Total Synthesis of (+)-Fendleridine (Aspidoalbidine) and (+)-1-Acetylaspidoalbidine

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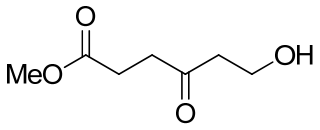
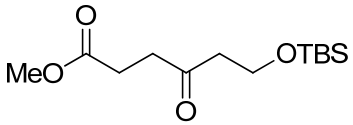
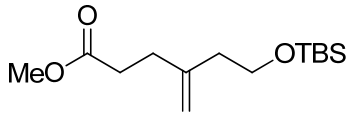


Methyl 6-Hydroxy-4-oxohexanoate (12). A solution of lactone **11**[1] (1.0 g, 7.8 mmol) in MeOH (29 mL) was cooled to 0 °C and treated with K_2CO_3 (221 mg, 1.6 mmol). The reaction mixture was stirred for 30 min at 0 °C, filtered, and the filtrate was concentrated under reduced pressure. Flash chromatography (SiO_2, 60% EtOAc–Hexanes) afforded **12** (1.14 g, 91%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (dd, *J* = 5.5, 11.5 Hz, 2H), 3.58 (s, 3H), 2.88 (t, *J* = 6 Hz, 1H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.61 (t, *J* = 5.5 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 173.1, 57.6, 51.6, 44.7, 37.3, 27.3; IR (film) ν_{max} 3461, 2954, 1731, 1708, 1200, 1041 cm^{-1}; HRMS-ESI-TOF *m/z* 183.0628 ($C_7H_{12}O_4$ + Na^+ requires 183.0631)

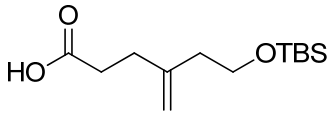


Methyl 6-(*tert*-Butyldimethylsilyloxy)-4-oxohexanoate (13). A solution of **12** (1.03 g, 6.4 mmol) and imidazole (0.88 g, 12.86 mmol) in DMF (26 mL) was treated with *tert*-butyldimethylsilyl chloride (1.45 g, 9.64 mmol). The reaction mixture was stirred at 25 °C for 4 h and quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (25 mL). The mixture was extracted with EtOAc (25 mL × 3), and the combined organic phase was washed with H_2O (15 mL × 2), saturated aqueous NaCl (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 30% EtOAc–hexanes) afforded **13** (1.61 g, 91%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (t, *J* = 7.5 Hz, 2H), 3.66 (s, 3H), 2.77 (t, *J* = 8.5 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 8.5 Hz, 2H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 173.2, 58.7, 51.7, 45.6, 38.1, 27.5, 25.8 (3C), 18.2, –5.5 (2C); IR (film) ν_{max} 2943, 2849, 1743, 1713, 1473, 1437, 1361, 1255, 1208, 1167, 1091, 1008, 944, 832, 779 cm^{-1}; HRMS-ESI-TOF *m/z* 275.1671 ($C_{13}H_{26}O_4Si$ + H^+ requires 275.1679)

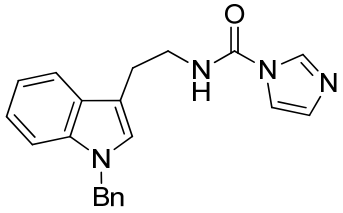


Methyl 6-(*tert*-Butyldimethylsilyloxy)-4-methylenehexanoate (14). A solution of Ph_3PCH_2Br (2.58 g, 7.21 mmol) in THF (35 mL) was cooled to 0 °C and treated dropwise with *n*-BuLi (2.9 mL, 7.21 mmol, 2.5 M). The reaction mixture was stirred at 0 °C for 30 min, and cooled to –78 °C before a solution of **13** (1.80 g, 6.56 mmol) in THF (7 mL) was added by cannula. After addition of the ketone was complete, the reaction mixture was stirred at –78 °C for 1 h, warmed to 25 °C, and stirred for an addition hour. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and the mixture was extracted with diethyl ether (20 mL × 3). The combined organic phase was washed with H_2O (10 mL), saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash

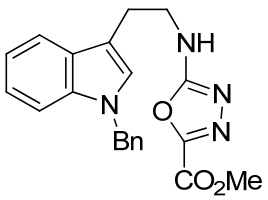
chromatography (SiO_2, 5% EtOAc–hexanes) afforded **14** (1.58 g, 88%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (d, *J* = 1.5 Hz, 1H), 4.76 (d, *J* = 1.5 Hz, 1H), 3.70 (t, *J* = 8.5 Hz, 2H), 3.66 (s, 3H), 2.47 (dd, *J* = 1.5, 11.5, Hz, 1H), 2.45 (d, *J* = 10.5 Hz, 1H), 2.35 (br dd, *J* = 8.5, 10.5 Hz, 2H), 2.24 (br t, *J* = 8.5 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 145.2, 114.0, 62.2, 51.6, 39.5, 32.5, 31.3, 25.9 (3C), 18.3, –5.4 (2C); IR (film) ν_{max} 2952, 2857, 1741, 1252, 1094 cm^{-1}; HRMS-ESI-TOF *m/z* 273.1880 ($C_{14}H_{28}O_3Si$ + H requires 273.1877).



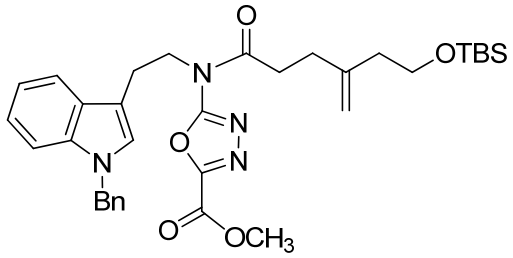
6-(*tert*-Butyldimethylsilyloxy)-4-methylenehexanoic Acid (15). A solution of **14** (5.42 g, 19.9 mmol) in THF (90 mL), MeOH (60 mL), and H_2O (30 mL) was treated with LiOH (1.91 g, 79.6 mmol) at 25 °C. The reaction mixture was stirred for 1.5 h before the MeOH and THF were removed under reduced pressure. The mixture was diluted with H_2O (30 mL) and was extracted with EtOAc (60 mL × 2), before the aqueous phase was acidified with 2 N HCl to pH 1 and extracted with EtOAc (60 mL × 3). The combined organic phase was washed with H_2O (20 mL), saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo to afford **15** (4.94 g, 96%) as a clear oil, which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (br s, 1H), 4.78 (m, 2H), 3.71 (t, *J* = 9.0 Hz, 2H), 2.52 (dd, *J* = 1.5, 10.5 Hz, 1H), 2.50 (d, *J* = 10.5 Hz, 1H), 2.36 (dd, *J* = 8.5, 10.5 Hz, 2H), 2.26 (br t, *J* = 8.5 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 144.9, 111.2, 62.3, 39.5, 32.5, 31.0, 25.9 (3C), 18.3, –5.3 (2C); IR (film) ν_{max} 2928, 1709, 1468, 1252, 1095, 831 cm^{-1}; HRMS-ESI-TOF *m/z* 257.1571 *m/z* ($C_{13}H_{26}O_3Si$ – H requires 257.1578).



