Carbamoylmethyl Radical Cyclization: Formal Synthesis of (−)-Trachelanthamidine

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Tributyltin hydride-mediated radical cyclization of the (2*S*)-*N*-(α-chloroacetyl)-2-ethenylpyrrolidines 13a, b and 15 and the bis(phenylthio)acetyl congener 14 derived from (*S*)-prolinol gave (1*R*,7a*S*)-hexahydro-1-methyl-3*H*-pyrrolizin-3-one (17) and its derivatives 16a, b in highly regio- and diastereo-selective manner. This radical cyclization was successfully applied to the formal total synthesis of (−)-trachelanthamidine.

Keywords carbamoylmethyl radical; (*S*)-prolinol; α-chlorosulfide; tributyltin hydride; radical cyclization; 5-*exo*-trig cyclization; diastereoselectivity; pyrrolizidin-3-one; (−)-trachelanthamidine; Barbier–Wieland degradation

During the last decade, the use of radical cyclizations for the construction of nitrogen-containing heterocycles has increased dramatically.[1] Recently, we[2] and others[3] have reported a new entry to γ-butyrolactams **3** by tributyltin hydride (Bu_3SnH)-mediated cyclization of *N*-allyl-α-haloacetamides **1** *via* carbamoylmethyl radicals **2**. One of the striking features of this cyclization is its high 5-*exo* selectivity; only the five-membered lactam **3** (R = Me) is formed even from the 2-methylprop-2-enyl congener **1** (R = Me).[2b] This behavior is in contrast to that of the α-acylamino radicals **4**, which give a mixture of the 5-*exo* **5** and 6-*endo* products **6**, unless appropriate substituents are placed on the double bond.[4] We have now extended the carbamoylmethyl radical cyclization to the synthesis of the optically active pyrrolizidinone ring system using (*S*)-prolinol (**7**) as the starting material.[5]

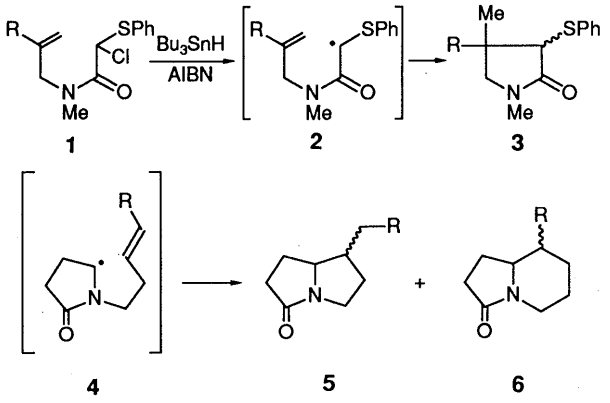

Chart 1

Initially, we set out to examine the diastereoselectivity of the radical cyclization of the α-chloroacetamides **13a, b** and **15**, as well as the bis(phenylthio)acetamide **14**. These compounds were synthesized from (*S*)-prolinol (**7**) as outlined in Chart 2. Thus, oxidation of (*S*)-*N*-ethoxycarbonylprolinol (**8**), readily prepared from **7**, with sulfur trioxide (SO_3)–pyridine in dimethyl sulfoxide (DMSO)–dichloromethane at 0 °C[6] gave the aldehyde **9**[7] in 74% yield. The aldehyde **9** was then converted to the alkene **10** by means of the Wittig reaction with methylenetriphenylphosphorane. Hydrolysis of **10** with potassium hydroxide–hydrazine hydrate in refluxing ethylene glycol[8] followed by treatment of the resulting amine **11** with phenylthio- or methylthio-acetyl chloride or dichloroacetyl chloride gave the corresponding acetamides **12a, b** and **15** in 58, 76, and 72% yields, respectively. Chlorination of **12a, b** with *N*-chlorosuccinimide (NCS) furnished the α-chlorosulfides **13a, b** quantitatively. Treatment of **13a** with sodium benzenethiolate gave the bis(phenylthio)acetamide **14**.

Cyclization of these radical precursors **13a, b** and **14** was effected by treating them with 1.1 molar eq of Bu_3SnH and a catalytic amount of azobisisobutyronitrile (AIBN) in boiling benzene to give the pyrrolizidin-3-ones **16a** (49%), **16b** (60%), and **16a** (67%),[9] along with the reduction products **12a** (13%), **12b** (24%), and **12a** (25%), respectively. Since the products **16a, b** were found to be a mixture of at least three isomers, they were reduced to the pyrrolizidin-3-one **17**[10] by heating with Raney nickel in boiling ethanol in 77 and 93% yields, respectively.

