A New Strategy for the Synthesis of (±)-Lupinine and (±)-Epilupinine via Cyclization of α-Sulfinyl Carbanions

Manat Pohmakotr,* Anusorn Seubsai, Pornthep Numeechai, Patoomratana Tuchinda

Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand
Fax +66(2)6445126; E-mail: scmpk@mahidol.ac.th

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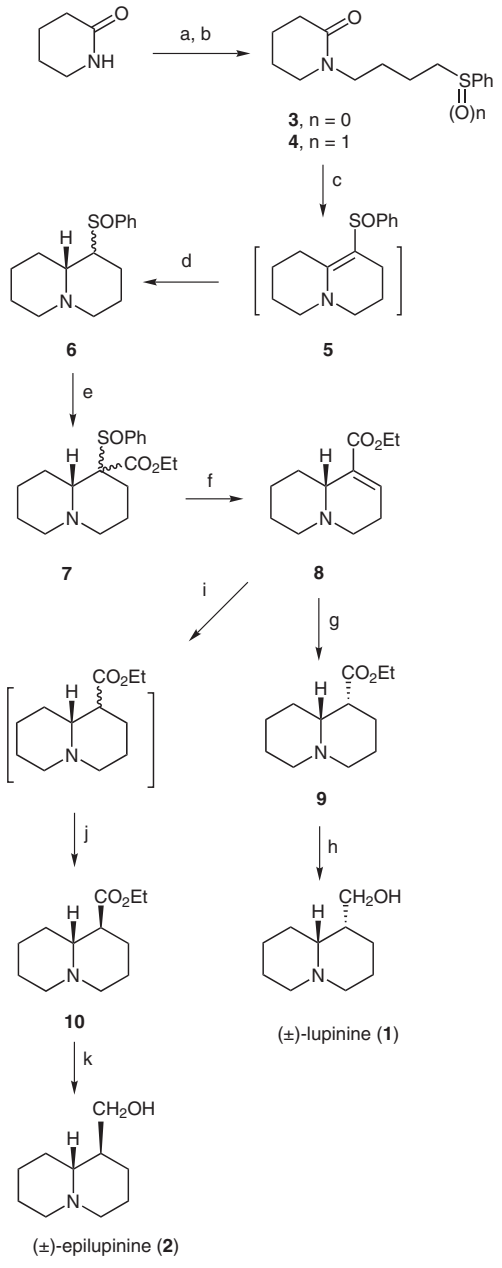
Abstract: (±)-Lupinine and (±)-epilupinine have been prepared starting from commercially available δ-valerolactam. The synthetic route involves the advantages of the cyclization based on α-sulfinyl carbanions.

Key words: (±)-lupinine, (±)-epilupinine, α-sulfinyl carbanion, cyclization

Quinolizidine alkaloids are important class of compounds as they are frequently encountered in a large number of natural products. Among these compounds, the lupin alkaloids are of particular interest due to their wide range of biological activities. Lupinine and epilupinine belonging to this class of alkaloid have been isolated from the aerial parts of plants in genus *Lupinus*, such as *Lupinus leteus, Lupinus albu.*[1] growing wild in North Africa, South Europe, North America, and Australia. Their relatively simple bicyclic quinolizidine structures and the interesting biological activities have challenged organic chemists to find an efficient approach to the synthesis of lupinine and epilupinine.[2]

We have recently developed a general route to 1-azabicyclo[m.n.0]alkanes including the quinolizidine skeleton via cyclization based on α-sulfinyl carbanions.[3] It is anticipated that the use of this method would permit a simple preparation of (±)-lupinine (**1**) and (±)-epilupinine (**2**). As summarized in Scheme 1, our strategy involves an intramolecular nucleophilic addition of α-sulfinyl carbanion onto the carbonyl group of the amide moiety leading to the key intermediate quinolizidine containing a phenylsulfinyl group. The synthesis started with N-alkylation of the readily available δ-valerolactam with 4-bromo-1-phenylsulfanylbutane employing NaH in DMF at 0 °C to room temperature to give sulfide **3** in 91% yield. This was followed by oxidation with $NaIO_4$ in aqueous methanol at 0 °C to room temperature to provide the corresponding sulfoxide **4** in 91% yield. The key cyclization step for the construction of the quinolizidine derivative **5** was carried out by treatment of the sulfoxide **4** with 2.2 equivalents of



