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

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Received 12 February 2008
Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

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 albus, 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 NaIO4 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(CH2)4Br, 0 °C to r.t.; (b) NaIO4, MeOH, H2O, 0 °C; (c) LiHMDS, THF, −78 °C to r.t.; (d) NaBH4, 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) H2, PtO2, MeOH; (h) LiAlH4, Et2O; (i) Mg, MeOH, 2 h; (j) NaOEt, EtOH, reflux, overnight; (k) LiAlH4, Et2O.
lithium hexamethyldisilazide (LiHMDS) in THF overnight at −78 °C to room temperature, followed by reduction of the labile unsaturated quinolizidine 5 with NaBH₄ 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-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-sulfanyl 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 sulfanylquinolizidine 6 and sulfoxide elimination. Thus, lithiation of the diastereomeric mixture of 6 with lithium diisopropylamide (LDA) 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 PtO₂ 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 LiAlH₄ in anhydrous diethyl ether furnished (±)-lupinine (1) in 80% yield. 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 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). Finally, (±)-epilupinine (2) was prepared in 71% yield by reduction of trans-quinoline ester 10 with LiAlH₄ in diethyl ether.

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

The ¹H and ¹³C NMR spectra were recorded on Bruker DPX-300 (300 MHz) spectrometer in CDCl₃ using tetramethylsilane as an internal standard. Melting points were recorded on a Büchi 501 Melt-Point Apparatus and were uncorrected. The IR spectra were recorded on a GX FT-IR system Perkin-Elmer IR spectrometer. The high-resolution mass spectra were recorded on an HR-TOF-MS Micromass spectrometer. The elemental analyses were performed on a Carlo Erba elemental analyzer. All glassware and syringes were oven-dried and kept in a desiccator before use. The molarity of THF was distilled over CaH₂. Merck silica gel 60H and 60 PF₂₄ were used for column chromatography and preparative TLC, respectively.

1-(4-Phenylsulfonylbutyl)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-δ-valerolactam (5.0 g, 50 mmol) at 0 °C under argon. After stirring for 1 h until the generation of H₂ ceased, and 1-bromo-4-phenylsulfonylbutane (1.394 g, 55 mmol) was then added. After stirring the mixture overnight (15 h) at 0 °C to r.t., it was quenched with H₂O (2 × 50 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with H₂O (2 × 50 mL) and brine (50 mL), and dried (Na₂SO₄). Filtration followed by evaporation in vacuo afforded a residue, which was purified by column chromatography (SiO₂, 80% in hexanes) to give 3 as a pale yellow liquid; yield: 12.09 g (91%).

IR (neat): 1638, 1584, 1494, 1481, 1465, 1333, 1300, 741, 692 cm⁻¹.

¹H NMR (300 MHz, CDCl₃); 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, CH₂CON), 1.67–1.58 (m, 4 H).

¹³C NMR (75 MHz, CDCl₃); δ = 169.4 (C=O), 136.3 (C), 129.0 (2 CH), 128.7 (2 CH), 125.7 (CH), 47.6 (CH₂), 46.2 (CH₃), 33.2 (CH₂), 32.2 (CH₂), 26.2 (CH₂), 25.9 (CH₃), 23.1 (CH₃), 21.2 (CH₂).

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

On the other hand, the reaction of +BuLi (in hexane) was determined by ¹H NMR spectroscopy. However, the major 1,8-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-sulfanyl 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 sulfanylquinolizidine 6 and sulfoxide elimination. Thus, lithiation of the diastereomeric mixture of 6 with lithium disopropylamide (LDA) 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 PtO₂ 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 LiAlH₄ in anhydrous diethyl ether furnished (±)-lupinine (1) in 80% yield. 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 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). Finally, (±)-epilupinine (2) was prepared in 71% yield by reduction of trans-quinoline ester 10 with LiAlH₄ in diethyl ether.

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

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directly subjected to reduction by using NaBH₄, as follows. To a solution of the crude product 5 in MeOH (160 mL) at 3–5 °C under argon, was added NaBH₄ (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 H₂O (2 × 50 mL) and brine (50 mL), and dried (Na₂SO₄). Filtration followed by evaporation in vacuo gave a residue, which was purified by column chromatography (SiO₂, 2% MeOH in EtOAc containing 0.15% NH₄OH) 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, CDCl₃); 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), 2.20–2.18 (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).