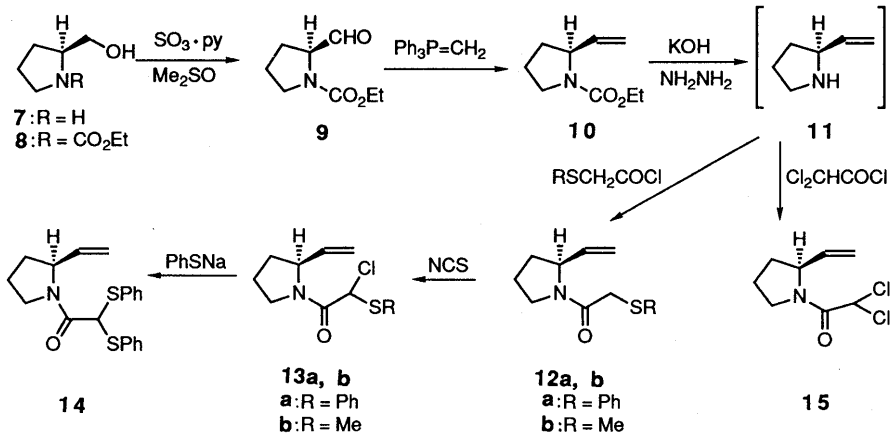

Chart 2

Treatment of the dichloroacetamide **15** with 2.2 molar eq of Bu_3SnH and AIBN directly gave **17** in 56% yield; the reduction product **12a** was not detected in the reaction mixture. An examination of the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum (300 MHz) of **17** thus obtained indicated the presence of a mixture of two diastereomers in a ratio of *exo* : *endo* = > 95 : < 5, irrespective of the precursors. This is in marked contrast to the cyclization of the α-acylamino radicals **4**, which give predominantly the pyrrolizidinones **5** bearing the *endo*-substituent at C-1.[4]

The observed high *exo*/*endo* selectivity could be the result of an attack of the radical center on the double bond *via* a transition state which minimizes steric repulsion between the substituent at C-1 and the C_7–C_{7a} bond of the newly forming pyrrolizidine ring. In view of the high diastereoselectivity of the cyclization of the carbamoylmethyl radicals, we were encouraged to apply this method to the synthesis of (−)-trachelanthamidine (**28**).[11]

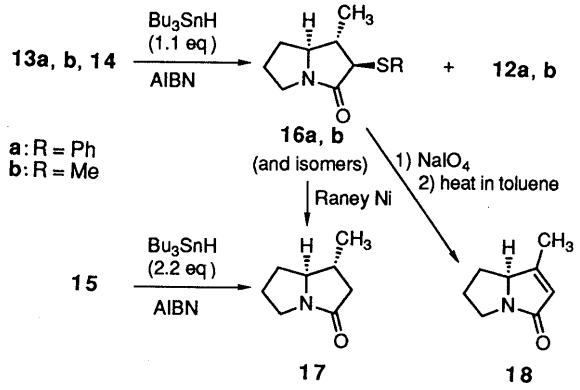

Chart 3

The radical precursor **22** was prepared in a straightforward manner, as outlined in Chart 4. The aldehyde **20**, prepared from (*S*)-prolinol (**7**) by *N*-acylation with phenylthioacetic acid and 1,3-dicyclohexylcarbodiimide (DCC) followed by oxidation of the resulting alcohol **19** with SO_3–pyridine, was treated with triethyl phosphonoacetate in the presence of diisopropylethylamine (DIPEA) and lithium chloride in acetonitrile[12] to afford the unsaturated ester **21** in 84% overall yield from **7**. Chlorination of **21** with NCS gave the α-chlorosulfide **22** in quantitative yield.

Cyclization of **22** with Bu_3SnH (1.1 molar eq) and AIBN in refluxing toluene proceeded very rapidly and cleanly to give the pyrrolizidin-3-one **23** in 77% yield as a mixture of two diastereomers in a ratio of 63 : 37. The reduction product **21** was not detected. Desulfurization of **23** with Raney nickel gave the ester **25** in 79% yield; its ^{1}H-NMR spectrum (300 MHz) showed it to be a single isomer, indicating that the two isomers of **23** differ in the configuration of the phenylthio group. The stereochemical relationship between the ethoxycarbonylmethyl and phenylthio groups of the major isomer of **23** was ascertained by the oxidative *syn* elimination of the thio group. Thus, oxidation of **23** with sodium metaperiodate in aqueous acetone followed by heating of the resulting sulfoxide in toluene gave the unsaturated lactam **24** in 56% yield, along with the unchanged sulfoxide (31%). The optical purity of the lactam **24** was estimated to be approximately 90% [determined by high-performance liquid chromatography (HPLC) on a Chiralcel OD column].[13] The stereochemistry of the ethoxycarbonylmethyl group in **23** was confirmed by its conversion to the known aldehyde **27** (*vide infra*).

