STEREOSELECTIVE SYNTHESIS OF (±)-EPILUPININE

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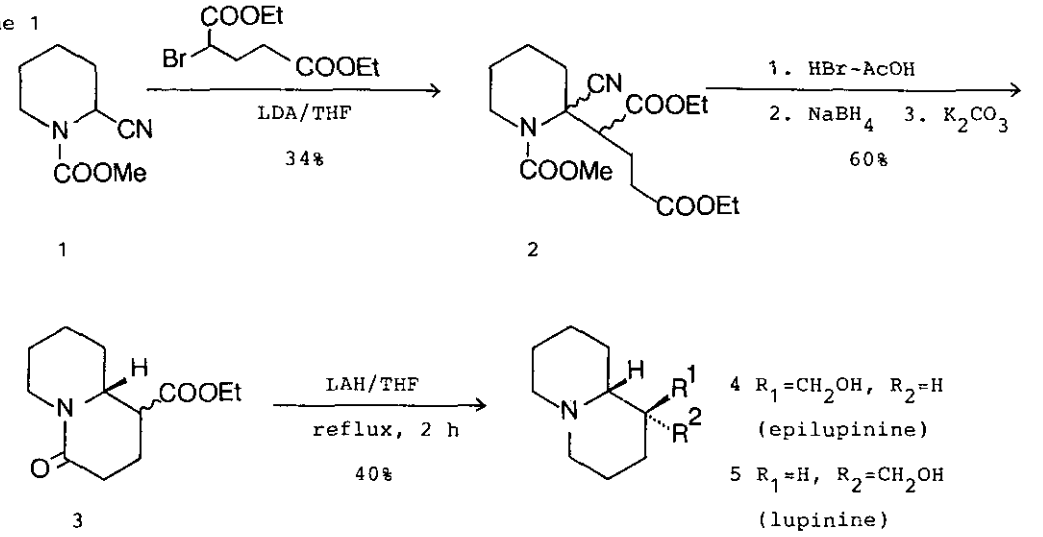
Abstract — Synthesis of lupin alkaloids starting from 2-piperidinone was attempted by three methods, one of which leads the stereoselective formation of (±)-epilupinine.

The conversion of lactams to α-substituted cyclic amines has recently been described by us.[1] The reaction involved was found to provide a useful means for the synthesis of alkaloids such as (±)-roxburghilin,[2a] (±)-coniine,[2b] (±)-2-epilasubine II,[2c] (+)-tilivalline,[2d] and (±)-elaeokanine C.[2e] The present paper reports the synthesis of lupin alkaloids, with special attention to a stereoselective route to (±)-epilupinine,[3] starting from 2-piperidinone.