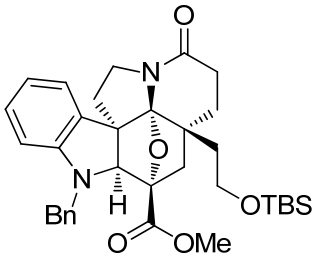
***N*-(2-(1-Benzylindol-3-yl)ethyl)-imidazole-1-carboxamide (8).** A solution of **7**[2] (4.08 g, 16.3 mmol) in CH_2Cl_2 (95 mL) was added to a solution of carbonyl diimidazole (4.00 g, 24.5 mmol) in THF (19 mL) at 0 °C. The reaction mixture was slowly warmed to 25 °C, and stirred for 10 h, before being concentrated under reduced pressure. Flash chromatography (SiO_2, EtOAc) afforded **8** (5.60 g, 97%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (s, 1H), 7.46 (d, *J* = 9.6 Hz, 1H), 7.16–7.18 (m, 6H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.99–6.96 (m, 3H), 6.84 (s, 1H), 6.76 (s, 1H), 5.10 (s, 2H), 3.57 (dd, *J* = 6.5, 12.5 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.8, 137.3, 136.7, 135.5, 129.5, 128.7 (2C), 127.8, 127.6, 126.7 (2C), 126.2, 122.0, 119.3, 118.7, 116.2, 111.6, 109.2, 49.8, 41.3, 25.0; IR (film) ν_{max} 3029, 2925, 1698, 1543, 1467, 1285, 735 cm^{-1}; HRMS-ESI-TOF *m/z* 344.1710 ($C_{21}H_{20}N_4$ + H^+ requires 345.1722).



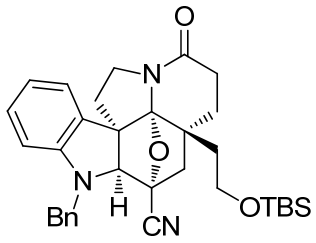
Methyl 5-(2-(1-Benzylindol-3-yl)ethylamino)-1,3,4-oxadiazole-2-carboxylate (5). A solution of **8** (5.44 g, 15.8 mmol) in THF (125 mL) was treated with acetic acid (0.98 mL, 15.8 mmol) and methyl 2-hydrazinyl-2-oxoacetate (**9**, 1.85 g, 15.8 mmol). The mixture was warmed at 35 °C for 12 h, cooled to 25 °C and concentrated under reduced pressure. The resulting yellow oil was diluted with CH_2Cl_2 and washed with aqueous citric acid (10%, 100 mL). The mixture was extracted quickly with CH_2Cl_2 (50 mL × 3), and the combined organic phase was dried over Na_2SO_4, concentrated to provide **10** as a white solid, and immediately used in the following reaction. For **10**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.28–7.22 (m, 4H), 7.15 (dt, *J* = 7.0, 1.0 Hz, 1H), 7.10–7.07 (m, 3H), 6.95 (s, 1H), 5.47 (t, *J* = 5.5 Hz, 1H), 5.23 (s, 2H), 3.82 (s, 3H), 3.50 (q, *J* = 7.0 Hz, 2H), 2.94 (t, *J* = 7.0, 2H). A solution of **10** (7.13 g, 18 mmol) and Et_3N (6.35 mL, 45.2 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (3.793 g, 19.9 mmol). The solution was warmed to 25 °C slowly over 6 h and was poured into saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (50 mL × 3). The combined organic phase was washed with H_2O, saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) afforded **5** (5.52 g, 81%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (d, *J* = 7.5 Hz, 1H), 7.31–7.25 (m, 4H), 7.21–7.18 (m, 1H), 7.14–7.10 (m, 3H), 6.99 (s, 1H), 5.62 (t, *J* = 5.5 Hz, NH), 5.27 (s, 2H), 3.97 (s, 3H), 3.78 (q, *J* = 6.6 Hz, 2H), 3.13 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.5, 154.8, 150.9, 137.3, 136.9, 128.8 (2C), 127.70, 127.66, 126.8 (2C), 126.5, 122.2, 119.4, 118.7, 110.8, 109.9, 53.2, 49.9, 43.6, 25.2; IR (film) ν_{max} 3230, 1730, 1622, 1149, 1064, 740 cm^{-1}; HRMS-ESI-TOF *m/z* 377.1613 ($C_{21}H_{20}N_4O_3$ + H^+ requires 377.1608).



Compound 4. A solution of **5** (3.34 g, 8.87 mmol) and DMAP (1.626 g, 13.3 mmol) in CH_2Cl_2 (50 mL) was treated with EDCI (2.552 g, 13.3 mmol). Carboxylic acid **6** (3.44 g, 13.3 mmol) was added to the reaction mixture as a solution in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 25 °C for 10 h and poured into saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted with EtOAc (50 mL × 3). The combined organic phase was washed H_2O (20 mL × 2), saturated aqueous NaCl (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (SiO_2, 20% EtOAc–hexanes) afforded **4** (4.034 g, 74%) as a thick oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (d, *J* = 7.2 Hz, 1H), 7.21–7.12 (m, 4H), 7.08–6.99 (m, 4H), 6.83 (s, 1H), 5.13 (s, 2H), 4.70 (d, *J* = 16.2 Hz, 2H), 4.16 (t, *J* = 2.1 Hz, 2H), 3.89 (s, 3H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.33 (t, *J* = 7.8 Hz, 2H), 2.18 (t, *J* = 7.2 Hz, 2H), 0.81 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.7, 161.9, 153.9, 153.1, 144.9, 137.2, 136.5, 128.6 (2C), 128.2, 127.6, 127.5, 126.7 (2C), 121.8, 119.2, 118.9, 111.2, 110.5, 109.6, 62.1, 53.5, 49.7, 47.5, 39.5, 34.6, 31.0, 25.8 (3C), 24.1, 18.2, –5.4 (2C); IR (film) ν_{max} 2919, 2856, 1748, 1708, 1563, 1103, 731 cm^{-1}; HRMS-ESI-TOF *m/z* 617.3148 ($C_{34}H_{44}N_4O_5Si$ + H^+ requires 617.3154).