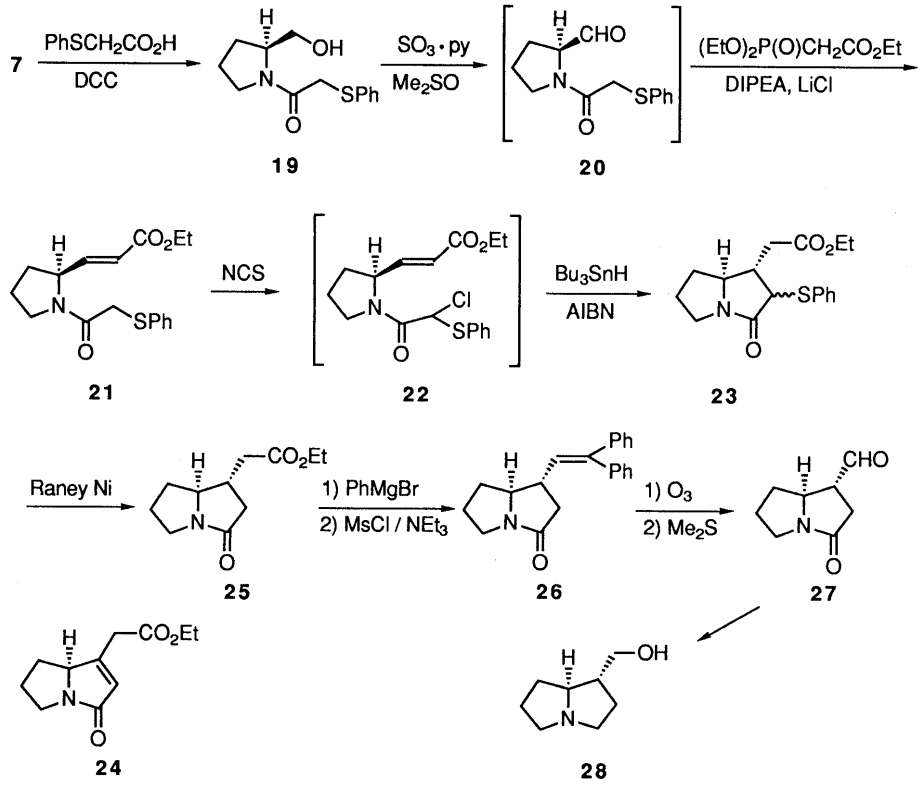

Chart 4

Finally, the ester **25** was converted into the aldehyde **27** by using Barbier–Wieland degradation.[14] Thus, reaction of **25** with excess phenylmagnesium bromide followed by treatment of the resulting alcohol with methanesulfonyl chloride in triethylamine gave the diphenylethene **26** in 69% yield. Ozonolysis of **26** followed by treatment with dimethyl sulfide afforded the aldehyde **27** in 69% yield, and this has already been converted into (−)-trachelanthamidine (**28**) by us.[15]

In summary, the radical cyclization of the *N*-(α-chloroacetyl)- and *N*-[bis(phenylthio)acetyl]-2-ethenylpyrrolidines was found to proceed in a highly regio- and diastereoselective manner to give the (1*R*,7a*S*)-1-methylpyrrolizidine derivatives. Further applications of this reaction to the synthesis of alkaloids are in progress in our laboratory.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer and ^{13}C-NMR spectra with a Varian XL-300 (75 MHz) spectrometer, using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. High-resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Optical rotations were measured with a JASCO DIP-360 polarimeter. Optical purity was determined by using a JASCO HPLC instrument with a ultraviolet (UV) detector (870-UV). Column chromatography was carried out on Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

(*S*)-(−)-1-Ethoxycarbonylpyrrolidine-2-methanol (8) Ethyl chloroformate (12.8 g, 118.6 mmol) was added to a stirred solution of **7** (10.0 g, 98.9 mmol) in 4 N NaOH solution (60 ml) at 0 °C, and the mixture was stirred at the same temperature for 30 min, then at room temperature for 30 min. The reaction mixture was neutralized with 10% HCl and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. The residue was distilled to give **8** (15.6 g, 91%), bp 108 °C (2 mmHg) [lit.[15] bp 160 °C (15 mmHg)], $[\alpha]_D^{24}$ −61.9° (*c*=1.17, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3420, 1680. ^{1}H-NMR (60 MHz) δ: 1.27 (3H, t, *J*=7 Hz), 1.48—2.17 (4H, m), 3.10—3.77 (5H, m), 3.8—4.7 (1H, m), 4.09 (2H, q, *J*=7 Hz).

(*S*)-(−)-1-Ethoxycarbonylpyrrolidine-2-carbaldehyde (9) SO_3–pyridine (36.8 g, 231 mmol) was added portionwise to a solution of **8** (10.0 g, 57.7 mmol) and triethylamine (56.3 ml, 404 mmol) in DMSO (58 ml) and CH_2Cl_2 (6 ml) at 0 °C, and the mixture was stirred at the same temperature for 1 h and diluted with Et_2O. The ethereal solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was distilled at 101 °C (3 mmHg) to give **9** (7.3 g, 74%), $[\alpha]_D^{22}$ −90.80° (*c*=0.25, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1700. ^{1}H-NMR (60 MHz) δ: 1.23 (3H, t, *J*=7 Hz), 1.50—2.33 (4H, m), 3.27—3.73 (2H, m), 4.12 (2H, q, *J*=7 Hz), 3.9—4.4 (1H, m), 9.48 (1H, br s). *Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.92; H, 7.65; N, 8.10.

