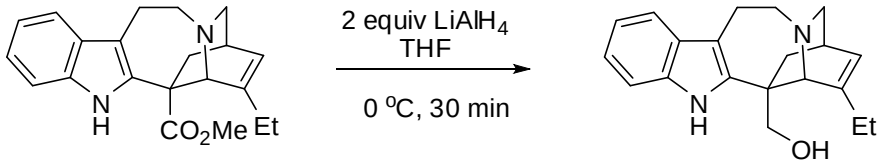
4 **9**

Compound 9. Catharanthine **4** (85 mg, 0.25 mmol) was dissolved in absolute EtOH (2 mL) and a solution of 1 N NaOH (3 mL) was added. The resulting mixture was warmed to 70 °C for 16 h. The reaction mixture was cooled to 0 °C before it was acidified by dropwise addition of 2 N HCl. The mixture was extracted into EtOAc (3 ×15 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 1:2:2 MeOH/EtOAc/CH_2Cl_2) provided **9** (56 mg, 70% yield). Spectral data was as previously reported.[1]



4 **10**

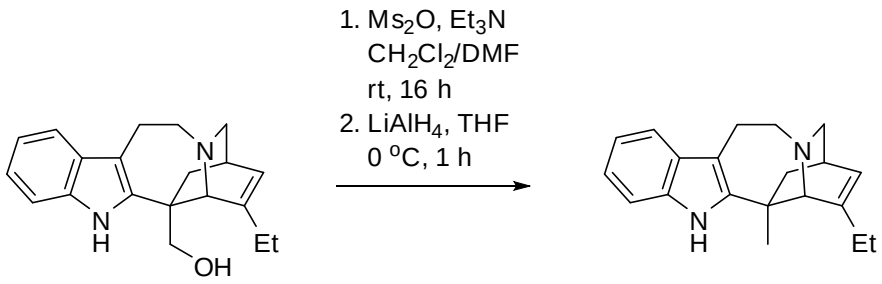
Compound 10. Catharanthine **4** (85 mg, 0.25 mmol) was dissolved in absolute EtOH (2 mL) and a solution of 1 N NaOH (3 mL) was added. The resulting mixture was warmed to 70 °C for 16 h. The reaction mixture was acidified by dropwise addition of 2 N HCl. The mixture was extracted into EtOAc (3 ×15 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 1:2:2 MeOH/EtOAc/CH_2Cl_2) provided **10** (59 mg, 85% yield). Spectral data was as previously reported.[1]



4 **11**

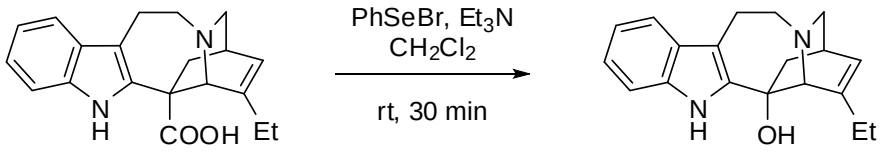
Compound 11. Catharanthine **4** (44.6 mg, 0.133 mmol) was added to a suspension of $LiAlH_4$ (9.9 mg, 0.27 mmol) in THF (2 mL) at 0 °C and the solution was stirred for 10 min. The reaction was carefully quenched by addition of a solution of saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 15% MeOH−EtOAc) provided **11** (32 mg, 77% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (br s, NH, 1H), 7.48−7.46 (m, 1H), 7.31−7.28 (m, 1H), 7.15−7.13 (m, 2H), 5.89 (d, *J* = 7.1 Hz, 1H), 3.68 (d, *J* = 11.1 Hz, 1H), 3.65 (s, 1H), 3.57 (d, *J* = 11.1 Hz, 1H), 3.32−3.29 (m, 2H), 3.17−3.14 (m, 2H), 2.93−2.90 (m, 1H), 2.84−2.82

(m, 1H), 2.72−2.63 (m, 2H), 2.50−2.44 (m, 1H), 2.28−2.20 (m, 1H), 1.63 (d, *J* = 12.3 Hz, 1H), 1.49 (d, *J* = 12.8 Hz, 1H), 1.15 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 150.1, 134.7, 128.4, 121.4, 120.9, 118.9, 118.1, 110.6, 109.7, 68.8, 62.4, 52.6, 50.7, 47.7, 36.3, 30.2, 26.7, 20.6, 10.3; IR (film) ν_{max} 3352, 2926, 1736, 1461, 1240, 1045, 741 cm^{-1}; HRMS ESI–TOF *m/z* 309.1971 ($C_{20}H_{24}N_2O$ + H^+, required 309.1961); $[\alpha]^{23}_D$ +0.07 (*c* 0.83, MeOH).