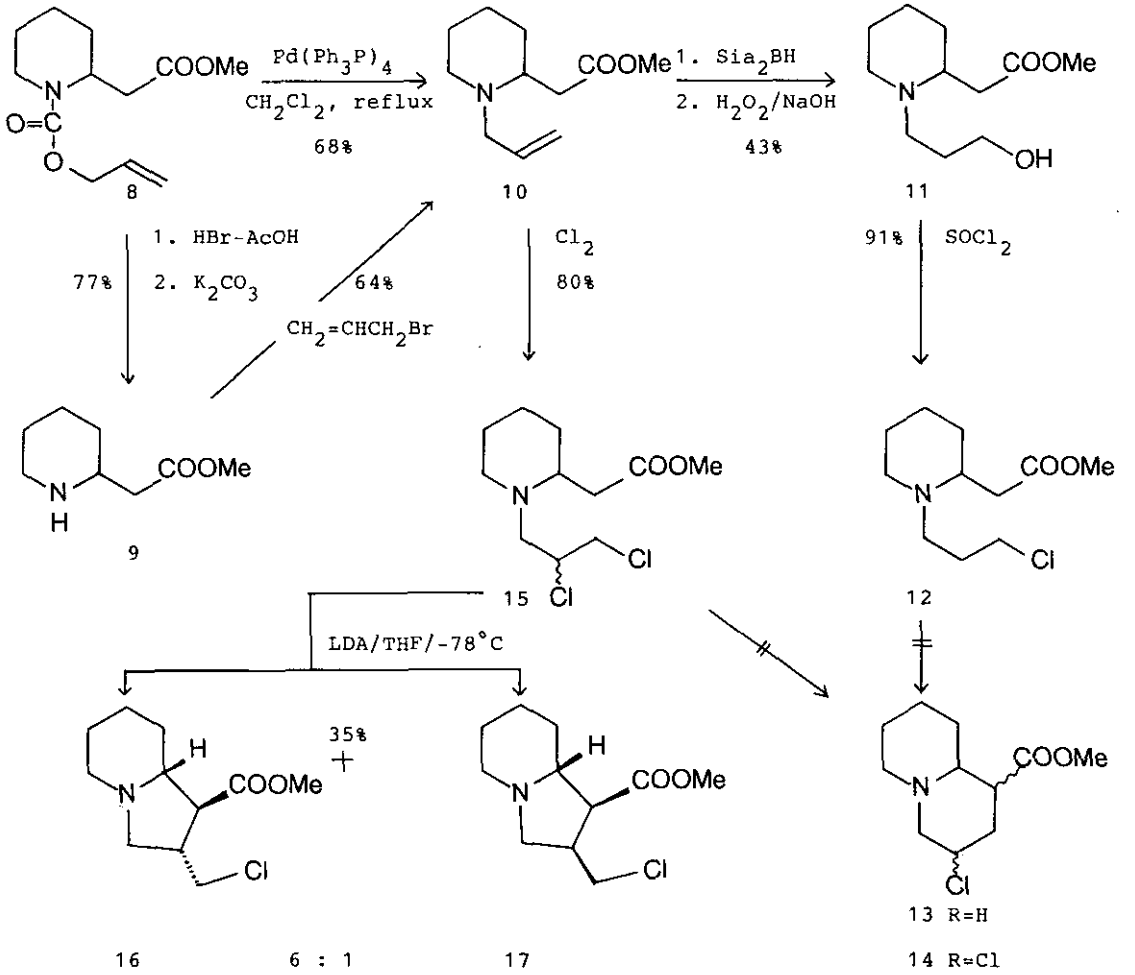
Synthesis of lupin alkaloids was attempted by the three methods depicted in Schemes 1, 2, and 3.

A mixture of (±)-epilupinine (4) and (±)-lupinine (5) was first made by the method in Scheme 1. The alkylation of α-cyanocarbamate (1), readily available from 2-piperidinone,[2b] with diethyl α-bromoadipate in the presense of lithium diisopropylamide (LDA) gave α-alkylated carbamate (2) in 34% yield (87% yield based on the consumed 1). This compound was separated by chromatography into two diastereomers at a 6:1 ratio. Treatment of the major isomer of 2 with 25% hydrobromic acid-acetic acid followed by reduction with sodium borohydride in ethanol gave quinolizidinone (3) in 60% yield. Although compound (3) was a mixture of diastereomers, it was reduced without separation with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) to give a mixture of (±)-epilupinine (4) and (±)-lupinine (5) in 40% yield. The ^{1}H-nmr spectrum of this mixture indicated 4 and 5 to be present at a 3:1 ratio. Chromatographic separation on alumina gave (±)-epilupinine (4) and (±)-lupinine (5), respectively.

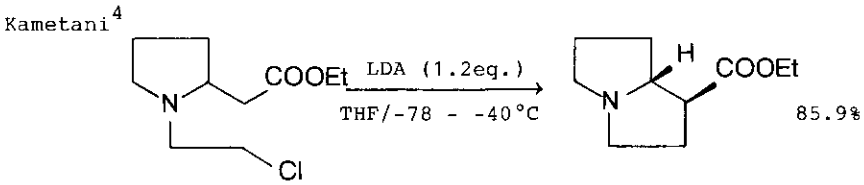
Scheme 1



Scheme 2

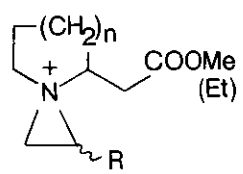


The second approach to lupin alkaloids is shown in Scheme 2. Kametani et al.[4] has reported that treatment of 1-(2-chloroethyl)-2-ethoxycarbonylmethylpyrrolidine (6) with LDA gave a thermodynamically more stable ester (7) as the sole product in 85.9% yield. We applied the same cyclization in this study to the synthesis of



