Total Synthesis of the Marine Alkaloid (±)-Lepadiformine *via* a Radical Carboazidation

Pascal Schär and Philippe Renaud*

*Departement für Chemie und Biochemie, Universität Bern,
Freiestrasse 3, CH-3012 Bern, Switzerland*

philippe.renaud@ioc.unibe.ch

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Section A: *General Experimental Procedures*

Techniques. All reactions were performed under a nitrogen atmosphere in oven-dried (120 °C) flasks and standard precautions against moisture were taken. A dry ice/acetone bath was used to obtain a temperature of –78 °C. An ice bath was used to obtain 0 °C. Silica gel 60 (40-60 µm, SdS) was used for flash column chromatography. Thin-layer chromatography was performed on Merck silica gel 60 F₂₅₄ plates. Visualization of TLC plates was carried out either with 254 nm UV light or by dipping in a solution of KMnO₄ (3 g), K₂CO₃ (20 g), 5% NaOH (3 mL) in H₂O (300 mL) and subsequent heating. Anhydrous magnesium sulfate was used as the drying reagent and organic solvents were removed under reduced pressure using a rotary evaporator.

Materials. Commercial reagents were used as received. Solvents for reactions (THF, Et₂O, CH₂Cl₂, benzene and toluene) were filtered over columns of dried alumina under a positive pressure of argon. Solvents for extractions and flash column chromatography were of technical grade and were distilled prior to use. Ammonia saturated ether (NH₃-sat. Et₂O) refers to the supernatant organic layer of a biphasic mixture of diethyl ether and saturated aqueous ammonium hydroxide.

Instrumentation. Melting points were measured on a Büchi B-545 apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE-300 spectrometer operating at 300 MHz for ¹H and 75 MHz for ¹³C at rt unless otherwise stated. Some ¹H and ¹³C NMR spectra and two-dimensional NMR spectra were recorded on a Bruker DRX-400 spectrometer by the NMR group of Professor Bigler at the University of Bern. Chemical shift data are reported in units of δ (ppm) using as the internal standard either residual CHCl₃ (δ = 7.27 for ¹H NMR spectra and δ = 77.16 for ¹³C NMR spectra) or Si(CH₃)₄ (δ = 0 for ¹H NMR and ¹³C NMR spectra). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad) for ¹H spectra and q (quaternary), t (tertiary), s (secondary) and p (primary) for ¹³C spectra as determined by the DEPT experiment. Coupling constants, *J*, are reported in Hz. Infrared spectra were recorded on a Jasco FT-IR-460 Plus spectrometer equipped with a Specac MKII Golden Gate Single Reflection Diamond ATR System and are reported in wave numbers (cm⁻¹). Low and high-resolution mass spectra were recorded on a Waters Micromass Autospec Q mass spectrometer in EI mode at 70 eV. Gas chromatographic mass spectra (GC-MS) analyses were performed on a Finnigan Trace GC

2000 gas chromatograph equipped with an autosampler and a Trace MS mass selective detector. Microanalyses were obtained from Ilse Beetz, Mikroanalytisches Laboratorium, 96317 Kronach, Germany.

Section B: Synthesis of Compounds

3-(2-Oxo-cyclohexyl)-propionic acid ethyl ester (**6**).¹

and pyrrolidine (17.07 g, 240 mmol) in benzene (80 mL) were refluxed under water separation using a Dean&Stark apparatus. After 6 h the solvent and excess pyrrolidine were removed under reduced pressure and the crude enamine was dissolved in THF (75 mL). Addition of ethyl acrylate (30.04 g, 300 mmol) and refluxing for 4 hours was followed by addition of water (10 mL) and another hour of refluxing for hydrolysis. The solvent was removed under reduced pressure and the crude product was diluted with Et₂O. The organic phase was washed with dilute hydrochloric acid and brine, dried, and the solvent was removed. Distillation (0.5 mbar / 88° C) gave **6** (34.37 g, 173 mmol, 87 %).

Colorless liquid. Physical and spectral data were in accordance with literature values. ¹H NMR (300MHz, CDCl₃) δ 4.10 (q, *J* = 7.4 Hz, 2H), 2.44 - 2.21 (m, 5H), 2.16 - 1.96 (m, 3H), 1.93 - 1.30 (m, 5H), 1.23 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 211.6, 172.9, 59.6, 49.2, 41.6, 33.7, 31.3, 27.6, 24.7, 24.4, 13.7. IR (ATR) ν 2933, 2861, 1730, 1706, 1448, 1374, 1309, 1162, 1130, 1095, 1032, 856.

