Synthesis of a Pyridone Alkaloid, Cerpegin

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A new pyridone alkaloid, cerpegin, was synthesized in five steps starting from the Michael reaction between phenylthioacetonitrile and 2-methoxycarbonyl-4-methyl-2-penten-4-olide. Catalytic hydrogenation of a nitrile group in the presence of a conjugated carbon–carbon double bond was performed by addition of 1 eq of concentrated HCl.

Key words cerpegin; pyridone alkaloid; 2-methoxycarbonyl-4-methyl-2-penten-4-olide; phenylthioacetonitrile; *Ceropegia juncea*

A new pyridone alkaloid, cerpegin, was isolated from *Ceropegia juncea*, and its structure was elucidated as 1,1,5-trimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (**1**).[1] *Ceropegia juncea* ROXB. is reported to be the source of "Soma," a plant drug of the Ayurvedic system of medicine with a wide variety of uses.[2] Although the total alkaloidal fraction of the alcoholic extracts of this plant exhibited promising tranquilizing, hypotensive and local anesthetic activities in experimental animals,[1] it is not clear whether **1** itself has those activities or not. Because of the novelty of its structure and our continuing interest in the synthesis of heterocyclic compounds possessing fused furanone moieties,[3] we undertook the synthesis of **1**. The first total synthesis of **1** was recently reported by Kelly and Walsh.[4] They synthesized **1** in about five steps starting from 2-nicotinic acid. We now report an alternative synthesis of **1** that involves the Michael addition of phenylthioacetonitrile (**2**)[5] to 2-methoxycarbonyl-4-methyl-2-penten-4-olide (**3**).[6,7] We chose the above Michael reaction at the beginning of the synthesis because Wang *et al.* have reported **2** is a good Michael donor[8] and we have used **3** as a Michael acceptor in the synthesis of furobenzothiazepinone derivatives.[3c] In addition, the phenylthio group is useful for the introduction of a carbon–carbon double bond after Michael addition.

Thus, 2-lithiophenylthioacetonitrile, prepared by treatment of **2** with lithium diisopropylamide (LDA), was reacted with **3** in tetrahydrofuran (THF) at −78 °C for 5 min and then at room temperature for 3 h. Acidic work-up (10% HCl) gave the adduct **4** as a mixture of two diastereomers in 93% yield. This mixture was separated into each isomer by preparative SiO_2 thin layer chromatography in a ratio of about 3 : 2. From inspection of the ^{1}H-NMR spectra of the isomers, these might be diastereomers involving the phenylthio and nitrile groups. Oxidation of **4** (the mixture of diastereomers) with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride furnished **5** as a single isomer in 80% yield, and this was successively heated in toluene for 2 h, but the yield of the desired α,β-unsaturated lactone **6** was only 32%. When the same elimination reaction was performed in the presence of calcium carbonate (0.5 molar eq against **5**) as an additive,[9] the yield of **6** was lowered to 14% (Table 1, run 2). Replacement of toluene by benzene as