Scheme 1 *Reagents and conditions:* (a) NaH, DMF, $PhS(CH_2)_4Br$, 0 °C to r.t.; (b) $NaIO_4$, MeOH, H_2O, 0 °C; (c) LiHMDS, THF, –78 °C to r.t.; (d) $NaBH_4$, MeOH, 0 °C; (e) LDA (1.5 equiv), THF, –78 °C (1 h); ethyl chloroformate (2.2 equiv), –78 °C, 2 h and r.t., 1 h; (f) toluene, reflux; (g) H_2, PtO_2, MeOH; (h) $LiAlH_4$, Et_2O; (i) Mg, MeOH, 2 h; (j) NaOEt, EtOH, reflux, overnight; (k) $LiAlH_4$, Et_2O.

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lithium hexamethyldisilazide (LiHMDS) in THF overnight at –78 °C to room temperature, followed by reduction of the labile unsaturated quinolizidine **5** with $NaBH_4$ in methanol at 0 °C. The expected quinolizidine **6** was obtained in 94% overall yield as a mixture of two diastereomers, the ratio of which ratio could not be determined by ^1H NMR spectroscopy. However, the major 1,8*a*-*cis*-isomer could be obtained by fractional crystallization from ethyl acetate.

The formation of compound **5** resulted from the intramolecular nucleophilic addition of the α-sulfinyl carbanion derived from the sulfoxide lactam **4** onto the amide group followed by dehydration during workup.

The key starting intermediate **8** was prepared in two steps by carboethoxylation of the sulfinylquinolizidine **6** and sulfoxide elimination. Thus, lithiation of the diastereomeric mixture of **6** with lithium diisopropylamide (LDA)[4] in THF followed by treatment with ethyl chloroformate gave compound **7**, which was subjected to sulfoxide elimination by refluxing in anhydrous toluene to give the required compound **8** in 48% yield after chromatographic purification.

Having compound **8** in hand, the preparation of (±)-lupinine (**1**) and (±)-epilupinine (**2**) was performed as summarized in Scheme 1. Catalytic hydrogenation of unsaturated ester **8** using PtO_2 as a catalyst in methanol afforded *cis*-quinolizidine ester **9** in 80% yield as the sole isomer. Reduction of the ester group of **9** with $LiAlH_4$ in anhydrous diethyl ether furnished (±)-lupinine (**1**) in 80% yield.[5a,b] On the other hand, the reaction of **8** with Mg in methanol under reflux provided a mixture of *cis*- and *trans*-isomers of the corresponding mixture of methyl and ethyl ester derivatives of **10**. Treatment of **10** with sodium ethoxide in refluxing ethanol was done in order to equilibrate the less stable *cis*-isomer to the thermodynamically more stable *trans*-isomer of the quinolizidine ester **10** and to perform transesterification of the methyl ester into the ethyl ester (78% yield).[6] Finally, (±)-epilupinine (**2**) was prepared in 71% yield by reduction of *trans*-quinoline ester **10** with $LiAlH_4$ in diethyl ether.[5a]

In summary, we have demonstrated a short entry to (±)-lupinine (**1**) and (±)-epilupinine (**2**) starting from commercially available δ-valerolactam by using the synthetic utilities of cyclization based on α-sulfinyl carbanions.

The ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Melting points were recorded on a Büchi 501 Melting Point Apparatus and were uncorrected. The IR spectra were recorded on a GX FT-IR system Perkin-Elmer IR spectrometer. The mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded on HR-TOF-MS Micromass spectrometer. The elemental analyses were performed by a Perkin-Elmer Elemental Analyzer 2400 CHN. All glassware and syringes were oven-dried and kept in a desiccator before use. The molarity of *n*-BuLi (in hexane) was determined by titration with diphenylacetic acid in THF at 0 °C. THF was distilled from sodium benzophenone ketyl. *i*-Pr_2NH, hexamethyldisilazane, and toluene were dried by distilling over CaH_2. Merck silica gel 60H and 60 PF_{245} were used for column chromatography and preparative TLC, respectively.

