86969-49-5; (*Z*)-**6d**, 86969-53-1; **6e**, 23854-03-7; (*E*)-**6f**, 86969-50-8; (*Z*)-**6f**, 86969-54-2; (*E*)-**6g**, 61973-99-7; (*Z*)-**6g**, 61973-98-6; (*E*)-**6h**, 86969-51-9; (*Z*)-**6h**, 86969-55-3; **7a**, 74458-30-3; **7b**, 74458-31-4; **7c**, 74458-33-6; **7d**, 74458-36-9; **7j**, 86969-47-3; **8**, 74458-38-1; **9**, 74458-39-2; **10**, 74458-37-0; **11**, 86969-38-2; **12e**, 86969-39-3; **12f**, 86969-40-6; **12g**, 86969-41-7; **12h**, 86969-43-9; **12i**, 86969-45-1; **13g**, 86969-42-8; **13h**, 86969-44-0; **13i**, 86969-46-2; **14a**, 86969-61-1; **14b**, 86969-62-2; **15a**, 86969-63-3; **15b**, 86969-64-4; **16b**, 86969-65-5; **16c**, 86969-75-7; **17a**, 86993-46-6; **17b**, 86969-66-6; **17c**, 86969-67-7; **18**, 86969-68-8; (*E,E*)-**19a**, 86969-57-5; (*Z,E*)-**19a**, 86969-56-4; (*E,E*)-**19b**, 86969-58-6; (*Z,E*)-**19b**, 86969-59-7; (*Z,E*)-**19c**, 86969-60-0; (*Z,Z*)-**19c**, 86969-76-8; **20a**, 86969-69-9; **20b**, 86993-47-7; **20c**, 86969-70-2; **21**, 74458-42-7; **22**, 74458-40-5; **23**, 86969-71-3; **24**, 74458-41-6; **25**, 86969-72-4; **26**, 86969-73-5.

Supplementary Material Available: Mass spectral data for compounds **7**, **9**, and **14–20** (1 page). Ordering information is given on any current masthead page.

Novel Synthesis of the Pyrrolizidine Skeleton by Sulfenocycloamination. Total Synthesis of (±)-Retronecine and (±)-Turneforcidine†

Tatsushi Ohsawa, Masataka Ihara, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Tetsuji Kametani*

Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

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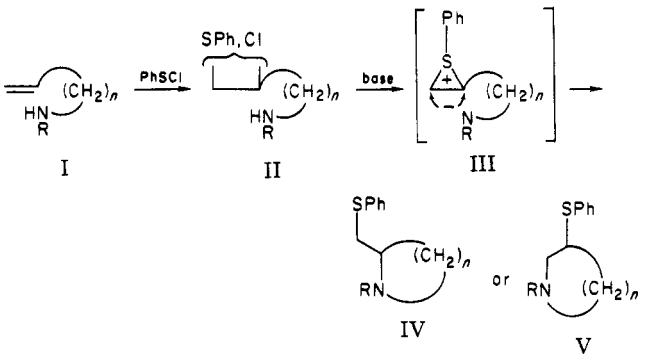
The ω-unsaturated amines **1**, **6**, and **7** were converted into pyrrolidines **4** and **8** and piperidine **9**, respectively, by treatment of their hydrochlorides with benzenesulfenyl chloride followed by base-induced ring closure. This novel sulfenocycloamination ring closure was applied to the synthesis of the pyrrolizidine ring (e.g., **20**) and to the total synthesis of (±)-retronecine (**32**) and (±)-turneforcidine (**34**).

In the past decade several new methods for forming C–N bonds have been devised. For example, ring closures of suitably substituted amines to nitrogen heterocycles have been effected by palladium chloride,[1] benzeneselenyl chloride,[2] mercuric acetate,[3,4] and sodium hydride–cuprous halides.[5] In our investigation of C–N bond-forming reactions we have focused on the use of benzenesulfenyl halides because of their strong electrophilicity for double bonds[6–8] and their ready availability. We now report on the cyclization of some ω-unsaturated alkenylamines (I), as shown in Scheme I. The ring closure, which can be called "sulfenocycloamination", probably proceeds via an *epi*-sulfonium ion III. We also report the application of this ring closure to a facile and efficient synthesis of the pyrrolizidine ring system,[9] culminating in the total synthesis of (±)-retronecine and (±)-turneforcidine.[10]

Sulfenocycloamination. As shown in Scheme I, there are two possibilities for ring formation: endo and exo cyclization. We examined these possibilities by running the sulfenocycloamination on amines with different chain lengths between the nitrogen and the olefinic group. In the reaction of benzenesulfenyl chloride with 3-butenylaniline (**1**),[11] (all reactions of benzenesulfenyl chloride were carried out on the amine hydrochlorides to avoid reaction with the basic amino nitrogen), a mixture of adducts **2a** and **2b** (Scheme II) was formed. Treatment of this mixture with potassium carbonate and sodium iodide gave the single product **4** in 90% overall yield. The reaction proceeds entirely by endo ring closure; there was no evidence for a four-membered ring product that would have resulted from exo closure. The fact that both **2a** and **2b** were converted into **4** is evidence for the common *epi*-sulfonium ion intermediate **3**. Although sodium iodide was not essential in the ring closure, the reaction was sluggish in its absence. Potassium hydroxide in benzene–water with tetrabutylammonium bromide as a phase-transfer catalyst[8] was examined in the ring closure, but the reaction did not give a clean result. The five-membered-ring structure of

Scheme I



† All compounds reported in this paper are racemic. For convenience, only one enantiomer is shown.