6 7

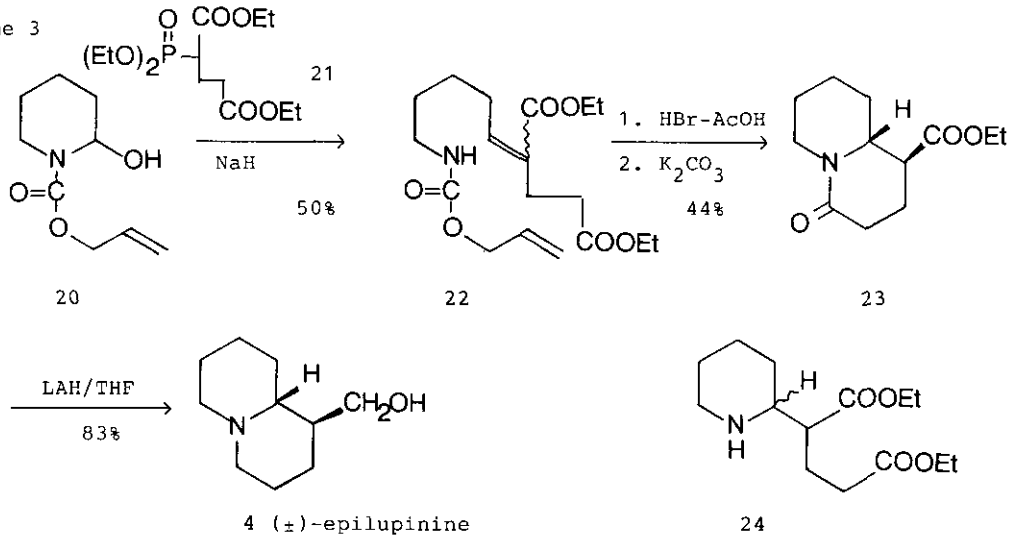
quinolizidine derivatives, using compounds (12 and 15). The hydroboration of N-allylpiperidine (10), obtained by the palladium-catalyzed reaction[2e] of allyl carbamate (8) or by the deprotection of 8 with hydrobromic acid followed by allylation of aminoester (9),[2c] with disiamylborane gave aminoalcohol (11) in 43% yield. Its subsequent treatment with thionyl chloride gave chloroamine (12) in 91% yield. Reaction of 12 with LDA, however, failed to give quinolizidine (13). The addition of chlorines to olefine (10) gave dichloroamine (15) in 80% yield. The cyclization of 15 with LDA in THF did not give the desired quinolizidine (14) but a mixture of indolizidines in 35% yield, whose separation was affected by chromatography into two isomers in a 6:1 ratio. The structure of 16 appeared to be that of the less polar compound (major) and that of 17, to be the structure for the more polar compound (minor). The ir spectra of both 16 and 17 showed Bohlmann bands due to trans-indolizidine ring. Their ^{1}H-nmr spectra showed signals for the methylene protons of chloromethyl (CH_2Cl) at 3.55 ppm (2H, d, J=6.5Hz) for 16 and at 3.53 (1H, dd, J=10.6Hz, 6.3Hz) and 3.33 ppm (1H, dd, J=10.6Hz, 8.2Hz) for 17. The ^{13}C-nmr spectra of 16 and 17 showed signals for CH_2Cl at 48.2 and 45.0 ppm, respectively. The chemical shifts and coupling patterns of these signals support that the structures of the cyclization products having the indolizidine ring and CH_2Cl groups. The higher yield of 16 than that of 17 and the steric compression shifts of the CH_2Cl signals in their ^{13}C-nmr spectra indicate the trans configuration between the 1- and 2-substituents for 16 and cis for 17, assuming the methoxycarbonyl groups to be situated at the more stable position (equatorial) of trans-indolizidine. Even the molecular models support this speculation. Too, the reaction rate of the iodomethylation of 17 far exceeded that of 16. The reason why the formation



18 n=1, R=H
19 n=2, R=CH_2Cl

of trans-quinolizidine is more difficult than that of trans-pyrrolizidine and indolizidine remains to be elucidated. β-Haloamines such as 6 and 15 may possibly cyclize to 7 and 16 (and 17), respectively, via aziridinium intermediates (18 and 19).[4]