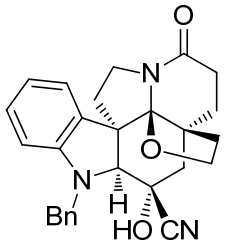


Compound 3. A solution of **4** (388 mg, 0.63 mmol) in anhydrous, degassed 1,2-dichlorobenzene (113 mL) was placed in a round bottom flasked equipped with a reflux condenser. The vessel was evacuated and refilled with argon three times and the solution was warmed at 180 °C for 48 h. The cooled reaction mixture was loaded on a SiO_2 column equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with hexanes (200 mL) and the column flushed with EtOAc (50 mL). The EtOAc was evaporated and the residue was purified by flash chromatography (SiO_2, 20–35% EtOAc–hexanes) to yield **3** (263 mg, 71%) as a colorless foam: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.21–7.11 (m, 5H), 7.12 (d, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.58 (t, *J* = 7.4 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.37 (d, *J* = 16.0 Hz, 1H), 4.16 (s, 1H), 3.94–3.79 (m, 2H), 3.66 (s, 3H), 3.33–3.28 (m, 2H), 2.42 (d, *J* = 12.8 Hz, 1H), 2.34–2.26 (m, 3H), 2.17–2.09 (m, 2H), 1.74 (d, *J* = 12.8 Hz, 1H), 1.68 (dt, *J* = 3.8, 7.0 Hz, 1H), 1.05 (dt, *J* = 14.4, 5.5 Hz, 1H), 0.71 (s, 9H), 0.50 (dt, *J* = 6.9, 14.1 Hz, 1H), –0.17 (s, 3H), –0.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.2 170.3, 152.8, 137.9, 129.6, 128.6 (2C), 128.3, 127.5 (2C), 127.2, 123.8, 118.5, 108.3, 106.5, 86.0, 79.9, 65.0, 59.8, 52.6, 51.9, 46.9, 42.2, 40.1, 37.4, 32.8, 29.5, 28.8, 25.8 (3C), 18.0, –5.5 (2C); IR (film) ν_{max} 2945, 2853, 1668, 1394, 1087, 835 cm^{-1}; HRMS-ESI-TOF *m/z* 588.3019 ($C_{34}H_{44}N_2O_5Si + H^+$ requires 589.3098).



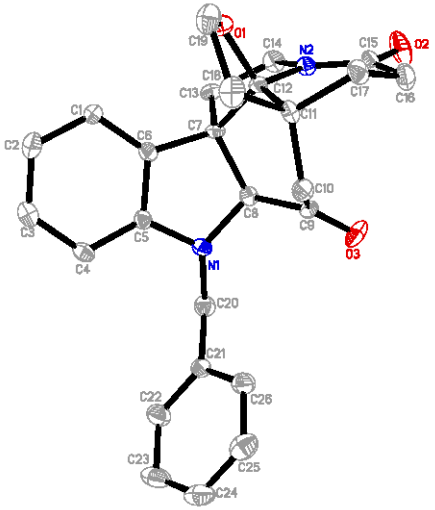
Compound 16. A solution of **3** (40 mg, 0.07 mmol) in MeOH (4.9 mL) in a heavy-wall reaction vessel was cooled to 0 °C. Ammonia gas was bubbled through the solution for 30 min, and the vessel was sealed and warmed at 70 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The yellow residue was dissolved in dioxane (0.68 mL) and pyridine (24 μL, 0.30 mmol) and cooled to 0 °C. Trifluoroacetic anhydride (21 μL, 0.15 mmol) was added to the mixture, and the solution was allowed to warm to 25 °C. After 1 h, the reaction mixture was diluted with EtOAc and was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 30% EtOAc–hexanes) provided **16** (35 mg, 90%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.33–7.23 (m, 5H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.70 (t, *J* = 7.8, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.48 (d, *J* = 15.6 Hz, 1H), 4.41 (d, *J* = 15.6 Hz, 1H), 4.31 (s, 1H), 3.98–3.89 (m, 2H), 3.35 (dd, *J* = 4.8, 7.2 Hz, 2H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.41–2.27 (m, 3H), 2.24–2.14 (m, 2H), 1.88 (d, *J* = 13.2 Hz, 1H), 1.77 (dd, *J* = 4.8, 13.2 Hz, 1H), 1.05 (dt, *J* = 4.2, 15.0

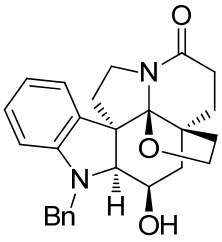
Hz, 1H), 0.79 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.1, 152.0, 136.8, 129.9, 128.9 (2C), 128.3, 128.0 (2C), 127.9, 124.0, 119.1, 118.0, 108.4, 107.7, 82.2, 74.5, 64.5, 59.4, 52.9, 46.9, 42.0, 41.7, 37.3, 32.5, 29.4, 28.5, 25.8 (3C), 18.0, –5.6 (2C); IR (film) ν_{max} 2954, 2928, 2852, 2360, 2340, 1673, 1487, 1391, 1091, 836 cm^{-1}; HRMS-ESI-TOF *m/z* 556.2985 ($C_{33}H_{41}N_3O_3Si$ + H^+ requires 556.2990).