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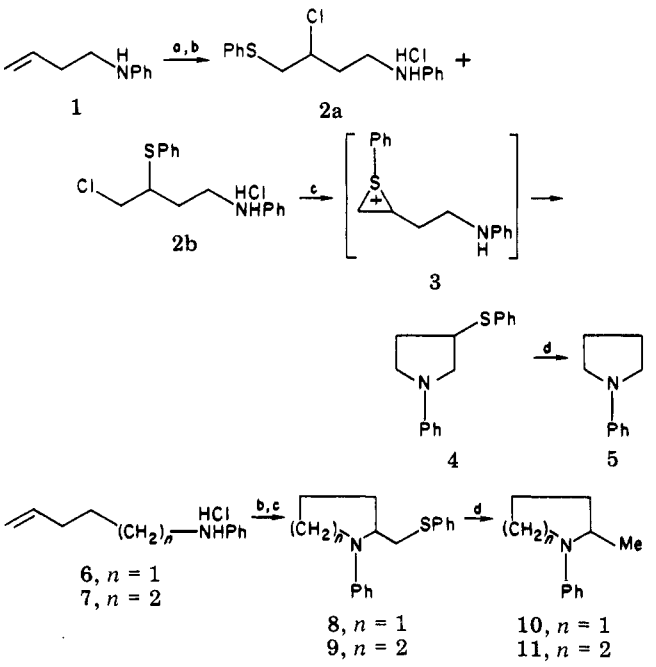
Scheme II[a]



[a] (a) HCl, MeOH, Et_2O; (b) PhSCl, CH_2Cl_2; (c) K_2CO_3, NaI, MeCN; (d) Raney nickel (W_2), EtOH.

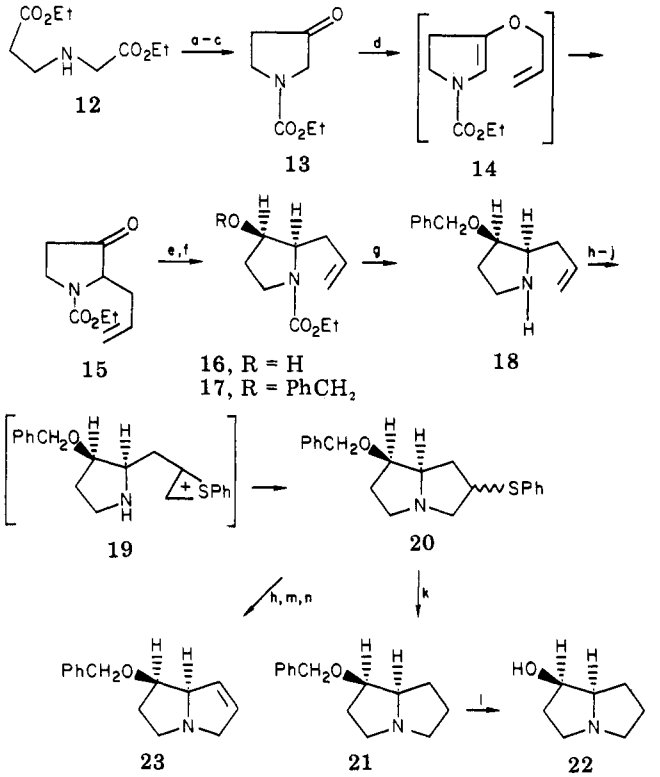
4 was confirmed by converting it to the known compound 5[12] by reductive desulfurization with Raney nickel.

On the other hand, similar sulfenocycloamination of the longer chain amines 6 and 7[13] gave as single products the pyrrolidine 8 and the piperidine 9, respectively. The reactions reflect exclusive exo ring closure; the corresponding six- and seven-membered products of endo ring closure were not detected. The structures of 8 and 9 were confirmed by reductive desulfurization with Raney nickel to give 2-methylpyrrolidine (10)[14] and 2-methylpiperidine (11),[13] respectively.

Synthesis of the Pyrrolizidine Skeleton by Sulfenocycloamination. We applied the sulfenocycloamination reaction to the construction of a pyrrolizidine ring system[15] as a model study and then to the total synthesis of (±)-retronecine and (±)-turneforcidine. The key to the synthesis of amino olefin 18, which was the substrate for sulfenocycloamination, was a [3,3] sigmatropic rearrangement[16] in the formation of 15 from 13. The reaction sequence of our model study is shown in Scheme III.

Refluxing the 3-pyrrolidinone 13 in xylene with allyl alcohol in the presence of a catalytic amount of camphorsulfonic acid and anhydrous sodium sulfate[16] furnished, probably through an allyl enol ether intermediate, 14, the single product 15 in 27% conversion and 86% yield, based on unrecovered 13. The structure of 15 was based on spectral data, including the observation that the ^1H NMR signal of one of the C-2 hydrogens in 13 was not present in the spectrum of 15. Ketone 15 was reduced stereoselectively with sodium borohydride to alcohol 16 in 62% yield. The stereochemistry of 16 was assumed to be cis, which was confirmed by its conversion into the

Scheme III[a]



[a] (a) $ClCO_2Et$, K_2CO_3, $CHCl_3$; (b) NaOEt, PhH; (c) 10% H_2SO_4, EtOH; (d) HO⟋⟋, CSA, xylene, Na_2SO_4; (e) $NaBH_4$, MeOH; (f) $PhCH_2Br$, NaH, DMF; (g) KOH, diethylene glycol; (h) HCl, Et_2O, MeOH; (i) PhSCl, CH_2Cl_2; (j) K_2CO_3, NaI, MeCN; (k) Raney nickel, EtOH; (l) $PdCl_2$, H_2, MeOH-$CHCl_3$; (m) MCPBA, CH_2Cl_2; (n) Δ, xylene.

known pyrrolizidine 22.[17] After conversion of 16 into the benzyl ether 17 by reaction with benzyl bromide and sodium hydride in 79% yield, the carbamate group was hydrolyzed with potassium hydroxide in diethylene glycol to give the olefinic amine 18 in 86% yield.

