[Chem. Pharm. Bull. 34(11)4523—4526(1986)]

An Efficient Total Synthesis of (±)-Epilupinine and (±)-Lupinine from a Common Quinolizidine Intermediate[1)]

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(Received April 23, 1986)

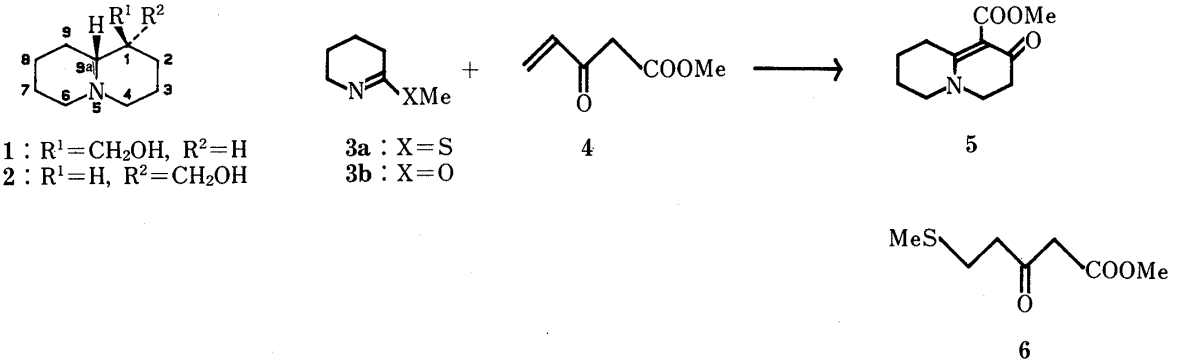
A common intermediate, the quinolizidine (**5**) obtained by annulation of a cyclic thioimidate (**3**) with Nazarov's reagent (**4**) in the presence of mercuric chloride, was stereospecifically transformed into (±)-epilupinine (**1**) and (±)-lupinine (**2**).

Keywords——(±)-epilupinine; (±)-lupinine; quinolizidine; cyclic thioimidate; Nazarov's reagent; annulation; mercuric chloride; Lawesson's reagent

Various total syntheses of the quinolizidine alkaloids, (±)-epilupinine (**1**) and (±)-lupinine (**2**) have still been well reported in recent years.[2)] We are interested in exploring the utilization of cyclic thioimidates in a heterocyclic synthesis,[3,4)] and we describe here the use of a quinolizidine intermediate obtained by Robinson annulation of a cyclic thioimidate with methyl 3-oxo-4-pentenoate (Nazarov's reagent) in the efficient syntheses of **1** and **2**.

Robinson annulation using Nazarov's reagent (**4**) is an attractive synthetic route to functionalized 6-membered ring compounds.[5)] Although it is already known that the treatment of a cyclic imidate (**3b**) with **4** gives a quinolizidine product (**5**) (54%),[5e)] we found that the reaction of **3a** with **4** in the presence of mercuric chloride afforded **5** in 62% yield, together with methyl 5-methylthio-3-oxopentenoate (**6**) (25%). Mercuric chloride might have worked as a scavenger of methanethiol. We were able to develop efficient total syntheses of **1** and **2** from the readily accessible **5**.

Transformation of **5** into **1** is shown in Chart 2. Stereospecific reduction of **5** with diisobutylaluminum hydride (DIBAL) in the presence of triethylamine (Et_3N) in tetrahydrofuran (THF) at −50 °C gave the saturated β-ketoester (**7**) in 55% yield.[6)] The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed a signal due to C_1-H at δ 3.24 (d, J=11 Hz) and its coupling constant strongly indicated *trans* relative configuration between C_1-H and C_{9a}-H. This selective conversion (**5**→**7**) can be attributed to thermodynamic control.



