Synthetic Studies on Pyrrolizidine Alkaloid Antitumor Agents. Enantioselective Synthesis of Retronecine and Its Enantiomer from D-Glucose

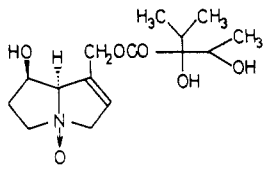
Yoshio Nishimura,* Shinichi Kondo, and Hamao Umezawa

Institute of Microbial Chemistry, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141, Japan

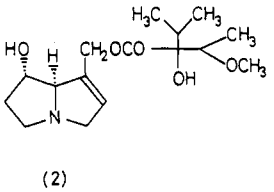
Received April 4, 1985

The first enantioselective synthesis of retronecine (3) and its enantiomer 4 has been achieved from D-glucose in a totally stereospecific fashion through a sequence involving as the key steps (a) the cyclization to the pyrrolidine ring by intramolecular nucleophilic attack of the primary amine, generated by reduction of the azide group of 6 derived from D-glucose (6 → 7), (b) the formation of the hydroxymethyl group by Wittig reaction followed by hydroboration and oxidation (13 → 17), (c) the cyclization to the bicyclic system (pyrrolizidine ring) by intramolecular nucleophilic attack of the secondary amine, generated by hydrogenolysis of the *N*-benzyloxycarbonyl group (17 → 18), (d) the differentiation of C-1 and C-7 of a pivotal intermediate, pyrrolizidine diol 18, by selective removal of each protecting group (18 → 19 and 20), (e) the hydroxymethylation to the carbanion stabilized by α-sulfoxide followed by sulfoxide-based elimination (22 → 25; 24 → 26), and (f) the removal of the protecting group ((2-methoxyethoxy)methyl and benzyl or benzyl ether) (25 → 3; 26 → 4). Synthetic retronecine and its enantiomer showed only weak cytotoxicity to leukemia L-1210 cells (IC_{50}: more than 100 μg/mL) and no significant difference between two compounds was revealed.

The pyrrolizidine alkaloids[1] containing $\Delta^{1,2}$-unsaturated dihydroxynecine base[2] (retronecine[1] and heliotridine[1,3]) are associated with a wide range of potent biological effects.[3c,4] Indicine *N*-oxide (1)[5] shows marked antitumor activity, while heliotrine (2)[3] is an established carcinogen. Due to their intriguing chemical structures and their pharmacological activities, the $\Delta^{1,2}$-unsaturated dihydroxypyrrolizidine alkaloids have been attractive synthetic targets.



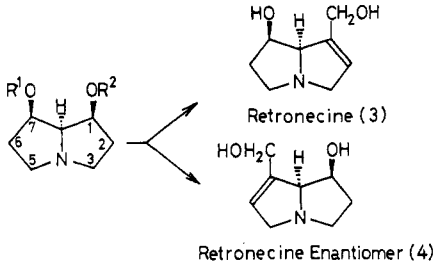
(1)



(2)

In order to understand the structural features necessary for the antitumor action, we undertook the synthesis of retronecine (3) and its enantiomer 4. Although syntheses of simpler, less oxidized necine bases in optically active form[6,7] have been reported, little is known about the synthesis of the more complex necine bases such as retronecine[8] or heliotridine.[8h]

Here we report the first enantioselective synthesis of retronecine (3) and its enantiomer 4. In the previous syntheses of such necine bases,[6-8] all carbon atoms required were in place before the construction of the pyrrolizidine ring. Our approach to retronecine and its enantiomer involves, as the key step, the introduction of the allylic alcohol part at either C-1 or C-7 of the same intermediate by differentiation of each position.



Cyclization of 3-azido-1,2-*O*-isopropylidene-5,6-di-*O*-mesyl-α-D-glucofuranose (6)[9] [mp 112–113 °C, $[\alpha]^{20}_D$ −50.8°

(1) Review: (a) Bull, L. B.; Culvenor, C. C.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland Publishing Co.; Amsterdam, 1968. (b) Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 247.

(2) For a review, see: Warren, F. L. *Fortschr. Chem. Org. Naturst.* **1966**, *24*, 329.

(3) (a) Men'Shikov, G. P. *Ber. Dtsch. Chem. Ges. B* **1932**, *65*, 974. (b) Zalkow, L. H.; Bonett, S.; Gelbaum, L.; Gordon, M. M.; Patil, B. B.; Shani, A.; Van Derveer, D. *J. Nat. Prod.* **1979**, *42*, 603. (c) Atal, C. K. *Ibid.* **1978**, *41*, 312.

(4) (a) Matlocks, A. R. "Phytochemical Ecology"; Harborne, J. B., Ed.; Academic Press: London, 1972, 179. (b) Smith, L. W.; Culvenor, C. C. *J. Nat. Prod.* **1981**, *44*, 129. (c) Hartwell, J. *Cancer Treat. Rep.* **1976**, *60*, 1031. (d) Leterndre, L.; Smithson, W. A.; Gilchrist, G. S.; Bergert, E. U.; Hoagland, C. H.; Ames, M. M.; Powis, G.; Korach, J. S. *Cancer (Philadelphia)* **1981**, *47*, 437.

(5) (a) Kugelman, M.; Liu, W. C.; Axelrod, M.; McBride, J. J.; Rao, K. V. *J. Nat. Prod.* **1976**, *39*, 125. (b) Kovach, J. S.; Ames, M. M.; Dowis, G.; Moertel, C. G.; Hahn, R. G.; Cregan, E. T. *Cancer Res.* **1979**, *39*, 4540.

(6) (a) Robins, D. J.; Sakdorat, S. *J. Chem. Soc., Chem. Commun.* **1979**, 1181. (b) Robins, D. J.; Sakdorat, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 909. (c) Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096. (d) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.