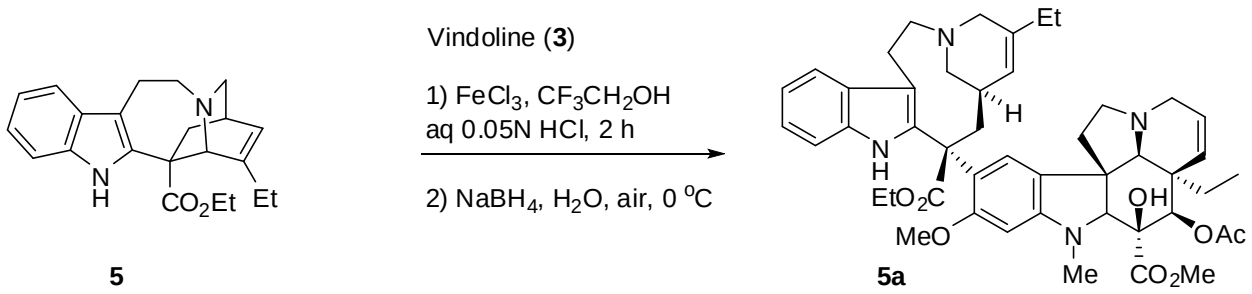
11 **12**

Compound 12. A solution of compound **11** (79 mg, 0.26 mmol) in anhydrous 1:1 CH_2Cl_2/DMF (2.5 mL) at 0 °C was treated with methanesulfonyl anhydride (54 mg, 0.31 mmol) and Et_3N (109 µL, 0.78 mmol). The resulting reaction mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 10% MeOH−EtOAc). A solution of $LiAlH_4$ (3.3 mg, 0.088 mmol) in anhydrous THF (440 µL) was treated with the mesylate product (17 mg, 0.044 mmol) at 0 °C. The reaction mixture was stirred for 1 h before careful quench with a drop of an aqueous solution of NH_4Cl. EtOAc (2 mL) was added and the solution was washed with saturated aqueous NH_4Cl (1 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 10% MeOH−EtOAc) provided **12** (27 mg, 32% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br s, NH, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.17−7.09 (m, 2H), 5.89 (d, *J* = 6.8 Hz, 1H), 3.49−3.43 (m, 2H), 3.37−3.29 (m, 1H), 2.96−2.87 (m, 2H), 2.73−2.71 (m, 1H), 2.54−2.45 (m, 1H), 2.20−2.11 (m, 1H), 1.86 (d, *J* = 10.8 Hz, 2H), 1.53 (d, *J* = 11.8 Hz, 2H), 1.29 (s, 3H), 1.13 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 134.1, 130.1, 128.9, 121.4, 119.4, 118.1 (2C), 110.2, 109.1, 65.6, 53.0, 47.7, 41.54, 41.52, 30.4, 27.8, 27.2, 23.5, 10.3; IR (film) ν_{max} 2928, 1461, 1261, 1100, 730 cm^{-1}; HRMS ESI–TOF *m/z* 293.2017 ($C_{20}H_{24}N_2$ + H^+, required 293.2012); $[\alpha]^{23}_D$ +17 (*c* 0.26, $CHCl_3$).