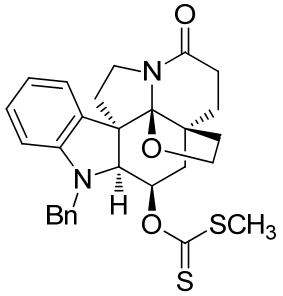
Compound 18. A solution of **16** (40 mg, 0.072 mmol) in THF (0.4 mL) and pyridine (0.4 mL) in a teflon reaction vessel was treated with HF/pyridine (0.35 mL, 3.9 mmol) complex dropwise at 0 °C. The reaction mixture was stirred at 0 °C until complete (30 min), diluted with EtOAc (5 mL) and quenched very slowly with the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (15 mL × 3). The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford **18** (31 mg, 100%) as a white solid, which was used without further purification: ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.33 (d, *J* = 7.8 Hz, 1H), 7.26–7.20 (m, 6H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 7.2 Hz, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 4.40 (d, *J* = 15.6 Hz, 1H), 3.99–3.95 (m, 1H), 3.87 (t, *J* = 8.4 Hz, 1H), 3.63 (s, 1H), 3.41 (dd, *J* = 9.6, 11.4 Hz, 1H), 2.99 (m, 1H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.37 (d, *J* = 14.4 Hz, 1H), 2.25 (m, 1H), 2.05–1.98 (m, 2H), 1.94 (dt, *J* = 6.0, 13.2, 1H), 1.64 (br s, OH), 1.59 (m, 1H), 0.89–0.81 (m, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 169.1, 150.8, 137.0, 130.8, 128.63 (2C), 128.59, 128.3 (2C), 127.6, 125.7, 122.6, 119.4, 110.5, 100.0, 71.3, 71.2, 59.8, 58.7, 53.5, 43.6, 41.4, 41.2, 37.0, 33.7, 30.4, 20.7; IR (film) ν_{max} 3119, 2870, 1631, 1468, 1042, 745 cm^{-1}; HRMS-ESI-TOF *m/z* 442.2125 ($C_{27}H_{27}N_3O_3$ + H^+ requires 442.2134).

A single crystal X-ray crystal of **18** conducted on white needles from EtOH revealed its transformation to the corresponding ketone (CCDC751262).[3]



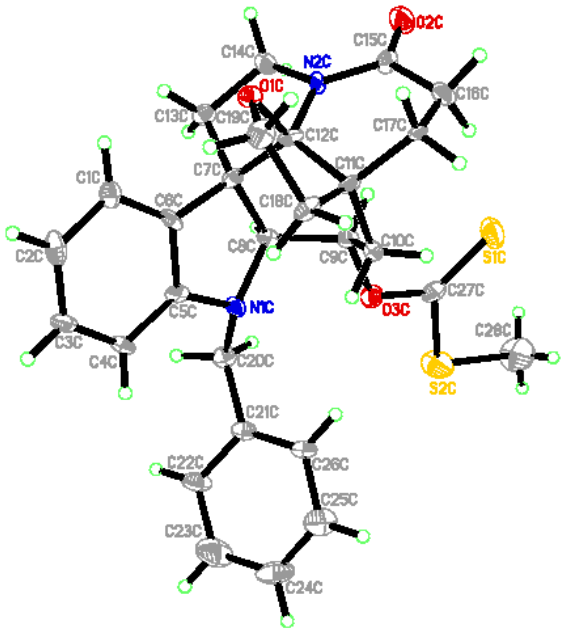


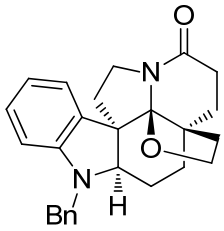
Compound 19. A solution of cyanohydrin **18** (84 mg, 0.19 mmol) in THF (1.9 mL) was treated with Na-selectride (0.56 mL of 1 M in THF, 0.56 mmol). After 2 min, the reaction mixture was concentrated under reduced pressure. Flash chromatography (SiO_2, 3% MeOH–EtOAc) provided alcohol **19** (67 mg, 85%) as a white solid: ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.28 (m, 4H), 7.20 (m, 2H), 6.98 (t, J = 7.2 Hz, 1H), 6.56 (t, J = 7.2 Hz, 1H), 6.37 (d, J = 7.8 Hz, 1H), 4.96 (d, J = 3.6 Hz, 1H), 4.76 (d, J = 16.2 Hz, 1H), 4.45 (d, J = 16.2 Hz, 1H), 3.61 (s, 1H), 3.86 (dd, J = 7.2, 16.8 Hz, 1H), 3.76–3.68 (m, 1H), 3.53 (t, J = 8.4 Hz, 2H), 3.48 (t, J = 10.2 Hz, 1H), 3.24–3.20 (m, 1H), 2.37–2.26 (m, 3H), 1.99 (t, J = 12.6 Hz, 1H), 1.94–1.92 (m, 1H), 1.89 (dd, J = 6.6, 12 Hz, 1H), 1.76 (dd, J = 7.2, 12.6 Hz, 1H), 1.63 (d, J = 12.6 Hz, 2H), 1.36 (q, J = 10.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 170.0, 153.2, 139.4, 129.6, 128.6, 128.2 (2C), 127.4 (2C), 126.5, 125.6, 117.1, 107.1, 100.1, 70.8, 67.6, 66.4, 59.1, 53.5, 41.4, 41.3, 40.5, 38.19, 38.16, 33.2, 29.7; IR (film) ν_{max} 3332, 2941, 2883, 1619, 1412, 1034, 1012, 738 cm^{-1}; HRMS-ESI-TOF *m/z* 417.2170 ($C_{26}H_{28}N_2O_3 + H^+$ requires 417.2173).