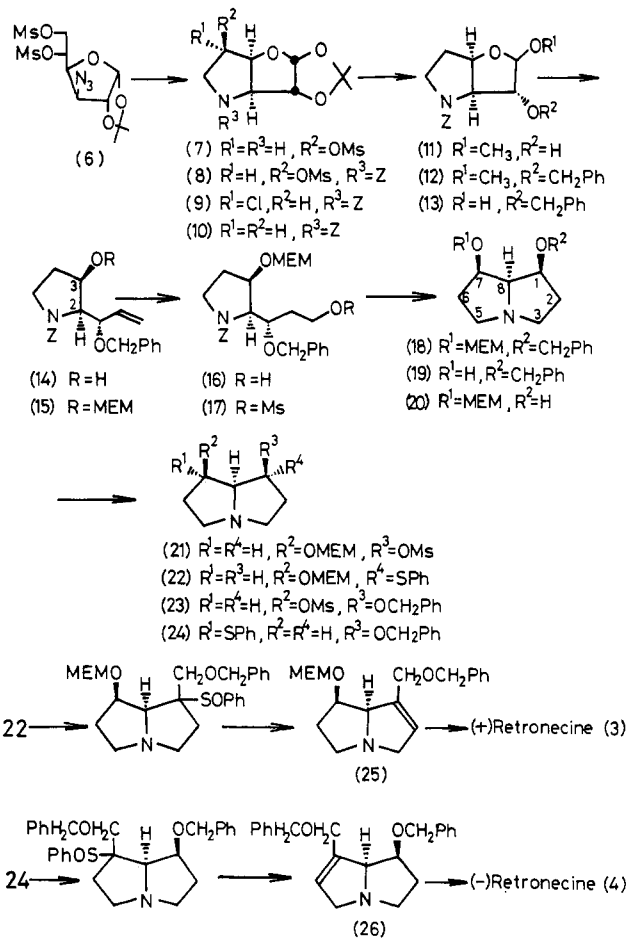
(7) For recent synthetic efforts to this class of alkaloids in racemic form: (a) Kraus, G. A.; Neuenschwander, K. *Tetrahedron Lett.* **1980**, *21*, 3841. (b) Munchowski, J. M.; Nelson, P. H. *Tetrahedron Lett.* **1980**, *21*, 4585. (c) Flitsch, W.; Wernsmann, P. *Tetrahedron Lett.* **1981**, *22*, 719. (d) Chamberlin, A. R.; Chung, Y. L. *Tetrahedron Lett.* **1982**, *23*, 2619. (e) Hart, D. J.; Yang, T.-K. *Tetrahedron Lett.* **1982**, *23*, 2761. (f) Robins, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1289. (g) Macdonald, T. L.; Narayanan, B. A. *J. Org. Chem.* **1983**, *48*, 1131. (h) Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1983**, *48*, 3644. (i) Earlier examples are reviewed: Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, 1734.

(8) Recent work on total synthesis of retronecine in racemic form: (a) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373. (b) Keck, G. E; Nickell, D. G. *Ibid.* **1980**, *102*, 3634. (c) Vedejs, E.; Martinez, G. R. *Ibid.* **1980**, *102*, 7993. (d) Niwa, H.; Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 125. (e) Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1983**, *48*, 4644. Very recently chiral synthesis of (+)-retronecine: (f) Rüeger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331. (g) Buchanan, J. G.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1299. (h) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. Added in proof: (i) The synthesis of (−)-heliotridine has recently been reported after the submission of our article, see: Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235.

(9) This compound was obtained from 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucopyranose (Kovar, J.; Jary, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 2619) by treatment with mesyl chloride in pyridine.

0022-3263/85/1950-5210$01.50/0

Scheme I



($CHCl_3$)] by catalytic reduction with Raney Ni gave pyrrolidinylisopropylidenefuranose **7**[10] quantitatively. Compound **7** was converted to the corresponding deoxy derivative **10** by the sequence of N-(benzyloxy)-carbonylation [benzyl *S*-4,6-dimethylpyrimid-2-yl thiocarbonate,[11] triethylamine, methanol; **8**, 100% yield], chlorination (lithium chloride, *N,N*-dimethylformamide; **9**, 85%), and tin hydride reduction (tributylstannane, toluene; 100%). Methanolysis of **10** by treatment with 10% hydrogen chloride in methanol afforded the methyl glycoside **11** in a yield of 75%, and subsequent benzylation with benzyl chloride and sodium hydride in *N,N*-dimethylformamide followed by acid hydrolysis with 3 M aqueous hydrogen chloride–acetic acid (1:1) produced compound **13**[12] in a yield of 86% for the two steps. Treatment of **13** with methylenetriphenylphosphorane gave vinyl alcohol **14** in a yield of 71%. Compound **14** was transformed into mesylate **17** by (methoxyethoxy)-methylation ((2-methoxyethoxy)methyl chloride, imidazole, methylene chloride; **15**, 93%), hydroboration and oxidation [(i) 9-borabicyclo[3.3.1]nonane, tetrahydrofuran, (ii) 30% hydrogen peroxide in water, aqueous sodium hydroxide; **16**, 100%], and mesylation (mesyl chloride; 92%). Cyclization of **17** by the same catalytic reduction mentioned above gave a pivotal intermediate, pyrrolizidine diol **18**, quantitatively. The differentiation of C-1 and C-7 of pyrrolizidine diol **18** was accomplished by selective removal of each protecting group. Acid hydrolysis of **18** with 1 M aqueous hydrogen chloride gave the 7-hydroxy derivative **19** quantitatively, while catalytic hydrogenolysis of **18** with Raney Ni in refluxing ethanol afforded 1-hydroxy derivative **20** quantitatively. The transformation of **20** and **19** to retronecine and its enantiomer, respectively, involve hydroxymethylation at carbon bearing an α-sulfur substituent followed by sulfoxide-based elimination.[13] Treatment of **20** with mesyl chloride in pyridine gave mesylate **21** (86% yield), and subsequent sulfide formation with sodium thiophenolate in *N,N*-dimethylformamide afforded the corresponding sulfide **22** in a yield of 65%. Oxidation of the hydrochloride of **22**, prepared with hydrogen chloride in methanol at 0 °C, with *m*-chloroperbenzoic acid in dichloromethane produced the corresponding sulfoxide[14] in a yield of 84%. Benzyloxymethylation of the sulfoxide [(i) lithium diisopropylamide, tetrahydrofuran, −78 °C, (ii) benzyl chloromethyl ether,[15] −78 °C → room temperature] afforded the corresponding (benzyloxy)methyl phenyl sulfoxide (77% yield), and subsequent syn elimination (xylene, reflux) furnished the olefin **25** in a yield of 69%. The stereochemistry of the benzyloxymethyl group was supposed as β by the ease of syn elimination toward C-2.

Hydrolysis of **25** with 3 M aqueous hydrogen chloride followed by benzyl ether cleavage with lithium in liquid ammonia[8c] resulted in crystalline retronecine (**3**) in a yield of 56%. Its spectral properties (IR, ^1H NMR, ^{13}C NMR, mass spectrum), melting point, and specific rotation were superimposable with those of the natural material.[16]

Conversion of **19** to **26** was achieved through the same sequence used for **20** → **25**. Mesylate **23** (88% yield), sulfide **24** (69% yield), (benzyloxy)methyl phenyl sulfoxide (91% yield), and olefin **26**[17] (62% yield) were obtained. The benzyl ether cleavage of **26** by the same manner mentioned above resulted in crystalline retronecine enantiomer **4** in a yield of 73%. The enantiomer **4** was identical in all respects with the synthetic and the natural retronecine except for the sign of the specific rotation.