Scheme 3



20 22 23

4 (±)-epilupinine 24

Finally the stereoselective synthesis of (±)-epilupinine (4) was carried out as shown in Scheme 3. The Wittig-Horner reaction of α-hydroxycarbamate (20)[2c] with phosphonate (21)[5] gave the unsaturated ester (22) in 50% yield as the sole product, whose geometric configuration was not examined. Deprotection of 22 with hydrobromic acid in acetic acid followed by basification with potassium carbonate gave pure trans-quinolizidine (23)[6] in 44% yield along with aminoester (24) in 10.7% yield. Reduction of 23 with $LiAlH_4$ in THF gave pure (±)-epilupinine (4) in 83% yield. The spectral data (ir and ^{1}H-nmr) of the synthetic (±)-epilupinine in this report showed complete agreement with those of an authentic sample provided by Prof. Nagao.

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on Hitachi 200-10 spectrophotometer and Hitachi M-80 spectrometer, respectively. ^{1}H-Nmr spectra were recorded on a Varian EM-390 instrument. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane).

(±)-Epilupinine (4) and (±)-Lupinine (5) (Scheme 1) -- A solution of n-BuLi (4.4 mmol) in hexane was added at -78°C to a solution of diisopropylamine (1.23 g, 12.1 mmol) in THF (50 ml) under an Ar atmosphere. This was followed 15 min later by adding a solution of 1 (680 mg, 4 mmol) and HMPA (723 mg, 4 mmol) in THF (1 ml) and the mixture was stirred at -78°C for 30 min. A solution of diethyl α-bromoadipate (3.0 g, 12 mmol) in THF (2 ml) was then added and the reaction mixture was stirred at -78 °C for 1 h and then at room temp. for 1 h. Neutralization was effected by adding aqueous NH_4Cl solution, followed by extraction with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Chromatographic separation on silica gel (Wako C-200) by elution with hexane-acetone (2:1) gave 416 mg of the starting material (1) and 486 mg (34% yield; 87% yield based on the consumed 1) of 2-cyano-2-(1,3-diethoxycarbonyl-1-propyl)-1-methoxycarbonylpiperidine (2). This diastereomeric mixture could be separated into two isomers (ratio 6:1) by high resolution chromatography on silica gel under the same conditions. The ir, ^{1}H-nmr, and ms spectra of two isomers (oil) were superimposable on each other. Ms m/z: 354 (M^+). Ir ($CHCl_3$) cm^{-1}: 1720, no absorption for CN. ^{1}H-Nmr ($CDCl_3$) δ: 1.15-1.40 (m, 6H, $OCH_2\underline{CH}_3$ x 2), 1.50-2.60 (m, 11H, CH_2 x 5, CH), 3.65-3.82 (m, 5H, CH_2N, OCH_3), 3.90-4.30 (m, 4H, $O\underline{CH}_2CH_3$ x 2). A solution of the major isomer of 2 (200 mg, 0.56 mmol) in 25% HBr-AcOH (2 ml) was stirred at room temp. for one day followed by evaporation under reduced pressure. The residue was dissolved in EtOH (2 ml) and reduced with excess $NaBH_4$ (114 mg, 3 mmol) by refluxing for 2 h. The reaction mixture was evaporated, basified with K_2CO_3 solution, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give 76 mg (60%) of 1-ethoxycarbonyl-trans-4-quinolizidinone (3) (a mixture of diastereomers) as a colorless oil. Ms m/z: 225 (M^+). Ir ($CHCl_3$) cm^{-1}: 1725, 1625. ^{1}H-Nmr ($CDCl_3$) δ: 1.12-1.26 (t x 2, J=7Hz, 3H, $OCH_2\underline{CH}_3$), 1.26-2.92 (m, 12H, CH_2 x 5, CH x 2), 3.33-3.82 (m, 1H, HCHN), 4.15 (q x 2, 2H, J=7Hz, $O\underline{CH}_2CH_3$), 4.63-4.90 (m, 1H, HCHN). To a solution of 3 (60 mg, 0.27 mmol) in THF (4 ml) was added $LiAlH_4$ (20 mg, 0.53 mmol). The reaction mixture was refluxed for 2 h under an Ar atmosphere, decomposed with a small amount of H_2O, basified with K_2CO_3, and extracted with ether. The extract was dried over K_2CO_3 and evaporated to give a colorless oil (18 mg, 40%), which was chromatographed on alumina by a procedure similar to that in the literature[3c] to give (±)-epilupinine (4) (13 mg) and crude (±)-lupinine (5) (5 mg). The former was identical with the authentic sample described after and the latter was confirmed as iodomethylate of 5, mp 285°C (lit.[3c] mp 285°C); Anal. Calcd for $C_{11}H_{22}INO$: C, 42.45; H, 7.13; N, 4.50. Found: C, 42.64; H, 7.13; N, 4.44.