Compound 20. A suspension of NaH (9 mg of a 60% dispersion in mineral oil, 0.24 mmol) in THF (2.0 mL) was stirred for 15 min and the solvent was decanted. The resulting solid was suspended in THF (0.66 mL) and was cooled to 0 °C. Imidazole (0.1 mg) and alcohol **19** (22 mg, 0.05 mmol) in THF (0.2 mL) were added to this suspension. The reaction mixture was stirred for 1 h at 0 °C before CS_2 (9 μL, 0.16 mmol) was added and the reaction mixture was warmed to 25 °C. After 1 h, the reaction mixture was treated with MeI (9 μL, 0.15 mmol). After 1 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 60% EtOAc–hexanes) provided **20** (23 mg, 92%) as a colorless oil. The enantiomers of **20** (10 mg/injection) were separated (α = 1.39) on a semipreparative ChiralCel OD column (2 × 25 cm, 30% *i*-PrOH–hexanes, 7 mL/min flow rate) providing natural (–)-**20** (t_R = 19.2 min) and *ent*-(–)-**20** (t_R = 26.5 min). For natural enantiomer (–)-**20**: $[\alpha]_D^{25}$ –3.3 (*c* 1.7, $CHCl_3$), unnatural enantiomer (+)-**20**: $[\alpha]_D^{25}$ +3.0 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.25 (m, 1H), 7.20–7.13 (m, 5H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.63 (t, *J* = 7.8 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 5.65 (dt, *J* = 3.0, 13.2 Hz, 1H), 4.56 (d, *J* = 16.2 Hz, 1H), 4.23 (d, *J* = 16.2 Hz, 1H), 3.88–3.84 (m, 1H), 3.72–3.66 (m, 3H), 3.29 (td, *J* = 7.3, 11.5 Hz, 1H), 2.56–2.52 (m, 1H), 2.40–2.33 (m, 2H), 2.36 (s, 3H), 2.24 (t, *J* = 12.6 Hz, 1H), 1.94–1.88 (m, 2H), 1.84–1.82 (m, 2H), 1.68 (dd, *J* = 7.0, 12.8 Hz, 1H), 1.55–1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 215.3, 171.3, 153.4, 138.5, 129.2 (2C), 128.5, 128.3 (2C), 127.4 (2C), 127.1, 126.0, 118.6, 108.3, 100.7, 80.4, 68.6, 67.3, 60.7, 55.0, 42.3, 41.7, 38.6, 34.8, 34.1, 30.5, 19.3; IR (film) ν_{max} 2945, 2874, 1660, 1486, 1405, 1208, 1059 cm^{-1}; HRMS-ESI-TOF *m/z* 507.1777 ($C_{28}H_{30}N_2O_3S_2 + H^+$ requires 507.1771).

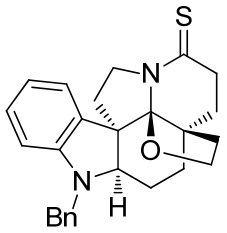
A single crystal X-ray structure of (–)-**20** was established using white needles grown from *i*PrOH confirming the structure and relative stereochemistry of **20** and establishing the absolute stereochemistry (CCDC deposition number 751263).[4]



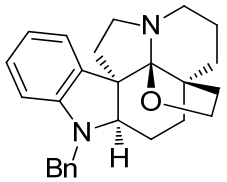


Compound 21. A solution of **20** (22 mg, 0.04 mmol) in toluene (0.9 mL) was degassed under argon with sonication. AIBN (0.7 mg, 0.004 mmol) was added to the mixture as a solution in THF (10 mg/mL, 70 μL), followed by freshly prepared Bu_3SnH (136 μL, 0.42 mmol).[5] The reaction mixture was sealed and warmed at 100 °C for 1 h, cooled to 25 °C, and concentrated under reduced pressure. The crude residue was filtered through a silica gel plug and flushed with hexanes (500 mL). The crude product was eluted with EtOAc (100 mL) and was concentrated under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) afforded **21** (13.0 mg, 77%) as a colorless residue: natural enantiomer (–)-**21**: $[\alpha]_D^{25}$ –35 (*c* 0.2, $CHCl_3$), unnatural enantiomer (+)-**21**: $[\alpha]_D^{25}$ +31 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.39 (d, *J* = 7.8 Hz, 1H), 7.32–7.30 (m, 2H), 7.27–7.25 (m, 3H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.65 (t, *J* = 7.8 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 4.47 (d, *J* = 16.2 Hz, 1H), 4.25 (d, *J* = 16.2 Hz, 1H), 4.02–3.98 (m, 1H), 3.89 (t, *J* = 9.0 Hz, 1H), 3.69 (t, *J* = 10.8 Hz, 1H), 3.43 (t, *J* = 3.5 Hz, 1H), 3.36 (td, *J* = 7.6, 11.5 Hz, 1H), 2.52–2.39 (m, 2H), 2.05–1.96 (m, 2H), 1.83–1.55 (m, 7H), 1.46–1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.1, 151.8, 138.4, 129.6, 128.6 (2C), 128.3, 127.2, 127.1 (2C), 126.0, 117.4, 105.9, 101.2, 67.8, 66.6, 57.8, 49.8,

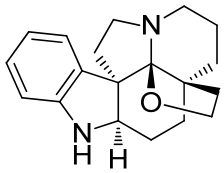
41.8, 40.7, 40.5, 37.5, 33.3, 30.0, 29.3, 23.3; IR (film) ν_{max} 2934, 2869, 1654, 1491, 1405 cm^{-1}; HRMS-ESI-TOF *m/z* 401.2225 ($C_{26}H_{28}N_2O_2 + H^+$ requires 410.2223).



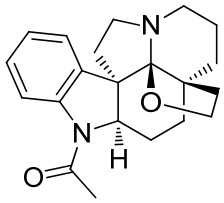
Compound 22. A solution of **21**(18.6 mg, 0.046 mmol) in toluene (0.55 mL) was treated with Lawesson's reagent (22 mg, 0.056 mmol). The mixture was warmed to 60 °C for 1 h, cooled to 25 °C, and concentrated under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) afforded **22** (16.4 mg, 85%) as a colorless residue: natural enantiomer (–)-**22**: $[\alpha]_D^{25}$ –96 (*c* 0.4, $CHCl_3$), unnatural enantiomer (+)-**22**: $[\alpha]_D^{25}$ +87 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.36 (dd, *J* = 1.8, 9.0 Hz, 1H), 7.33–7.23 (m, 5H), 7.08 (td, *J* = 1.2, 7.8 Hz, 1H), 6.63 (td, *J* = 1.2, 9.0 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 4.47 (d, *J* = 19.8 Hz, 1H), 4.25 (d, *J* = 19.8 Hz, 1H), 4.16 (dd, *J* = 9.1, 13.6 Hz, 1H), 4.04–3.99 (m, 1H), 3.96–3.92 (m, 1H), 3.62–3.56 (m, 1H), 3.51 (t, *J* = 3.6 Hz, 1H), 3.07 (dt, *J* = 4.9, 16.4 Hz, 1H), 2.95–2.88 (m, 1H), 2.51–2.44 (m, 1H), 1.98–1.93 (m, 2H), 1.87 (dt, *J* = 5.2, 13.9 Hz, 1H), 1.75–1.52 (m, 5H), 1.32–1.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.5, 151.8, 138.3, 128.9, 128.9, 128.7 (2C), 127.1 (2C), 126.0, 117.3, 105.7, 101.3, 67.6, 67.4, 57.7, 49.7, 48.9, 42.8, 42.7, 40.9, 37.7, 35.2, 31.2, 23.4; IR (film) ν_{max} 2928, 2879, 1491, 1452, 1038, 734 cm^{-1}; HRMS-ESI-TOF *m/z* 417.2004 ($C_{26}H_{28}N_2OS + H^+$ requires 417.1995).