Synthetic retronecine and its enantiomer showed only weak cytotoxicity to leukemia L-1210 cells (IC_{50}: more than 100 μg/mL) and no significant difference between two compounds was revealed. The result suggested that for the appearance of cytotoxicity, at least one of the hydroxy groups on the base moiety must be esterified.

Further chemical modification studies of retronecine and its enantiomer are to examine the structural features responsibility for the antitumor action.

Experimental Section

General Methods. Melting points were determined with a Yamato apparatus and were uncorrected. IR spectra were determined on a Hitachi Model 260-10 spectrophotometer. Optical rotations were measured with a Parkin-Elmer Model 241 polarimeter. The ^1H NMR spectra were recorded with Varian XL-100, Varian EM-390, Bruker WM250, and JEOL GX-400 spectrometers. Chemical shifts were expressed in values (ppm) with tetramethylsilane as an internal standard. Proton noise decoupled FT ^{13}C NMR spectra were taken at 25.2 MHz on a Varian XL-100 and at 100.4 MHz on a JEOL GX-400 spectrometer using tet-

(10) The IR, ^1H NMR, and mass spectral data of all new compounds reported here were in accord with the structures assigned.

(11) Nagasawa, T.; Kuroiwa, K.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269.

(12) β-Isomer could not be isolated by pure state. The mixture of α- and β-isomer was subjected to Wittig reaction.

(13) For the similar elimination based on selenium, see: (a) Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1734. (b) Reference 8c.

(14) The diastereomeric mixture was obtained and was not separated into each isomer.

(15) Purchased from Aldrich Chemical Co. For the hydroxymethyl synthon, see: (a) Caine, D.; Smith, T. L., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7568. (b) McGuirk, P. R.; Collum, D. B. *Ibid.* **1982**, *104*, 4496.

(16) The authentic sample of natural retronecine was provided by Prof. T. Furuya, Kitasato University, Tokyo.

(17) This compound in racemic form was synthesized by Ohsawa et al. See ref 7h.

ramethylsilane as a reference. The mass spectra were taken by a Hitachi RMU-6M mass spectrometer for electron-impact ionization or RMU-7M for field-desorption and for secondary ionization.

(1*S*,3*R*,7*R*,8*S*,11*R*)-11-[(Methylsulfonyl)oxy]-5,5-dimethyl-2,4,6-trioxa-9-azatricyclo[6.3.0.0^{3,7}]undecane (7). The 3-azido-3-deoxy-1,2-*O*-isopropylidene-5,6-di-*O*-mesyl-α-D-glucofuranose (**6**, 26 g) in a mixture of ethyl acetate (500 mL) and methanol (200 mL) was stirred with Raney Ni (W4, 10 g) under a hydrogen atmosphere for 2 h. The Raney Ni was filtered off, and the filtrate was evaporated to give a residue, which was subjected to the column chromatography on silica gel. Elution with toluene–acetone (3:1) gave the pyrrolidinylisopropylidenefuranose **7** (18.6 g, 100%), which was recrystallized from acetone: mp 113–114 °C; $[\alpha]^{20}_D$ +61° ($CHCl_3$); IR (KBr) 3380, 1345 and 1175 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.32 and 1.50 (3 H, s each, isopropylidene), 1.66 (1 H, br s, NH), 2.98 (1 H, dd, J = 9, 11 Hz, 5-H), 3.13 (3 H, s, CH_3SO_2), 3.31 (1 H, dd, J = 7, 11 Hz, 5′-H), 3.94 (1 H, d, J = 4.4, 3-H), 4.50 (1 H, s, J = 3.5, 2-H), 4.84 (1 H, ddd, J = 4, 7, 9 Hz, 6-H), 4.92 (1 H, t, J = 4, 7-H), 5.97 (1 H, d, J = 3.5 Hz, 1-H); ^{13}C NMR ($CDCl_3$) δ 26.8 and 27.5 (s each, isopropylidene), 38.8 (q, CH_3SO_2), 48.1 (t, C-5), 65.5 (d, C-3), 78.3, 80.9, 87.3, 107.3 (d, C-1), 112.7 (s, C-9); mass spectrum (SIMS), m/z 280 (M^+ + 1), 222, 180, 126, 75, 56, 44.

(1*S*,3*R*,7*R*,8*S*,11*R*)-9-[(Benzyloxy)carbonyl]-11-[(methylsulfonyl)oxy]-5,5-dimethyl-2,4,6-trioxa-9-azatricyclo-[6.3.0.0^{3,7}]undecane (8). To a solution of **7** (18 g) in methanol (500 mL) was added triethylamine (60 mL) and benzyl *S*-4,6-dimethylpyrimid-2-yl thiocarbonate (26.5 g) in one portion, and the resulting mixture was stirred at room temperature for 2 h. Evaporation of the solvent gave an oil, which was dissolved in chloroform. The solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with toluene–acetone (10:1) gave compound **8** (23 g, 100%), which was recrystallized from a mixture of ether–ethyl acetate (5:1) to give one isomer as a colorless crystal: mp 125–126 °C; $[\alpha]^{20}_D$ −26° ($CHCl_3$); IR (KBr) 1720, 1360, 1180 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.30 and 1.52 (3 H, s each, isopropylidene), 3.10 (3 H, s, CH_3SO_2), 3.40 and 4.10 (1 H, m each, 5,5′-H), 4.33 (1 H, d, J = 3.7 Hz, 2-H), 4.6–5.1 (3 H, m, 3,6,7-H), 5.18 (1 H, br s, CH_2-phenyl), 5.92 (1 H, d, J = 3.5 Hz, 1-H), 7.38 (5 H, s, phenyl); mass spectrum (SIMS), m/z 414 (M^+ + 1), 356, 324, 280, 266, 248, 91, 75, 57, 45.