1-Allyl-2-methoxycarbonylmethylpiperidine (10) -- Reaction of 9[2c] (400 mg, 2.55 mmol) with allyl bromide (309 mg, 2.55 mmol) in the presence of diisopropylamine (258 mg, 2.55 mmol) in MeOH (10 ml) gave 10 (322 mg, 64%). Oil, bp 97°C (3 mmHg). Ms m/z: 197 (M^+). Ir (neat) cm^{-1}: 1730, 1640. ^{1}H-Nmr ($CDCl_3$) δ: 1.18-1.85 (m, 6H, CH_2 x 3), 2.12-3.42 (m, 7H, NCH_2 x 2, CH_2CO, NCH), 3.66 (s, 3H, CH_3), 5.02-5.32 (m, 2H, $CH=C\underline{H}_2$), 5.62-6.12 (m, 1H, $C\underline{H}=CH_2$). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.81; H, 9.88; N, 7.02.

1-(1-Hydroxy-3-propyl)-2-methoxycarbonylpiperidine (11) -- A 0.5 M THF solution of

disiamylborane (Aldrich, 24 ml, 11.9 mmol) was added dropwise to N-allylamine (10) (1.17 g, 5.94 mmol) at 0°C under an Ar atmosphere followed by stirring for 2 h at 0°C. After adding H_2O (1.8 ml) and 3 M NaOH solution (8 ml, 23 mmol) at 0°C, 30% H_2O_2 (4 ml, 35 mmol) was introduced while maintaining the temperature of the reaction mixture at 30-50°C. The solution was stirred for 30 min at room temp. and extracted with ether five times. The extract was washed with brine, dried over $MgSO_4$, and evaporated to give an oil. This oil was dissolved in saturated HCl-MeOH (5 ml) and allowed to stand overnight. After evaporating the MeOH, the residue was dissolved in H_2O, basified with K_2CO_3 and evaporated to give an oil, which, on chromatographic separation on silica gel by elution with $CHCl_3$-MeOH (30:1), gave 550 mg (43%) of 11. Ms m/z: 215 (M^+, 3%), 142 ($M^+-CH_2COOCH_3$, 100%), exact ms calcd for $C_8H_{16}NO$: 142.1231. Found: 142.1260. Ir (neat) cm^{-1}: 3400, 1740. ^{1}H-Nmr ($CDCl_3$) δ:1.20-2.10 (m, 8H, CH_2 x 4), 2.20-3.20 (m, 7H, CH_2N x 2, CHN, CH_2CO), 3.63 (s, 3H, OCH_3), 3.73 (t, J=5Hz, CH_2O), 4.20 (br s, 1H, OH).

1-(1-Chloro-3-propyl)-2-methoxycarbonylmethylpiperidine (12) -- A solution of 11 (500 mg, 23 mmol) and $SOCl_2$ (5 ml, 5.75 mmol) in $CHCl_3$ (10 ml) was stirred at room temp. for 2 h followed by adding H_2O. The aqueous layer was basified with K_2CO_3 and extracted with $CHCl_3$. The combined extracts were washed with brine, dried over K_2CO_3, and evaporated. The residue was chromatographed on silica gel by elution with $CHCl_3$ and gave 494 mg (91%) of 12. Ms m/z: 233 (M^+, 3%), 160 ($M^+-CH_2COOCH_3$, 100%), exact ms calcd for $C_8H_{15}ClN$: 160.0893. Found: 160.0918. Ir (neat) cm^{-1}: 1730. ^{1}H-Nmr ($CDCl_3$) δ: 1.20-2.05 (m, 8H, CH_2 x 4), 2.10-3.10 (m, 7H, CH_2N x 2, CHN, CH_2CO), 3.50 (t,J=6Hz, 2H, CH_2Cl), 3.60 (s, 3H, OCH_3).