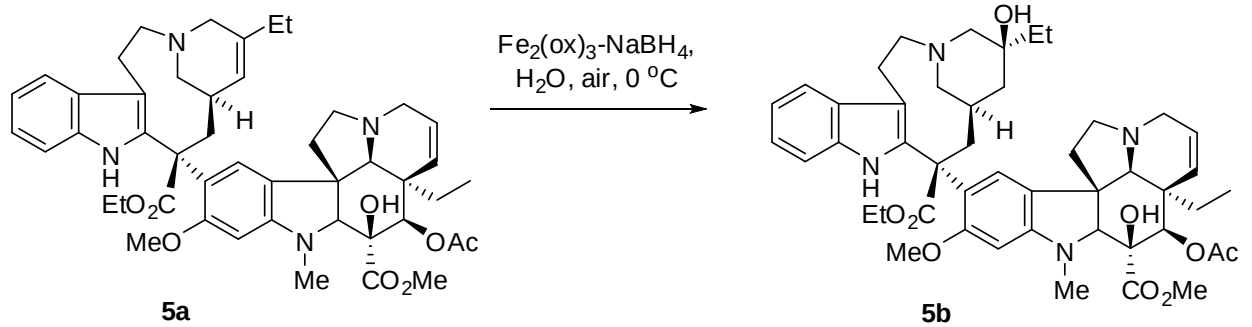


9 **13**

Compound 13. A solution of phenylselenyl bromide (22 mg, 0.09 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of **9** (20 mg, 0.06 mmol) and Et_3N (18 µL) in CH_2Cl_2 (1.5 mL) at room temperature under an atmosphere of Ar. After 30 min, the mixture was diluted with CH_2Cl_2 (5 mL) and washed with H_2O (2 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography (SiO_2, 10% MeOH−EtOAc) provided **13** (6 mg, 29% yield). Spectral data was as previously reported.[1]

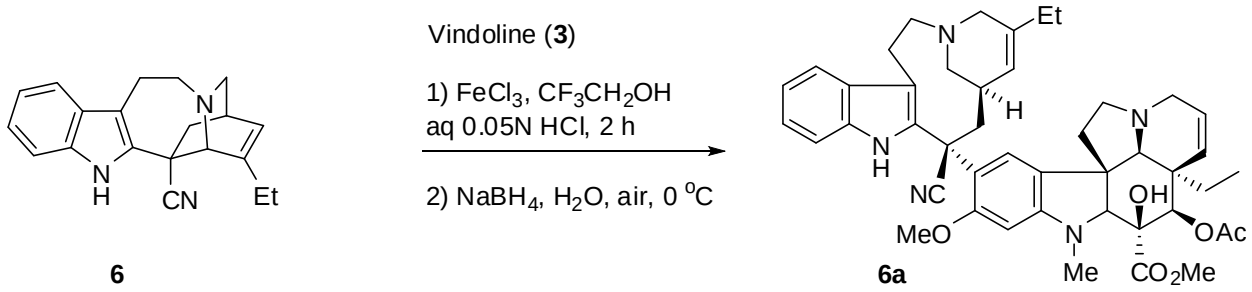


Compound 5a. Iron(III) chloride hexahydrate (42 mg, 0.16 mmol) was added to a solution of vindoline (**3**, 14 mg, 0.031 mmol) and **5** (11 mg, 0.031 mmol) in CF_3CH_2OH (0.12 mL), aqueous 0.1 N HCl (0.59 mL) and H_2O (0.59 mL) at 25 °C under Ar. The reaction mixture was stirred for 2 h at 25 °C. The solution was cooled to 0 °C and a solution of $NaBH_4$ (1.2 mg, 0.031 mmol) in H_2O (0.1 mL) was added. The resulting mixture was stirred for 30 min before being quenched by the addition of 30% aqueous NH_4OH (0.5 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 0−10% MeOH/EtOAc) afforded **5a** (32 mg, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (br s, 1H), 8.06 (s, 1H), 7.53−7.50 (m, 1H), 7.18−7.10 (m, 3H), 6.61−6.60 (m, 1H), 6.12 (s, 1H), 5.85 (dd, *J* = 10.0, 3.5 Hz, 1H), 5.49−5.47 (m, 2H), 5.28 (d, *J* = 9.0 Hz, 1H), 4.10−4.01 (m, 2H), 3.81 (s, 3H), 3.80 (s, 1H), 3.79 (s, 3H), 3.72 (s, 1H), 3.61 (s, 1H), 3.53−3.50 (m, 1H), 3.39−3.35 (m, 2H), 3.31−3.26 (m, 2H), 3.22−3.19 (m, 1H), 3.09−2.94 (m, 2H), 2.84−2.78 (m, 1H), 2.71 (s, 3H), 2.65 (s, 1H), 2.61−2.57 (m, 1H), 2.47−2.40 (m, 2H), 2.11 (s, 3H), 1.96−1.91 (m, 1H), 1.87−1.85 (m, 1H), 1.83−1.79 (m, 2H), 1.73−1.68 (m, 1H), 1.42−1.36 (m, 1H), 1.34−1.30 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); IR (film) ν_{max} 3467, 2963, 1738, 1458, 1226, 1040, 748 cm^{-1}; HRMS ESI-TOF *m/z* 807.4351 ($C_{47}H_{58}N_4O_8$ + H^+, required 807.4255); $[\alpha]^{23}_D$ +36 (*c* 0.38, $CHCl_3$).