1-(4-Phenylsulfanylbutyl)piperidin-2-one (3)

To a suspension of NaH (2.42 g, 55 mmol, 55% suspension in mineral oil) in DMF (100 mL) was slowly added a DMF (8 mL) solution of δ-valerolactam (5.0 g, 50 mmol) at 0 °C under argon. The mixture was stirred for 1 h until the generation of H_2 ceased, and 1-bromo-4-phenylsulfanylbutane (1.594 g, 55 mmol) was then added. After stirring the mixture overnight (15 h) at 0 °C to r.t., it was quenched with H_2O (2 × 50 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). Filtration followed by evaporation in vacuo afforded a residue, which was purified by column chromatography (SiO_2, 80% in hexanes) to give **3** as a pale yellow liquid; yield: 12.09 g (91%).

IR (neat): 1638, 1584, 1494, 1481, 1466, 1353, 1300, 741, 692 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.17 and 7.10–7.06 (2 m, 5 H), 3.28 (t, *J* = 6.8 Hz, 2 H), 3.15 (br s, 2 H), 2.87 (t, *J* = 6.5 Hz, 2 H,), 2.27 (br s, 2 H, CH_2CON), 1.67–1.58 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6 (C=O), 136.3 (C), 129.0 (2 CH), 128.7 (2 CH), 125.7 (CH), 47.6 (CH_2), 46.2 (CH_2), 33.2 (CH_2), 32.2 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 23.1 (CH_2), 21.2 (CH_2).

MS: *m*/*z* (%) = 264 (M^+ + 1), 154 (100), 112 (77), 84 (71), 56 (18).

Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.63; H, 8.04; N, 5.32. Found: C, 68.33; H, 8.22; N, 5.02.

1-(4-Phenylsulfinylbutyl)piperidin-2-one (4)

A solution of **3** (6.32 g, 24 mmol) in MeOH (15 mL) was slowly added to a cooled (0 °C) suspension of $NaIO_4$ (5.6487 g, 26 mmol) in MeOH (58 mL) and H_2O (14 mL). The mixture was stirred vigorously and slowly warmed up overnight (16 h) from 0 °C to r.t. The precipitate of $NaIO_3$ was filtered and washed with EtOAc (4 × 70 mL). The combined extracts were washed with H_2O (2 × 25 mL) and brine (25 mL), and dried (Na_2SO_4). Filtration followed by evaporation in vacuo gave a residue, which was purified by column chromatography (SiO_2, 100% EtOAc to 2% MeOH in EtOAc) to provide **4** as a colorless viscous liquid; yield: 6.073 g (91%).

IR (neat): 1634, 1496, 1467, 1444, 1044, 753, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.48 and 7.42–7.38 (2 m, 5 H), 3.2 (app t, *J* = 5.9 Hz, 2 H), 3.12 (br s, 2 H), 2.74 (q, *J* = 8.8 Hz, 2 H), 2.20 (br s, 2 H), 1.67–1.58 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4 (C=O), 143.2 (C), 130.6 (CH), 128.8 (2 CH), 123.6 (2 CH), 55.9 (CH_2), 44.4 (CH_2), 45.4 (CH_2), 31.8 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 20.9 (CH_2), 18.9 (CH_2).

MS: *m*/*z* (%) = 279 (M^+, 2), 262 (78), 165 (47), 154 (86), 112 (69), 84 (100), 56 (44).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{21}NO_2S$: 279.1298; found: 279.1291.