Sulfenocycloamination of 18 was effected by treating its hydrochloride with benzenesulfenyl chloride in methylene chloride at 0 °C, followed by cyclization with potassium carbonate and sodium iodide in acetonitrile to give the pyrrolizidine 20 as a mixture of two stereoisomers in 55% yield. The phenylthio group was easily removed with Raney nickel to afford in 92% yield the benzyl ether 21. This compound was debenzylated by hydrogenolysis over palladium chloride to furnish *cis*-1(1*H*,8*H*)-hydroxypyrrolizidine (22) in 88% yield. The spectral data of 22 were identical with those of authentic material prepared by a known method.[17] Moreover, the hydrochloride of 20 could be converted into the olefinic compound 23 in a yield of 25% by treatment with *m*-chloroperbenzoic acid in methylene chloride at −20 °C, followed by refluxing in xylene under argon.

Synthesis of (±)-Retronecine and (±)-Turneforcidine. Retronecine (32) is a necine base of several pyrrolizidine alkaloids,[15a] and its total synthesis in racemic form has been reported by four groups.[18] On the other hand, total synthesis of turneforcidine (34), a necine base of turneforcine isolated by a Russian group,[19] has not been

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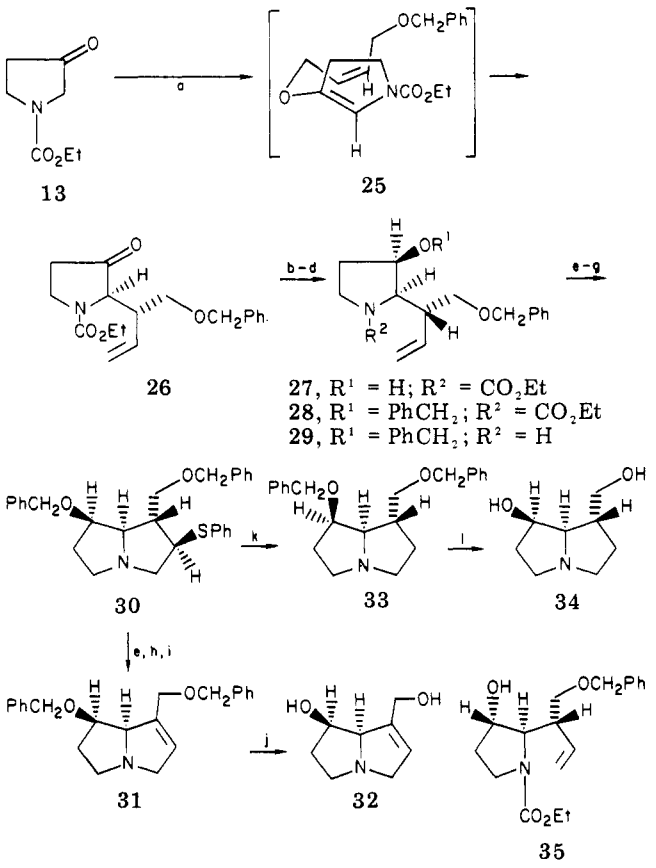
Scheme IV[a]



[a] (a) TsOH (catalyst), Na_2SO_4, xylene; (b) $NaBH_4$, MeOH; (c) NaH, $PhCH_2Br$, THF; (d) KOH, diethylene glycol; (e) HCl, Et_2O, MeOH; (f) PhSCl, CH_2Cl_2; (g) K_2CO_3, NaI, MeCN; (h) MCPBA, CH_2Cl_2; (i) Δ, xylene; (j) Li, liquid NH_3, THF; (k) Raney nickel, EtOH; (l) H_2, $PdCl_2$, MeOH-$CHCl_3$.

reported. We have applied our methodology to the syntheses of these two necine bases. The reaction sequences are shown in Scheme IV.

The 3-pyrrolidinone **13** was treated with the *cis*-butenediol derivative **24**[3] in the presence of a catalytic amount of *p*-toluenesulfonic acid and anhydrous sodium sulfate with azeotropic removal of water to give the ketone **26** in 77% yield in a regio- and stereoselective reaction that presumably proceeded via a chairlike transition state, **25**. The stereochemical relationship between C-2 and C-1′ of **26** was confirmed by its conversion into (±)-turneforcidine (**34**). In this case, reaction with *p*-toluenesulfonic acid as a catalyst gave a better result than that with camphorsulfonic acid. Subsequently, **26** was converted into the olefinic amine **29** by the same sequence used for **15** → **18** (Scheme III). Although the attack of hydride in the reduction of **26** occurred mainly on the less hindered side to give **27** (77% yield), a minor amount (10%) of the epimer **35** was also obtained.

