Supporting Information

Total Synthesis of the Tricyclic Marine Alkaloids (–)-Lepadiformine, (+)-Cylindricine C, and (–)-Fasicularin via a Common Intermediate Formed by Formic Acid-Induced Intramolecular Conjugate Azaspirocyclization

Hideki Abe, Sakae Aoyagi, and Chihiro Kibayashi*

School of Pharmacy, Tokyo University of Pharmacy & Life Science

Experimental Section

General Methods. Reported melting points are uncorrected. Unless otherwise stated ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a 400 MHz instrument. Chemical shifts are given in δ (ppm) relative to internal CHCl_3 (7.26 ppm for ^1H) and CDCl_3 (77.05 ppm for ^{13}C). Optical rotations were recorded on a JASCO P-1010 Digital Polarimeter. Analytical TLC was carried out with precoated silica gel 60F₂₅₄ plates (Merck). Flash column chromatography was performed on Silica gel 60N (spherical, neutral, 40–50 μm , Kanto Chemical Co., Inc.).

(2E)-1-Methyl-3-{1-[(4-methylphenyl)sulfonyl]-1-azaspiro[4.4]non-6-yl}prop-2-enyl Formate (12**).** To a cooled (0 °C), stirred solution of **8** (83.9 mg, 0.187 mmol) in CH₂Cl₂ (2 mL) was added dropwise formic acid (2 mL), and the mixture was stirred at room temperature for 40 h. The reaction mixture was neutralized with 28% aqueous NH₃ and extracted with CHCl₃ (30 mL × 2). The extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo. Chromatography (6:1 hexane/EtOAc) followed by recrystallization from hexane gave **12** (30.3 mg, 43%) as colorless pillars: mp 96–99 °C; ¹H NMR δ 1.288 and 1.292 (d, *J* = 6.4 Hz each, total 3H in 1:1 ratio), 1.32–1.60 (m, 4H), 1.63–1.94 (m, 5H), 2.41 (m, 3H), 2.55 (m, 1H), 3.32 (td, *J* = 6.4, 5.9 Hz, 1H), 3.35 (t, *J* = 6.6 Hz, 2H), 5.37 and 5.38 (quint, *J* = 6.2 Hz, and quint, *J* = 6.0 Hz, respectively, total 1H in 1:1 ratio), 5.46 and 5.49 (ddd, *J* = 15.5, 6.5, 0.8 Hz, and dd, *J* = 15.6, 5.7 Hz, respectively, total 1H in 1:1 ratio), 5.55 (ddd, *J* = 15.6, 5.9, 1.4 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.73 (dd, *J* = 8.2, 1.4 Hz, 2H), 8.00 (s, 1H); ¹³C NMR δ 20.0, 20.1, 20.4, 20.5, 21.5, 22.7, 26.8, 27.3, 35.07, 35.11, 36.6, 36.7, 47.6, 47.8, 49.9, 50.0, 71.0, 71.3, 76.4, 76.6, 127.1, 129.5, 130.7, 131.1, 132.56, 132.63, 138.6, 142.8, 160.4.

(2E)-1-Methyl-3-{1-[(4-methylphenyl)sulfonyl]-1-azaspiro[4.5]dec-6-yl}prop-2-enyl Formate (13). According to the procedure described for conversion of **8** to **12**, a solution of **9** (61.0 mg, 0.132 mmol) in CH₂Cl₂ (1.5 mL) was treated with formic acid (1.5 mL) and worked up. Chromatography followed by recrystallization from hexane gave **13** (26.4 mg, 55%) as colorless pillars: mp 99–102 °C; ¹H NMR δ 1.10–1.40 (m, 6H), 1.49 (m, 1H), 1.59–1.80 (m, 6H), 1.96 (m, 1H), 2.39 (m, 1H), 2.40 (s, 3H), 3.14 (m, 1H), 3.21–3.33 (m, 2H), 5.41 (m, 1H), 5.55 and 5.61 (ddd, *J* = 15.7, 7.0, 1.1 Hz, and dd, *J* = 16.0, 6.3 Hz, respectively, total 1H in 1:1 ratio), 5.73 and 5.78 (dd, *J* = 15.8, 6.6 Hz, and dd, *J* = 15.7, 5.9 Hz, respectively, total 1H in 1:1 ratio), 7.26 (d, *J* = 7.9 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H), 8.01 and 8.02 (s each, total 1H in 1:1 ratio); ¹³C NMR δ 20.4, 20.5, 21.5, 23.3, 24.4, 24.9, 29.2, 29.7, 32.2, 32.3, 37.0, 37.1, 46.2, 46.5, 49.5, 49.6, 71.2, 71.8, 72.7, 72.8, 127.20, 127.22, 129.4, 130.0, 130.3, 134.0, 134.5, 138.9, 142.6, 160.5; HRMS (ESI-TOF) *m/z* calcd for C₂₁H₂₉NO₄NaS ([M + Na]⁺) 414.1715, found 414.1723.

tert-Butyl 6-[(1E)-3-(Formyloxy)but-1-enyl]-1-azaspiro[4.5]decane-1-carboxylate (14). To a cooled (0 °C), stirred solution of **10** (138 mg, 0.446 mmol) in

toluene/THF (19:1, 4 mL) was added dropwise formic acid (4 mL), and the mixture was stirred at the same temperature for 1 h. The reaction mixture was neutralized with 28% aqueous NH_3 and extracted with Et_2O (30 mL x 2). The extracts were washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by chromatography (20:1 hexane/EtOAc) to give **14** (98.6 mg, 66%) as a colorless oil: ^1H NMR δ (for major amide rotamer) 1.12–1.88 (m, 23H), 2.40 (m, 1H), 3.13 (ddt, $J = 13.3$, 10.9, 7.6 Hz, 1H), 3.35 (ddd, $J = 12.3$, 7.7, 3.3 Hz, 1H), 3.41 (m, 1H), 5.38–5.47 (m, 2H), 5.60 (m, 1H), 8.01 (s, 1H); ^{13}C NMR δ (for major amide rotamer) 20.6, 20.7, 22.5, 24.2, 25.0, 28.7, 29.0, 29.3, 30.8, 34.2, 34.3, 42.7, 42.9, 48.7, 67.0, 71.4, 71.6, 78.4, 78.5, 129.8, 130.1, 134.9, 135.0, 153.4, 160.5; HRMS (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{32}\text{NO}_4$ ($[\text{M} + \text{H}]^+$) 338.2331, found 338.2317. Anal. Calcd for $\text{C}_{19}\text{H}_{31}\text{NO}_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.68; H, 8.93; N, 4.01.