1-Benzenesulfinyloctahydroquinolizidine (6)

n-BuLi (1.35 M in hexane; 52.93 mL, 71.45 mmol) was added to a cooled (–78 °C) THF (292 mL) solution of hexamethyldisilazane (HMDS) (1 mL, 4.8 mmol) under argon. After stirring at –78 °C for 40 min, a THF (64 mL) solution of **4** (9.061 g, 32 mmol) was added dropwise. The resulting mixture was allowed to stir and slowly warmed up overnight (15 h) from –78 °C to r.t. The resulting yellow solution was quenched with H_2O (100 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL) and dried (Na_2SO_4). Filtration followed by evaporation in vacuo to dryness afforded a viscous yellow liquid of crude 9-benzenesulfinyl-1,3,4,6,7,8-hexahydro-2*H*-quinolizine (**5**; yield: 8.22 g, 31 mmol), which was

directly subjected to reduction by using $NaBH_4$ as follows. To a solution of the crude product **5** in MeOH (160 mL) at 3–5 °C under argon, was added $NaBH_4$ (7.614 g, 201 mmol) in a small portion over 4 h. The mixture was stirred for 1 h at the same temperature, diluted with aq 1 N NaOH (100 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). Filtration followed by evaporation in vacuo gave a residue, which was purified by column chromatography (SiO_2, 2% MeOH in EtOAc containing 0.15% NH_4OH) to afford a white semi-solid of **6** as a mixture of two diastereomers; yield: 8.034 g (94%). The major diastereomer could be obtained by fractional crystallization from EtOAc to give 1,9-*cis*-**6** as a white solid; mp 112–113 °C). The minor diastereomer could not be separated.

IR (Nujol): 2749, 1463, 1446, 1302, 1084, 1034, 752, 690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.63 and 7.53–7.43 (2 m, 5 H), 3.01 (m, 2 H), 2.73 (t, *J* = 4.0 Hz, 1 H), 2.41 (app d, *J* = 11.9 Hz, 1 H), 2.30–2.18 (m, 2 H), 2.20–2.10 (m, 1 H), 2.14–2.06 (m, 1 H), 2.06–1.93 (m, 1 H), 1.89–1.80 (m, 1 H), 1.79–1.63 (m, 1 H), 1.55–1.46 (m, 3 H), 1.49–1.40 (m, 1 H), 1.38–1.27 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9 (C), 130.5 (CH), 129.0 (2 CH), 124.7 (2 CH), 66.3 (CH), 62.9 (CH), 56.8 (CH_2), 54.4 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 23.9 (CH_2), 22.9 (CH_2), 21.9 (CH_2).

MS: *m*/*z* (%) = 264 (M^+ + 1, 8), 246 (100), 136 (93), 110 (30).

Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.04; H, 8.04; N, 5.32. Found: C, 68.26; H, 8.15; N, 5.67.

3,6,7,8,9,9a-Hexahydro-4*H*-quinolizine-1-carboxylic Acid Ethyl Ester (8)

A solution of **6** (3.95 g, 15 mmol) in THF (30 mL) was added dropwise at –78 °C to a THF solution of LDA [prepared by reacting *i*-Pr_2NH (3.50 mL, 24.75 mmol) in THF (90 mL) with *n*-BuLi (1.35 M in hexane, 16.7 mL. 22.5 mmol) at –78 °C for 30 min] under argon. After stirring for 30 min, ethyl chloroformate (3.15 mL, 33 mmol) was added dropwise. The resulting mixture was stirred at –78 °C for 2 h and at r.t. for 1 h. It was quenched with H_2O (50 mL) and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried (Na_2SO_4). The organic phase was concentrated to give a yellow viscous liquid of the crude product 1-benzenesulfinyloctahydroquinolizine-1-carboxylic acid ethyl ester (**7**), which was directly subjected to sulfoxide elimination by refluxing in toluene as follows. A solution of the crude product **7** (3.954 g, 12 mmol) in anhyd toluene (140 mL) in the presence of $CaCO_3$ (0.5 g) was stirred at reflux under argon for 16 h. The mixture was filtered and the filtrate was evaporated to dryness to give a crude product, which was purified by column chromatography (SiO_2, 80% EtOAc in hexanes) to provide **8**[5a] as a yellow liquid; yield: 1.52 g (48%).