1 : R^1=CH_2OH, R^2=H
2 : R^1=H, R^2=CH_2OH

3a : X=S
3b : X=O

4

5

6

Chart 1

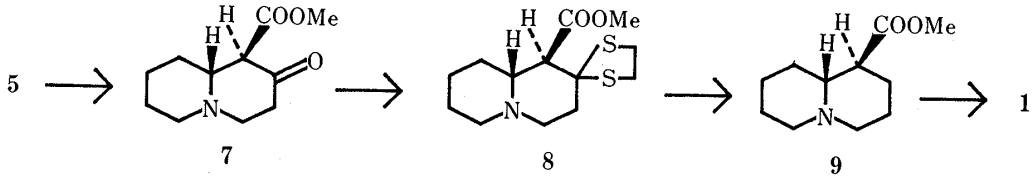


Chart 2

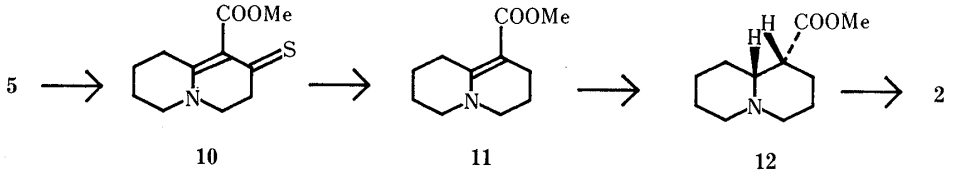


Chart 3

Treatment of **7** with 1,2-ethanedithiol in the presence of boron trifluoride etherate in trifluoroacetic acid afforded the thioketal (**8**) in 81% yield. Desulfurization of **8** with Raney Ni (W-2) in ethanol produced the ester (**9**) in 51% yield. The methoxycarbonyl group of **9** underwent reduction with lithium aluminum hydride ($LiAlH_4$) in boiling THF to give (±)-epilupinine (**1**) in 75% yield.

Conversion of **5** to **2** is depicted in Chart 3. Chemoselective thionation of **5** with Lawesson's reagent[7] in benzene at room temperature gave the enaminothioketone (**10**) in 79% yield, and this underwent desulfurization with Raney Ni (W-2) in ethanol to produce the enaminoester (**11**) in 65% yield. According to the method described previously[8] stereospecific reduction of **11** was performed with sodium borohydride in methanol to afford methyl lupinate (**12**) in 69% yield. Compound **12** was subsequently converted to (±)-lupinine (**2**) by reduction with $LiAlH_4$. Both **1** and **2** thus prepared had spectra (NMR and infrared (IR)) identical with those of the corresponding authentic materials.[2c]

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were taken with a JASCO A-102 spectrophotometer, NMR spectra with Varian EM360, JEOL PMX60SI, Varian XL200, and JEOL JNM-FX270 spectrometers ($SiMe_4$ as an internal reference and $CDCl_3$ as the solvent), and mass spectra (MS) with a JEOL JMS-D200 spectrometer. Column chromatography was performed on Silica gel 60 (230—400 mesh), under pressure.

Methyl 3,4,6,7,8,9-Hexahydro-2-oxo-2*H*-quinolizine-1-carboxylate (5)——The thioimidate (**3a**) (1.28 g) was added dropwise to a stirred solution of mercuric chloride (3 g) and Nazarov's reagent (**4**)[9] (1.29 g) in methanol (30 ml) at 0 °C. The mixture was stirred overnight at room temperature and filtered through celite. The filtrate was evaporated. Saturated aqueous $NaHSO_4$ was added to the residue, and the mixture was extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (ethyl acetate–methanol) to give methyl 5-methylthio-3-oxopentenoate (**6**) (436 mg, 25%) and the quinolizidine (**5**) (1.29 g, 62%). **6**: bp 110—115 °C/5 mmHg (Kugelrohr). IR ν_{max}^{film} cm^{-1}: 1740, 1710. ^{1}H-NMR δ: 2.10 (3H, s, SMe), 3.70 (3H, s, COOMe). High-resolution MS Calcd for $C_7H_{12}O_3S$: 176.0507. Found: 176.0509. **5**: mp 75—78 °C (from hexane–ethyl acetate); in lit.,[5e] **5** was isolated as an oil. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1620. ^{1}H-NMR δ: 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.07; H, 7.15; N, 6.68.