The hydrochloride of **29** was treated with benzenesulfenyl chloride, followed by potassium carbonate and sodium iodide, to give the sulfide **30** as the single isomer in 72% yield. The stereochemistry of the phenylsulfenyl group was assumed from a kinetic consideration of the addition reaction and was supported by the ease of syn elimination of the corresponding sulfoxide. Thus, the hydrochloride of **30** was treated with *m*-chloroperbenzoic acid to afford the sulfoxide, which then underwent syn elimination on refluxing in xylene to furnish the olefin **31** in a yield of 30%. Olefin **31** was debenzylated with lithium in liquid ammonia and tetrahydrofuran[18d] at −33 °C to afford (±)-retronecine (**32**), whose IR and ^1H NMR spectra were superimposable on those of natural retronecine.

Desulfurization of **30** with Raney nickel in refluxing ethanol gave in 96% yield the dibenzyl ether **33**, which was debenzylated by catalytic hydrogenolysis to furnish (±)-turneforcidine (**34**) in 94% yield. Its NMR spectrum was identical with that of the authentic compound.[20]

Experimental Section

IR spectra were taken with a Hitachi 260-10 spectrophotometer and NMR spectra with JEOL PMX-60 and JEOL PS-100 spectrometers. Ordinary mass spectra were obtained with a Hitachi M-52G, and high-resolution mass spectra were taken with a JEOL JMS-01SG-2 spectrometer.

***N*-(Pent-4-enyl)aniline (6).** *N*-(Pent-4-enoyl)aniline[21] (1.8 g, 10.3 mmol) was reduced with $LiAlH_4$ in ether, and the product was purified by chromatography on silica gel with *n*-hexane/benzene (50:50 v/v) as the eluant. Amine **6** (1.56 g, 94%) was obtained as an oil: ^1H NMR (CCl_4) δ 3.07 (2 H, t, J = 7 Hz, 1-CH_2), 3.33 (1 H, br s, NH), 4.73–5.17 (2 H, m, CH=CH_2), 5.42–6.10 (1 H, m, C*H*=CH_2), 6.27–6.66 (3 H, m, 2′,4′,6′-H), 6.80–7.17 (2 H, m, 3′,5′-H); mass spectrum, m/z 161 (M^+). Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.77; H, 9.25; N, 8.45.

Sulfenocycloamination. Preparation of 4, 8, and 9. The amine (**1, 6, 7**) was converted into its hydrochloride by treatment with ethereal HCl solution in MeOH at 0 °C. The hydrochloride (2.5 mmol) dissolved in 5–25 mL of CH_2Cl_2 was treated with benzenesulfenyl chloride (1.35 molar equiv) at 0 °C for 15 min. The solvent was evaporated and the residue chromatographed on silica gel with $CHCl_3$/MeOH (98:2 v/v) as the eluant. The resulting adduct hydrochlorides were dissolved in 30 mL of CH_3CN, K_2CO_3 (1.5 g, 10.9 mmol) and NaI (1.5 g, 10.0 mmol) were added, and the mixture was refluxed for 1.5 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to give a residue that was chromatographed on silica gel with *n*-hexane/benzene (4:1 v/v) as the eluant.

(±)-1-Phenyl-3-(phenylthio)pyrrolidine (4): oil; 90%; ^1H NMR (CCl_4) δ 1.63–2.60 (2 H, m, 4-CH_2), 6.27–6.73 (3 H, m, 2′,4′,6′-H), 6.83–7.43 (7 H, m, 3′,5′-H and SPh); mass spectrum, m/z 255 (M^+). Anal. Calcd for $C_{16}H_{17}NS$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.46; H, 6.73; N, 5.39.

(±)-1-Phenyl-2-[(phenylthio)methyl]pyrrolidine (8): oil; 76%; ^1H NMR (CCl_4) δ 3.57–4.00 (1 H, m, 2-CH), 6.13–7.50 (10 H, m, SPh and NPh); mass spectrum, m/z 269 (M^+). Anal. Calcd for $C_{17}H_{19}NS$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.55; H, 7.18; N, 5.05.

(±)-1-Phenyl-2-[(phenylthio)methyl]piperidine (9): oil; 64%; ^1H NMR (CCl_4) δ 3.53–4.07 (1 H, m, 2-CH), 6.53–7.47 (10 H, m, SPh and NPh); mass spectrum, m/z 283 (M^+). Anal. Calcd for $C_{18}H_{21}NS$: N, 4.94. Found: N, 4.98.

Elimination of the Phenylthio Group (5, 10, 11). The sulfide (**4, 8,** or **9**; 0.7 mmol) was treated with W_2 Raney nickel (1.5 g) in 10 mL of ethanol under reflux for 30 min. The catalyst was removed by filtration, the solvent evaporated, and the residue chromatographed on silica gel with *n*-hexane/benzene (4:1 v/v) as the eluant.

1-Phenylpyrrolidine (5) was obtained as an oil (57%) with spectral data identical with those of an authentic sample.[12]

(±)-2-Methyl-1-phenylpyrrolidine (10): oil; 73%; ^1H NMR (CCl_4) δ 1.15 (3 H, d, J = 7 Hz, 2-CH_3), 2.73–3.57 (2 H, m, 5-CH_2), 3.63–4.10 (1 H, m, 2-CH), 6.30–6.67 (3 H, m, 2′,4′,6′-H), 6.87–7.30

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(2 H, m, 3′,5′-H); mass spectrum, m/z 161 (M^+); picrate (ethanol) mp 122–123 °C (lit.[14] mp 132 °C).