t-2-Chloromethyl-r-1-methoxycarbonyl-c-8aH-trans-indolizidine (16) and c-2-Chloromethyl-r-1-methoxycarbonyl-c-8aH-trans-indolizidine (17) (Scheme 2) -- Dry chlorine was introduced into a solution of olefine 10 (1.5 g) in $CHCl_3$ (5 ml). After evaporation at room tomp., the residue was dissolved in a small amount of H_2O, basified with K_2CO_3, and extracted with ether several times. The extract was dried over K_2CO_3, and evaporated to give an oil, which, on chromatographic separation on silica gel by elution with $CHCl_3$, gave 1.63 g (80%) of 1-(1,2-dichloro-3-propyl)-2-methoxycarbonylmethylpiperidine (15). Ms (CI) m/z: 268 (M^++1). Ir (neat) cm^{-1}: 1740. ^{1}H-Nmr ($CDCl_3$) δ: 1.10-1.93 (m, 6H, CH_2 x 3), 2.11-3.50 (m, 7H, CH_2N x 2, CH_2CO, CHN), 3.67 (s, 3H, OCH_3), 3.85 (d, J=6Hz, 2H, CH_2Cl), 4.05 (m, 1H, CHCl). A solution of n-BuLi (3.4 mmol) in hexane was added at -78°C to a solution of diisopropylamine (824 mg, 8.15 mmol) in THF (30 ml) under an Ar atmosphere. After maintaining this solution at -78°C for 20 min, a solution of dichloroamine (15) (612 mg, 2.28 mmol) in THF (2 ml) was added dropwise over a period of 5 min. The reaction mixture was stirred at -78°C for 1 h and then warmed to room temp. followed by adding H_2O and extraction with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated. The oil obtained was chromatographed on silica gel by elution with $CHCl_3$ to give 214 mg (30%) of 16 from the first crop and 36 mg (5%) of 17 from the second crop. 16: Bp 148°C (1 mmHg). Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.02; H, 7.83; N, 6.04. Found: C, 57.32; H, 8.11; N, 5.82. Ms m/z: 231 (M^+). Ir (neat) cm^{-1}: 2800, 2720, 1740. ^{1}H-Nmr ($CDCl_3$) δ: 1.00-3.10 (m, 13H), 3.55 (d, J=6.5Hz, 2H, CH_2Cl), 3.68 (s, 3H, OCH_3).

100MHz ^{13}C-Nmr ($CDCl_3$) δ: 23.8, 25.0, 30.3, 42.7, 48.2, 52.0, 52.8, 54.2, 57.5, 67.7, 173.7. Iodomethylate, mp 199-201°C; Anal. Calcd for $C_{12}H_{21}ClINO_2$: C, 38.57; H, 5.66; N, 3.75. Found: C, 38.55; H, 5.64; N, 3.72. 17: Bp 142°C (1 mmHg). Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.02; H, 7.83; N, 6.04. Found: C, 57.21; H, 8.15; N, 5.82. Ms m/z: 231 (M^+). Ir (neat) cm^{-1} : 2800, 2750, 1730. ^{1}H-Nmr ($CDCl_3$) δ: 1.00-3.20 (m, 13H), 3.33 (1H, dd, J=10.6Hz, 8.2Hz), 3.53 (1H, dd, J=10.6Hz, 6.3Hz), 3.68 (s, 3H, OCH_3). 100 MHz ^{13}C-Nmr ($CDCl_3$) δ: 23.9, 25.1, 30.0, 40.4, 45.0, 51.3, 51.8, 52.8, 59.5, 66.6, 172.5. Iodomethylate, mp 120-122°C; Anal. Calcd for $C_{12}H_{21}ClINO_2$: C, 38.57; H, 5.66; N, 3.75. Found: C, 38.62; H, 5.45, N, 3.63.