Ethyl 3-(2-methylenecyclohexyl)-propionate (**7**).²

dissolved in THF (70 mL). The resulting dark blue solution was cooled to -78 °C and MeLi (6.9 mL of a 1.6 M solution in Et₂O, 11 mmol) was added dropwise. The resulting dark brown reaction mixture was stirred for 1 h, after which the ketone **6** (397 mg, 2.0 mmol) in THF (5 mL) was added. After 1 h at -78 °C, the reaction was allowed to warm to rt, then heated to reflux temperature for 1 h and left overnight at rt. The solvent was removed and the crude product filtered over a short column of silica gel (cyclohexane/*tert*-butyl methyl ether 1:1) to give **7** (380 mg, 1.94 mmol, 97 %).

Colorless liquid with a strong fruity smell. Physical and spectral data were in accordance with literature values.³ ¹H NMR (300MHz, CDCl₃) δ 4.67 (s, 1H), 4.57 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.29 (t, *J* = 7.7 Hz, 2H), 2.26 - 2.13 (m, 1H), 2.10 - 1.86 (m, 3H), 1.78 - 1.38 (m, 7H), 1.36 - 1.28 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 173.8, 151.5, 106.4, 60.0, 42.6, 34.2, 33.6, 32.4, 28.6, 27.1, 23.7, 14.2. IR (ATR) ν 2928, 2854, 1733, 1644, 1445, 1372, 1163, 1035, 889.

3-(2-Methylenecyclohexyl)-*N*-methoxy-*N*-methyl-propanamide (8).^{4, 5} A suspension of

N,O-dimethylhydroxylamine hydrochloride (4.88 g, 50 mmol) in CH₂Cl₂ (400 mL) was cooled to 0 °C and Me₂AlCl (42 mL of a 1.2 M solution in toluene, 50 mmol) was added over a period of 5 min. Cooling was removed and the mixture was stirred at rt for 1 h. To the resulting pink solution was added ester **7** (2.95 g, 15 mmol) in

CH₂Cl₂ (150 mL) dropwise over a period of 35 min. The reaction mixture was stirred at rt for 1 h and was then cooled to 0 °C. Phosphate buffer (40 mL, pH 8) was cautiously added and the mixture was filtered through Celite[®]. The organic phase was washed with brine, dried, and the solvent was removed. FC (hexanes/EtOAc 4:1) gave **8** (2.93 g, 13.9 mmol, 92 %).

Colorless liquid with a characteristic smell. Physical and spectral data were in accordance with literature values. ¹H NMR (300MHz, CDCl₃) δ 4.66 ("s", 1H), 4.58 ("s", 1H), 3.65 (s, 3H), 3.16 (s, 3H), 2.40 (t, *J* = 7.9 Hz, 2H), 2.30 - 2.14 (m, 1H), 2.10 - 1.86 (m, 3H), 1.80 - 1.25 (m, 7H). ¹³C NMR (75 MHz, CDCl₃) δ 174.5, 151.7, 106.0, 61.0, 42.7, 34.2, 33.8, 32.0, 29.8, 28.6, 26.6, 23.8. IR (ATR) ν 2927, 2853, 1663, 1443, 1412, 1383, 1175, 1115, 997, 887. MS (EI, 70ev) *m/z* (%) 211 (M⁺, 45), 180 (12), 151 (77), 133 (76), 123 (29), 116 (44), 109 (85), 103 (73), 93 (78), 81 (84), 67 (89), 61 (100), 41 (93). HRMS (EI) calcd for C₁₂H₂₁NO₂: 211.157229; found: 211.157100.

1-(2-Methylenecyclohexyl)-nonan-3-one (4).⁶ Magnesium turnings (2.43 g, 100 mmol) were

covered with Et₂O (~5 mL) and a few drops of 1-bromohexane were added for the reaction to start. The rest of the 1-bromohexane (16.51 g, 100 mmol) in Et₂O (25 mL) was added at such a rate that the reaction remained at a gentle reflux. After 1 h of stirring at rt all of the Mg had dissolved. The so prepared solution was added dropwise to a

solution of weinreb amide **8** (10.57 g, 50 mmol) in THF (500 mL) at -78 °C. Cooling was

removed and the reaction mixture was stirred for 2.5 h. 1 N HCl(aq) was added until the precipitate which formed dissolved again. The layers were separated and the aqueous layer was extracted with Et₂O (2 x 200 mL). The combined organic extracts were washed with brine, dried, and the solvent was removed. FC (hexanes/EtOAc 97:3) gave **4** (11.43 g, 48.4 mmol, 97 %).