6-[(5*E*,7*E*)-Nona-5,7-dienyl]-2,3,4,5-tetrahydropyridine (15). To a cooled (0 °C), stirred solution of **11** (20.7 mg, 64.0 μmol) in CH_3CN (0.6 mL) was added dropwise formic acid (0.6 mL), and the mixture was stirred at room temperature. After being stirred for 16 h, the mixture was neutralized with 28% aqueous NH_3 and extracted with CHCl_3 (30 mL x 2). The extracts were washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by chromatography (20:1 $\text{CHCl}_3/\text{MeOH}/28\%$ aqueous NH_3) to

give **15** (10.4 mg, 79%) as a pale yellow oil: ^1H NMR δ 1.33–1.41 (m, 2H), 1.46–1.55 (m, 4H), 1.60–1.66 (m, 2H), 1.70 (d, J = 6.4 Hz, 3H), 2.02–2.13 (m, 6H), 3.50–3.53 (m, 2H), 5.48–5.58 (m, 2H), 5.93–6.02 (m, 2H); ^{13}C NMR δ 18.0, 19.6, 21.9, 26.0, 29.0, 29.3, 32.4, 40.9, 49.1, 126.7, 130.4, 131.7, 131.8, 171.0; HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{24}\text{N}$ ($[\text{M} + \text{H}]^+$) 206.1909, found 206.1904.

tert-Butyl (1S)-[(9E,11E)-1-Benzyloxymethyl-4-oxo-9,11-octadeca-dienyl]-carbamate (6). To a cooled (0 °C), stirred solution of (*S*)-*N*-Boc-5-(benzyloxymethyl)-pyrrolidin-2-one (**7**) (1.32 g, 4.32 mmol) in THF (43 mL) was added dropwise a THF (31 mL) solution of 5,7-tetradecadienylmagnesium bromide (**16**), freshly prepared from (*5E,7E*)-1-bromo-5,7-tetradecadiene (4.25 g, 15.6 mmol). After being stirred at 0 °C for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and the mixture was extracted with CHCl_3 (300 mL $\times$ 2). The extracts were washed with water and dried over MgSO_4 , and the solvent was removed in vacuo. The residue was purified by chromatography (9:1 hexane/EtOAc) to give a white solid. It was then recrystallized from CHCl_3 /hexane to afford **6** (1.71 g, 79%) as white crystals: mp 52–54 °C; $[\alpha]_{\text{D}}^{29}$ –15.1 (c 1.0, CHCl_3); IR (KBr) 3364, 1703, 1686 cm^{-1} ; ^1H NMR δ 0.88 (t, J = 6.9 Hz, 3H), 1.21–1.47 (m, 19H), 1.53–1.60 (m, 2H), 1.70–1.89 (m, 2H), 2.01–2.08 (m, 4H), 2.36–2.40 (m, 2H), 2.44–2.28 (m, 2H), 3.41–3.50 (m, 2H), 3.71 (m, 1H), 4.48 and 4.52 (ABq, J =

12.0 Hz, 2H), 4.73 (m, 1H), 5.48–5.61 (m, 2H), 5.94–6.02 (m, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR δ 14.1, 22.6, 23.4, 26.3, 28.4, 28.9, 29.0, 29.4, 31.8, 32.3, 32.6, 39.3, 42.8, 50.0, 72.3, 73.2, 79.2, 127.6, 127.7, 128.4, 130.2, 130.8, 131.5, 132.8, 138.1, 155.7, 210.6; EIMS m/z (relative intensity) 499 (M^+ , 7), 426 (9), 399 (23), 381 (20), 336 (21), 288 (46), 140 (100). Anal. Calcd for $\text{C}_{31}\text{H}_{49}\text{NO}_4$: C, 74.51; H, 9.88; N, 2.80. Found: C, 74.51; H, 9.76; N, 2.74.

***tert*-Butyl (2*S*,5*S*,6*S*)-2-Benzoyloxymethyl-6-[(1*E*,3*S*/*R*)-3-(formyloxy)non-1-enyl]-1-azaspiro[4.5]decane-1-carboxylate (**5**).** To a cooled (0 °C), stirred solution of **6** (154 mg, 0.309 mmol) in toluene/THF (19:1, 3 mL) was added dropwise formic acid (3 mL). After being stirred at 0 °C for 2 h, the mixture was neutralized with 28% aqueous NH_3 and extracted with Et_2O (30 mL $\times$ 2). The extracts were washed with brine and dried over MgSO_4 , and the solvent was removed in vacuo. The residue was purified by chromatography (20:1 hexane/ EtOAc) to give an inseparable 1.6:1 (based on ^1H NMR) diastereomeric mixture of **5** (143 mg, 88%) as a colorless oil: IR (neat) 2926, 2858, 1725, 1693 cm^{-1} ; ^1H NMR δ (for major amide rotamer) 0.87 (t, J = 6.6 Hz, 3H), 1.21–1.79 (m, 29H), 2.07 (m, 1H), 2.53 (m, 1H), 3.27 (t, J = 8.7 Hz, 1H), 3.34 (m, 1H), 3.46 (m, 1H), 3.98 (m, 1H), 4.51 (s, 2H), 5.28 (m, 1H), 5.37 (A part of ABX, J = 15.2, 7.6 Hz, 1H), 5.54 (B

part of ABX, $J = 15.2, 8.7$ Hz, 1H), 7.26–7.35 (m, 5H), 8.04 and 8.05 (s each, total 1H in 1.6:1 ratio); ^{13}C NMR δ (for major amide rotamer) 14.1, 22.6, 24.1, 25.0, 25.1, 26.4, 28.6, 29.0, 29.9, 31.3, 31.8, 34.6, 38.0, 42.3, 58.9, 68.1, 71.4, 73.1, 75.3, 78.8, 127.5, 128.4, 128.6, 136.5, 138.5, 152.9, 160.6; EIMS m/z (relative intensity) 527 (M^+ , 32), 381 (100). Anal. Calcd for $\text{C}_{32}\text{H}_{49}\text{NO}_5$: C, 72.83; H, 9.36; N, 2.65. Found: C, 72.77; H, 9.38; N, 2.69.

***tert*-Butyl (2*S*,5*S*,6*S*)-2-Benzylloxymethyl-6-[(1*E*,3*S*/*R*)-3-hydroxynon-1-enyl]-1-azaspiro[4.5]decane-1-carboxylate (24a and 24b).** To a solution of **5** (134 mg, 0.254 mmol) in MeOH (2 mL) was added saturated aqueous K_2CO_3 (2 mL), and the mixture was stirred at room temperature for 2 h. The mixture was extracted with CHCl_3 (20 mL $\times$ 2), and the extracts were washed with brine and dried over MgSO_4 . After the solvent was removed in vacuo, the resulting residue was purified by chromatography (4:1 hexane/EtOAc) to give a 1.6:1 mixture of **24a** and **24b** (124 mg, 98%) as a colorless oil. The diastereomeric ratio and stereochemical assignment of the diastereomers **24a** and **24b** were analyzed with a Shimazu Shim-pak CLC-SIL column using hexane–2-propanol (100:1). The major isomer had a shorter retention time (12 min) and was identified as the 3'*S*-isomer ($\alpha\text{-OH}$) **24a** by comparison of the retention time with that of **24a** prepared by

reduction of **25** with (*S*)-BINAL-H (vide infra). The minor isomer with a longer retention time (16 min) was identified as the 3'*R*-isomer (β -OH) **24b** by comparison of the retention time with that of **24b** prepared by reduction of **25** with (*R*)-BINAL-H (vide infra).