(1*S*,3*R*,7*R*,8*S*,11*S*)-9-[(Benzyloxy)carbonyl]-11-chloro-5,5-dimethyl-2,4,6-trioxa-9-azatricyclo[6.3.0.0^{3,7}]undecane (9). To a solution of **8** (2.9 g) in dry *N*,*N*-dimethylformamide (40 mL) was added lithium chloride (0.9 g), and the mixture was stirred at 130 °C for 17 h. Evaporation of the solvent gave a viscous oil, which was dissolved in chloroform. The solution was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a solid, which was subjected to a column chromatography on silica gel. Elution with toluene–acetone (5:1) gave a solid of **9** (2.12 g, 85%), which was recrystallized from ethyl acetate to give a colorless crystal: mp 78–79 °C; $[\alpha]^{20}_D$ −60.8° ($CHCl_3$); IR (KBr) 1720 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.31 and 1.32 (total 3 H, s each, isopropylidene), 1.52 and 1.53 (total 3 H, s each, isopropylidene), 3.73 and 3.75 (total 1 H, dd each, J = 4, 13 Hz, 5-H), 3.92 and 4.10 (total 1 H, d each, J = 13 Hz, 5′-H), 4.26 and 4.27 (total 1 H, d each, J = 4 Hz, 6-H), 4.54 and 4.57 (total 1 H, d each, J = 4 Hz, 3-H), 4.69 and 4.87 (total 1 H, d each, J = 3.5 Hz, 2-H), 4.83 and 4.85 (total 1 H, d each, J = 3.5 Hz, 7-H), 5.16, 5.21 and 5.28 (total 2 H, s, AB q, respectively, CH_2-phenyl), 5.79 and 5.81 (total 1 H, d each, 1-H); mass spectrum (SIMS), m/z 354 (M^+ + 1), 296, 206, 91, 75, 57, 45.

(1*R*,3*R*,7*R*,8*S*)-9-[(Benzyloxy)carbonyl]-5,5-dimethyl-2,4,6-trioxa-9-azatricyclo[6.3.0.0^{3,7}]undecane (10). The solution of the mixture of chloride **9** (1.44 g) and tributylstannane (7 mL) in dry toluene (15 mL) was refluxed under vigorously stirring for 1 day. Evaporation of the solvent gave an oil, which was subjected to a column chromatography on silica gel. Elution with toluene–acetone (20:1) gave a colorless solid of **10** (1.32 g), which was recrystallized from acetone to give a colorless crystal: mp 88–89 °C; $[\alpha]^{20}_D$ −62.8° ($CHCl_3$); IR (KBr) 1715 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.31 and 1.52 (3 H, s each, isopropylidene), 1.5–2.3 (2H, m, 6,6′-H), 3.1–4.0 (2H, m, 5,5′-H), 4.22 (1 H, d, J = 4 Hz, 3-H), 4.5–5.3 (4 H, m, 2,7-H and CH_2-phenyl), 5.82 (1 H, d, J = 3.5 Hz, 1-H), 7.38 (5 H, br s, phenyl); mass spectrum (EI), m/z 319 (M^+), 304, 261, 203, 170, 159, 155, 127, 113, 100, 91, 78, 75.

(1*R*,3*R*,4*R*,5*S*)- and (1*R*,3*S*,4*R*,5*S*)-5-[(Benzyloxy)-carbonyl]-3-methoxy-2-oxa-6-azabicyclo[3.3.0]octan-4-ol (11). The solution of **10** (1.89 g) in 10% hydrogen chloride in methanol (18 mL) was stirred at 50 °C for 1 h. Evaporation of the solvent gave an oil, which was dissolved in chloroform. The solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography over silica gel. Elution with toluene–acetone (5:1) gave the 3*R* isomer (1.06 g, 61%) and 3*S* isomer (0.18 g, 10%) of **11** as an oil. 3*R* isomer: $[\alpha]^{20}_D$ −155° ($CHCl_3$); IR (KBr) 3430, 1700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.97 (2 H, m, 6,6′-H), 3.47 (3 H, s, OCH_3), 4.0–4.4 (2 H, m, 2,3-H), 4.80 (1 H, dt, J = ~3, ~5 Hz, 7-H), 4.97 (1 H, d, J = 4 Hz, 1-H), 5.18 (2 H, s, CH_2-phenyl), 7.37 (5 H, br s, phenyl); mass spectrum (SIMS), m/z 294 (M^+ + 1), 262, 244, 218, 204, 172, 91, 75, 57, 45. 2*S* isomer: $[\alpha]^{20}_D$ +15° ($CHCl_3$); IR (KBr) 3420, 1700, 1680 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.0 (2 H, br m, 6,6′-H), 3.31 (3 H, s, OCH_3), 4.14 (1 H, d, J = 5.5 Hz, 3-H), 4.85 and 5.14 (AB q, CH_2-phenyl), 4.98 (1 H, br t, J = 5.5 Hz, 7-H), 5.10 (1 H, d, J = 2 Hz, 1-H), 7.32 (5 H, br s, phenyl); mass spectrum (SIMS), m/z 294 (M^+ + 1), 262, 244, 172, 91, 75, 57, 45.

(1*R*,3*R*,4*R*,5*S*)- and (1*R*,3*S*,4*R*,5*S*)-4-(Benzyloxy)-5-[(benzyloxy)carbonyl]-3-methoxy-2-oxa-6-azabicyclo-[3.3.0]octane (12). To a solution of the 2*R* isomer of **11** (153.3 mg) in dry *N*,*N*-dimethylformamide (2 mL) was added NaH (50% in oil, 25 mg). After the mixture stirred at room temperature for 30 min, benzyl bromide (0.62 mL) was added to the mixture. Then the resulting mixture was stirred at room temperature for 1 h. After quenching with a small amount of water, evaporation of the solvent gave a viscous solid. The solid was dissolved in chloroform, and the chloroform solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the solvent gave an oil. The oil was subjected to the preparative thin-layer chromatography on silica gel developed with toluene–acetone (5:1) to give an oil of **12** (189 mg, 94%): $[\alpha]^{20}_D$ −116.8° ($CHCl_3$); IR (KBr) 1700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.92 (2 H, m, 6,6′-H), 3.30 (1 H, dt, J = 9, 15 Hz 5-H), 3.42 (3 H, s, OCH_3), 3.85 (2 H, br m, 3.5-H), 4.3–4.7 (2 H, m, 2,7-H), 4.7–5.0 (3 H, m, 1-H and OCH_2-phenyl), 5.20 (2 H, s, $COOCH_2$-phenyl), 7.28 and 7.38 (5 H, br s each, two phenyls); mass spectrum (SIMS), m/z 384 (M^+ + 1), 352, 308, 294, 263, 91, 75, 57, 45.

The procedures used for the preparation of the 3*S* isomer of **12** were similar to those used for the preparation of the 3*R* isomer of **12**: $[\alpha]^{20}_D$ −30.5° ($CHCl_3$); IR (KBr) 1700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.0 (2 H, m, 6,6′-H), 3.30 (3 H, s, OCH_3), 4.94 and 5.17 (2 H, s each, $COOCH_2$-phenyl and OCH_2-phenyl), 5.0 (1 H, br t, J = 5.5 Hz, 7-H), 5.18 (1 H, d, J = ~2 Hz, 1-H), 7.0–7.5 (10 H, br m, two phenyls); mass spectrum (SIMS), m/z 384 (M^+ + 1), 352, 308, 294, 263, 91, 75, 57, 45.