Colorless liquid. Physical and spectral data were in accordance with literature values. ¹H NMR (300MHz, CDCl₃) δ 4.66 (s, 1H), 4.55 (s, 1H), 2.40 (t, *J* = 7.54 Hz, 2H), 2.38 (t, *J* = 7.35 Hz, 2H), 2.25 - 2.13 (m, 1H), 2.06 - 1.95 (m, 2H), 1.94 - 1.80 (m, 1H), 1.77 - 1.20 (m, 15H), 0.88 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 211.4, 151.9, 106.2, 42.9, 42.7, 40.8, 34.2, 33.8, 31.6, 28.9, 28.7, 25.8, 23.9, 23.8, 22.5, 14.0. IR (ATR) ν 2926, 2854, 1713, 1644, 1446, 1409, 1370, 1068, 888. MS (EI, 70ev) *m/z* (%) 236 (M⁺, 9), 218 (38), 179 (18), 166 (24), 151 (53), 133 (63), 108 (74), 93 (70), 81 (63), 67 (67), 55 (100), 43 (79). HRMS (EI) calcd for C₁₆H₂₈O: 236.214016; found: 236.214160.

Ethyl 3-[(1*RS*,2*RS*)-1-azido-2-(3-oxononyl)cyclohexyl]propanoate (3**).** A mixture of olefin

4 (3.55 g, 15 mmol), ethyl iodoacetate (2.14 g, 10 mmol), 3-pyridinesulfonyl azide (5.50 g, 30 mmol) and hexabutyldistannane (8.70 g, 15 mmol) in benzene (20 mL) was heated to 60 °C and di-*tert*-butylhyponitrite (52 mg, 0.3 mmol) was added three times in intervals of 2 h. After 4 h, additional

ethyl iodoacetate (1.07 g, 5 mmol) was added to the reaction mixture. After a total reaction time of 6 h, the solvent was removed. FC (large volumes of hexanes to remove tin residues, then 5-20 % of EtOAc in hexanes) gave **3** (4.42 g, 12.1 mmol, 81 %) as an approximately 3:2 mixture of diastereomers in favour of the desired *trans* isomer.

Mixture of diastereomers: Anal. calcd for C₂₀H₃₅N₃O₃: C, 65.72; H, 9.65; N, 11.50; found: C, 65.76; H, 9.66; N, 11.61.

trans-**3** (major, 1*RS*,2*RS*): colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 4.09 (q, *J* = 7.1 Hz, 2H), 2.50-2.20 (m, 6H), 1.90-1.10 (m, 24H), 0.83 (t, *J* = 6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 210.9 (q), 173.4 (q), 66.5 (q), 60.6 (s), 43.4 (t), 42.9 (s), 40.9 (s), 32.2 (s), 31.6 (s), 28.9 (s), 28.4 (s), 27.1 (s), 26.6 (s), 26.6 (s), 23.9 (s), 23.1 (s), 22.5 (s), 22.3 (s), 14.2 (p), 14.0 (p). IR (KBr, neat) ν 2932, 2861, 2097 (N₃), 1736 (CO₂), 1716 (CO).

cis-**3** (minor, 1*RS*,2*SR*): colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 4.20 (q, *J* = 7.1 Hz, 2H), 2.55-2.30 (m, 6H), 2.13 (t, *J* = 8.3 Hz, 2H), 1.96-1.82 (m, 2H), 1.78-1.69 (m, 1H), 1.67-1.14

(m, 19H), 0.88 (t, $J = 6.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 211.1 (q), 173.1 (q), 66.0 (q), 60.7 (s), 42.9 (s), 42.1 (t), 40.0 (s), 33.1 (s), 32.8 (s), 31.6 (s), 29.0 (s), 28.9 (s), 26.6 (s), 24.9 (s), 23.9 (s), 22.9 (s), 22.5 (s), 21.8 (s), 14.2 (p), 14.0 (p). IR (KBr, neat) ν 2933, 2858, 2097 (N_3), 1736 (CO_2), 1716 (CO).