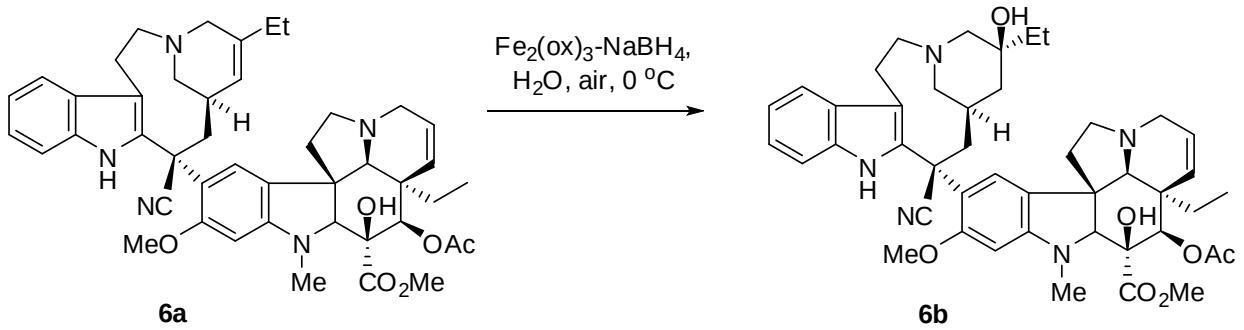


Compound 5b. A solution of iron(III) oxalate hexahydrate (90 mg, 0.19 mmol) in H_2O (80 mL) was cooled to 0 °C and air was bubbled through the mixture for 10 min. A solution of compound **5a** (15 mg, 0.019 mmol) dissolved in CF_3CH_2OH (0.9 mL), aqueous 0.1 N HCl (0.45 mL) and H_2O (0.45 mL) was transferred by pipette to this aqueous iron(III) oxalate solution and $NaBH_4$ (14 mg, 0.37 mmol) in H_2O (1 mL) was added to the mixture at 0 °C. The resulting mixture was stirred for 30 min before being quenched by the addition of 30% aqueous NH_4OH (3 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2. The combined organic layer was dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure. PTLC (SiO_2, Et_3N:MeOH:EtOAc = 3:3:97) afforded **5b** (4 mg, 26%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.52 (d, *J* = 7.66 Hz, 1H), 7.17−7.08 (m, 3H), 6.62 (s, 1H), 6.11 (s, 1H), 5.86−5.83 (m, 1H), 5.48 (s, 1H), 5.28 (d, *J* = 9.9 Hz, 1H), 4.07−4.01 (m, 2H), 3.94 (t, *J* = 14.7 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 1H), 3.78 (s, 3H), 3.73 (s, 2H), 3.67−3.61 (m, 2H), 3.41−3.36 (m, 2H), 3.30−3.28 (m, 2H), 3.15−3.13 (m, 2H), 2.83−2.80 (m, 3H), 2.71 (s, 3H), 2.65 (s, 1H), 2.46−2.42 (m, 2H), 2.32−2.30 (m, 2H), 2.20−2.15 (m, 1H), 2.10 (s, 3H), 1.88−1.77 (m, 2H), 1.50−1.40 (m, 2H), 1.33−1.30 (m, 2H), 1.11 (t, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H); IR (film) ν_{max} 3467, 2927, 1737, 1226, 1039, 735 cm^{-1}; HRMS ESI-TOF *m/z* 825.4422 ($C_{47}H_{60}N_4O_9$ + H^+, required 825.4433); $[\alpha]^{23}_D$ +37 (*c* 0.14, $CHCl_3$).