(±)-2-Methyl-1-phenylpiperidine (11): oil; 82%; ^1H NMR (CCl_4) δ 0.92 (3 H, d, J = 7 Hz, 2-CH_3), 2.53–3.33 (2 H, m, 6-CH_2), 3.50–4.03 (1 H, m, 2-CH), 6.53–7.30 (5 H, m, NPh); mass spectrum, m/z 175 (M^+); picrate (ethanol) mp 164–165 °C (lit.[13] mp 166.8–167.2 °C).

1-(Ethoxycarbonyl)-3-pyrrolidinone (13) was prepared from **12** (Scheme III) in 59% yield (cf. ref 22 and 23).

(±)-1-(Ethoxycarbonyl)-2-(prop-1-en-3-yl)pyrrolidin-3-one (15). A mixture of **13** (10.17 g, 64.8 mmol), allyl alcohol (10.2 g, 176 mmol), D-camphor-10-sulfonic acid (400 mg), and anhydrous sodium sulfate (25 g) in xylene (200 mL) was refluxed for 20 h. The sodium sulfate was removed by filtration and the filtrate evaporated to give a residue that was chromatographed on silica gel. Elution with benzene/acetone (98.5:1.5 v/v) gave **15**: 3.43 g (27% conversion, 86% yield based on unrecovered **13**); colorless oil; IR ($CHCl_3$) 1760, 1690 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.27 (3 H, t, J = 7 Hz, OCH_2CH_3), 4.13 (2 H, q, J = 7 Hz, OCH_2CH_3), 4.83–6.10 (3 H, m, CH=CH_2); mass spectrum, m/z 198 (M^+ + 1). Anal. Calcd for $C_{10}H_{15}NO_3 \cdot 0.25H_2O$: C, 59.53; H, 7.74; N, 6.94. Found: C, 59.57; H, 7.70; N, 6.86. Elution of the column with benzene/acetone (98:2 v/v) afforded 6.98 g of recovered **13**.

(±)-1-(Ethoxycarbonyl)-3β-hydroxy-2β-(prop-1-en-3-yl)-pyrrolidine (16). To a stirred solution of **15** (1.7 g, 8.6 mmol) in methanol (30 mL) was added sodium borohydride (200 mg, 5.4 mmol) in small portions at 0 °C. The resulting mixture was stirred at room temperature for 30 min and evaporated to give a residue, which was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give a residue, which was chromatographed on silica gel with benzene/acetone (96:4 v/v) as an eluant, giving **16**: 1.06 g (62%); oil; IR ($CHCl_3$) 1700 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.25 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.73–2.17 (2 H, m, 4-CH_2), 4.10 (2 H, q, J = 7 Hz, OCH_2CH_3), 4.83–5.37 (2 H, m, CH=CH_2), 5.57–6.30 (1 H, m, CH=CH_2); mass spectrum, m/z 200 (M^+ + 1). Anal. Calcd for $C_{10}H_{17}NO_3$: N, 7.03. Found: N, 6.80.

(±)-3β-(Benzyloxy)-1-(ethoxycarbonyl)-2β-(prop-1-en-3-yl)pyrrolidine (17). After a mixture of **16** (1.9 g, 9.5 mmol) and 60% sodium hydride (640 mg, 16.7 mmol) in dimethylformamide (20 mL) was stirred at room temperature, a solution of benzyl bromide (2.2 g, 12.9 mmol) in dimethylformamide (5 mL) was introduced, and the reaction mixture was stirred at room temperature for 1 h. Excess crystalline ammonium chloride was added to the mixture, which was then extracted with benzene. The extract was washed with aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to afford a residue, which was chromatographed on silica gel. Elution with benzene/acetone (99:1 v/v) furnished the benzyl ether **17**: 2.19 g (79%); colorless oil; IR ($CHCl_3$) 1690 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.70–2.17 (2 H, m, 4-CH_2) 2.20–2.67 (2 H, m, 2′-CH_2), 3.17–3.53 (2 H, t, J = 8 Hz, 5-CH_2), 4.48 (2 H, s, OCH_2Ph), 4.80–5.23 (2 H, m, CH=CH_2), 5.43–6.23 (1 H, m, CH=CH_2), 7.23 (5 H, br s, OCH_2Ph); mass spectrum, m/z 290 (M^+ + 1). Anal. Calcd for $C_{17}H_{23}NO_3$; C, 70.56; H, 8.01; N, 4.84. Found: C, 70.42; H, 8.03; N, 4.75.

(±)-3β-(Benzyloxy)-2β-(prop-1-en-3-yl)pyrrolidine (18). A mixture of **17** (3.41 g, 11.8 mmol) and potassium hydroxide (2 g, 41 mmol) in diethylene glycol (50 mL) was heated under reflux for 15 h and, after cooling, poured into saturated ammonium chloride solution. The product was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give the crude product, which was purified by chromatography on silica gel, eluting with chloroform/methanol (95:5 v/v) to afford the amine **18**: 2.21 g (86%); viscous oil; ^1H NMR ($CDCl_3$) δ 4.33 and 4.60 (each 1 H, each d, each J = 12 Hz, OCH_2Ph), 4.87–6.27 (3 H, m, CH=CH_2), 7.30 (5 H, s, OCH_2Ph); mass spectrum, m/z 218 (M^+ + 1). Anal. Calcd for $C_{14}H_{19}NO \cdot 0.25H_2O$: C, 75.81; H, 8.86; N, 6.31. Found: C, 75.31; H, 8.88; N, 6.02.