(5RS,7aSR,11aSR)-5-Hexyldecahydro-3H-pyrrolo[2,1-*j*]quinolin-3-one (2). A mixture of

azides **3** (dr 3:2, 366 mg, 1.0 mmol) in ethanol (10 mL) was hydrogenated at a hydrogen pressure of 55 bar in the presence of Pd/CaCO_3 (100 mg, 5% w/w) at 100 °C for 3 days. The catalyst was removed by filtration over Celite[®] and the solvent was removed under reduced pressure to give 322 mg of a crude product which was diluted in $(\text{CH}_2\text{Cl})_2$ (15 mL). To this solution was added Me_2AlCl (5 mL of a 2.4 M solution in $(\text{CH}_2\text{Cl})_2$, 12 mmol) and the reaction mixture was

heated to reflux (90 °C) over 3 days. After cooling to rt, the reaction mixture was diluted in ice-cold EtOAc (100 mL) and 0.5 M $\text{Na}_2\text{HPO}_4(\text{aq})$ (4 mL) was cautiously added. The organic layer was dried, and the solvent was removed. FC (cyclohexane/*tert*-butyl methyl ether 4:1 – 1:1) gave **2** (120 mg, 0.43 mmol, 43 %; 72 % based on *trans*-**3**) as a single diastereomer.

Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 3.19 (ddd, $J = 17.0, 8.7, 6.6$ Hz, 1H), 2.53 (dd, $J = 13.7, 5.0$ Hz, 1H), 2.48 (dddd, $J = 16.2, 12.9, 8.2, 0.4$ Hz, 1H), 2.14 (dd, $J = 16.2, 9.0$ Hz, 1H), 1.90 (ddd, $J = 12.5, 8.2, 0.4$ Hz, 1H), 1.79 (tdd, $J = 12.7, 9.0, 1.7$ Hz, 2H), 1.76-1.24 (m, 20H), 1.19 (qd, $J = 12.5, 3.5$ Hz, 1H), 0.90 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 176.5 (q), 66.3 (q), 51.8 (t), 42.7 (t), 33.4 (s), 32.0 (s, 2C), 31.8 (s), 30.6 (s), 29.3 (s), 28.0 (s), 27.4 (s), 26.3 (s), 24.6 (s), 23.7 (s), 22.8 (s), 22.3 (s), 14.3 (p). IR (ATR) ν 2923, 2855, 2361, 1684, 1414, 1339. MS (EI, 70ev) m/z (%) 277 (M^+ , 48), 234 (100), 220 (20), 192 (67), 150 (19), 136 (20), 110 (14), 67 (20), 55 (14), 41 (17). HRMS (EI) calcd for $\text{C}_{18}\text{H}_{31}\text{NO}$: 277.240565; found: 277.240780.

(5RS,7aSR,11aSR)-5-Hexyldecahydro-3H-pyrrolo[2,1-j]quinolin-3-thione (10). To

lactam **2** (111 mg, 0.40 mmol) was added neat Lawesson's reagent⁷ (121 mg, 0.30 mmol). After 5 min the reaction was diluted with toluene (4 mL), and immersed in an oil bath set at 120 °C. After 30 min, the reaction mixture was allowed to cool and the solvent was removed under reduced pressure. FC (26 g silica gel; CH_2Cl_2) gave **10** (113 mg, 0.385 mmol, 96 %).

Yellow oil. ¹H NMR (300 MHz, $CDCl_3$) δ 5.16-4.99 (m, 1H), 3.07-2.79 (m, 2H), 2.21-2.04 (m, 1H), 2.04-1.08 (m, 24H), 0.83 (t, J = 6.8 Hz, 3H). ¹³C NMR (75 MHz, $CDCl_3$) δ 201.1 (q), 76.6 (q), 56.4 (t), 45.9 (s), 43.3 (t), 31.8 (s), 31.7 (s), 31.4 (s), 28.9 (s), 28.7 (s), 27.8 (s), 27.4 (s), 26.7 (s), 25.8 (s), 23.8 (s), 22.5 (s), 21.5 (s), 14.0 (p). MS (EI, 70ev) m/z (%) 292 ($[M-H]^+$, 69), 260 (100), 250 (7), 236 (12), 222 (10), 208 (7), 190 (8), 166 (10), 136 (7), 93 (7), 81 (8), 67 (13), 55 (11), 41 (13). HRMS (EI) calcd for $C_{18}H_{30}NS$ ($[M-H]^+$): 292.209897; found: 292.210140.

(3RS,5SR,7aRS,11aRS)-5-Hexyl-3-(2-phenylethenyl)-decahydro-pyrrolo[2,1-j]quinoline (11).⁸

A mixture of thiolactam **10** (88 mg, 0.30 mmol) and iodomethane (62 μ L, 1.0 mmol) in THF (3 mL) was stirred at rt overnight. The reaction mixture was cooled to -78 °C, and to it was added a solution of lithium acetylide, prepared by the dropwise addition of *n*-BuLi (2.4 M in hexanes, 0.4 mmol) to phenyl acetylene (51 mg, 0.5 mmol) in THF (2 mL) at -78 °C. The mixture was then allowed to warm to -30 °C over 3 h, when $LiAlH_4$

(228 mg, 6 mmol) was added. The mixture was allowed to warm to rt and then refluxed over 48 h. It was diluted in EtOAc (30 mL) and quenched with 10 % NaOH(aq). The organic layer was dried, and the solvent was removed. FC (18 g silica gel; cyclohexane/ NH_3 -sat. Et_2O 1:1) gave **11** (88 mg, 0.24 mmol, 80 %) as a single stereoisomer.