This mixture was used for the next step without separation.

tert-Butyl (2*S*,5*S*,6*S*)-2-Benzylloxymethyl-6-[(1*E*)-3-oxonon-1-enyl]-1-azaspiro-[4.5]decane-1-carboxylate (25**).** To a solution of the above described mixture of **24a** and **24b** (293 mg, 0.586 mmol) in CH₂Cl₂ was added 88% activated manganese oxide (1.76 g), and the mixture was stirred at room temperature. After 3 h, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by chromatography (9:1 hexane/EtOAc) to give **25** (266 mg, 91%) as a colorless oil: $[\alpha]_D^{27}$ -106 (*c* 1.24, CHCl₃); IR (neat) 1682, 1624 cm⁻¹; ¹H NMR δ (for major amide rotamer) 0.88 (t, *J* = 6.6 Hz, 3H), 1.24–1.82 (m, 27H), 2.08 (m, 1H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.57 (m, 1H), 3.28 (dd, *J* = 8.6, 8.5 Hz, 1H), 3.47 (m, 1H), 3.56 (m, 1H), 3.95 (m, 1H), 4.50 (s, 2H), 6.07 (d, *J* = 15.6 Hz, 1H), 6.66 (dd, *J* = 15.6, 8.3 Hz, 1H), 7.26–7.35 (m, 5H); ¹³C NMR δ (for major amide rotamer) 14.1, 22.5, 23.9, 24.3, 24.7, 26.4, 28.6, 29.0, 29.1, 31.5, 31.7, 37.8, 41.0, 42.5, 59.1, 68.3, 71.3, 73.1, 79.2, 127.4, 127.6, 128.4, 129.7, 138.4, 148.0, 153.0, 200.6; EIMS *m/z* (relative intensity) 497 (*M*⁺, 18), 397 (33), 396 (36), 276

(100). Anal. Calcd for $C_{31}H_{47}NO_4$: C, 74.81; H, 9.52; N, 2.81. Found: C, 74.61; H, 9.35; N, 2.86.

***tert*-Butyl (2*S*,5*S*,6*S*)-2-Benzyloxymethyl-6-[(1*E*,3*S*)-hydroxynon-1-enyl]-1-aza-spiro[4.5]decane-1-carboxylate (**24a**).** To a cooled (0 °C), stirred suspension of lithium aluminum hydride (101 mg, 2.67 mmol) in THF (1.7 mL) under N_2 was added dropwise a solution of EtOH (124 mg, 2.70 mmol) in THF (1.3 mL) followed by a solution of (*S*)-1,1'-bi-2-naphthol (780 mg, 2.73 mmol) in THF (4.2 mL). After being stirred at room temperature for 1 h, the mixture was allowed to cool to -78 °C. To this mixture was added dropwise a solution of **25** (266 mg, 0.534 mmol) in THF (1.1 mL), and the mixture was stirred at the same temperature for 5 h. After the reaction was quenched with water (2 mL), the mixture was diluted with Et₂O (20 mL) and filtered through Celite. Evaporation of the solvent in vacuo followed by chromatography (4:1 hexane/acetone) afforded **24a** (246 mg, 92%) as a colorless oil: $[\alpha]_D^{26} -73.8$ (*c* 0.90, CHCl₃); IR (neat) 3444, 1692 cm^{-1} ; ¹H NMR δ (for major amide rotamer) 0.87 (t, *J* = 7.0 Hz, 3H), 1.17–1.82 (m, 30H), 2.07 (m, 1H), 2.54 (m, 1H), 3.26 (dd, *J* = 8.7, 8.6 Hz, 1H), 3.33 (m, 1H), 3.49 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.98–4.14 (m, 2H), 4.46–4.58 (m, 2H), 5.39–5.58 (m, 2H), 7.26–7.36 (m, 5H); ¹³C

NMR δ (for major amide rotamer) 14.1, 22.6, 24.1, 25.1, 25.4, 26.5, 28.6, 29.3, 29.9, 31.3, 31.8, 37.4, 38.0, 41.9, 59.1, 68.3, 71.5, 72.7, 73.1, 78.9, 127.5, 127.6, 128.4, 132.3, 133.7, 138.5, 153.0; EIMS m/z (relative intensity) 399 ($M^+ - \text{Boc}$, 17), 398 (48), 260 (100). Anal. Calcd for $\text{C}_{31}\text{H}_{49}\text{NO}_4$: C, 74.51; H, 9.88; N, 2.80. Found: C, 74.46; H, 9.83; N, 2.86.

***tert*-Butyl (2*S*,5*S*,6*S*)-2-Benzoyloxymethyl-6-[(3*S*)-3-hydroxynonyl]-1-azaspiro-[4.5]decane-1-carboxylate (26).** To a solution of **24a** (103 mg, 0.206 mmol) in EtOAc (4 mL) was added platinum oxide (2.34 mg, 10.3 μmol), and the resulting suspension was stirred under hydrogen (1 atm) for 30 min. After the catalyst was removed by filtration through Celite, the filtrate was concentrated in vacuo and the residue was purified by chromatography (7:1 hexane/EtOAc) to give **26** (89.0 mg, 86%) as a colorless oil: $[\alpha]_D^{26} -44.0$ (c 1.1, CHCl_3); IR (neat) 3445, 1694, 1681 cm^{-1} ; ^1H NMR δ (for major amide rotamer) 0.86–1.01 (m, 5H), 1.10–2.61 (m, 35H), 3.29 (m, 1H), 3.47–3.55 (m, 2H), 4.08 (m, 1H), 4.52 (s, 2H), 7.26–7.36 (m, 5H); ^{13}C NMR δ (for major amide rotamer) 14.1, 22.7, 24.2, 25.6, 25.8, 26.4, 26.9, 28.6, 29.4, 29.8, 30.8, 31.9, 35.4, 37.4, 38.4, 40.0, 59.1, 68.7, 71.4, 72.8, 73.1, 78.9, 127.5, 128.4, 138.5, 153.1; EIMS m/z (relative intensity) 401 ($M^+ - \text{Boc}$, 2), 383 (5), 340 (16), 326 (32), 264 (100). Anal. Calcd for $\text{C}_{31}\text{H}_{51}\text{NO}_4$: C, 74.21; H, 10.25; N, 2.79. Found: C, 74.25; H, 10.20; N, 2.83.

(3S)-1-[(2S,5S,6S)-2-Benzyloxymethyl-1-azaspiro[4.5]dec-6-yl]-3-nonanol (27).