(*S*)-(−)-2-Ethenyl-1-ethoxycarbonylpyrrolidine (10) DMSO (8 ml) was added to a flask containing NaH (60% mineral oil dispersion) (0.9 g, 22.5 mmol) (washed several times with dry hexane), and the mixture was heated with stirring at 65—70 °C until the evolution of hydrogen gas ceased. After cooling of this solution to 0 °C, a solution of methyltriphenylphosphonium bromide (8.0 g, 22.5 mmol) in DMSO (20 ml) was added, and the mixture was stirred at room temperature for 1 h. A solution of the aldehyde **9** (3.5 g, 20.4 mmol) in DMSO (10 ml) was added to the above solution and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into water and extracted with hexane. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 4:1) to give **10** (3.25 g, 94%) as an oil, $[\alpha]_D^{22}$ −22.22° (*c*=0.27, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1700. ^{1}H-NMR (60 MHz) δ: 1.25 (3H, t, *J*=7 Hz), 1.6—2.2 (4H, m), 3.3—3.6 (2H, m), 3.9—4.5 (1H, m), 4.1 (2H, q, *J*=7 Hz), 4.85—5.25 (2H, m), 5.80 (1H, ddd, *J*=17, 9, 5.5 Hz). Exact MS *m/z*: Calcd for $C_9H_{15}NO_2$: 169.1101. Found: 169.1107.

(*S*)-(2)-Ethenyl-1-[(phenylthio)acetyl]pyrrolidine (12a) The carbamate **10** (1.75 g, 10.3 mmol) was added to a mixture of KOH (17.75 g, 269 mmol), hydrazine monohydrate (2.5 ml, 51.7 mmol), and ethylene glycol (30 ml), and the mixture was heated under reflux for 3 h. After cooling, the reaction mixture was extracted with Et_2O and the extract was dried (NaOH). Triethylamine (1.57 g, 15.5 mmol) and a solution of (phenylthio)acetyl chloride[17] (2.88 g, 15.5 mmol) in Et_2O (10 ml) were added successively to the above ethereal solution containing the amine **11** at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and the organic layer was separated. The aqueous layer was further extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **12a** (1.49 g, 58% based on **10**) as an oil, $[\alpha]_D^{22}$ −67.49° (*c*=0.56, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640. ^{1}H-NMR (60 MHz) δ: 1.33—2.38 (4H, m), 3.28—3.81 (2H, m), 3.67 (2H, s), 4.18—4.88 (1H, m), 4.78—5.27 (2H, m), 5.41—6.14 (1H, m), 6.68—7.74 (5H, m). *Anal.* Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.78; H, 7.02; N, 5.75.

(*S*)-2-Ethenyl-1-[(methylthio)acetyl]pyrrolidine (12b) Using a similar procedure to that described above for the preparation of **12a**, compound **10** (5.9 g, 35 mmol) was deprotected with KOH (51.2 g, 912 mmol) and hydrazine monohydrate (8.5 ml) in ethylene glycol (98 ml), and the resulting ethereal solution of the amine **11** was treated with (methylthio)acetyl chloride (4.4 g, 35 mmol) in Et_2O (10 ml) in the presence of triethylamine (3.54 g, 35 mmol) to give **12b** (4.9 g, 76% based on **10**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640. ^{1}H-NMR (60 MHz) δ: 1.53—2.13 (4H, m), 2.22 (3H, s), 3.20 (2H, s), 3.37—3.77 (2H, m), 4.38—4.82 (1H, m), 4.82—5.35 (2H, m), 5.50—6.10 (1H, m). Exact MS *m/z*: Calcd for $C_9H_{15}NOS$: 185.0873. Found: 185.0876.

Preparation and Cyclization of 1-[Chloro(phenylthio)acetyl]-2-ethenylpyrrolidine (13a) NCS (130 mg, 0.97 mmol) was added to a solution of **12a** (200 mg, 0.80 mmol) in CCl_4 (15 ml) at 0 °C and the mixture was stirred at room temperature for 5 h. The precipitated succinimide was filtered off. The filtrate was concentrated and the crude chloride **13a** thus obtained was immediately dissolved in benzene (20 ml), then the mixture was heated at reflux. A solution of Bu_3SnH (260 mg, 0.9 mmol) and AIBN (13 mg, 0.08 mmol) in benzene (30 ml) was added to the above solution over a period of 30 min, and the mixture was further refluxed for 8 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 1:1). The first fraction gave **12a** (26 mg, 13%).