(±)-*cis*-1β(1*H*,8*H*)-(Benzyloxy)-6α- and -6β-(phenylthio)pyrrolizidine (20). The hydrochloride of **18** (1 g, 4.6 mmol), prepared with ethereal hydrogen chloride solution in methanol at 0 °C, was treated with benzenesulfenyl chloride (1 g, 7 mmol) in methylene chloride (50 mL) at 0 °C under stirring for 15 min. After evaporation of the solvent, the residue was chromatographed on silica gel with chloroform/methanol (98:2 v/v) as an eluant to give a mixture of the adducts, which was reacted with potassium carbonate (1.9 g, 13.8 mmol) and sodium iodide (1.38 g, 9.2 mmol) in refluxing acetonitrile (30 mL) for 1 h. Evaporation of the solvent afforded a residue, which was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give a residue, which was purified by chromatography on silica gel, eluting with chloroform/methanol (98:2 v/v) to afford the sulfide **20** as a mixture of stereoisomers: 820 mg (55%); ^1H NMR ($CDCl_3$) δ 4.23–4.77 (2 H, m, OCH_2Ph), 6.73–7.57 (10 H, m, OCH_2Ph and S*Ph*); mass spectrum, m/z 325 (M^+). Anal. Calcd for $C_{20}H_{23}NOS$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.34; H, 6.97; N, 4.11.

(±)-*cis*-1(1*H*,8*H*)-(Benzyloxy)pyrrolizidine (21). The sulfide **20** (400 mg, 1.23 mmol) in ethanol (15 mL) was refluxed with Raney nickel (W_2, 3 g) under a nitrogen atmosphere for 1 h. The Raney nickel was filtered off, and the filtrate was evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with chloroform/methanol (97:3 v/v) gave the benzyloxy compound **21**: 245 mg (92%); viscous syrup; ^1H NMR ($CDCl_3$) δ 4.45 and 4.68 (each 1 H, each d, each J = 12 Hz, OCH_2Ph), 7.33 (5 H, s, OCH_2Ph); mass spectrum, m/z 337 (M^+); exact mass calcd for $C_{14}H_{19}NO$ 217.1465, found 217.1445.

(±)-*cis*-1(1*H*,8*H*)-Hydroxypyrrolizidine (22). A mixture of the benzyloxy compound **21** (245 mg, 1.13 mmol) and palladium chloride (100 mg) in methanol (10 mL) and chloroform (1 mL) was stirred under a hydrogen atmosphere at room temperature for 12 h. The catalyst was filtered off, and the filtrate was evaporated to give a residue, which was chromatographed on alumina (grade III). Elution with chloroform/methanol (90:10 v/v) afforded the hydroxy compound **22** (125 mg, 88%) as a viscous syrup, the NMR spectrum of which was identical with that of an authentic sample.[17]

(±)-*cis*-1(1*H*,8*H*)-(Benzyloxy)-1,2,3,8-tetrahydro-5*H*-pyrrolizine (23). To a stirred solution of the hydrochloride of the sulfide **20** (55 mg, 0.17 mmol), prepared with ethereal hydrogen chloride in methanol at 0 °C, in methylene chloride (5 mL) was added 70% *m*-chloroperbenzoic acid (42 mg, 0.17 mmol) in one portion at −20 °C, and the resulting mixture was stirred at the same temperature for 5 min. After addition of 10% potassium hydroxide solution (5 mL), the reaction mixture was extracted with methylene chloride. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give a residue, which was dissolved in xylene (5 mL). After heating under reflux for 1 h, the solvent was evaporated to afford a residue, which was chromatographed on silica gel with chloroform/methanol (97.5:2.5 v/v) as eluant, giving **23** (9 mg, 25%): ^1H NMR ($CDCl_3$) δ 4.47 (2H, s, OCH_2Ph), 5.73 (2H, s, -CH=CH-), 7.20 (5H, s, OCH_2Ph); mass spectrum m/z 215 (M^+); exact mass calcd for $C_{14}H_{17}NO$ 215.1311, found: 215.1312.

(±)-2(*R)-[3(*R**)-[4-(Benzyloxy)but-1-enyl]]-1-(ethoxycarbonyl)pyrrolidin-3-one (26).** A mixture of the 3-pyrrolidinone **13** (1.9 g, 12.1 mmol), the *cis*-2-butenediol derivative[3] **24** (3.5 g, 19.7 mmol), *p*-toluenesulfonic acid (300 mg), and anhydrous sodium sulfate (10 g) in xylene (80 mL) was refluxed for 8 h with a Dean–Stark apparatus. After the mixture cooled, the sodium sulfate was filtered off, and the filtrate was evaporated to give a residue, which was purified by chromatography on silica gel. Elution with benzene/acetone (98.5:1.5 v/v) afforded compound **26**: 2.96 g (77%); pale yellow oil; IR ($CHCl_3$) 1750, 1690 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (3 H, t, J = 7 Hz, OCH_2CH_3), 2.10–2.50 (2 H, m, 4-CH_2), 4.40 (2 H, s, OCH_2Ph), 4.87–5.33 (2 H, m, CH=CH_2), 5.50–6.30 (1 H, m, CH=CH_2), 7.20 (5 H, s, OCH_2Ph); mass spectrum, m/z 318 (M^+ + 1). Anal. Calcd for $C_{18}H_{23}NO_4 \cdot 0.25H_2O$: C, 67.16; H, 7.35; N, 4.35. Found: C, 67.44; H, 7.31; N, 4.37.