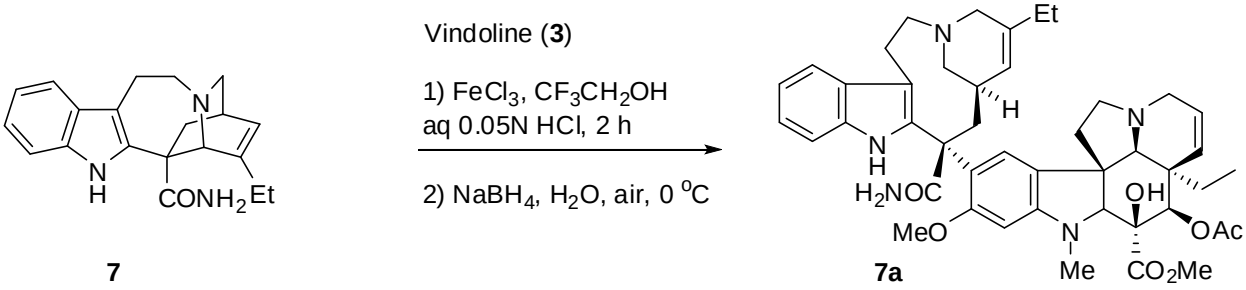


Compound 6a. Iron(III) chloride hexahydrate (53 mg, 0.20 mmol) was added to a solution of vindoline (**3**, 18 mg, 0.04 mmol) and **6** (12 mg, 0.04 mmol) in CF_3CH_2OH (0.14 mL), aqueous 0.1 N HCl (0.74 mL) and H_2O (0.74 mL) at 25 °C under Ar. The reaction mixture was stirred for 2 h at 25 °C. The solution was cooled to 0 °C and a solution of $NaBH_4$ (1.5 mg, 0.04 mmol) in H_2O (0.1 mL) was added. The resulting mixture was stirred for 30 min before being quenched by the addition of 30% aqueous NH_4OH (0.5 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 0−10% MeOH/EtOAc) afforded **6a** (57 mg, 95%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (br s, 1H), 7.16−6.99 (m, 3H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.29 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.07 (d, *J* = 2.2 Hz, 1H), 5.94−5.89 (m, 1H), 5.85 (dd, *J* = 10.2, 4.9 Hz, 1H), 5.45 (s, 2H), 5.27−5.23 (m, 2H), 3.79 (s, 1H), 3.787 (s, 3H), 3.782 (s, 3H), 3.75 (s, 1H), 3.66 (s, 1H), 3.61−3.56 (m, 2H), 3.51−3.47 (m, 1H), 3.44−3.40 (m, 1H), 3.32 (s, 1H), 3.13−3.10 (m, 1H), 2.68 (s, 1H), 2.67 (s, 3H), 2.66 (s, 2H), 2.55−2.49 (m, 1H), 2.41−2.26 (m, 2H), 2.17 (s, 2H), 2.09 (s, 1H), 2.07 (s, 3H), 1.66−1.62 (m, 2H), 1.27−1.25 (m, 2H), 0.88 (t, *J* = 5.3 Hz, 3H), 0.49 (t, *J* = 7.4 Hz, 3H); IR (film) ν_{max} 3454, 2961, 1737, 1230, 1039, 732 cm^{-1}; HRMS ESI-TOF *m/z* 760.4089 ($C_{45}H_{53}N_5O_6$ + H^+, required 760.4068); $[\alpha]^{23}_D$ +9 (*c* 0.14, $CHCl_3$).