(1*R*,4*R*,5*S*)-4-(Benzyloxy)-5-[(benzyloxy)carbonyl]-2-oxa-6-azabicyclo[3.3.0]octan-3-ol (13). The solution of **12** (170 mg) in a mixture of acetic acid and 3 M hydrogen chloride (3:1, 2.1 mL) was stirred at 70 °C for 2 h. Evaporation of the solvent gave an oil, which was dissolved in chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil. The oil was subjected to the preparative thin-layer chromatography on silica gel developed with toluene–acetone (5:1) to give an oil of **13** (150 mg, 92%): IR (KBr) 3400, 1695, 1420, 1115 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.5–2.3 (2H, br m, 6,6′-H), 5.19 (2 H, s, $COOCH_2$-phenyl (?)), 5.30 and 5.43 (total 1 H, d each, J = 2, 4 Hz, 1-H), 7.4 (10H, br s, two phenyls); mass spectrum (SIMS), m/z 370 (M^+ + 1), 352, 262, 91, 75, 57, 45.

(−)-(2*S*,3*R*)-1-[(Benzyloxy)carbonyl]-2-[(*S*)-1-(benzyloxy)prop-2-enyl]-3-hydroxypyrrolidine (14). To a stirring suspension of methyltriphenylphosphonium bromide (15.4 g) in tetrahydrofuran (70 mL) was added butyllithium in hexane (1.6 M/L, 26.9 mL), and the mixture was stirred at room temperature for 30 min. A solution of **13** (5.29 g) in tetrahydrofuran (40 mL) was added to the mixture, and then the resulting mixture was stirred at 50 °C for 5 h. After being quenched with saturated aqueous NH_4Cl solution, the mixture was extracted with ether.

The ether solution was washed with NaCl-saturated aqueous solution, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography over silica gel. Elution with toluene–acetone (3:1) gave an oil of **14** (3.7 g, 71%): $[\alpha]^{20}_D$ −25.2° ($CHCl_3$); IR (KBr) 3430, 1700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.9 (2 H, m, 4,4′-H), 3.29 (1 H, br s, OH), (2 H, m, 5,5′-H), 4.2 (1 H, m, 2-H), 4.35–4.8 (4 H, m, 3,6-H and OCH_2-phenyl (?)), 5.09 (2 H, s, $COOCH_2$-phenyl (?)), 5.1–5.4 (2 H, br m, 8,8′-H), 5.8–6.3 (1 H, m, 7-H), 7.3 (10 H, br s, two phenyls); mass spectrum (SIMS), m/z 368 (M^+ + 1), 260, 234, 91, 75, 57, 45.

(−)-(2*S*,3*R*)-1-[(Benzyloxy)carbonyl]-2-[(*S*)-1-(benzyloxy)prop-2-enyl]-3-[(methoxyethoxy)methoxy]pyrrolidine (15). To a solution of **14** (3.7 g) in dichloromethane (50 mL) were added *N*,*N*-diisopropylethylamine (3.53 mL) and (2-methoxyethoxy)methyl chloride (2.3 mL), and the mixture was stirred at 45 °C for 5 h. After quenching with water, evaporation of the solvent gave an oil. The oil was dissolved in chloroform, and the chloroform solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to the column chromatography on silica gel. Elution with toluene–acetone (5:1) gave an oil of **15** (4.27 g, 93%): $[\alpha]^{20}_D$ −7.3° ($CHCl_3$); IR (KBr) 1710 and 1415 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.13 (2 H, m, 4,4′-H), 3.35 (3 H, s, OCH_3), 4.73 (2 H, s, $-OCH_2O-$), 5.12 (2 H, s, $COOCH_2$-phenyl (?)), 5.2 (2 H, m, 8,8′-H), 5.7–6.3 (1 H, m, 7-H), 7.3 and 7.37 (5 H, s each, phenyl); mass spectrum (SIMS), m/z 456 (M^+ + 1), 322, 186, 75, 57, 45.

(−)-(2*R*,3*R*)-1-[(Benzyloxy)carbonyl]-2-[(*S*)-1-(benzyloxy)-3-hydroxypropyl]-3-[(methoxyethoxy)methoxy]pyrrolidine (16). To a solution of **15** (4.27 g) in tetrahydrofuran (45 mL) was added 9-borabicyclo[3.3.1]nonane (3.54 g) in one portion at room temperature, and the mixture was stirred at 60 °C for 1.5 h. Both 2 M aqueous NaOH (10.08 mL) and 30% aqueous hydrogen peroxide (6.46 mL) were added to the mixture, and then the resulting mixture was stirred at 45 °C for 2 h. After evaporation of the solvent, the residue was extracted with ether. The ether solution was washed with NaCl-saturated aqueous solution, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to the column chromatography on silica gel. Elution with toluene–acetone (3:1) gave an oil of **16** (4.06 g, 100%): $[\alpha]^{20}_D$ −32.6° ($CHCl_3$); IR (KBr) 3450 and 1700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.1–2.6 (4 H, m, 4,4′,7,7′-H), 3.37 (3 H, s, OCH_3), 3.61 (2 H, br s, OCH_2-phenyl (?)), 4.78 (2 H, s, $-OCH_2O-$), 5.04 and 5.2 (2 H, AB q, J = 13 Hz, $COOCH_2$-phenyl (?)), 7.32 and 7.37 (5 H, s each, two phenyls); mass spectrum (SIMS), m/z 474 (M^+ + 1), 384, 354, 340, 277, 91, 75, 59, 45.

(−)-(2*R*,3*R*)-1-[(Benzyloxy)carbonyl]-2-[(*S*)-1-(benzyloxy)-3-[(methylsulfonyl)oxy]propyl]-3-[(methoxyethoxy)methoxy]pyrrolidine (17). To a solution of **16** (4.06 g) in dry pyridine (50 mL) was added mesyl chloride (0.796 mL) at −40 °C, and the mixture was stirred at room temperature for 1 h. After quenching with water, evaporation of the solvent gave an oil. The oil was dissolved in chloroform, and the chloroform solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography over silica gel. Elution with toluene–acetone (10:1) gave an oil of **17** (4.2 g, 92%): $[\alpha]^{20}_D$ −33° ($CHCl_3$); IR (KBr) 1700, 1415, 1360, 1330, 1180 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.7–2.5 (4 H, m, 4,4′,7,7′-H), 2.90 (3 H, br s, CH_3SO_2), 3.37 (3 H, s, OCH_3), 4.78 (2 H, s, $-OCH_2O-$), 5.03 and 5.2 (2 H, AB q, J = 13 Hz, $COOCH_2$-phenyl (?)), 7.31 and 7.37 (5 H, s each, phenyl); mass spectrum (SIMS), m/z 552 (M^+ + 1), 462, 418, 342, 186, 91, 75, 57, 45.