1-Benzyl Fendleridine (23). A solution of Raney nickel in H_2O was washed with H_2O (1 mL × 2), MeOH (1 mL × 2), and THF (1 mL × 2) and finally diluted with THF (1 mL). A solution of thioamide **22** (16.4 mg, 0.039 mmol) in THF (3.3 mL) was treated with the Ra–Ni solution (15 drops) at 0 °C. The mixture was stirred rapidly for 1 h at 0 °C, warmed to 25 °C and stirred for an additional 1 h, before being filtered through Celite (CH_2Cl_2). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, 4% MeOH–EtOAc) to afford **23** (12 mg, 80%) as a white residue: natural enantiomer (–)-**23**: $[\alpha]_D^{25}$ –27 (*c* 0.2, $CHCl_3$), unnatural enantiomer (+)-**23**: $[\alpha]_D^{25}$ +22 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.43 (d, *J* = 7.2 Hz, 1H), 7.34–7.31 (m, 5H), 7.02 (td, *J* = 6.6, 0.6 Hz, 1H), 6.67 (t, *J* = 7.8 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 4.13 (d, *J* = 15.0 Hz, 1H), 3.93 (dt, *J* = 7.2, 10.8 Hz, 1H), 3.83 (t, *J* = 8.4 Hz, 1H), 3.29 (dd, *J* = 4.1, 7.8 Hz, 1H), 2.97–2.90 (m, 2H), 2.77 (td, *J* = 2.6, 11.4 Hz, 1H), 2.63–2.62 (m, 1H), 2.22 (ddd, *J* = 6.5, 9.0, 13.3 Hz, 1H), 2.03–1.93 (m, 2H), 1.85 (q, *J* = 10.8 Hz, 1H), 1.71–1.60 (m, 3H), 1.56–1.48 (m, 3H), 1.33 (br d, *J* = 10.8 Hz, 1H), 1.29 (dd, *J* = 6.6, 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.0, 138.8, 134.8, 128.5 (2C), 127.5 (2C), 127.3, 126.9, 125.7, 117.8, 106.4, 101.8, 71.4, 64.8, 57.7, 49.5, 49.0, 43.9, 38.5, 38.1, 36.7, 34.5, 27.2, 21.5, 21.4; IR (film) ν_{max} 2931, 2869, 1600, 1478, 1453, 1024 cm^{-1}; HRMS-ESI-TOF *m/z* 387.2435 ($C_{26}H_{30}N_2O + H^+$ requires 387.2431).



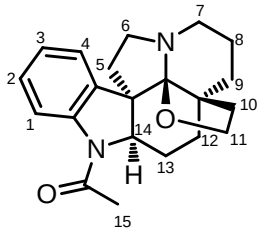
Fendleridine (1). A solution of liquid ammonia (0.8 mL) in a 10 mL vial was cooled to −78 °C and was treated with freshly cut Na (15 mg, 0.65 mmol). After 5 min, a solution of *t*-BuOH (0.030 mL) in THF (0.25 mL) was added to the blue solution, followed by a solution of **23** (6.6 mg, 17 μmol) in THF (0.5 mL). The reaction mixture was stirred at −78 °C for 30 min at which time the blue color had disappeared. The reaction mixture was quenched with the addition of solid NH_4Cl (0.1 g), and the ammonia was allowed to slowly evaporate (–40 to 0 °C). The residue was dissolved in CH_2Cl_2 (10 mL) and was filtered through a plug of cotton. The filtrate was concentrated under reduced pressure to afford fendleridine (**1**, 5.0 mg, 100%) as off-white solid: natural enantiomer (+)-**1**: $[\alpha]_D^{25}$ +43 (*c* 1.1, $CHCl_3$), unnatural enantiomer (–)-**1**: $[\alpha]_D^{25}$ –41 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.46 (d, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.90 (br s, NH), 4.01–3.98 (m, 2H), 3.40 (dd, *J* = 4.8, 9.6 Hz, 1H), 3.01 (td, *J* = 4.3, 8.7 Hz, 1H), 2.92 (dt, *J* = 7.3, 14.6 Hz, 1H), 2.79 (td, *J* = 2.6, 11.5 Hz, 1H), 2.65 (d, *J* = 11.4 Hz, 1H), 2.25 (ddd, *J* = 6.3, 9.1, 15.0 Hz, 1H), 1.92–1.55 (m, 7H), 1.52 (dd, *J* = 4.6, 7.7 Hz, 1H), 1.45 (dt, *J* = 4.4, 13.6 Hz, 1H), 1.35 (d, *J* = 13.1 Hz, 1H), 1.23 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.0, 134.4, 127.1, 125.9, 119.3, 109.9, 101.9, 66.3, 64.8, 58.8, 49.1, 43.9, 39.1, 35.7, 35.6, 33.9, 27.0, 26.8, 21.3; IR (film) ν_{max} 3332, 2929, 2856, 1597, 1460, 1034 cm^{-1}; HRMS-ESI-TOF *m/z* 297.1961 ($C_{19}H_{24}N_2O + H^+$ requires 297.1960).