The second fraction gave hexahydro-1-methyl-2-phenylthio-3*H*-pyrrolizin-3-one (**16a**) (97 mg, 49%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1700. ^{1}H-NMR (300 MHz) δ: 1.11—1.38 (1H, m, 7-H), 1.22 (3H, d, *J*=6.6 Hz, Me), 1.88 (1H, ddq, *J*=11.5, 8.0, 6.6 Hz, 1-H), 1.93—2.20 (3H, m, 6-H_2, 7-H), 3.11 (1H, dddd, *J*=11.6, 8.5, 4.8, 1.3 Hz, 5-H), 3.43 (1H, td, *J*=8.0, 5.9 Hz, 7a-H), 3.55 (1H, dt, *J*=11.6, 7.6 Hz, 5-H), 3.67 (1H, br d, *J*=11.5 Hz, 2-H), 7.21—7.32 (3H, m), 7.52—7.61 (2H, m) (very weak signals due to the other stereoisomers also appeared). Exact MS *m/z*: Calcd for $C_{14}H_{17}NOS$: 247.1029. Found: 247.1014.

Preparation and Cyclization of 1-[Chloro(methylthio)acetyl]-2-ethenylpyrrolidine (13b) NCS (147 mg, 1.1 mmol) was added portionwise to a solution of **12b** (170 mg, 0.91 mmol) in $CHCl_3$ (20 ml) at 0 °C and the mixture was stirred at room temperature for 15 h. The solvent was removed by evaporation and CCl_4 was added to the residue, then precipitated succinimide was filtered off. The filtrate was concentrated to give **13b**, which was immediately dissolved in benzene (20 ml), and the mixture was heated at reflux. A solution of Bu_3SnH (300 mg, 1.0 mmol) and AIBN (15 mg, 0.09 mmol) in benzene (30 ml) was added to the above solution over a period of 30 min, and the mixture was further refluxed for 2 h. The solvent was removed by evaporation and the residue was purified by chromatography on silica gel (benzene–AcOEt, 4:3). The first fraction gave **12b** (42 mg, 24%).

The second fraction gave hexahydro-1-methyl-2-methylthio-3*H*-pyrrolizin-3-one (**16b**) (102 mg, 60%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1690. ^{1}H-NMR (300 MHz) δ: 1.26 (3H, d, *J*=7.1 Hz, 1-Me), 1.28—1.49 (1H, m, 7-H), 1.85—2.17 (4H, m, 1-H, 6-H_2, 7-H), 2.18 (3H, s, SMe), 3.05—3.16 (1H, m, 5-H), 3.31 (1H, d, *J*=11.2 Hz, 2-H), 3.39—3.68 (2H, m, 5-H, 7a-H) (very weak signals due to the other stereoisomers also appeared). Exact MS *m/z*: Calcd for $C_9H_{15}NOS$: 185.0873. Found: 185.0873.

Preparation and Cyclization of 1-[Bis(phenylthio)acetyl]-2-ethenylpyrrolidine (14) Benzenethiol (186 mg, 1.7 mmol) was added to a solution of sodium ethoxide in EtOH, prepared from Na (39 mg, 1.7 mmol) and anhydrous EtOH (3 ml). A solution of the chloride **13a** [prepared from **12a** (350 mg, 1.4 mmol) and NCS (227 mg, 1.69 mmol)] in EtOH (3 ml) was added to the above solution and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into water (20 ml) and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1) to give **14** (396 mg, 79%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1650.

^{1}H-NMR (60 MHz) δ: 1.38—2.13 (4H, m), 3.23—3.71 (2H, m), 3.81—4.29 (1H, m), 4.35—5.24 (2H, m), 5.03 (1H, s), 5.37—6.17 (1H, m), 7.01—7.71 (10H, m). *Anal.* Calcd for $C_{20}H_{21}NOS_2$: C, 67.41; H, 5.94; N, 3.93. Found: C, 67.34; H, 5.74; N, 3.90.

A mixture of Bu_3SnH (530 mg, 1.83 mmol) and AIBN (35 mg, 0.21 mmol) in benzene (40 ml) was added dropwise to a solution of **14** (500 mg, 1.4 mmol) in boiling benzene (20 ml) over a period of 50 min and the mixture was further refluxed for 4 h, then cooled to room temperature. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1). The first fraction gave **12a** (88 mg, 25%) and the second fraction gave **16a** (231 mg, 67%).

Hexahydro-1-methyl-3*H*-pyrrolizin-3-one (17) From **16a**: A solution of **16a** (100 mg, 0.40 mmol) in EtOH (5 ml) was added to a suspension of Raney nickel (*ca.* 2 g) in EtOH (3 ml) and the mixture was heated under reflux for 1.5 h. The catalyst was filtered off, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane–AcOEt–MeOH, 10 : 10 : 1) to give **17**[10] (43 mg, 77%) as an oil: IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1695. ^{1}H-NMR (300 MHz) δ: 1.16 (3H, d, J=6.6 Hz, Me), 1.33—1.46 (1H, m, 7-H), 1.92—2.22 (4H, m, 1-H, 6-H$_2$, 7-H), 2.41 (1H, br dd, J=15.9, 11.0 Hz, 2-H), 2.53 (1H, dd, J=15.9, 8.3 Hz, 2-H), 3.04 (1H, dddd, J=11.8, 8.7, 4.3, 1.3 Hz, 5-H), 3.49 (1H, td, J=7.8, 6.0 Hz, 7a-H), 3.55 (1H, dt, J=11.8, 7.2 Hz, 5-H) [a trace doublet (<5%) appeared at δ 0.98 corresponding to the methyl proton of the 1β-methyl isomer].