(±)-2(*R)-[3(*R**)-[4-(Benzyloxy)but-1-enyl]]-1-(ethoxycarbonyl)-3(*R**)-hydroxypyrrolidine (27).** To a solution of **26** (5.87 g, 18.5 mmol) in methanol (100 mL) was added sodium borohydride (1 g, 26.3 mmol) in small portions at room temperature. After the mixture was stirred at room temperature for 10 min, the solvent was evaporated to give a residue, which was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give a residue, which was chromatographed

on silica gel with benzene/acetone (97.5:2.5 v/v) as the eluant, affording (±)-2(*R**)-[3(*R**)-[4-(benzyloxy)but-1-enyl]]-1-(ethoxycarbonyl)-3(*S**)-hydroxypyrrolidine (**35**): 560 mg (10%); oil; IR ($CHCl_3$) 1690 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (3 H, t, J = 7 Hz, OCH_2CH_3), 4.05 (2 H, q, J = 7 Hz, OCH_2CH_3), 4.50 (2 H, s, OCH_2Ph), 4.77–6.50 (3 H, m, $CH{=}CH_2$), 7.27 (5 H, s, OCH_2Ph); mass spectrum, m/z 320 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67,69; H, 7.89; N, 4.39. Found: C, 67.43; H, 7.91; N, 4.10. Further elution with benzene/acetone (97:3 v/v) gave the isomeric 3(*R**)-hydroxypyrrolidine **27**: 4.53 g (77%); oil; IR ($CHCl_3$) 1680 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.17 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.62–2.08 (2 H, m, 4-CH_2), 4.45 (2 H, s, OCH_2Ph), 4.87–5.27 (2 H, m, $CH{=}CH_2$), 5.47–6.27 (1 H, m, $CH{=}CH_2$), 7.23 (5 H, s, OCH_2Ph); mass spectrum, m/z 320 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{25}NO_4{\cdot}0.5H_2O$: C, 65.28; H, 7.98; N, 4.27. Found: C, 65.93; H, 7.75; N, 4.45.

(±)-3(*R)-(Benzyloxy)-2(*R**)-[3(*R**)-[4-(benzyloxy)but-1-enyl]]-1-(ethoxycarbonyl)pyrrolidine (28).** After a mixture of **27** (2.45 g, 7.7 mmol) and 60% sodium hydride (430 mg, 10.7 mmol) in tetrahydrofuran (50 mL) was refluxed, a solution of benzyl bromide (2 g 11.7 mmol) in tetrahydrofuran (5 mL) was introduced, and the resulting mixture was stirred under reflux for 1 h. After addition of excess crystalline ammonium chloride, the mixture was extracted with benzene. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to afford a residue, which was chromatographed on silica gel with benzene/acetone (99:1 v/v) as an eluant, affording the benzyl ether **28**: 2.55 g (81%); oil; IR ($CHCl_3$) 1690 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.19 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.77–2.22 (2 H, m, 4-CH_2), 4.23–4.70 (4 H, m, $2OCH_2Ph$), 4.85–6.07 (3 H, m, $CH{=}CH_2$), 6.83–7.50 (10 H, m, $2OCH_2Ph$); mass spectrum, m/z 409 (M^+). Anal. Calcd for $C_{25}H_{31}NO_4{\cdot}0.5H_2O$: C, 71.74; H, 7.71; N, 3.34. Found: C, 71.89; H, 7.53; N, 3.30.

(±)-3(*R)-(Benzyloxy)-2(*R**)-[3(*R**)-[4-(benzyloxy)but-1-enyl]]pyrrolidine (29).** A mixture of **28** (2.45 g, 6.0 mmol) and potassium hydroxide (1.5 g, 23.3 mmol) in diethylene glycol (20 mL) was heated under reflux for 15 h and, after cooling, poured into saturated ammonium chloride solution. After extraction with chloroform, the extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent, followed by chromatography on silica gel with chloroform/methanol (95:5 v/v) as the eluant gave the amine **29**: 1.87 g (92%); viscous oil; ^1H NMR ($CDCl_3$) δ 4.15 and 4.50 (each 1 H, each d, each J = 12 Hz, OCH_2Ph), 4.40 (2 H, s, OCH_2Ph), 4.97–5.40 (2 H, m, $CH{=}CH_2$), 5.63–6.30 (1 H, m, $CH{=}CH_2$), 7.23 (10 H, s, $2OCH_2Ph$); mass spectrum, m/z 338 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{27}NO_2{\cdot}0.25H_2O$: C, 77.26; H, 8.11; N, 4.09. Found: C, 77.31; H, 7.98; N, 3.95.

(±)-*cis*-1β(1*H*,8*H*)-(Benzyloxy)-7α-[(benzyloxy)methyl]-6β-(phenylthio)pyrrolizidine (30). To a solution of the hydrochloride of **29** (1.7 g, 5.04 mmol), prepared as described for **18**, in methylene chloride (20 mL) was added benzenesulfenyl chloride (750 mg, 5.26 mmol) in methylene chloride (5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and then evaporated to give a residue, which was purified by chromatography on silica gel with chloroform/methanol (97:3 v/v) as the eluant, giving the adducts which were dissolved in acetonitrile (30 mL). The resulting solution was treated with potassium carbonate (2 g, 14.5 mmol) and sodium iodide (2 g, 13.3 mmol) under reflux for 30 min and evaporated. The residue was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give a residue, which was chromatographed on silica gel. Elution with chloroform/methanol (98:2 v/v) gave the sulfide **30**: 1.16 g (72%), viscous oil; ^1H NMR ($CDCl_3$) δ 4.35 and 4.60 (each d, each 1 H, each J = 12 Hz, OCH_2Ph), 4.43 (2 H, s, OCH_2Ph), 6.97–7.67 (15 H, m, $2OCH_2Ph$ and SPh); mass spectrum, m/z 445 (M^+). Anal. Calcd for $C_{27}H_{29}NO_2S$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.42; H, 7.01; N, 3.03.