(+)-(1*S*,7*R*,8*R*)-1-(Benzyloxy)-7-[(methoxyethoxy)methoxy]pyrrolizidine (18). The mesylate **17** (14.5 g) in a mixture of methanol and ethyl acetate (4:1, 500 mL) was stirred with Raney Ni (W4, 5 g) under a hydrogen atmosphere for 1 day. The Raney Ni was filtered off, and the filtrate was evaporated to give an oil, which was subjected to the column chromatography on silica gel. Elution with chloroform–methanol–ammonia (100:10:1) gave an oil of **18** (8.3 g, 100%): $[\alpha]^{20}_D$ +5.4° ($CHCl_3$); IR (KBr) 2925, 2875, 1460 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.76–2.0 (2 H, m, 2,6-H), 2.0–2.24 (2 H, m, 2′,6′-H), 2.66–2.87 (2 H, m, 3,5-H), 3.1–3.27 (2 H, m, 3′,5′-H), 3.36 (3 H, s, OCH_3), 3.37 (1 H, dd, J = 5, 6 Hz, 8-H), 4.18 (1 H, dd, J = 6, 12 Hz, 7-H), 4.29 (1 H, dd, J = 5, 10 Hz, 1-H), 4.54 and 4.60 (2 H, AB q, J = 12 Hz, $-OCH_2O-$), 4.74 and 4.80 (2 H, AB q, J = 7.5 Hz, OCH_2-phenyl), 7.2–7.5 (5 H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ 31.5 (t, C-6 (?)), 32.8 (t, C-2 (?)), 54.5 (t, C-5 (?)), 54.6 (t, C-3 (?)), 59.0 (q, OCH_3), 66.9 (t, CH_2-phenyl), 69.9 (d, C-8), 71.8 and 72.2 (t each, $-OCH_2CH_2O-$), 78.7 (d, C-7 (?)), 80.7 (d, C-1 (?)), 95.3 (t, $-OCH_2O-$), 127.4, 127.5, 128.2 (phenyl); mass spectrum (SIMS), m/z 322 (M^+ + 1), 262, 232, 214, 154, 111, 91, 72, 59.

(+)-(1*S*,7*R*,8*R*)-1-Hydroxy-7-(benzyloxy)pyrrolizidine (19). Compound **18** (4 g) was dissolved in 3 M HCl (40 mL), and the mixture was allowed to stand at room temperature overnight. After neutralization with solid $NaHCO_3$, the solvent was evaporated to give a viscous oil. The oil was dissolved in chloroform, and the chloroform solution was washed with NaCl-saturated aqueous solution, dried over $MgSO_4$, and filtered. Evaporation of the solvent gave a colorless solid. The solid was recrystallized from ethyl acetate–ethanol (4:1) gave a very hygroscopic crystal of **19** (3.08 g, 100%): $[\alpha]^{20}_D$ +8.4° ($CHCl_3$); IR (KBr) 3500, 1975, 1900, 1825, 1100 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.7–2.4 (4 H, m, 2,2′,6,6′-H), 2.6–3.3 (4 H, m, 3,3′,5,5′-H), 3.48 (1 H, dd, J = 4.5, 6.5 Hz, 8-H), 4.22 (1 H, br s, OH), 4.2–4.5 (2 H, m, 1,7-H), 4.53 and 4.70 (2 H, AB q, J = 7 Hz, OCH_2-phenyl), 7.37 (5 H, br s, phenyl); mass spectrum (EI), m/z 233 (M^+), 184, 143, 91; mass spectrum (SIMS), m/z 234 (M^+ + 1), 177, 142, 91, 82, 59.

(−)-(1*S*,7*R*,8*R*)-1-Hydroxy-7-[(methoxyethoxy)methoxy]pyrrolizidine (20). Compound **18** (1.15 g) in ethanol (30 mL) was refluxed with Raney Ni (W4, 500 mg) under bubbling hydrogen gas for 20 h. The Raney Ni was filtered off, and the filtrate was evaporated to give an oil. The oil was subjected to the preparative thin-layer chromatography on silica gel developed with chloroform–methanol–ammonia (10:1:0.1) to give an oil of **20** (545 mg, 100%): $[\alpha]^{20}_D$ −8.2° ($CHCl_3$); IR (KBr) 3470, 2950, 2900, 1120, 1050 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.7–2.3 (4 H, m, 2,2′,6,6′-H), 3.55 (3 H, s, OCH_3), 4.43 (1 H, dd, J = 4.5, 6.5 Hz, 1-H), 4.60 (1 H, dd, J = 7, 13 Hz, 7-H), 4.83 (2 H, s, $-OCH_2O-$); mass spectrum (EI), m/z 231 (M^+), 156, 142, 125, 99, 82; mass spectrum (SIMS), m/z 232 (M^+ + 1), 149, 82, 59, 41.

(+)-(1*S*,7*R*,8*S*)-1-[(Methylsulfonyl)oxy]-7-[(methoxyethoxy)methoxy]pyrrolizidine (21). To a solution of **20** (237 mg) in dry pyridine (3 mL) was added mesyl chloride (0.119 mL), and the mixture was allowed to stand at room temperature for 1 h. After being quenched with water, the solution was evaporated to give a viscous solid. The solid was dissolved in chloroform, and the chloroform solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil subjected to the preparative thin-layer chromatography on silica gel developed with chloroform–methanol–ammonia (100:10:1) to give an oil of **21** (273 mg, 86%): $[\alpha]^{20}_D$ +32.8° ($CHCl_3$); IR (KBr) 2940, 2875, 1360, 1180 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.05 (3 H, s, CH_3SO_2), 3.40 (3 H, s, OCH_3), 4.45 (1 H, dd, J = 7, 13 Hz, 7-H), 4.80 (2 H, s, OCH_2-phenyl), 5.13 (1 H, dd, J = 4.5, 6.5 Hz, 1-H); mass spectrum (FD), m/z 310 (M^+ + 1), 213.