From **16b**: Under similar conditions, **16b** (100 mg, 0.53 mmol) was desulfurized with Raney nickel (*ca.* 2 g) to give **17** (69 mg, 93%), whose ^{1}H-NMR spectrum was essentially the same as that of **17** obtained from **16a**.

Preparation and Cyclization of 1-(Dichloroacetyl)-2-ethenylpyrrolidine (15) Using a similar procedure to that described for the preparation of **12a**, the ethereal solution of **11**, obtained by alkaline hydrolysis of **10** (2.2 g, 13.0 mmol), was treated with dichloroacetyl chloride (2.30 g, 15.6 mmol) and triethylamine (1.58 g, 15.6 mmol), and work-up gave **15** (1.95 g, 72%), mp 32—33 °C (from hexane). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1685, 1665. ^{1}H-NMR (60 MHz) δ: 1.53—2.41 (4H, m), 3.40—3.90 (2H, m), 4.26—4.84 (1H, m), 4.84—5.38 (2H, m, CH=C$\underline{H}_2$), 5.48—6.26 (1H, m, C$\underline{H}$=CH$_2$), 6.13 (1H, s, COCHCl$_2$). *Anal.* Calcd for $C_8H_{11}Cl_2NO$: C, 46.18; H, 5.33; N, 6.73. Found: C, 45.95; H, 5.40; N, 6.95.

A solution of Bu_3SnH (840 mg, 2.88 mmol) and AIBN (19 mg, 0.12 mmol) in toluene (20 ml) was added to a boiling solution of **15** (500 mg, 2.4 mmol) in toluene (30 ml) over a period of 30 min and the mixture was refluxed for 3 h. Then a solution of Bu_3SnH (840 mg) and AIBN (19 mg) in toluene (20 ml) was added to this mixture, and the whole was refluxed for 3 h. Work-up gave **17** (188 mg, 56%) as an oil.

5,6,7,7a-Tetrahydro-1-methyl-3*H*-pyrrolizin-3-one (18) From **16a**: A solution of $NaIO_4$ (285 mg, 1.33 mmol) in H_2O (4 ml) was added to a solution of the sulfide **16a** (300 mg, 1.21 mmol) in acetone (6 ml) at 0 °C over 1 h and the mixture was stirred at room temperature for 16 h. After removal of the precipitated salts, the filtrate was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (AcOEt) to give **16a** (71 mg, 24%) and the sulfoxide (200 mg, 63%). The sulfoxide (147 mg, 0.56 mmol) was dissolved in toluene (10 ml) containing $NaHCO_3$ (118 mg, 1.4 mmol) and the mixture was heated under reflux for 1.5 h. The salts were removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **18**[10] (56 mg, 73% based on **16a**) as an oil. $[\alpha]_D^{22}$ −30.0° (c=0.25, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1705. ^{1}H-NMR (300 MHz) δ: 1.1—1.25 (1H, m), 2.04 (3H, d, J=1.6 Hz, Me), 2.05—2.35 (3H, m), 3.25 (1H, ddd, J=11.2, 8.5, 2.9 Hz, 5-H), 3.48 (1H, dt, J=11.2, 8.7 Hz, 5-H), 4.09 (1H, dd, J=10.5, 6.1 Hz, 2-H), 5.69 (1H, quintet, J=1.6 Hz, 2-H). ^{13}C-NMR (75 MHz) δ: 14.9 (Me), 28.6, 29.2 (C-6, C-7), 42.3 (C-5), 69.8 (C-7a), 122.8 (C-2), 161.9 (C-1), 176.8 (C-3).

From **16b**: Using a similar procedure to that described above, **18** (125 mg, 72%) was obtained from **16b** (235 mg, 1.26 mmol).

(*S*)-1-[(Phenylthio)acetyl]pyrrolidine-2-methanol (19) A solution of DCC (5.7 g, 33 mmol) in CH_2Cl_2 (15 ml) was added dropwise at 0 °C to a solution of **7** (3.0 g, 30 mmol), (phenylthio)acetic acid (5.5 g, 33 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.36 g, 0.3 mmol) in CH_2Cl_2 (50 ml). The mixture was stirred at room temperature. Precipitated 1,3-dicyclohexylurea was filtered off, and the filtrate was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated to give **19** (7.2 g, 95%) as colorless crystals, mp 42—44 °C (from AcOEt–hexane), $[\alpha]_D^{22}$ −53.65° (c=0.4, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3450, 1625. ^{1}H-NMR (60 MHz) δ: 1.47—2.35 (4H, m), 3.10—4.33 (5H, m), 3.67 (2H, s, CH_2S), 4.0—4.55 (1H, br, OH), 7.2—7.6 (5H, m, aromatic protons). *Anal.* Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 61.90; H, 6.86; N, 5.47.