13C NMR (75 MHz, CDCl₃); δ = 145.9 (C), 130.5 (CH₃), 129.0 (2 CH), 124.7 (2 CH), 66.3 (CH), 62.9 (CH₂), 56.8 (CH₂), 54.4 (CH₂), 28.5 (CH₂), 24.9 (CH₃), 23.9 (CH₃), 22.9 (CH₂), 21.9 (CH₂).

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

3.6,7,8,9,9a-Hexahydro-4H-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 n-BuLi (1.35 M in hexane, 16.7 mL) at –78 °C for 30 min for 30 min under argon. After stirring for 30 min, ethyl chloroformate (3.15 mL, 33 mmol) at –78 °C to a THF solution of LDA (3.95 g, 15 mmol) in THF (30 mL) 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 H₂O (50 mL) and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with H₂O (50 mL) and brine (50 mL) and dried (Na₂SO₄). The organic phase was concentrated to give a yellow viscous liquid of the crude product 1-benzenesulfinyloctahydroquinolizine-1-carboxylic Acid Ethyl Ester (8) as a pale yellow liquid; yield: 1.52 g (48%).

IR (neat): 1714, 1466, 1255, 1173, 1097, 1051 cm⁻¹.

1H NMR (300 MHz, CDCl₃); 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, 2 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).

13C NMR (75 MHz, CDCl₃); δ = 166.4 (C=O), 136.7 (CH₃), 133.8 (C), 60.2 (CH), 59.9 (CH₂), 55.9 (CH₃), 48.8 (CH₂), 28.5 (CH₃), 26.3 (CH₂), 24.9 (CH₃), 24.4 (CH₄), 14.1 (CH₃).

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.⁶

Ethyl (IR*,9αR*)-Octahydro-2H-quinolinol-1-ylmethanol (±)-Lupinine (1)

A solution of 9a (83 mg, 0.393 mmol) in anhyd Et₂O (3 mL) was directly subjected to a stirred suspension of LiAlH₄ (33 mg, 0.865 mmol) in anhyd Et₂O (2 mL) at 0 °C under argon. The resulting mixture was refluxed under argon was washed with H₂O (2 × 25 mL) and brine (50 mL), and dried (Na₂SO₄). Filtration followed by evaporation in vacuo to give 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, CDCl₃); δ = 4.12 (br s, 1 H, OH), 4.07 (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).

13C NMR (75 MHz, CDCl₃); δ = 65.6 (CH₂), 64.9 (CH), 56.9 (2 CH₂), 38.2 (CH₃), 30.9 (CH), 29.4 (CH₂), 25.3 (CH₃), 24.5 (CH₂), 22.8 (CH₂).

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 (IR*,9αS*)-Octahydro-2H-quinolinol-1-ylmethanol (±)-Epilupinine (10)

A solution of 8 (1.033 g, 0.48 mmol) in MeOH (5 mL) and Mg turnings (0.12 g, 4.80 mmol) was stirred and refluxed under argon for 3 h, then cooled to r.t. and diluted with H₂O (50 mL). The white precipitate was filtered and washed with EtOAc (4 × 50 mL). The combined organic layers were washed with H₂O (2 × 50 mL) and brine (25 mL), and dried (Na₂SO₄). The organic phase was concentrated to give a pale yellow viscous liquid of a crude product containing a mixture of ethyl and methyl octahydro-2H-quinolinol-1-ylmethanol (90.1 mg), which was directly subjected to epimerization and transesterification by using NaOEt in EtOH as follows. A solution of the crude product in EtOH (2 mL) at r.t. under argon was added to 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 H2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H2O (15 mL) and brine (15 mL) and dried (Na2SO4). The organic phase was concentrated to give a pale yellow viscous liquid of the crude product, which was purified by TLC on silica gel (SiO2, 0.15% NH4OH 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.

References


Acknowledgment

We thank the Center for Innovation in Chemistry: Postgraduate Education and Research Program in Chemistry (PERCH-CIC), the Thailand Research Fund (BRG49800005), and the Commission of Higher Education (CHE-RES-RG) for financial support.

Synthesis 2008, No. 11, 1733–1736 © Thieme Stuttgart · New York