IR (neat): 1714, 1466, 1255, 1173, 1097, 1051 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.78–6.76 (m, 1 H), 4.19–1.03 (m, 2 H), 2.98–2.94 (m, 1 H), 2.89–2.84 (m, 1 H), 2.78–2.73 (m, 1 H), 2.48–2.33 (m, 1 H), 2.46–2.33 (m, 1 H), 2.17–2.11 (m, 1 H), 2.11–2.05 (m, 1 H), 2.02–2.01 (m, 1 H), 1.76–1.71 (m, 1 H), 1.64–1.45 (m, 2 H), 1.45–1.31 (m, 1 H,), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.20–1.06 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C=O), 136.7 (CH), 133.8 (C), 60.2 (CH), 59.9 (CH_2), 55.9 (CH_2), 48.8 (CH_2), 28.5 (CH_2), 26.3 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 14.1 (CH_3).

MS: *m*/*z* (%) = 210 (M^+ + 1, 100), 209 (M^+, 39), 180 (94), 137 (53), 136 (40), 124 (47).

These spectroscopic data are in agreement with those reported in the literature.[5a]

Ethyl (1*R**,9a*R**)-Octahydro-2*H*-quinolizine-1-carboxylate (9)

To a solution of **8** (70 mg, 0.364 mmol) in anhyd MeOH (2 mL) was added PtO_2 (8.25 mg, 0.0364 mmol). The reaction flask was connected via a two-way tap connected to a balloon of H_2 at atmospheric pressure and a vacuum pump. It was evacuated and flushed with H_2 several times to remove the air. Then it was stirred for 16 h while maintaining an atmosphere of H_2 at a slight positive pressure. At the end of this time, the H_2 was disconnected and the reaction flask was flushed with N_2. The catalyst was removed by filtration, followed by evaporation in vacuo to provide a residue, which was purified by TLC (SiO_2, 0.15% NH_4OH in EtOAc) to give **9** as a pale yellow liquid; yield: 61 mg (80%).

IR (neat): 1733, 1444, 1373, 1318, 1146, 1035 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.11 (m, 2 H, OCH_2), 2.87–2.84 (m, 2 H), 2.05 (t, *J* = 4.1 Hz, 1 H), 2.15–1.93 (m, 4 H), 1.90–1.80 (m, 1 H), 1.75–1.65 (m, 1 H), 1.65–1.40 (m, 6 H), 1.30–1.15 (m, 1 H), 1.18 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4 (C=O), 62.6 (CH), 59.8 (CH_2), 56.9 (CH_2), 54.6 (CH_2), 44.4 (CH), 28.5 (CH_2), 26.1 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 22.1 (CH_2), 14.2 (CH_3).

MS: *m*/*z* (%) = 211 (M^+, 14), 182 (60), 137 (100), 110 (57), 98 (40), 82 (39).

These spectroscopic data are in agreement with those reported in the literature.[5a,b]

1*R**,9a*R**)-Octahydro-2*H*-quinolizine-1-ylmethanol [(±)-Lupinine (1)]

A solution of **9a** (83 mg, 0.393 mmol) in anhyd Et_2O (3 mL) was added to a stirred suspension of $LiAlH_4$ (33 mg, 0.865 mmol) in anhyd Et_2O (2 mL) at 0 °C under argon. The resulting mixture was refluxed for 4 h, cooled to 0 °C, and quenched by sequential addition of EtOAc (5 mL) and H_2O (0.5 mL). The mixture was filtered through Celite. The filtrate was evaporated to give a crude product, which was purified by TLC on silica gel (SiO_2, 0.15% NH_4OH in EtOAc) to give (±)-lupinine (**1**) as a pale yellow solid; yield: 49 mg (74% yield); mp 55–56 °C (EtOAc) (Lit.[5a] mp 55–57 °C).

IR (neat): 3391, 1468, 1445, 1351, 1296, 1067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.12 (br s, 1 H, OH), 4.07 (d, *J* = 7.0 Hz, 1 H), 3.63 (d, *J* = 10.8 Hz, 1 H), 2.81–2.74 (m, 2 H), 2.12–1.64 (m, 7 H), 1.60–1.45 (m, 6 H), 1.30–1.25 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.6 (CH_2), 64.9 (CH), 56.9 (2 CH_2), 38.2 (CH), 30.9 (CH), 29.4 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 22.8 (CH_2).