Ethyl (*S*)-3-[1-(Phenylthioacetyl)pyrrolidin-2-yl]propenoate (21) Using a similar procedure to that described for the preparation of **9**, **19** (3.34 g, 13.3 mmol) was oxidized with SO_3-pyridine (8.45 g, 53.1 mmol) and triethylamine (13.3 ml, 93 mmol) in DMSO (13 ml) and CH_2Cl_2 (20 ml). Work-up gave the crude aldehyde **20** (3.0 g), which was used for the next reaction without purification.

DIPEA (2.78 ml, 13.3 mmol) and triethyl phosphonoacetate (3.13 ml, 15.9 mmol) were added to a solution of the crude aldehyde **20** and LiCl (675 mg, 15.9 mmol) in dry MeCN (50 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred for 2 h, diluted with water and concentrated *in vacuo*. The residue was extracted with ether and the extract was washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **21** (3.77 g, 89% based on **19**) as an oil. $[\alpha]_D^{22}$ −85.6° (c=0.5, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720, 1650. ^{1}H-NMR (60 MHz) δ: 1.30 (3H, t, J=7 Hz with further small splitting, OCH$_2$C$\underline{H}_3$), 1.5—2.5 (4H, m), 3.66 (2H, s, CH_2S), 3.3—3.66 (1H, m), 4.13 (2H, q, J=7 Hz with further small splitting, OC$\underline{H}_2$CH$_3$), 4.33—4.86 (2H, m, 2-H), 5.80 (1H, d, J=16 Hz, CH=C$\underline{H}$–CO$_2$Et), 6.53—7.0 (1H, m, –C$\underline{H}$=CH–CO$_2$Et), 7.0—7.5 (5H, m, aromatic protons). *Anal.* Calcd for $C_{17}H_{21}NO_3S \cdot 1/4H_2O$: C, 63.04; H, 6.69; N, 4.32. Found: C, 63.22; H, 6.75; N, 4.44.

Preparation and Cyclization of Ethyl 3-[Chloro(phenylthio)acetyl]pyrrolidin-2-ylpropenoate (22) NCS (294 mg, 2.2 mmol) was added portionwise to a solution of **21** (638 mg, 2.9 mmol) in CCl_4 (30 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in toluene (140 ml) and the solution was heated at reflux. A solution of Bu_3SnH (0.6 ml, 2.2 mmol) and AIBN (33 mg, 0.2 mmol) in toluene (30 ml) was added dropwise over 2 h, and the mixture was further refluxed for 2 h. After evaporation of the solvent, Et_2O (10 ml) and a 8% aqueous solution of KF (10 ml) were added and the whole mixture was stirred for 1 h. The ethereal layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give an isomeric mixture (63 : 27, determined by ^{1}H-NMR spectroscopy) of ethyl hexahydro-3-oxo-2-phenylthio-3*H*-pyrrolizin-1-ylacetate (**23**) (496 mg, 77%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720, 1675. ^{1}H-NMR (300 MHz) δ: 1.22, 1.26 (total 3H, t, J=8.0 Hz, –OCH$_2$C$\underline{H}_3$), 1.05—1.43 (1H, m), 1.55—1.72 (1H, m), 1.96—2.33 (2H, m), 2.44—2.94 (3H, m), 2.99—3.15 (1H, m), 3.35—3.60 (2H, m), 3.81 and 4.02 (total 1H, d each, J=13.0, 7.0 Hz, respectively, 2-H), 4.07 and 4.13 (total 2H, q, both J=8.0 Hz, OC$\underline{H}_2$CH$_3$), 7.26—7.30 and 7.56—7.60 (total 5H, m, aromatic protons). Exact MS m/z: Calcd for $C_{17}H_{21}NO_3S$: 319.1241. Found: 319.1249.

Ethyl 5,6,7,7a-Tetrahydro-3-oxo-3*H*-pyrrolizin-1-ylacetate (24) A solution of $NaIO_4$ (83 mg, 0.39 mmol) in water (5 ml) was added to a solution of the sulfide **23** (82 mg, 0.26 mmol) in acetone (9 ml) and the mixture was stirred at 0 °C for 1 h and then at room temperature for 18 h. The precipitated solid was filtered off, acetone was evaporated off, and the aqueous solution was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. The residual crude sulfoxide was dissolved in toluene (3 ml) and $NaHCO_3$ (33 mg) was added. The mixture was refluxed for 12 h, the solvent was evaporated off, and the residue was chromatographed on silica gel (AcOEt) to give **24** (32 mg, 58%) and the unreacted sulfoxide (27 mg, 31%). Compound **24** has $[\alpha]_D^{22}$ −23.47 (c=0.21, EtOH). The optical purity of this compound was estimated by HPLC analysis on a Chiralcel OD column (Daicel Chemical Industries, Ltd.) (4.6 mm × 250 mm) with hexane–2-propanol (9 : 1) as the eluant (flow rate 1.0 ml/min) at 40 °C. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725, 1705. ^{1}H-NMR (300 MHz) δ: 1.33 (3H, t, J=7.2 Hz, –OCH$_2$C$\underline{H}_3$), 1.36—2.78 (4H, m, 6-H, 7-H), 3.45 (2H, s, C$\underline{H}_2$CO$_2$Et), 3.03—3.78 (2H, m, 5-H), 4.10—4.58 (1H, m, 8-H), 4.15 (2H, q, J=7.2 Hz, OC$\underline{H}_2$CH$_3$), 5.93 (1H, s, 2-H). Exact MS m/z: Calcd for $C_{11}H_{15}NO_3$: 209.2392. Found: 209.2399.