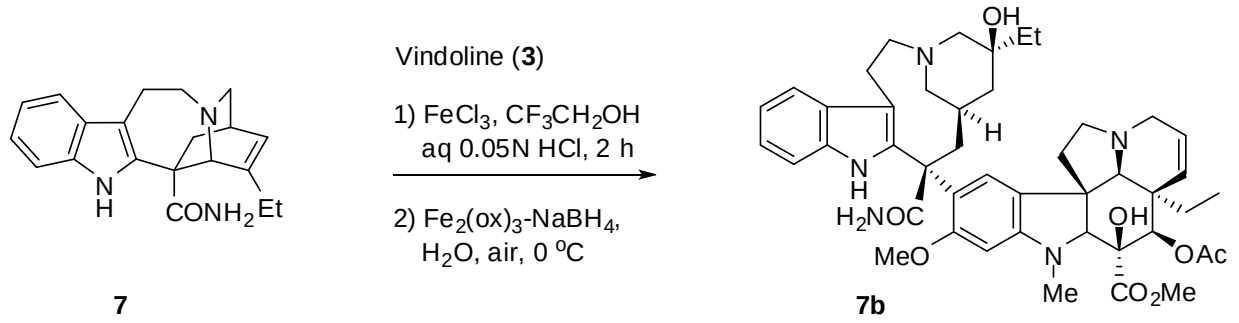
6a **6b**

Compound 6b. Prepared following the procedure detailed for **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.55−7.51 (m, 1H), 7.23−7.21 (m, 3H), 7.08−7.07 (m, 1H), 6.98 (d, *J* = 6.1 Hz, 1H), 6.14 (s, 1H), 6.05 (s, 1H), 5.96−5.91 (m, 1H), 5.82−5.81 (m, 1H), 5.51−5.39 (m, 2H), 5.29 (s, 1H), 5.24 (d, *J* = 10.7 Hz, 1H), 5.18 (s, 1H), 4.06 (t, *J* = 6.7 Hz, 1H), 3.83 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.68−3.63 (m, 1H), 3.58−3.56 (m, 2H), 3.41 (d, *J* = 6.5 Hz, 1H), 3.38−3.33 (m, 2H), 3.15−3.05 (m, 1H), 2.85−2.81 (m, 1H), 2.74 (s, 3H), 2.68 (s, 1H), 2.65 (s, 1H), 2.53−2.46 (m, 3H), 2.42−2.40 (m, 1H), 2.08 (s, 3H), 2.02−2.00 (m, 1H), 1.71−1.66 (m, 1H), 1.62−1.58 (m, 1H), 1.42−1.36 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.75 (t, *J* = 7.3 Hz, 3H); IR (film) ν_{max} 3455, 2927, 1740, 1615, 1459, 1241, 1040, 740 cm^{-1}; HRMS ESI-TOF *m/z* 778.4182 ($C_{45}H_{55}N_5O_7$ + H^+, required 778.7174); $[\alpha]^{23}_D$ −18 (*c* 0.17, $CHCl_3$).

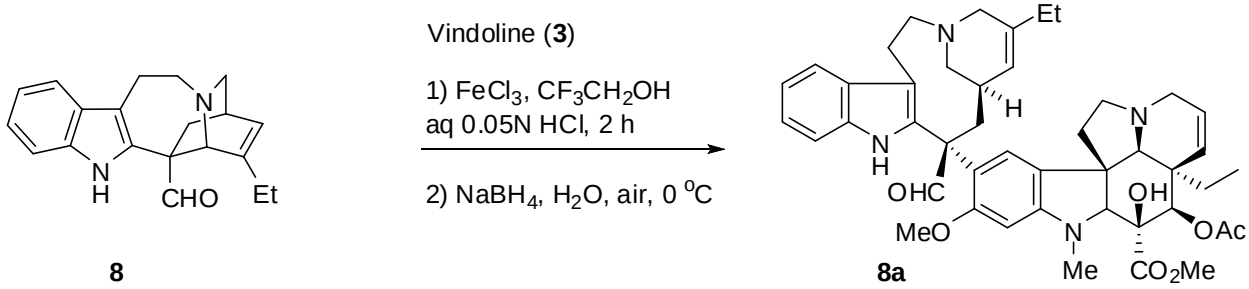


7 **7a**

Compound 7a. Iron(III) chloride hexahydrate (61 mg, 0.22 mmol) was added to a solution of vindoline (**3**, 20 mg, 0.045 mmol) and **7** (14 mg, 0.045 mmol) in CF_3CH_2OH (0.17 mL), aqueous 0.1 N HCl (0.84 mL) and H_2O (0.84 mL) at 25 °C under Ar. The reaction mixture was stirred for 2 h at 25 °C. The solution was cooled to 0 °C and a solution of $NaBH_4$ (1.7 mg, 0.045 mmol) in H_2O (0.1 mL) was added. The resulting mixture was stirred for 30 min before being quenched by the addition of 30% aqueous NH_4OH (0.5 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 0−10% MeOH/EtOAc) afforded **7a** (29 mg, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (br s, 1H), 8.37 (s, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.21−7.09 (m, 3H), 6.73 (br s, 1H), 6.14 (s, 1H), 5.83 (dd, *J* = 9.3, 4.4 Hz, 1H), 5.47 (br s, 2H), 5.45 (s, 2H), 5.26 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.49−3.29 (m, 6H), 3.19−3.11 (m, 2H), 2.99−2.97 (m, 1H), 2.96−2.80 (m, 2H), 2.79 (s, 1H), 2.71 (s, 3H), 2.63 (s, 1H), 2.46−2.42 (m, 2H), 2.22−2.15 (m, 1H), 2.10 (s, 3H), 1.96−1.89 (m, 2H), 1.77−1.68 (m, 2H), 1.67−1.58 (m, 1H), 1.42−1.34 (m, 1H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); IR (film) ν_{max} 3366, 2963, 1742, 1674, 1241, 1040, 748 cm^{-1}; HRMS ESI-TOF *m/z* 778.4165 ($C_{45}H_{55}N_5O_7$ + H^+, required 778.4174); $[\alpha]^{23}_D$ +23 (*c* 0.82, $CHCl_3$).