MS: *m*/*z* (%) = 169 (M^+, 42), 168 (89), 152 (94), 138 (82), 110 (61), 98 (100), 83 (50).

These spectroscopic data are in agreement with those reported in the literature.[7]

Ethyl (1*R**,9a*S**)-Octahydro-2*H*-quinolizine-1-carboxylate (10)[6a,b]

A solution of **8** (1.033 g, 0.48 mmol) in MeOH (5 mL) and Mg turnings (0.12 g, 4.80 mmol) were stirred and refluxed under argon for 3 h, then cooled to r.t. and diluted with H_2O (50 mL). The white precipitate was filtered and washed with EtOAc (4 × 50 mL). The combined organic layers were washed with H_2O (2 × 25 mL) and brine (25 mL), and dried (Na_2SO_4). The organic phase was concentrated to give a pale yellow viscous liquid of a crude product containing a mixture of ethyl and methyl octahydro-2*H*-quinolizine-1-ylmethanol (90.1 mg), which was directly subjected to epimerization and transesterification by using in NaOEt in EtOH as follows. A solution of the crude product in EtOH (2 mL) at r.t. under argon was added to a NaOEt solution in EtOH [2 mL, prepared by reacting Na (40 mg, 1.74 mmol) with EtOH (2 mL)]. The mixture was stirred

under reflux overnight (16 h). After cooling the mixture to r.t., it was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL) and dried (Na_2SO_4). The organic phase was concentrated to give a pale yellow viscous liquid of the crude product, which was purified by TLC on silica gel (SiO_2, 0.15% NH_4OH in EtOAc) to give **10** as a pale yellow liquid of; yield: 79 mg (78%).

IR (neat): 1733, 1445, 1259, 1172, 1131, 1035 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.07 (q, *J* = 7.1 Hz, 2 H), 2.75 (t, *J* = 11.3 Hz, 2 H), 2.24–2.16 (m, 1 H), 2.07–1.92 (m, 3 H), 1.88–1.83 (m, 1 H), 1.64–1.37 (m, 7 H), 1.28–1.13 (m, 2 H), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8 (C=O), 63.5 (CH), 60.2 (CH_2), 56.6 (CH_2), 55.9 (CH_2), 49.3 (CH), 30.7 (CH_2), 28.6 (CH_2), 25.6 (CH_2), 24.4 (CH_2), 24.2 (CH_2), 14.2 (CH_3).

MS: *m*/*z* (%) = 211 (M^+, 20), 182 (100), 178 (31), 138 (69), 110 (62), 96 (60), 83 (43).

These spectroscopic data are in agreement with those reported in the literature.[6a,b]

(1*R,9a*S**)-Octahydro-2*H*-quinolizine-1-ylmethanol [(±)-Epilupinine (2)]**

As described for (±)-lupinine (**1**), a solution of **10** (80 mg, 0.38 mmol) in anhyd Et_2O (3 mL) was added to a stirred suspension of $LiAlH_4$ (32 mg, 0.83 mmol) in anhyd Et_2O (2mL) at 0 °C under argon to give (±)-epilupinine (**2**) as a colorless solid; yield. 45 mg (71%); mp 80–81 °C (Lit.[7a] mp 79–80 °C.

IR (neat): 3347, 1466, 1358, 1296, 1113, 1067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (dq, *J* = 15.7, 3.2 Hz, 2 H), 2.77 (t, *J* = 11.9 Hz, 2 H), 2.03–1.44 (m, 3 H), 1.86–1.55 (m, 8 H), 1.45–1.35 (m, 1 H), 1.30–1.10 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.3 (CH), 64.1 (CH_2), 56.5 (CH_2), 56.1 (CH_2), 43.1 (CH), 28.9 (CH_2), 27.7 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 24.1 (CH_2).

MS: *m*/*z* (%) = 169 (M^+, 44), 168 (93), 152 (91), 138 (84), 124 (68), 110 (64), 96 (100), 82 (83).

These spectroscopic data are in agreement with those reported in the literature.[7]

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