To a solution of **26** (238 mg, 0.475 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (541 mg, 4.75 mmol), and the mixture was stirred at room temperature. After 3 h, the mixture was basified with saturated aqueous NaHCO_3 at 0 °C and extracted with CHCl_3 (20 mL x 2). The extracts were dried over K_2CO_3 and the solvent was removed in vacuo. The residue was purified by chromatography (200:9:1 $\text{CHCl}_3/\text{MeOH}/28\%$ aqueous NH_3) to give **27** (174 mg, 91%) as a colorless oil: $[\alpha]_D^{26} -33.2$ (c 0.98, MeOH); IR (neat) 3376, 2925 cm^{-1} ; ^1H NMR δ 0.89 (t, $J = 6.7$ Hz, 3H), 0.92–1.10 (m, 2H), 1.14–1.43 (m, 15H), 1.54–1.73 (m, 9H), 1.83 (m, 1H), 2.10–2.62 (br m, 2H), 3.35 (m, 1H), 3.41 (A part of ABX, $J = 9.2, 5.3$ Hz, 1H), 3.50 (B part of ABX, $J = 9.2, 4.6$ Hz, 1H), 3.61 (m, 1H), 4.52 and 4.53 (ABq, $J = 12.1$ Hz, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR δ 14.1, 22.7, 24.7, 25.4, 25.8, 27.6, 29.3, 29.5, 30.0, 30.5, 31.9, 36.4, 37.8, 40.9, 48.7, 59.3, 65.7, 73.2, 73.3, 73.7, 127.5, 127.6, 128.4, 138.6; EIMS m/z (relative intensity) 402 ($\text{M}^+ + 1$, 23), 358 (3), 316 (7), 280 (100). Anal. Calcd for $\text{C}_{26}\text{H}_{43}\text{NO}_2$: C, 77.75; H, 10.79; N, 3.49. Found: C, 77.48; H, 10.63; N, 3.40.

(3*S*,5*R*,7*aS*,11*aS*)-3-Benzoyloxymethyl-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]-quinoline (28). To a cooled (0 °C), stirred solution of **27** (84.2 mg, 0.210 mmol) in CH₂Cl₂ (2 mL) were successively added triphenylphosphine (220 mg, 0.839 mmol), carbon tetrabromide (278 mg, 0.839 mmol), and triethylamine (84.9 mg, 0.839 mmol). After the mixture was stirred at room temperature for 1 h, saturated aqueous NaHCO₃ (5 mL) was added and the mixture was extracted with CHCl₃ (20 mL x 2). The extracts were dried over K₂CO₃ and the solvent was removed in vacuo. The resulting residue was purified by chromatography (200:9:1 CHCl₃/MeOH/28% aqueous NH₃) to give **28** (66.2 mg, 82%) as a pale yellow oil: $[\alpha]_D^{27}$ -22.0 (*c* 0.71, MeOH); IR (neat) 2927, 2856, 1454, 1090 cm⁻¹; ¹H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.03 (qd, *J* = 12.4, 3.2 Hz, 1H), 1.12–1.73 (m, 25H), 2.01 (m, 1H), 3.05–3.14 (m, 2H), 3.30 (m, 1H), 3.56 (dd, *J* = 8.7, 4.0 Hz, 1H), 4.51 (s, 2H), 7.23–7.33 (m, 5H); ¹³C NMR δ 14.1, 22.7, 24.1, 24.5, 26.5, 27.7, 28.1, 29.3, 29.7, 31.0, 31.9, 34.5, 37.9, 41.4, 53.8, 57.6, 67.6, 73.2, 77.9, 127.4, 127.6, 128.3, 138.8; EIMS *m/z* (relative intensity) 384 (M⁺ + 1, 0.5), 383 (M⁺, 0.5), 340 (1), 292 (1), 262 (39), 91 (100). Anal. Calcd for C₂₆H₄₁NO: C, 81.41; H, 10.77; N, 3.65. Found: C, 81.13; H, 10.79; N, 3.79.

[(3*S*,5*R*,7*aS*,11*aS*)-5-Hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl]methanol

[(-)-Lepadiformine] (3). To a solution of **28** (66.2 mg, 0.173 mmol) in MeOH (2 mL) was added palladium hydroxide on carbon (70 mg), and the mixture was stirred under hydrogen (1 atm) at room temperature for 18 h. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo and the residue was purified by chromatography (150:9:1 CHCl₃/MeOH/28% aqueous NH₃) to give **3** (44.1 mg, 87%) as a colorless oil: $[\alpha]_{\text{D}}^{28} -15.0$ (*c* 0.37, MeOH); IR (neat) 3418, 2918, 2857, 1463 cm⁻¹; ¹H NMR δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.01 (qd, *J* = 12.4, 3.3 Hz, 1H), 1.13–1.82 (m, 26H), 3.14 (m, 1H), 3.21 (d, *J* = 8.0 Hz, 1H), 3.30–3.38 (m, 2H), 3.42–3.83 (br s, 1H); ¹³C NMR δ 14.1, 22.67, 22.69, 23.3, 24.3, 26.4, 27.6, 27.7, 28.3, 29.6, 30.6, 31.9, 34.2, 38.3, 40.2, 53.3, 58.4, 62.4, 67.3; HRMS (ESI-TOF) *m/z* calcd for C₁₉H₃₆NO ([M + H]⁺) 294.2797, found 294.2779. Anal. Calcd for C₁₉H₃₅NO: C, 77.76; H, 12.02; N, 4.77. Found: C, 77.65; H, 12.01; N, 4.85.

Lepadiformine Hydrochloride (3·HCl). The free base **3** was dissolved in MeOH (4 mL). To this solution was added 1 M aqueous HCl (0.04 mL), and then the solution was evaporated to dryness in vacuo to give the hydrochloride salt of **3** as a colorless gum: $[\alpha]_{\text{D}}^{26} +2.6$ (*c* 0.54, CHCl₃); ¹H NMR δ 0.82 (t, *J* = 6.6 Hz, 3H), 1.00 (m, 1H), 1.17–1.39 (m, 12H), 1.47 (m, 1H), 1.62–1.80 (m, 5H), 1.86–2.03 (m, 4H), 2.10–2.12 (m, 2H), 2.28–2.46 (m, 2H), 3.55–3.62 (m, 3H), 4.12 (d, *J* = 13.0 Hz, 1H), 4.73 (br s, 1H), 10.06 (br s, 1H); ¹³C

NMR δ 14.0, 19.3, 22.5, 22.6, 23.3, 24.4, 25.0, 26.4, 26.5, 29.1, 29.9, 30.8, 31.7, 33.8, 36.2, 58.9, 59.9, 63.5, 77.2.