1-Acetyl Fendleridine (2, **1-Acetylaspidoalbidine).** A solution of fendleridine (**1**, 5.2 mg, 17.5 μmol) in pyridine (0.2 mL) was treated with acetic anhydride (0.1 mL) at 25 °C. The mixture was stirred for 30 min, before being concentrated under reduced pressure. The residue was purified by PTLC (SiO_2, 5% MeOH–CH_2Cl_2) to afford 1-acetylfendleridine (**2**, 4.8 mg, 81%) as a white residue: natural enantiomer (+)-**2**: $[\alpha]_D^{25}$ +38 (*c* 0.2, $CHCl_3$), +42 (*c* 0.2, MeOH), unnatural enantiomer (–)-**2**: $[\alpha]_D^{25}$ –37 (*c* 0.2, $CHCl_3$), –42 (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.16 (t, *J* = 8.5 Hz, 1H), 4.08 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.86 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.02 (td, *J* = 8.7, 4.2 Hz, 1H), 2.92 (dd, *J* = 9.1, 15.4 Hz, 1H), 2.79 (t, *J* = 9.6 Hz, 1H), 2.65 (d, *J* = 10.8 Hz, 1H), 2.25 (s, 3H), 2.13–2.06 (m, 1H), 1.99–1.66 (m, 8H), 1.55 (d, *J* = 12.1 Hz, 1H), 1.43 (dd, *J* = 13.9, 3.3 Hz, 1H), 1.36 (br d, *J* = 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.1, 141.1, 137.8, 127.3, 124.75, 124.67, 117.8, 102.0, 68.8, 65.0, 58.2, 48.9, 43.9, 39.6, 37.1, 34.6, 33.0, 26.4, 25.3, 23.4, 21.0; IR (film) ν_{max} 2920, 2851, 1658, 1458, 1396, 1258 cm^{-1}; HRMS-ESI-TOF *m/z* 339.2067 ($C_{21}H_{26}N_2O_2 + H^+$ requires 339.2071).

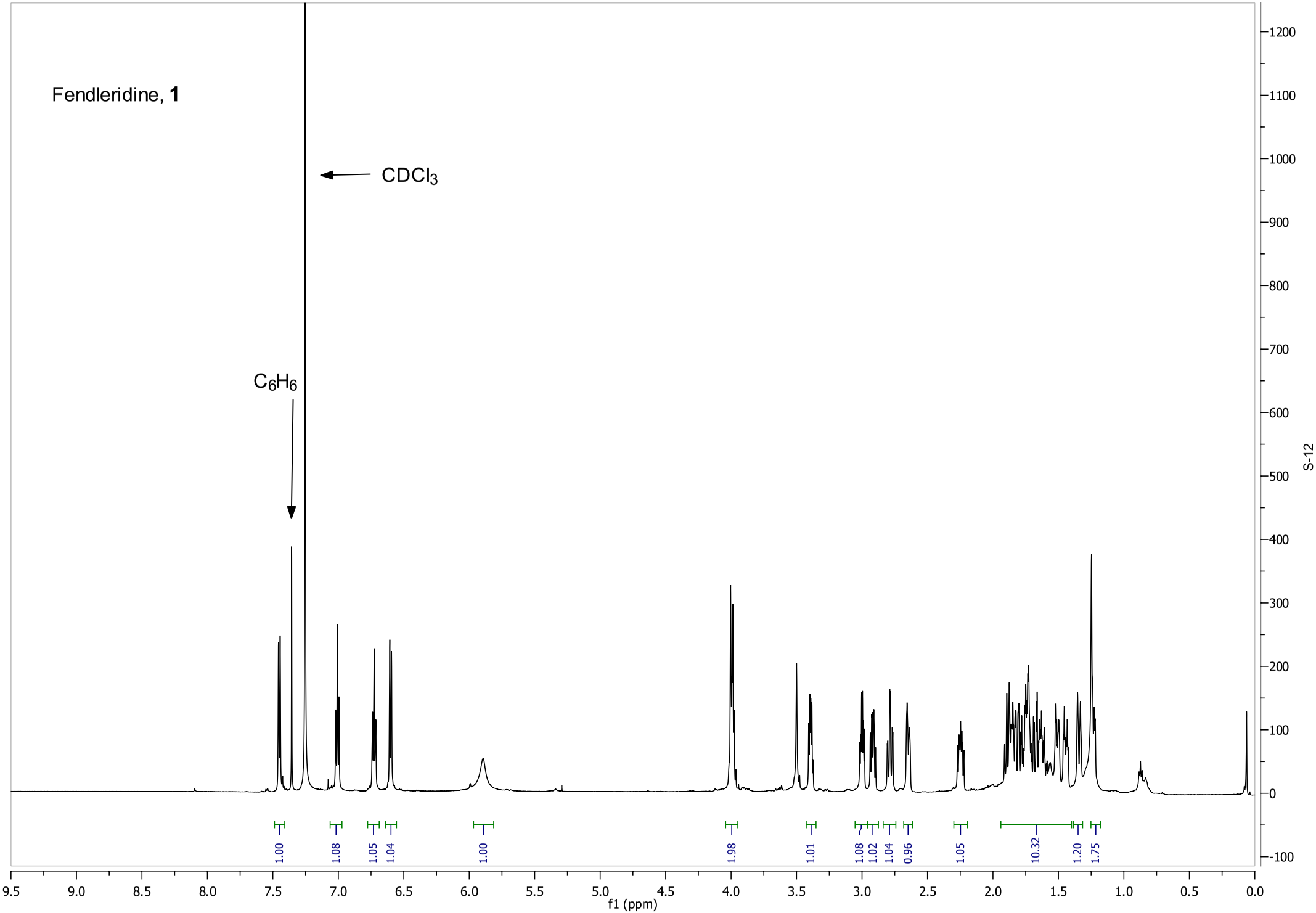
Spectral data was in accordance with the literature values,[6] and the ^{1}H NMR of synthetic **2** was in full agreement with a copy of the spectrum of authentic **2**.