Yellow oil. ¹H NMR (300 MHz, $CDCl_3$) δ 7.42-7.21 (m, 4H), 7.20-7.09 (m, 1H), 6.32 (d, J = 15.8 Hz, 1H), 6.14 (dd, J = 15.8, 7.7 Hz, 1H), 3.80-3.61 (m, 1H), 3.23-3.04 (m, 1H), 1.93-0.93 (m, 27H), 0.76 (t, J = 6.8 Hz, 3H). ¹³C NMR (75 MHz, $CDCl_3$) δ 139.4 (t), 137.9 (q), 128.4 (t, 2C), 126.9 (t), 126.7 (t), 126.1 (t, 2C), 67.4 (q), 61.9 (t), 53.5 (t), 40.5 (s), 39.4 (t), 35.1 (s), 32.4 (s), 32.0 (s), 30.4 (s), 29.6 (s), 27.7 (s), 27.7 (s), 26.6 (s), 24.7 (s), 23.5 (s), 23.3 (s), 22.7 (s), 14.1 (p). MS (EI, 70ev) m/z (%) 365 (M^+ , 7), 322 (29), 277 (12),

234 (68), 192 (42), 150 (12), 122 (46), 105 (76), 91 (53), 77 (100), 55 (45), 41 (53). HRMS (EI) calcd for C₂₆H₃₉N: 365.308251; found: 365.308170.

(±)-Lepadiformine (1). Acetyl chloride (57 μL, 0.8 mmol) was given to dry MeOH (10 mL).

After 1 h, this solution was added to neat **11** (40 mg, 0.11 mmol) and the resulting mixture was stirred for 2 h, after which it was cooled to -78 °C. A stream of ozonized oxygen was bubbled through the solution for 90 s followed by a stream of pure oxygen for 3 min. The reaction mixture was diluted with 50% aqueous EtOH (12 mL; precooled to -20 °C), external cooling was removed, NaBH₄ (152 mg, 4 mmol) was cautiously added and the reaction

was left overnight. Conc. HCl(aq) (0.5 ml) was added and the solution was stirred for 30 min. It was basified with half sat. Na₂CO₃(aq) and extracted with EtOAc (50 mL). The organic layer was washed with H₂O and brine (each 10 mL), dried, and the solvent was removed. FC (NH₃-sat. Et₂O) gave **1** (25 mg, 0.085 mmol, 77 %).

Colorless oil. Physical and spectral data were in accordance with literature values.³ ¹H NMR (500 MHz, CDCl₃) δ 3.43-3.28 (m, 2H), 3.21 (d, *J* = 8.4 Hz, 1H), 3.18-3.07 (m, 1H), 1.85-1.10 (m, 27H), 1.02 (qd, *J* = 12.5, 3.5 Hz, 1H), 0.88 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 67.4 (q), 62.5 (s), 58.5 (t), 53.4 (t), 40.3 (s), 38.4 (t), 34.3 (s), 32.0 (s), 30.7 (s), 29.8 (s), 28.4 (s), 27.8 (s), 27.7 (s), 26.4 (s), 24.4 (s), 23.4 (s), 22.8 (s, 2C), 14.2 (p). MS (EI, 70ev) *m/z* (%) 293 (M⁺, 5), 262 (100), 250 (26), 220 (8), 208 (10), 178 (5), 176 (5), 67 (6), 55 (6). HRMS (EI) calcd for C₁₉H₃₅NO: 293.271865; found: 293.271790.

7
 $C_{12}H_{20}O_2$

11-S

8
 $C_{12}H_{21}NO_2$

4
C₁₆H₂₈O

trans-3
 $\text{C}_{20}\text{H}_{35}\text{N}_3\text{O}_3$

trans-3
 $\text{C}_{20}\text{H}_{35}\text{N}_3\text{O}_3$

400 MHz

61-S

cis-**3**
 $C_{20}H_{35}N_3O_3$

cis-**3**
 $C_{20}H_{35}N_3O_3$

500 MHz

2
C₁₈H₃₁NO

10
 $C_{18}H_{31}NS$

11
C₂₆H₃₉N

Section D: References

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