Methyl (1*R,9a*R**)-1,3,4,6,7,8,9,9a-Octahydro-2-oxo-2*H*-quinolizine-1-carboxylate (7)**——Diisobutylaluminum hydride (1.0 M solution in *n*-hexane) (3.6 ml) was added to THF (3 ml) under argon at −50 °C, then triethylamine (0.52 ml) was added to that solution. The resulting mixture was stirred for 0.5 h, then added to a solution of the quinolizidine (**5**) (540 mg) in THF (13 ml) at −50 °C *via* a syringe. The whole was stirred at the same temperature for 4 h, then the reaction was quenched by the addition of 2 N NaOH. The mixture was extracted with ether and successively with CH_2Cl_2. Each extract was washed with brine, dried over K_2CO_3, and evaporated. The combined residues were chromatographed on silica gel (ethyl acetate–methanol) to give the β-ketoester quinolizidine (**7**) (300 mg, 55%) as a viscous oil. IR ν_{max}^{film} cm^{-1}: 2860, 2810, 2770, 1740, 1710. ^{1}H-NMR δ: 3.24 (1H, d, J=11 Hz, 1-H), 3.73 (3H, s, COOMe). High-resolution MS Calcd for $C_{11}H_{17}NO_3$: 211.1206. Found: 211.1164.

Methyl (1*S,9a*R**)-1,3,4,6,7,8,9,9a-Octahydro-2,2-ethylenedithio-2*H*-quinolizine-1-carboxylate (8)**——A mixture of the quinolizidine (**7**) (197 mg), ethanedithiol (1.1 ml), and $BF_3 \cdot Et_2O$ (1.1 ml) in trifluoroacetic acid (11 ml) was stirred at room temperature for 15 h. The reaction mixture was evaporated, and ice cold saturated aqueous $NaHCO_3$ was added to the residue. The mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (ethyl acetate–methanol) to give the thioketal (**8**) (216 mg, 81%) as a solid, mp 59—62 °C (from diisopropyl ether). IR ν_{max}^{Nujol} cm^{-1}: 2810, 1730. ^{1}H-NMR δ: 2.79 (1H, d, J=11 Hz, 1-H), 3.23 (4H, s, SCH_2CH_2S), 3.71 (3H, s, COOMe). *Anal.* Calcd for $C_{13}H_{21}NO_2S$: C, 54.32; H, 7.36; N, 4.87. Found: C, 54.34; H, 7.39; N, 4.89.

Methyl (1*S,9a*R**)-1,2,3,6,7,8,9,9a-Octahydro-4*H*-quinolizine-1-carboxylate (9)**——A mixture of the thioketal (**8**) (216 mg) and W-2 Raney Ni (2.2 g) in ethanol (10 ml) was refluxed for 0.5 h, then filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel (ethyl acetate–methanol) to give the ester (**9**) (75 mg, 51%) as a viscous oil. IR ν_{max}^{film} cm^{-1}: 2800, 1720. ^{1}H-NMR δ: 3.69 (3H, s, COOMe). High-resolution MS Calcd for $C_{11}H_{19}NO_2$: 197.1415. Found: 197.1395.

(±)-Epilupinine (1)——A solution of the ester (**9**) (74 mg) in THF (1 ml) was added to a suspension of lithium aluminum hydride (9.1 mg) in THF (1 ml). The reaction mixture was refluxed for 0.5 h, cooled, then treated sequentially with water (0.1 ml), 15% aqueous NaOH (0.1 ml), and water (0.1 ml), and dried over Na_2SO_4. The mixture was filtered and the solid was washed with THF. The combined solutions were evaporated. The residue was chromatographed on alumina (ethyl acetate–methanol) to give (±)-epilupinine (**1**) (51 mg, 76%) as a solid, mp 79—80 °C (from hexane–diisopropyl ether) (lit.,[2c] 81—82.5 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 2870, 2820, 2780, 2690, 1640. ^{1}H-NMR δ: 1.20—2.10 (15H, m), 2.84 (2H, m), 3.66 (2H, m). The synthetic compound was completely identical with an authentic sample[2c] in terms of spectral properties (NMR and IR).