***tert*-Butyl (2*S*,5*S*,6*R*)-2-[(Benzyloxy)methyl]-6-{(2*R*,3*R*)-3-[(1*S*)-1-hydroxy-heptyl]oxiranyl}-1-azaspiro[4.5]decane-1-carboxylate (30).** To a cooled (0 °C), stirred solution of **24a** (51.0 mg, 0.102 mmol) in CH₂Cl₂ (1 mL) was added sodium hydrogen phosphate (43.5 mg, 0.306 mmol) followed by *m*-chloroperbenzoic acid (34.3 mg, 0.153 mmol). After the mixture was stirred at 0 °C for 4 h, dimethyl sulfide (3.80 mg, 61.2 μ mol) was added and the mixture was stirred at 0 °C for an additional 1 h. The reaction was quenched with water (3 mL) and extracted with Et₂O (10 mL $\times$ 2). The extracts were washed with saturated aqueous NaHCO₃ and brine, and dried over MgSO₄. The solvent was removed and the residue was subjected to chromatography (5:1 hexane/EtOAc), the first fraction of which gave **30** (36.0 mg, 68%) as a colorless oil: $[\alpha]_D^{20}$ -56.4 (*c* 1.1, CHCl₃); IR (neat) 3475, 1691 cm⁻¹; ¹H NMR δ (for major amide rotamer) 0.83–0.93 (m, 3H), 1.10–1.91 (m, 30H), 2.24 (m, 1H), 2.47 (m, 1H), 2.48 (m, 1H), 2.72–2.80 (m, 2H), 3.31 (t, *J* = 8.7 Hz, 1H), 3.49 (dd, *J* = 9.0, 3.3 Hz, 1H), 3.71 (m, 1H), 4.08 (m, 1H), 4.51 and 4.53 (ABq, *J* = 12.5 Hz, 2H), 7.27–7.36 (m, 5H); ¹³C NMR δ (for major amide rotamer) 14.1, 22.6, 23.9, 24.7, 25.9, 26.2, 27.5, 28.6, 29.3, 31.5, 31.7, 33.5, 38.2, 41.7, 56.0, 58.8,

60.3, 66.7, 69.0, 71.0, 73.1, 79.2, 127.50, 127.53, 128.4, 138.3, 152.7; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{49}NO_5Na$ ($[M + Na]^+$) 538.2508, found 538.3630. Anal. Calcd for $C_{31}H_{49}NO_5$: C, 72.20; H, 9.58; N, 2.72. Found: C, 71.98; H, 9.48; N, 2.72.

The second fraction yielded *tert*-butyl (2*S*,5*S*,6*R*)-2-[(benzyloxy)methyl]-6-[(2*S*,3*S*)-3-[(1*S*)-1-hydroxy-heptyl]oxiranyl]-1-azaspiro[4.5]decane-1-carboxylate (**31**) (7.2 mg, 14%) as white crystals: 1H NMR δ (for major amide rotamer) 0.88 (t, $J = 6.7$ Hz, 3H), 1.10–2.02 (m, 30H), 2.17 (dd, $J = 13.0, 6.3$ Hz, 1H), 2.52 (td, $J = 12.8, 3.2$ Hz, 1H), 2.57–2.69 (m, 3H), 3.32 (t, $J = 8.8$ Hz, 1H), 3.40 (m, 1H), 3.51 (dd, $J = 9.2, 3.2$ Hz, 1H), 4.20 (m, 1H), 4.53 (s, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR δ (for major amide rotamer) 14.1, 22.6, 23.9, 24.7, 25.2, 26.4, 27.1, 28.6, 29.3, 31.4, 31.7, 34.6, 38.1, 40.0, 57.7, 58.6, 60.0, 66.7, 71.3, 71.6, 72.9, 78.9, 127.4, 127.5, 128.4, 138.6, 153.2.

***tert*-Butyl (2*S*,5*S*,6*R*)-2-[(Benzyloxy)methyl]-6-[(1*S*,3*S*)-1,3-dihydroxynonyl]-1-azaspiro[4.5]decane-1-carboxylate (**32**).** To a cooled (0 °C), stirred suspension of lithium aluminum hydride (102 mg, 2.68 mmol) in Et_2O (5 mL) was added dropwise a solution of **30** (230 mg, 0.446 mmol) in Et_2O (4 mL), and the mixture was stirred at room temperature. After 4 h, the mixture was quenched with 2 M aqueous NaOH (0.4 mL) at 0 °C, diluted with $CHCl_3$ (20 mL), and filtered through Celite. The filtrate was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by

chromatography (3:1 hexane/EtOAc) to give **32** (194 mg, 84%) as a colorless oil: $[\alpha]_D^{20}$ -28.7 (c 1.0, CHCl_3); IR (neat) 3444, 1694, 1668 cm^{-1} ; ^1H NMR δ (for major amide rotamer) 0.88 (t, J = 6.8 Hz, 3H), 1.19–1.55 (m, 23H), 1.60–1.77 (m, 5H), 1.84 (m, 1H), 1.94 (m, 1H), 2.06 (m, 1H), 2.17–2.31 (m, 2H), 2.38–2.47 (m, 2H), 2.60 (m, 1H), 3.31 (dd, J = 8.9, 8.7 Hz, 1H), 3.54 (dd, J = 8.9, 3.2 Hz, 1H), 3.78 (m, 1H), 3.97 (m, 1H), 4.14 (m, 1H), 4.52 and 4.54 (ABq, J = 12.2 Hz, 2H), 7.26–7.36 (m, 5H); ^{13}C NMR δ (for major amide rotamer) 14.1, 22.7, 23.1, 24.1, 25.5, 25.7, 25.9, 28.6, 29.3, 31.4, 31.8, 37.3, 39.2, 43.3, 44.5, 59.5, 67.7, 68.4, 70.1, 71.4, 73.1, 79.1, 127.5, 127.6, 128.4, 138.5, 153.2; HRMS (ESI-TOF) m/z calcd for $\text{C}_{31}\text{H}_{51}\text{NO}_5\text{Na}$ ($[\text{M} + \text{Na}]^+$) 540.3665, found 540.3716.

***tert*-Butyl (2*S*,5*S*,6*R*)-2-[(Benzyloxy)methyl]-6-[(1*S*,3*S*)-1-hydroxy-3-[(methylsulfonyl)oxy]nonyl]-1-azaspiro[4.5]decane-1-carboxylate (**33**).** To a cooled (0 °C), stirred solution of **32** (149 mg, 0.288 mmol) in CH_2Cl_2 (4 mL) were successively added triethylamine (43.7 mg, 0.432 mmol), 4-dimethylaminopyridine (17.6 mg, 0.144 mmol), and methanesulfonyl chloride (33.0 mg, 0.288 mmol), and stirring was continued at room temperature. After 1 h, the reaction was quenched with 1 M aqueous HCl (3 mL) and extracted with CHCl_3 (10 mL $\times$ 2). The extracts were washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by chromatography (4:1 hexane/EtOAc) to give **33** (126 mg, 73%) as a colorless oil: $[\alpha]_D^{20}$ -28.8 (c 0.98, CHCl_3);

IR (neat) 3542, 1693, 1681, 1668 cm^{-1} ; ^1H NMR δ (for major amide rotamer) 0.88 (t, J = 6.6 Hz, 3H), 1.20–1.50 (m, 21H), 1.59–1.98 (m, 9H), 2.15–2.29 (m, 2H), 2.41–2.57 (m, 3H), 3.02 (s, 3H), 3.30 (dd, J = 8.8, 8.6 Hz, 1H), 3.52 (dd, J = 8.8, 3.2 Hz, 1H), 3.87 (br d, J = 10.8 Hz, 1H), 4.14 (m, 1H), 4.47–4.59 (m, 2H), 4.86 (m, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR δ (for major amide rotamer) 14.1, 22.5, 23.2, 24.1, 25.0, 25.6, 25.7, 28.5, 29.0, 31.2, 31.6, 35.6, 38.3, 39.2, 42.1, 44.0, 59.5, 64.4, 68.4, 71.5, 73.1, 79.0, 81.4, 127.5, 127.6, 128.3, 138.5, 153.0; HRMS (ESI-TOF) m/z calcd for $\text{C}_{32}\text{H}_{53}\text{NO}_7\text{Na}$ ($[\text{M} + \text{Na}]^+$) 618.3440, found 618.3309.