(−)-(1*S*,7*R*,8*R*)-1-(Benzyloxy)-7-[(methylsulfonyl)oxy]pyrrolizidine (23). Procedures used were similar to those used for the preparation of **20** from **21** described above; the yield 88%: $[\alpha]^{20}_D$ −35.9° ($CHCl_3$); IR (KBr) 2930, 2875, 1350, 1175 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.8 (3 H, s, CH_3SO_2), 3.52 (1 H, dd, J = 5, 6.7 Hz, 8-H), 4.33 (1 H, dd, J = 6.7, 13.5 Hz, 1-H), 4.57 (2 H, s, OCH_2-phenyl), 5.08 (1 H, dd, J = 5, 8 Hz, 7-H), 7.37 (5 H, s, phenyl); mass spectrum (FD), m/z 312 (M^+ + 1), 216, 215.

(−)-(1*R*,7*R*,8*S*)-7-[(Methoxyethoxy)methoxy]-1-(phenylthio)pyrrolizidine (22). To a solution of sodium thiophenoxide prepared from thiophenol (0.36 mL) and sodium hydroxide (130 mg) in *N*,*N*-dimethylformamide (6 mL) was added a solution of mesylate **21** (670 mg) in *N*,*N*-dimethylformamide (1 mL), and the resulting mixture was stirred at 50 °C for 2 h. After quenching with water, the solvent was evaporated to give a viscous solid, which was dissolved in chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the solvent of the filtrate gave an oil. The oil was subjected to the preparative thin-layer chromatography on silica gel developed with chloroform–methanol–ammonia (150:10:1) to give an oil of **22** (457 mg, 65%): $[\alpha]^{20}_D$ −35° ($CHCl_3$); IR ($CHCl_3$) 2940, 2890, 1480, 1440, 1090, 1050 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.88–2.16 (3 H, m, 2,2′,6-H), 2.37 (1 H, m, 6′-H), 2.54–2.66 (2 H, m, 5,5′-H), 3.17 (1 H, br t, J = 9 Hz, 3-H), 3.25 (1 H, dt, J = 6.5,

9 Hz, 3′-H), 3.38 (3 H, s, OCH_3), 3.88 (1 H, dd, J = 7, 15 Hz, 7-H), 4.04 (1 H, br t, J = 4.5 Hz, 1-H), 4.60 and 4.73 (2 H, AB q, J = 7 Hz, -OCH_2O-); ^{13}C NMR ($CDCl_3$), δ 34.4 (C-6 (?)), 35.7 (C-2 (?)), 43.6 (C-1), 52.3 (C-5 (?)), 54.2 (C-3 (?)), 59 (OCH_3), 67.3 and 71.7 (-OCH_2CH_2O-), 74.9 (C-8), 76.1 (C-7), 94.7 (-OCH_2O-), 127.1, 129, 131.8 (phenyl); mass spectrum (SIMS), m/z 324 (M^+ + 1), 216, 186, 94, 75, 57, 45.

(+)-(1*S*,7*S*,8*R*)-1-(Benzyloxy)-7-(phenylthio)pyrrolizidine (24). Procedures used were similar to those used for the preparation of **22** from **21** described above; the yield was 69%: $[\alpha]^{20}_D$ +74° ($CHCl_3$); IR ($CHCl_3$) 2940, 2860, 1480, 1460, 1100, 1070 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.75–2.15 (3 H, m, 2,2′,6-H), 2.32 (1 H, m, 6-H), 2.5–2.65 (2 H, m, 5,5′-H), 3.05 (1 H, br t, J = 10 Hz, 3-H), 3.15 (1 H, dt, J = 7, 10 Hz, 3′-H), 3.5 (1 H, dd, J = 4.5, 6 Hz, 8-H), 3.76 (1 H, br t, J = 4.5 Hz, 7-H), 3.99 (1 H, dd, J = 6, 15 Hz, 1-H), 4.31 and 4.51 (2 H, AB q, J = 12 Hz, OCH_2-phenyl), 7.1–7.4 (5 H, m, phenyl); mass spectrum (SIMS), m/z 326 (M^+ + 1), 216, 186, 91, 75, 57, 45.

(-)-9-*O*-Benzyl-7-*O*-[(methoxyethoxy)methoxy]retronecine (25). To a stirred solution of the hydrochloride of the sulfide **22** (296 mg), prepared with ethereal hydrogen chloride in methanol at 0 °C, in methylene chloride (30 ml) was added 85% *m*-chloroperbenzoic acid (167 mg) in one portion at −30 °C, and the mixture was stirred at −30 °C for 30 min. After addition of a 10% aqueous potassium hydroxide solution (2 mL), the mixture was extracted with dichloromethane. The extract was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave a residue, which was subjected to the preparative thin-layer chromatography developed with chloroform–methanol–ammonia (100:10:1). The corresponding sulfoxide (233 mg, 84%) was obtained. To a solution of lithium diisopropylamine, prepared from diisopropylamine (0.198) and butyllithium in hexane (1.6 M/L, 0.858 mL) at −15 °C, in tetrahydrofuran (1.5 mL) was added a solution of sulfoxide (233 mg) in tetrahydrofuran (1.5 mL) and hexamethylphosphoramide (1.5 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 1.5 h. Benzyl chloromethyl ether (0.135 mL) was added to the mixture at −78 °C, and the mixture was stirred from −78 °C to room temperature. After addition of water, the reaction mixture was extracted with dichloromethane. The extract was washed with NaCl-saturated aqueous solution, dried over $MgSO_4$, and filtered. Evaporation of the filtrate afforded a residue, which was subjected to the preparative thin-layer chromatography on silica gel developed with chloroform–methanol (5:1). The corresponding (benzyloxy)methyl phenyl sulfoxide (240 mL, 77%) was obtained. The (benzyloxy)methyl phenyl sulfoxide (240 mg) was dissolved in xylene (3 mL). After heating under reflux for 10 min, the solvent was evaporated to afford a residue, which was purified by preparative thin-layer chromatography on silica gel developed with chloroform–methanol–ammonia (100:10:1), giving **25** (120 mg, 69%): $[\alpha]^{20}_D$ −23° ($CHCl_3$); IR ($CHCl_3$) 2930, 2870, 1450, 1360, 1090, 1040 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.8–2.0 (1 H, m, 6-H), 2.12 (1 H, br dd, J = 7, 13 Hz, 6′-H), 2.61 (1 H, m, 5-H), 3.22 (1 H, br t, J = 8 Hz, 5′-H), 3.37 (3 H, s, OCH_3), 3.91 (1 H, br dt, J = 2, 15 Hz, 3-H), 4.10 and 4.16 (2 H, AB q, J = 12.5 Hz, 9,9′-H), 4.20 (1 H, br t with a small coupling, J = 4 Hz, 7-H), 4.30 (1 H, br m, 8-H), 4.48 and 4.57 (2 H, AB q, J = 12 Hz, -OCH_2O- (?)), 4.66 and 4.74 (2 H, AB q, J = 7 Hz, OCH_2-phenyl), 5.73 (1 H, d, J = 2 Hz, 2-H), ^{13}C NMR ($CDCl_3$) δ 33.5 (C-6), 53.8 (C-5), 59.0 (OCH_3), 62.6 (C-9), 67.2 (OCH_2-phenyl (?)), 67.3 (C-3), 71.7 and 72.3 (-OCH_2CH_2O- (?)), 76.2 (C-8), 77.4 (C-7), 94.5 (-OCH_2O-), 125.2 (C-2), 127.6, and 128.3 (phenyl), 136.7 (C-1); mass spectrum (SIMS), m/z 334 (M^+ + 1), 217, 201, 199, 109, 107, 91, 75, 57, 45.