Ethyl (1*S*,7a*S*)-Hexahydro-3-oxo-3*H*-pyrrolizin-1-ylacetate (25) A mixture of **23** (1.1 g, 3.4 mmol) and Raney nickel (*ca.* 18 ml) in EtOH (30 ml) was refluxed for 6 h. The catalyst was filtered off, the filtrate was concentrated, and the residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **25** (569 mg, 79%) as an oil, $[\alpha]_D^{22}$ −35.8° (c=0.6, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725, 1700. ^{1}H-NMR (300 MHz) δ: 1.27 (3H, t, J=7.1 Hz, OCH$_2$C$\underline{H}_3$), 1.35—1.53 (1H, m), 1.85—2.20 (4H, m), 2.45—2.67 (4H, m), 3.05 (1H, ddd, J=12.0, 9.0, 4.0 Hz), 3.35—3.66 (2H, m), 4.15 (2H, q, J=7.1 Hz, OC$\underline{H}_2$CH$_3$). ^{13}C-NMR δ: 14.23, 26.87, 31.41, 38.22, 38.61 (C-1), 41.24, 41.67, 60.70, 67.29 (C-7a), 171.63, 173.29. Exact MS m/z: Calcd for $C_{11}H_{17}NO_3$: 211.1206. Found: 211.1199.

(1*S*,7a*S*)-Hexahydro-1-(2,2-diphenylethenyl)-3*H*-pyrrolizin-3-one (26) A solution of **25** (211 mg, 1 mmol) in anhydrous tetrahydrofuran (THF) (15 ml) was added dropwise to an ethereal solution of phenylmagnesium bromide [prepared from bromobenzene (0.42 ml, 4 mmol) and magnesium (96 mg, 4 mmol) in anhydrous THF (1 ml)] at −78 °C under a nitrogen atmosphere. After 10 min, the solvent was evaporated off. The residue was dissolved in CH_2Cl_2 and the solution was washed with saturated NH_4Cl solution, dried ($MgSO_4$), and concentrated to give the crude alcohol, which was directly used for the next reaction. Methanesulfonyl chloride (0.097 ml, 1 mmol) was added to a solution of the crude alcohol in CH_2Cl_2 (2 ml) at 0 °C, and then triethylamine (0.14 ml, 1 mmol) was added. The mixture was stirred for 45 min at 0 °C, then diluted with CH_2Cl_2, and the whole was washed with brine, 5% HCl and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to give **26** (209 mg, 69%) as an oil, $[\alpha]_D^{22}$ −47.7° (c=0.6, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1700. ^{1}H-NMR (300 MHz) δ: 1.16—1.27 (1H, m), 1.92—2.03 (3H, m), 2.44—2.52 (1H, m), 2.68—2.90 (2H, m), 2.99—3.07 (1H, m), 3.46 (1H, dt, J=12.7, 8.3 Hz), 3.78 (1H, dt, J=9.2, 6.0 Hz), 6.09 (1H, d, J=10.7 Hz, an olefinic proton), 7.10—7.41 (10H, m, aromatic protons). Exact MS m/z: Calcd for $C_{21}H_{21}NO$: 303.1622. Found: 303.1628.

(1*R*,7a*S*)-Hexahydro-3-oxo-3*H*-pyrrolizine-1-carbaldehyde (27) A stream of ozone was passed through a solution of **26** (303 mg, 1 mmol) in MeOH (25 ml) for 30 min at −78 °C. Dimethyl sulfide (0.13 ml) was added, and the reaction mixture was stirred at room temperature overnight and concentrated. The residue was dissolved in Et_2O and the solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 3 : 1) to give **27** (95 mg, 69%) as an oil, $[\alpha]_D^{22}$ −34.5° (c=0.20, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1700. ^{1}H-NMR (60 MHz) δ: 0.95—1.68 (1H, m), 1.68—2.40 (3H, m), 2.40—3.28 (3H, m), 3.28—4.27 (3H, m), 9.87 (1H, br s, CHO). Exact MS m/z: Calcd for $C_8H_{11}O_2N$: 153.0789. Found: 153.0790.

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