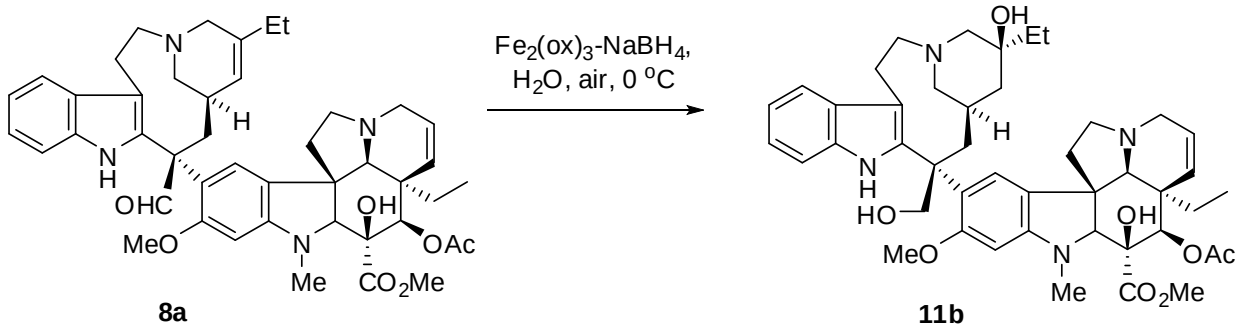


Compound 7b. Iron(III) chloride hexahydrate (64 mg, 0.24 mmol) was added to a solution of vindoline (**3**, 22 mg, 0.0483 mmol) and **7** (15.3 mg, 0.048 mmol) in CF_3CH_2OH (0.18 mL), aqueous 0.1 N HCl (0.89 mL) and H_2O (0.89 mL) at 25 °C under Ar. The reaction mixture was stirred for 2 h at 25 °C. Meanwhile, in a separate flask, a solution of iron(III) oxalate hexahydrate (230 mg, 0.48 mmol) in H_2O (190 mL) was cooled to 0 °C and air was bubbled through the mixture for 10 min. The coupling solution was transferred by pipette to this aqueous iron (III) oxalate solution and $NaBH_4$ (36 mg, 0.94 mmol) in H_2O (2.0 mL) was added to the mixture at 0 °C. The resulting mixture was stirred for 30 min before being quenched by the addition of 30% aqueous NH_4OH (3 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. PTLC (SiO_2, Et_3N:MeOH:EtOAc = 3:3:97) afforded **7b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.18−7.13 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.87−6.85 (br s, 1H), 6.13 (s, 1H), 5.82 (dd, *J* = 10.3, 4.2 Hz, 1H), 5.45 (s, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.25−4.17 (m, 2H), 4.06 (dd, *J* = 6.77 Hz, 1H), 3.79 (s, 6H), 3.76 (s, 1H), 3.67−3.62 (m, 2H), 3.55−3.50 (m, 2H), 3.37 (dd, *J* = 16.1, 5.4 Hz, 1H), 3.31−3.20 (m, 2H), 3.08−3.05 (m, 2H), 2.95−2.91 (m, 2H), 2.81 (d, *J* = 16.3 Hz, 1H), 2.72 (s, 3H), 2.61 (s, 1H), 2.46−2.42 (m, 2H), 2.25−2.19 (m, 2H), 2.09 (s, 3H), 2.07−2.00 (m, 2H), 1.77−1.69 (m, 1H), 1.56−1.53 (m, 1H), 1.38−1.35 (m, 1H), 1.31−1.30 (m, 2H), 0.92 (t, *J* = 8.7 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); IR (film) ν_{max} 3415, 2962, 1740, 1668, 1612, 1228, 1035, 732 cm^{-1}; HRMS ESI-TOF *m/z* 796.4275 ($C_{45}H_{57}N_5O_8$ + H^+, required 796.4280); $[\alpha]^{23}_D$ +25 (*c* 0.15, $CHCl_3$).