(3*S*,5*R*,7*S*,7*aR*,11*aS*)-3-[(Benzyloxy)methyl]-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-7-ol (34). To a cooled (0 °C), stirred solution of **33** (119 mg, 0.200 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (455 mg, 3.99 mmol), and the mixture was stirred at room temperature for 30 min. After the mixture was allowed to cool to 0 °C, CHCl_3 (3 mL) and saturated aqueous NaHCO_3 (3 mL) were added and the mixture was stirred at room temperature for 30 min. The two-phase system was separated, and the aqueous layer was extracted with CHCl_3 (10 mL $\times$ 2). The combined organic layers were dried over K_2CO_3 and concentrated in vacuo. The residue was purified by chromatography (200:9:1 $\text{CHCl}_3/\text{MeOH}/28\%$ aqueous NH_3) to give **34** (67.4 mg, 84%) as a pale yellow oil: $[\alpha]_{\text{D}}^{20}$ -44.1 (c 0.89, CH_2Cl_2); IR (neat) 3388 cm^{-1} ; ^1H NMR δ 0.88 (t, J =

6.9 Hz, 3H), 1.14–1.42 (m, 15H), 1.50–1.63 (m, 6H), 1.72 (m, 1H), 1.78 (ddd, $J = 12.4, 7.3, 2.7$ Hz, 1H), 1.90 (ddd, $J = 14.9, 12.4, 8.1$ Hz, 1H), 1.93–2.01 (m, 2H), 3.12 (dd, $J = 9.0, 8.8$ Hz, 1H), 3.19–3.30 (m, 2H), 3.56 (dd, $J = 8.8, 4.1$ Hz, 1H), 3.63 (m, 1H), 4.49 and 4.52 (ABq, $J = 12.1$ Hz, 2H), 7.23–7.33 (m, 5H); ^{13}C NMR δ 14.1, 22.6, 24.6, 26.1, 27.5, 29.0, 29.4, 29.6, 31.9, 33.5, 34.6, 41.0, 46.8, 52.3, 57.7, 66.9, 68.8, 73.2, 77.7, 127.5, 127.6, 128.3, 138.2; HRMS (ESI-TOF) m/z calcd for $\text{C}_{26}\text{H}_{42}\text{NO}_2$ ($[\text{M} + \text{H}]^+$) 400.3216, found 400.3186. Anal. Calcd for $\text{C}_{26}\text{H}_{41}\text{NO}_2$: C, 78.15; H, 10.34; N, 3.50. Found: C, 78.18; H, 10.23; N, 3.58.

(3*S*,5*R*,7*aS*,11*aS*)-3-[(Benzyloxy)methyl]-5-hexyloctahydro-1*H*-pyrrolo[2,1-*j*]-quinolin-7(7*aH*)-one (36). To a cooled ($-78\text{ }^{\circ}\text{C}$) solution of oxalyl chloride (37.7 mg, 0.297 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise a solution of dimethylsulfoxide (46.5 mg, 0.595 mmol) in CH_2Cl_2 (0.3 mL), and the mixture was stirred at the same temperature for 30 min. To this mixture was added dropwise a solution of **34** (59.4 mg, 0.149 mmol) in CH_2Cl_2 (0.6 mL) and the mixture was stirred at the same temperature. After 1.5 h, to this mixture was added dropwise triethylamine (90.2 mg, 0.892 mmol), and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1.5 h and then at room temperature for 1 h. The reaction was quenched with water (3 mL) and the mixture was extracted with CHCl_3 (10 mL $\times$ 2). The

extracts were dried over MgSO_4 and concentrated in vacuo to give a crude mixture of the tricyclic compounds **35** and **36** (2:1 ratio) as a pale yellow oil. This mixture was dissolved in MeOH (2 mL), and to this solution was added saturated aqueous K_2CO_3 (1 mL). After being stirred for 2 h, the mixture was extracted with CHCl_3 (10 mL x 2). The extracts were dried over K_2CO_3 and concentrated in vacuo to give a crude residue, which was purified by chromatography (8:1 hexane/EtOAc) to afford **36** (51.1 mg, 86%) as a pale yellow oil: $[\alpha]_D^{21} +26.3$ (c 1.2, CH_2Cl_2); IR (neat) 3390, 1704 cm^{-1} ; ^1H NMR δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.16–1.43 (m, 13H), 1.45 (m, 1H), 1.52–1.67 (m, 4H), 1.92 (m, 1H), 2.02–2.11 (m, 2H), 2.14–2.27 (m, 4H), 3.11 (t, $J = 9.8$ Hz, 1H), 3.17 (m, 1H), 3.42–3.48 (m, 2H), 4.50 and 4.56 (ABq, $J = 12.1$ Hz, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR δ 14.1, 21.9, 22.6, 23.0, 24.5, 26.9, 27.1, 29.3, 31.8, 35.0, 35.2, 35.9, 43.0, 51.0, 55.5, 55.7, 70.0, 73.2, 75.5, 127.6, 127.7, 128.4, 138.5, 211.2; HRMS (ESI-TOF) m/z calcd for $\text{C}_{26}\text{H}_{40}\text{NO}_2$ ($[\text{M} + \text{H}]^+$) 398.3059, found 398.3081.

(3*S*,5*R*,7*aS*,11*aS*)-5-Hexyl-3-(hydroxymethyl)octahydro-1*H*-pyrrolo[2,1-*j*]-quinoline-7(7*aH*)-one [(+)-Cylindricine C] (1c). To a solution of **36** (50.7 mg, 0.128 mmol) in MeOH (2 mL) was added palladium hydroxide on carbon (60 mg), and the resulting suspension was stirred under hydrogen (1 atm) for 16 h. The catalyst was

removed by filtration and the filtrate was evaporated in vacuo. The residue was purified by chromatography (6:1 hexane/EtOAc) to give **1c** (28.5 mg, 73%) as a colorless oil: $[\alpha]_D^{21} +63.1$ (c 0.44, CH_2Cl_2); ^1H NMR δ 0.86 (t, J = 6.8 Hz, 3H), 1.18–1.50 (m, 15H), 1.59–1.72 (m, 4H), 1.82 (m, 1H), 2.10 (dd, J = 12.1, 7.9 Hz, 1H), 2.15–2.32 (m, 4H), 2.85 (br s, 1H), 3.28 (m, 1H), 3.41 (m, 1H), 3.48–3.54 (m, 2H); ^{13}C NMR δ 14.0, 21.9, 22.6, 22.8, 24.3, 27.1, 28.7, 29.3, 31.7, 35.2, 35.9, 36.4, 42.6, 50.3, 55.3, 56.6, 66.4, 70.7, 210.5; HRMS (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{34}\text{NO}_2$ ($[\text{M} + \text{H}]^+$) 308.2590, found 308.2595.