Methyl 3,4,6,7,8,9-Hexahydro-2-thioxo-2*H*-quinolizine-1-carboxylate (10)——A mixture of the quinolizidine (**5**) (1.4 g) and *p*-methoxyphenylthiophosphine sulfide dimer (707 mg) in dry benzene (30 ml) was stirred at room temperature for 1 h and filtered through celite. The filtrate was evaporated. The residue was chromatographed on silica gel (ethyl acetate) to give the thione (**10**) (887 mg, 79%) as a solid, mp 156—160 °C (from diisopropyl ether–CH_2Cl_2). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1590. ^{1}H-NMR δ: 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.47; H, 6.74; N, 5.99.

Methyl 2,3,6,7,8,9-Hexahydro-4*H*-quinolizine-1-carboxylate (11)——A mixture of the thione (**10**) (450 mg) and W-2 Raney Ni (2.25 g) in ethanol (22.5 ml) was stirred at room temperature for 3 min, then filtered, and evaporated. The residue was chromatographed on silica gel (hexane–ethyl acetate) to give the enamino ester (**11**) (254 mg, 65%) as a syrup. IR ν_{max}^{film} cm^{-1}: 1670. ^{1}H-NMR δ: 3.62 (3H, s, COOMe). High-resolution MS Calcd for $C_{11}H_{17}NO_2$: 195.1259. Found: 195.1265.

Methyl (1*R,9a*R**)-1,2,3,6,7,8,9,9a-Octahydro-4*H*-quinolizine-1-carboxylate (12)**——The enaminoester (**11**) (224 mg) was dissolved in methanol (2 ml) and while the solution was stirred and kept between 5 and 10 °C, sodium borohydride (435 mg) was added in small portions during 1 h. The reaction mixture was stirred at room temperature for 15 min, diluted with water (5 ml), and extracted with ether. The extract was washed with brine, dried over K_2CO_3, and evaporated. The residue was chromatographed on silica gel (ethyl acetate–methanol) to give the ester (**12**) (155 mg, 69%) as a syrup. IR ν_{max}^{film} cm^{-1}: 2850, 2800, 2750, 1740. ^{1}H-NMR δ: 3.67 (3H, s, COOMe). High-resolution MS Calcd for $C_{11}H_{19}NO_2$: 197.1416. Found: 197.1439.

(±)-Lupinine (2)——A solution of the ester (**12** (99 mg) in THF (1.2 ml)) was added to a suspension of lithium aluminum hydride (11.4 mg) in THF (1.2 ml). The reaction mixture was refluxed for 0.5 h, cooled, then treated sequentially with water (0.1 ml) and 10% aqueous NaOH (0.1 ml), and then dried over Na_2SO_4. The mixture was filtered and the solid was washed with THF. The combined solutions were evaporated. The residue was chromatographed on alumina (ethyl acetate–methanol) to give (±)-lupinine (**2**) (63 mg, 74%) as a solid, mp 57—59 °C (from hexane) (lit.,[2c] 59—61 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3170, 2850, 2800, 2770, 2680. ^{1}H-NMR δ: 1.20—2.30 (14H, m), 2.83 (2H, m), 3.70 (1H, m), 4.17 (1H, m). The compound prepared was identical with an authentic sample[2c] in terms of spectral data (NMR and IR).

Acknowledgements We are grateful to Professor Y. Ban for providing spectral data of (±)-epilupinine and (±)-lupinine, and to the Ministry of Education, Sciences, and Culture (Japan), and Toyama Prefecture Centennial Foundation for research grants.

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