Compound 8a. Iron(III) chloride hexahydrate (41 mg, 0.15 mmol) was added to a solution of vindoline (**3**, 14 mg, 0.03 mmol) and **8** (9.2 mg, 0.03 mmol) in CF_3CH_2OH (0.11 mL), aqueous 0.1 N HCl (0.57 mL) and H_2O (0.57 mL) at 25 °C under Ar. The reaction mixture was stirred for 2 h at 25 °C. The solution was cooled to 0 °C and a solution of $NaBH_4$ (1.1 mg, 0.03 mmol) in H_2O (0.1 mL) was added. The resulting mixture was stirred for 30 min before being quenched by the addition of 30% aqueous NH_4OH (0.5 mL). The mixture was extracted with 10% MeOH in

CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 0−10% MeOH/EtOAc) afforded **8a** (30 mg, 49%): ^{1}H NMR (600 MHz, C_6D_6) δ 9.59 (s, 1H), 8.99 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.13−7.03 (m, 3H), 6.61 (s, 1H), 6.17 (s, 1H), 5.90 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.47 (s, 1H), 5.27 (d, *J* = 10.2 Hz, 1H), 4.06 (d, *J* = 6.7 Hz, 1H), 4.03 (s, 1H), 3.84 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.67−3.62 (m, 2H), 3.50−3.48 (m, 1H), 3.41−3.39 (m, 2H), 3.28−3.26 (m, 2H), 3.10−3.04 (m, 2H), 2.90−2.87 (m, 1H), 2.73 (s, 1H), 2.67 (s, 3H), 2.58−2.53 (m, 2H), 2.30−2.25 (m, 3H), 2.10 (s, 3H), 1.96 (s, 1H), 1.95−1.93 (m, 2H), 1.85−1.82 (m, 1H), 1.61−1.58 (m, 1H), 1.39−1.35 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); IR (film) ν_{max} 3456, 2930, 1738, 1240, 1041, 737 cm^{-1}; HRMS ESI-TOF *m/z* 763.4066 ($C_{45}H_{54}N_4O_7$ + H^+, required 763.4065); $[\alpha]^{23}_D$ +19 (*c* 0.32, $CHCl_3$).



8a **11b**

Compound 11b. Prepared following the procedure detailed for **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.47 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 4.0 Hz, 1H), 7.19−7.08 (m, 3H), 6.10 (d, *J* = 14.6 Hz, 1H), 5.81−5.76 (m, 1H), 5.47−5.39 (m, 1H), 5.28−5.21 (m, 1H), 5.11 (d, *J* = 9.2 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 4.06 (t, *J* = 6.6 Hz, 1H), 4.03 (s, 1H), 3.93 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.67−3.64 (m, 1H), 3.62 (s, 1H), 3.60−3.54 (m, 2H), 3.46 (s, 1H), 3.41 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.90 (s, 1H), 2.81 (s, 1H), 2.72 (s, 3H), 2.67−2.62 (m, 2H), 2.45−2.40 (m, 2H), 2.32 (s, 1H), 2.25−2.21 (m, 1H), 2.09 (s, 3H), 1.66−1.57 (m, 3H), 1.42−1.29 (m, 6H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 6.6 Hz, 3H); IR (film) ν_{max} 3367, 2925, 1735, 1615, 1238, 1039, 733 cm^{-1}; HRMS ESI-TOF *m/z* 783.4333 ($C_{45}H_{58}N_4O_8$ + H^+, required 783.4327); $[\alpha]^{23}_D$ +32 (*c* 0.12, $CHCl_3$).

References

[1] Kutney, J. P.; Honda, T.; Joshua, A. V.; Lewis, N. G.; Worth, B. R. *Helv. Chim. Acta* **1978**, *61*, 690.