(+)-7,9-Di-*O*-benzylretronecine (26). Procedures used were similar to those used for the preparation of **25** from **22** described above; the yield was 55% for three steps: $[\alpha^{20}_D$ +26.9° ($CHCl_3$); IR ($CHCl_3$) 2950, 2850, 1450, 1260, 1090, 1030 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.8 (1 H, m, 2-H), 2.11 (1 H, br dd, J = 5.5, 13 Hz, 2′-H), 2.65 (1 H, 7, 3-H), 3.21 (1 H, br t, J = 8 Hz, 3′-H), 3.39 (1 H, m 5-H), 3.91 (1 H, br d with a small coupling, J = 15 Hz, 5′-H), 4.01 (1 H, br t with a small coupling, J =4 Hz, 1-H), 4.10 and 4.17 (2 H, AB q, J = 12.5 Hz, 9,9′-H), 4.29 (1 H, br m, 8-H), 4.33 and 4.41 (2 H, AB q, J = 12 Hz, -OCH_2O- (?)), 4.54 (2 H, t, J = 12.5 Hz, OCH_2-phenyl (?)), 5.71 (1 H, d, J = ~1.5 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ 32.1 (C-2), 53.8 (C-3), 62.5 (C-5), 67.5 (C-9), 70.5 (-OCH_2CH_2O- (?)), 72.21 (OCH_2-phenyl (?)), 77.3 (C-8), 78.4 (C-1), 125.0 (C-6), 127.4, 127.5, 127.6 and 128.2 (phenyl), 136.8 (C-7); mass spectrum (SIMS), m/z 336 (M^+ + 1), 246, 186, 94, 91, 75, 57, 45.

(+)-Retronecine (3). Compound **25** (75 mg) was dissolved in 3 M HCl (2 mL), and the mixture was stirred for 1 day. After being neutralized with solid $NaHCO_3$, the mixture was evaporated to dryness. The residue was extracted with chloroform, and evaporation of the solvent gave a crude product. After a crude product obtained was stirred in a mixture of liquid ammonia (7 mL) and tetrahydrofuran (4 mL) with lithium (16 mg) at −33 °C for 5 h, isoprene (0.3 ml) and crystalline ammonium chloride (0.6 g) were added to the reaction mixture. Evaporation of the solvent afforded a residue, which was extracted with chloroform–methanol (1:1). After evaporation of the solvent, the residue was extracted with chloroform. The solvent was removed to give a residue, which was purified by the column chromatography on alumina (grade III). Elution with chloroform–methanol (4:1) afforded a colorless solid, which was recrystallized from acetone to furnish (+)-retronecine (**3**) (19 mg, 56%): mp 117–118 °C (lit.[16] mp 117–118 °C); $[\alpha]^{20}_D$ +53.1° (ethanol) (lit.[18] +50.2° (ethanol); +53.4° (ethanol)[16]); IR, NMR, and ^{13}C NMR spectra were identical with those of the natural retronecine.

(-)-Retronecine (4). After compound **26** (115 mg) was stirred in a mixture of liquid ammonia (11 mL) and tetrahydrofuran (6 mL) with lithium (25 mg) at −33 °C for 5 h, isoprene (0.46 mL) and crystalline ammonium chloride (0.9 g) were added to the reaction mixture. Evaporation of the solvent afforded a residue, which was extracted with chloroform–methanol (1:1). After evaporation of the solvent, the residue was extracted with chloroform. The solvent was removed to give a residue, which was purified by the column chromatography on alumina (grade III). Elution with chloroform–methanol (4:1) afforded a colorless solid, which was recrystallized from acetone to furnish (-)-retronecine (**4**) (37.3 mg, 73%): mp 117–118 °C; $[\alpha]^{20}_D$ −52.9° (ethanol); IR, NMR, and ^{13}C NMR spectra were identical with those of the natural retronecine.

Acknowledgment. We are very grateful to Prof. T. Furuya, Kitasato University, for generous gift of the natural retronecine. This work was supported in part by a Contract N01-CM-47593 with the Division of Cancer Treatment, National Cancer Institute, U.S.A., and by a Grant-in-Aid for Cancer Research from the Ministry of Education, Science and Culture, Japan, and from the Ministry of Health and Welfare, Japan.

Registry No. **3**, 480-85-3; **4**, 99032-02-7; **6**, 96625-41-1; **7**, 98944-18-4; **8**, 84730-22-3; **9**, 98944-19-5; **10**, 98944-20-8; (3*R*)-**11**, 98944-21-9; (3*S*)-**11**, 98944-22-0; (3*R*)-**12**, 98944-24-2; (3*S*)-**12**, 98944-23-1; (3*R*)-**13**, 98944-25-3; (3*S*)-**13**, 98944-40-2; **14**, 98944-26-4; **15**, 98944-27-5; **16**, 98944-28-6; **17**, 98944-29-7; **18**, 98944-30-0; **19**, 98944-31-1; **20**, 98944-32-2; **21**, 98944-33-3; **22**, 98944-35-5; **22** (sulfoxide, isomer 1), 99032-52-7; **22** (sulfoxide, isomer 2), 98944-41-3; **22**·HCl, 99032-01-6; **23**, 98944-34-4; **24**, 98944-36-6; **25**, 98944-37-7; **26**, 99094-33-4; $H_2C{=}C(CH_3)CH{=}CH_2$, 78-79-5; *S*-4,6-dimethylpyrimid-2-yl thiocarbonate, 42116-21-2; 7-[(methoxyethoxy)methoxy]-1-(phenylsulfoxyl)-1-((benzyloxy)methyl)pyrrolizidine, 98944-38-8; 1-(benzyloxy)-7-((benzyloxy)methyl)-7-(phenylsulfoxyl)pyrrolizidine, 98944-39-9.

(18) Adams, R.; Roger, E. F. *J. Am. Chem. Soc.* **1939**, *61*, 2815.