Stereoselective Synthesis of (±)-Epilupinine (4) (Scheme 3) -- A solution of tetraethyl α-phosphonoglutarate[5] (1.43 g, 4.4 mmol) in toluene (3 ml) was added to a solution of NaH (4.8 mmol) in toluene (12 ml) at 0-5°C followed by stirring at room temp. for 2 h. After carbamate (20) (814 mg, 4.4 mmol) was added to this solution, the reaction mixture was refluxed for 36 h and evaporated. The residue was mixed with H_2O and extracted with ether. The ether extract was dried over $MgSO_4$ and evaporated to give an oil (1.32 g), which, on chromatographic separation on silica gel by elution with hexane-acetone (10:1), gave 781 mg (50%) of 8-allyloxycarbonylamino-1,3-diethoxycarbonyl-3-octene (22) as a colorless oil. Ms (CI) m/z: 356 (M^++1). Ir ($CHCl_3$) cm^{-1}: 3450, 1700, 1620. ^{1}H-Nmr ($CDCl_3$) δ: 1.33 (t, J=7Hz, 3H, CH_3), 1.39 (t, J=7Hz, 3H, CH_3), 1.48-1.78 (m, 4H, CH_2 x 2), 2.12-2.88 (m, 6H, CH_2 x 3), 3.06-3.42 (m, 2H, CH_2N), 4.18 (q, J=7Hz, 2H, OCH_2CH_3), 4.30 (q, J=7Hz, 2H, OCH_2CH_3), 4.57 (m, 2H, $OCH_2CH=CH_2$), 5.12-5.51 (m, 2H, $OCH_2CH=CH_2$), 5.75-6.24 (m, 1H, $OCH_2CH=CH_2$), 6.89 (t, J=7.5, 1H, CH=CCOOEt). A solution of 22 (355 mg, 1 mmol) in 25% HBr-AcOH (5 ml) was stirred at room temp. for 2 h and evaporated. The residue was dissolved in H_2O and basified with K_2CO_3 followed by extraction with ether. The extract was washed with brine, dried over K_2CO_3, and evaporated to give an oil (236 mg), which, on chromatographic separation on alumina by elution with benzene-ether (4:1), gave 99 mg (44%) of 1,9a-trans-1-ethoxycarbonyl-trans-4-quinolizidinone (23) from the first crop and 29 mg (10.7%) of 2-(1,3-diethoxycarbonyl-1-propyl)piperidine (24). 23: Ms m/z: 225 (M^+). Ir ($CHCl_3$) cm^{-1}: 1720, 1620. ^{1}H-Nmr ($CDCl_3$) δ: 1.26 (t, J=7Hz, 3H, CH_3), 1.26-2.63 (m, 12H, CH_2 x 5, CH x 2), 3.39-3.72 (m, 1H, HCHN), 4.16 (q, J=7Hz, 2H, OCH_2), 4.63-4.94 (m, 1H, HCHN). 24: Ms (CI) m/z: 272 (M^++1). Ir ($CHCl_3$) cm^{-1}: 1723, 1622. ^{1}H-Nmr ($CDCl_3$) δ: 1.23 (t, J=7.5Hz, 3H, CH_3), 1.25 (t, J=7.5Hz, 3H, CH_3), 1.25-3.20 (m, 14H, CH_2 x 6, CH x 2), 4.10 (q, J=7.5Hz, 2H, OCH_2CH_3), 4.16 (q, J=7.5Hz, 2H, OCH_2CH_3). Reduction of 23 (134 mg, 0.6 mmol) with $LiAlH_4$ (46 mg, 1.2 mmol) in THF (7 ml) followed by extraction with ether, as described before for synthesis of 4 and 5, gave a crude oil (92 mg), which , on chromatographic separation on alumina by elution with $CHCl_3$-MeOH (40:1), gave 84 mg (83%) of (±)-epilupinine (4). Recrystallization from hexane gave colorless prisms, mp 82-83°C. Exact ms calcd for $C_{10}H_{19}NO$ m/z: 169.1466. Found: 169.1467. Ir ($CHCl_3$) cm^{-1}: 3600, 3400, 1800, 1750. ^{1}H-Nmr ($CDCl_3$) δ: 1.00-2.30 (14H), 2.70-3.00 (2H), 3.60 (m, 2H, CH_2OH), 4.60 (s, 1H, OH). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.67; H, 11.31; N, 8.24.

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6. Intramolecular Michael reaction of 22 using NaH was carried out without success (cf. reference 2c); the stereoselective synthesis of (±)-epilupinine by double Michael reactions (intramolecular Diels-Alder reaction) of 1-aza-1,3-diene derivatives is reported: see reference 3h.

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