(±)-*cis*-1β(1*H*,8*H*)-(Benzyloxy)-7α-[(benzyloxy)methyl]-pyrrolizidine (33). The sulfide **30** (250 mg, 0.56 mmol) was refluxed with Raney nickel (W_2, 2 g) in ethanol (10 mL) for 1.5 h under nitrogen. The catalyst was filtered off, and the filtrate was evaporated to give a residue, which was chromatographed on silica gel with chloroform/methanol (97.5:2.5 v/v), affording the dibenzyl ether **33**: 186 mg (95%); ^1H NMR ($CDCl_3$) δ 4.43 and 4.63 (each 1 H, each d, each J = 11 Hz, OCH_2Ph), 4.50 (2 H, s, OCH_2Ph), 7.27 (10 H, s, $2OCH_2Ph$); mass spectrum, m/z 337 (M^+); exact mass calcd for $C_{22}H_{27}NO_2$ 337.2040, found 337.2032.

(±)-Turneforcidine (34). A mixture of **33** (186 mg, 0.55 mmol) and palladium chloride (100 mg) in methanol (25 mL) and chloroform (1 mL) was stirred at room temperature under a hydrogen atmosphere for 12 h. The catalyst was filtered off, and the filtrate was evaporated to give a residue, which was purified by chromatography on alumina (grade III) with chloroform/methanol (90:10 v/v) as the eluant, affording (±)-turneforcidine (**34**; 81 mg, 93%) as a viscous oil, whose NMR spectrum was superimposable on the reported one[20] of natural turneforcidine.

(±)-*cis*-1(1*H*,8*H*)-(Benzyloxy)-7-[(benzyloxy)methyl]-2,3,4,8-tetrahydropyrrolizine (31). To a stirred solution of the hydrochloride of the sulfide **30** (600 mg, 1.35 mmol) in methylene chloride (30 mL) was added 70% *m*-chloroperbenzoic acid (335 mg, 1.36 mmol) in one portion at −20 °C, and the mixture was stirred for 15 min at the same temperature. After addition of 10% potassium hydroxide solution, the organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give the crude sulfoxide, which was dissolved in xylene (20 mL). The solution was heated under reflux for 30 min under an argon atmosphere. After evaporation of the solvent, the resulting residue was chromatographed on silica gel. Elution with chloroform/methanol (96:4 v/v) afforded the olefinic compound **31**: 139 mg (30%); viscous oil; ^1H NMR ($CDCl_3$) δ 4.28 and 4.53 (each 1 H, each d, each J = 13 Hz, OCH_2Ph), 4.47 (2 H, s, OCH_2Ph), 5.65 (1 H, br s, $CH_2CH{=}$), 7.20 and 7.23 (each 5 H, each s, $2OCH_2Ph$); mass spectrum, m/z 335 (M^+); exact mass calcd for $C_{22}H_{25}NO_2$ 335.1884, found 335.1878.

(±)-Retronecine (32). After **31** (120 mg, 0.36 mmol) was stirred in liquid ammonia (20 mL) and tetrahydrofuran (6 mL) with lithium (25 mg, 3.57 mmol) at −33 °C for 4 h, isoprene (0.5 mL) and crystalline ammonium chloride (1 g) were added to the reaction mixture. Evaporation of the solvent afforded a residue, which was extracted with chloroform/methanol (1:1 v/v). After evaporation of the solvent, the residue was extracted with chloroform. The solvent was removed to give a residue, which was purified by chromatography on alumina (grade III). Elution with chloroform/methanol (80:20 v/v) afforded a crude product, which was recrystallized from acetone to furnish (±)-retronecine (**32**): 25 mg (45%); needles; mp 131–132 °C (lit.[18a] mp 130–131 °C); IR and NMR spectra were identical with those of natural retronecine.

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Registry No. **1**, 29369-71-9; (±)-**4**, 86971-12-2; **5**, 4096-21-3; **6**, 86971-13-3; **6** (free base), 42331-17-9; **7**, 86971-14-4; (±)-**8**, 86971-15-5; (±)-**9**, 86971-16-6; (±)-**10**, 86971-17-7; (±)-**11**, 86971-18-8; **12**, 3783-61-7; **13**, 14891-10-2; (±)-**15**, 83455-91-8; (±)-**16**, 83455-92-9; (±)-**17**, 83455-93-0; (±)-**18**, 86971-19-9; (±)-**20** (isomer 1), 86971-20-2; (±)-**20** (isomer 2), 86971-21-3; (±)-**21**, 83455-96-3; (±)-**22**, 83509-35-7; (±)-**23**, 83455-97-4; **24**, 81028-03-7; (±)-**26**, 83925-25-1; (±)-**27**, 83925-26-2; (±)-**28**, 83925-27-3; (±)-**29**, 83925-28-4; (±)-**30**, 83925-23-9; (±)-**31**, 83925-22-8; (±)-**32**, 73466-19-0; (±)-**33**, 83925-21-7; (±)-**34**, 83946-88-7; (±)-**35**, 86971-22-4; PhSCl, 931-59-9; allyl alcohol, 107-18-6.