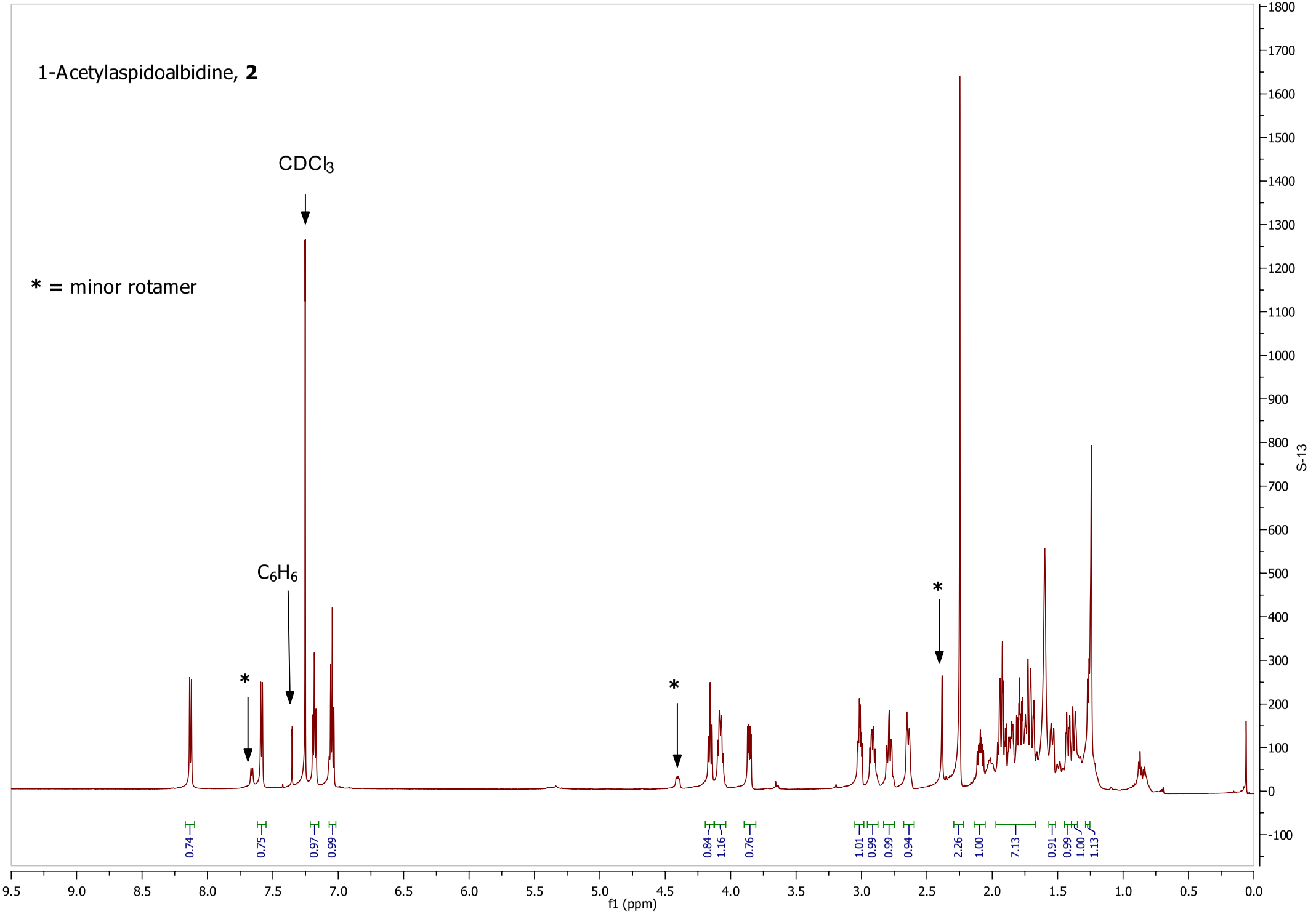
Supplemental Table 1. ^{1}H NMR comparison for natural 1-Acetylaspidoalbidine (**2**) and synthetic **2**.



δ, ppm (multiplicity, *J*, Hz)

Position	Natural (300 MHz, $CDCl_3$)[6]	Synthetic (600 MHz, $CDCl_3$)
4	8.1 (dd, *J* = 7.7, 1.3 Hz, 1H),	8.14 (d, *J* = 8.0 Hz, 1H),
1	7.6 (dd, *J* = 7.7, 1.3 Hz, 1H),	7.59 (d, *J* = 7.6 Hz, 1H),
2	7.2 (td, *J* = 7.7, 1.3 Hz, 1H),	7.19 (t, *J* = 7.7 Hz, 1H),
3	7.1 (td, *J* = 7.7 Hz, 1H)	7.05 (t, *J* = 7.5 Hz, 1H),
11	4.15 (t, *J* = 10.8 Hz, 1H)	4.16 (t, *J* = 8.5 Hz, 1H),
11'	4.05 (ddd, *J* = 10.8, 8.2, 6.0 Hz, 1H)	4.08 (dd, *J* = 10.2, 7.5 Hz, 1H),
14	3.85 (dd, *J* = 10.6, 5.8, 1H)	3.86 (dd, *J* = 10.9, 5.1 Hz, 1H),
6	3.0 (td, *J* = 8.5, 4.3 Hz, 1H),	3.02 (td, *J* = 8.7, 4.2 Hz, 1H),
6'	2.9 (m, 1H)	2.92 (dd, *J* = 15.4, 9.1 Hz, 1H),
7	2.8 (td, *J* = 8.5, 4.3 Hz, 1H)	2.79 (t, *J* = 9.6 Hz, 1H),
7'	2.6 (m, 1H)	2.65 (d, *J* = 10.8 Hz, 1H),
15'	2.3 (s, 3H)	2.25 (s, 3H),
5	2.1–1.6 (m, 8H)	2.13–2.06 (m, 1H),
5', 12, 13, 13', 10, 8, 9'		1.99–1.66 (m, 7H),
8	1.55 (m, 1H)	1.55 (d, *J* = 12.1 Hz, 1H),
12'	1.45 (dt, *J* = 13.7, 3.5 Hz, 1H)	1.43 (dd, *J* = 13.9, 3.3 Hz, 1H),
9'	1.35 (br d, *J* = 8.0 Hz, 1H)	1.38 (br d, *J* = 11.4 Hz, 1H);
10'	1.25 (dd, *J* = 12, 6.0 Hz, 1H)	1.26 (m, 1H)


Fendleridine, 1
CDCl3
C6H6
1.00
1.08
1.05
1.04
1.00
1.98
1.01
1.08
1.02
1.04
0.96
1.05
10.32
1.20
1.75
f1 (ppm)
S-12


1-Acetylaspidoalbidine, **2**
* = minor rotamer
$CDCl_3$
C_6H_6
*
*
*
0.74
0.75
0.97
0.99
0.84
1.16
0.76
1.01
0.99
0.99
0.94
2.26
1.00
7.13
0.91
0.99
1.00
1.13
f1 (ppm)
S-13

[1] Van der Ende, A. E.; Kravitz, E. J.; Harth, E. *J. Am. Chem. Soc.* **2008**, *130*, 8706.
[2] Liu, Y.; Luo, S.; Fu, X.; Fang, F.; Zhuang, Z.; Xiong, W.; Jia, X.; Zhai, H. *Org. Lett.* **2006**, *8*, 115.
[3] Atomic coordinates for the ketone derived from **18** (CCDC751262) have been deposited with the Cambridge Crystallographic Data Center.
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