***tert*-Butyl (2*S*,5*S*,6*S*)-2-Benzoyloxymethyl-6-[(1*E*)-3(*R*)-hydroxynon-1-enyl]-1-azaspiro[4.5]decane-1-carboxylate (**24b**).** According to the procedure described for conversion of **25** to **24a**, **25** (770 mg, 1.55 mmol) was treated with (*R*)-BINAL-H prepared from (*R*)-1,1'-bi-2-naphthol (2.26 g, 7.89 mmol) and worked up. Chromatography (6:1 hexane/EtOAc) afforded two fractions. The first fraction gave **24a** (64.9 mg, 8.4%) as a colorless oil.

The second fraction gave **24b** (584 mg, 76%) as a colorless oil: $[\alpha]_D^{20} -61.9$ (c 1.1, CHCl_3); IR (neat) 3433, 1681 cm^{-1} ; ^1H NMR δ (for major amide rotamer) 0.87 (t, J = 6.8 Hz, 3H), 1.14–1.83 (m, 30H), 2.10 (m, 1H), 2.53 (td, J = 12.8, 3.4 Hz, 1H), 3.26 (t, J = 8.8 Hz, 1H), 3.33 (m, 1H), 3.48 (dd, J = 9.0, 3.3 Hz, 1H), 3.94–4.04 (m, 2H), 4.50 and 4.51

(ABq, $J = 12.4$ Hz, 2H), 5.37–5.52 (m, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR δ (for major amide rotamer) 14.1, 22.7, 24.1, 25.1, 25.5, 26.5, 28.6, 29.4, 30.3, 31.3, 31.9, 37.4, 38.0, 42.3, 58.9, 68.2, 71.4, 73.0, 73.7, 78.8, 127.5, 127.6, 128.4, 133.7, 133.9, 138.5, 152.9; HRMS (ESI–TOF) m/z calcd for $\text{C}_{31}\text{H}_{50}\text{NO}_4$ ($[\text{M} + \text{H}]^+$) 500.3740, found 500.3745. Anal. Calcd for $\text{C}_{31}\text{H}_{49}\text{NO}_4$: C, 74.51; H, 9.88; N, 2.80. Found: C, 74.75; H, 9.59; N, 2.62.

***tert*-Butyl (2*S*,5*S*,6*S*)-2-Benzoyloxymethyl-6-[(3*R*)-3-hydroxynonyl]-1-azaspiro-[4.5]-decane-1-carboxylate (37).** To a solution of **24b** (95.7 mg, 0.191 mmol) in EtOAc (2 mL) was added platinum oxide (2.17 mg, 9.57 μmol), and the mixture was stirred under hydrogen (1 atm) for 15 min and filtered through Celite. The filtrate was concentrated in vacuo and purification of the residue by chromatography (6:1 hexane/EtOAc) afforded **37** (77.6 mg, 81%) as a colorless oil: $[\alpha]_{\text{D}}^{20} -43.7$ (c 1.1, CHCl_3); IR (neat) 3443, 1700, 1681 cm^{-1} ; ^1H NMR δ (for major amide rotamer) 0.88 (t, $J = 6.7$ Hz, 3H), 0.92–1.01 (m, 2H), 1.19–1.50 (m, 24H), 1.55–1.88 (m, 7H), 1.97 (br s, 1H), 2.05 (ddd, $J = 12.5, 7.6, 2.1$ Hz, 1H), 2.35 (td, $J = 12.7, 3.6$ Hz, 1H), 2.65 (m, 1H), 3.30 (t, $J = 8.8$ Hz, 1H), 3.53 (dd, $J = 8.9, 3.3$ Hz, 1H), 3.60 (m, 1H), 4.08 (m, 1H), 4.51 and 4.53 (ABq, $J = 12.1$ Hz, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR δ (for major amide rotamer) 14.1, 22.7, 24.1, 25.1, 25.7, 25.9, 26.3, 28.6, 28.9, 29.5, 30.7, 31.9, 34.0, 37.7, 38.5, 59.2, 68.7, 70.2, 71.3, 73.1, 79.2, 127.5, 127.6, 128.4, 138.4, 153.6; HRMS (ESI–TOF) m/z calcd for $\text{C}_{31}\text{H}_{52}\text{NO}_4$ ($[\text{M} + \text{H}]^+$) 502.3896,

found 502.3920. Anal. Calcd for $C_{31}H_{51}NO_4$: C, 74.21; H, 10.25; N, 2.79. Found: C, 74.23; H, 10.17; N, 2.72.

(3*R*)-1-[(2*S*,5*S*,6*S*)-2-Benzylloxymethyl-1-azaspiro[4.5]dec-6-yl]-3-nonanol (38).

To a solution of **37** (101 mg, 0.201 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (230 mg, 2.01 mmol), and the mixture was stirred at room temperature. After being stirred at room temperature for 3 h, the mixture was basified by the addition of saturated aqueous $NaHCO_3$ at 0 °C and extracted with $CHCl_3$ (10 mL x 2). The extracts were dried over K_2CO_3 and concentrated in vacuo. The residue was purified by chromatography (400:9:1 $CHCl_3$ /MeOH/28% aqueous NH_3) to give **38** (79.7 mg, 99%) as a colorless oil: $[\alpha]_D^{20}$ -38.4 (c 1.2, $CHCl_3$); IR (neat) 3376, 2925 cm^{-1} ; 1H NMR δ 0.88 (t, J = 6.8 Hz, 3H), 0.93–1.06 (m, 2H), 1.11–1.49 (m, 17H), 1.54–1.83 (m, 10H), 3.33 (m, 1H), 3.41 (dd, J = 9.5, 4.9 Hz, 1H), 3.52 (dd, J = 9.5, 4.2 Hz, 1H), 3.71 (m, 1H), 4.48 and 4.53 (ABq, J = 12.1 Hz, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR δ 14.1, 22.7, 24.8, 25.9, 26.2, 26.3, 28.97, 29.03, 29.6, 31.3, 31.9, 35.0, 37.8, 40.8, 45.5, 59.2, 66.0, 68.4, 72.0, 73.0, 127.50, 127.52, 128.4, 138.5; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{44}NO_2$ ($[M + H]^+$) 402.3372, found 402.3348. Anal. Calcd for $C_{26}H_{43}NO_2$: C, 77.75; H, 10.79; N, 3.49. Found: C, 77.75; H, 10.52; N, 3.37.

(3*S*,5*S*,7*aS*,11*aS*)-3-Benzylloxymethyl-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]-quinoline (**39**). To a cooled (0 °C), stirred solution of **38** (89.7 mg, 0.223 mmol) in CH₂Cl₂ (2 mL) were successively added triphenylphosphine (176 mg, 0.670 mmol), carbon tetrabromide (222 mg, 0.670 mmol), and triethylamine (67.8 mg, 0.670 mmol), and the mixture was stirred at room temperature for 2 h. After addition of saturated aqueous NaHCO₃ (5 mL), the resulting mixture was extracted with CHCl₃ (20 mL x 2) and the extracts were dried over K₂CO₃. Removal of the solvent in vacuo followed by purification by chromatography (200:9:1 CHCl₃/MeOH/28% aqueous NH₃) gave **39** (75.3 mg, 88%) as a pale yellow oil: $[\alpha]_D^{20} +4.1$ (*c* 1.1, MeOH); IR (neat) 2927, 2856 cm⁻¹; ¹H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.04 (td, *J* = 12.8, 3.6 Hz, 1H), 1.10–1.33 (m, 14H), 1.37 (dt, *J* = 13.1, 3.8 Hz, 1H), 1.44 (m, 1H), 1.49–1.70 (m, 7H), 1.74 (m, 1H), 1.83 (m, 1H), 2.01 (m, 1H), 2.17 (m, 1H), 3.10 (m, 1H), 3.37 (t, *J* = 8.9 Hz, 1H), 3.63 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.49 and 4.56 (ABq, *J* = 12.1 Hz, 2H), 7.23–7.35 (m, 5H); ¹³C NMR δ 14.2, 22.7, 23.7, 24.9, 26.0, 26.4, 26.6, 27.1, 29.7, 31.0, 31.5, 32.0, 37.4, 38.9, 43.7, 62.8, 65.3, 67.5, 73.1, 77.6, 127.4, 127.5, 128.3, 138.8; HRMS (ESI–TOF) *m/z* calcd for C₂₆H₄₂NO ([M + H]⁺) 384.3266, found 384.3291. Anal. Calcd for C₂₆H₄₁NO: C, 81.41; H, 10.77; N, 3.65. Found: C, 81.17; H, 10.71; N, 3.51.

[(3*S*,5*S*,7*aS*,11*aS*)-5-Hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl]methanol

(40). To a solution of **39** (64.9 mg, 0.169 mmol) in MeOH (2 mL) was added palladium hydroxide on carbon (70 mg) and the mixture was stirred under hydrogen (1 atm) for 18 h. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo. The residue was purified by chromatography (150:9:1 CHCl₃/MeOH/28% aqueous NH₃) to give **40** (47.0 mg, 95%) as a colorless oil: $[\alpha]_D^{20} +11.0$ (*c* 0.45, MeOH); IR (neat) 3419 cm⁻¹; ¹H NMR δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.05–1.16 (m, 2H), 1.21–1.80 (m, 23H), 1.86–1.94 (m, 2H), 2.23 (m, 1H), 3.07–3.14 (m, 2H), 3.31 (m, 1H), 3.53 (dd, *J* = 10.2, 5.8 Hz, 1H); ¹³C NMR δ 14.1, 22.7, 23.9, 24.5, 25.9, 26.0, 26.4, 27.0, 27.7, 29.6, 31.3, 32.0, 38.1, 39.6, 41.8, 60.3, 65.0, 66.3, 66.7; HRMS (ESI-TOF) *m/z* calcd for C₁₉H₃₆NO ([*M* + *H*]⁺) 294.2797, found 294.2793.

(3*R*,6*S*,8*aS*,12*aS*)-6-Hexyldodecahydropyrido[2,1-*j*]-quinolin-3-yl Thiocyanate

[(-)-Fasicularin (4)]. To a solution of DEAD (40% toluene solution, 0.124 mL, 0.316 mmol) in CH₂Cl₂ (1 mL) were added triphenylphosphine (82.8 mg, 0.316 mmol) and ammonium thiocyanate (30.0 mg, 0.394 mmol). To this mixture was added dropwise a solution of **40** (46.3 mg, 0.158 mmol) in CH₂Cl₂ (1.6 mL), and the mixture was stirred at

room temperature. After 10 min, saturated aqueous NaHCO_3 (5 mL) was added and the mixture was extracted with CHCl_3 (20 mL $\times$ 2). After the extracts were dried over K_2CO_3 and concentrated in vacuo, the products were separated into two fractions by column chromatography (15:1 hexane/EtOAc). The first fraction gave (–)-fasicularin (**4**) (24.9 mg, 47%) as a colorless oil: $[\alpha]_D^{21} -4.4$ (c 0.47, MeOH); IR (neat) 2152 cm^{-1} ; ^1H NMR (pyridine- d_5) δ 0.84 (t, $J = 6.6\text{ Hz}$, 3H), 0.96–1.58 (m, 23H), 1.78 (td, $J = 13.1, 4.4\text{ Hz}$, 1H), 1.88 (qd, $J = 12.4, 4.0\text{ Hz}$, 1H), 1.95 (m, 1H), 2.54 (d, $J = 12.2\text{ Hz}$, 1H), 2.91 (ddt, $J = 11.4, 5.9, 2.9\text{ Hz}$, 1H), 3.28 (ddd, $J = 14.6, 4.4, 1.8\text{ Hz}$, 1H), 3.39 (dd, $J = 14.3, 12.2\text{ Hz}$, 1H), 3.57 (m, 1H); ^{13}C NMR (pyridine- d_5) δ 14.3, 19.3, 22.7, 22.9, 24.0, 26.3, 27.2, 27.7, 29.5, 30.2, 32.1, 32.3, 34.1, 34.3, 40.2, 46.1, 46.5, 52.2, 56.3, 111.6; HRMS (ESI–TOF) m/z calcd for $\text{C}_{20}\text{H}_{35}\text{N}_2\text{S}$ ($[\text{M} + \text{H}]^+$) 335.2521, found 335.2523.

The second fraction yielded [(3*S*,5*S*,7*aS*,11*aS*)-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl]methyl thiocyanate (**41**) (24.9 mg, 47%) as a colorless oil: IR (neat) $2152, 2094\text{ cm}^{-1}$; ^1H NMR δ 0.89 (t, $J = 6.7\text{ Hz}$, 3H), 1.04–1.46 (m, 16H), 1.53–1.71 (m, 8H), 1.78–1.89 (m, 2H), 2.15 (m, 1H), 2.25 (m, 1H), 3.04 (m, 1H), 3.17–3.25 (m, 2H); ^{13}C NMR δ 14.2, 22.7, 24.0, 24.3, 26.3, 26.4, 26.9, 27.5, 28.5, 29.6, 31.1, 32.0, 38.0, 39.9, 41.6, 42.1, 60.9, 64.8, 67.2, 113.6; HRMS (ESI–TOF) m/z calcd for $\text{C}_{20}\text{H}_{35}\text{N}_2\text{S}$ ($[\text{M} + \text{H}]^+$) 335.2521, found 335.2502.

The later product **41** was dissolved in CH_3CN (2 mL) and the resulting solution was allowed to stir at room temperature for 72 h. After removal of the solvent in vacuo, the residue was subjected to chromatography (15:1 hexane/EtOAc) to give **4** (22.7 mg, 91%) along with the recovery of **41** (2.2 mg, 9%). In the chiral HPLC analysis of fasicularin (**4**)

on a Daicel Chiralpak AD-H [mobile phase, 500:1 hexane–2-propanol; flow rate, 0.5 mL/min; detection, UV (220 nm)], the authentic sample of racemic fascicularin⁶ gave peaks at different retention times (16 min and 17 min). The synthetic sample of (–)-fascicularin (**4**) gave a single peak at 17 min.