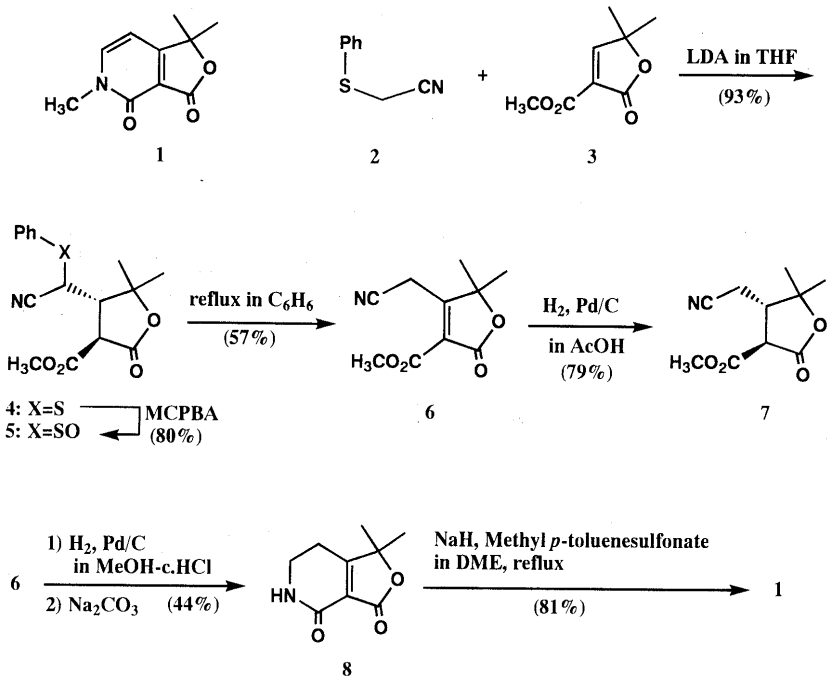

Chart 1

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the solvent and prolongation of the refluxing time (7 h) improved the yield to 57% (run 3). Addition of calcium carbonate (0.5 or 1.0 molar eq against **5**) lowered rather than improved the yield (runs 4 and 5). Chemoselective reduction of the nitrile group of **6** to an amine in the presence of the conjugated carbon–carbon double bond was a crucial step. Reaction of **6** with $NaBH_4$ or $NaBH_4$–$CoCl_2$ resulted in the recovery of **6** (in the former case) or formation of a complex mixture (in the latter case).[10] Catalytic hydrogenation of **6** over Pd–C in acetic acid or methanol under 1.6 atm of hydrogen at room temperature for 2 h gave the undesired compound **7** in 79% or 70% yield, respectively (Table 2, runs 1 and 2). When the catalytic hydrogenation of **6** was performed over Pd–C in the presence of excess concentrated HCl (13 or 1.3 molar eq against **6**) in methanol and the mixture was worked up under basic conditions (10% Na_2CO_3, pH *ca.* 9), the desired lactam **8** was obtained, but the yields were only 6 and 12%, respectively (Table 2, runs 3 and 4).[11,12] Reducing the amount of concentrated HCl to 1.0 molar eq against **6** resulted in improvement of the yield of **8** (25%, run 5). The best result was obtained in the case of run **6**. Thus, when the reaction was carried out over Pd–C in methanol in the presence of 1.0 molar eq concentrated HCl under 1 atm of hydrogen at room temperature for 3 h, **8** was obtained in 44% yield (run 6). The crucial points of the catalytic reduction are the addition of concentrated HCl just before starting the reaction and maintaining the pressure of hydrogen at 1 atm throughout the reaction. Replacement of concentrated HCl with *p*-toluenesulfonic acid or Pd–C with Raney-Ni did not improve the yield. The role of concentrated HCl in this chemoselective reduction is not clear at present.

Table 1. Preparation of **6** from **5**

Run	Solvent	$CaCO_3$ (mol)[a]	Reflux (h)	Yield (%)
1	Toluene	—	2	32
2	Toluene	0.5	2	14
3	Benzene	—	7	57
4	Benzene	0.5	7	51
5	Benzene	1.0	7	51

a) Molar equivalent against **5**.

Table 2. Catalytic Reduction of **6** with H_2 and Pd–C[a]

Run	conc.HCl[b] (mol)	Solvent	Stir.[c] (h)	Pressure (atm)	Yield (%)	
					7	**8**
1	—	MeOH	2	1.6	70	—
2	—	AcOH	2	1.6	79	—
3	13	MeOH	2	1.0—1.6	—	6
4	1.3	MeOH	1.5	1.0—1.6	—	12
5	1.0	MeOH	1.5	1.0—1.6	18	25
6	1.0	MeOH	3	1.0	—	44

a) 50% by weight with respect to **6** was used. *b*) Molar equivalent against **6**. *c*) Room temperature.

Next, as **8** was in hand, its *N*-methylation was examined. Reaction of **8** with CH_3I in the presence of NaH in *N*,*N*-dimethylformamide (DMF) at room temperature resulted in the formation of a complex mixture. When **8** was treated with methyl *p*-toluenesulfonate in the presence of NaH in 1,2-dimethoxyethane (DME) at refluxing temperature for 1 h, **1** was obtained directly in 81% yield. It is interesting that dehydrogenation reaction occurs concomitantly in the above alkylation reaction. The IR, ^{1}H-NMR and MS data of the synthetic **1** were identical with those of the natural product.[1,4]

Next, we tried to transform **7**, which was obtained by catalytic hydrogenation of **6** in the absence of concentrated HCl, into **1**. Further catalytic reduction of **7** in the presence of concentrated HCl and Pd–C in methanol followed by basic work-up gave **9** in 74% yield. Treatment of **9** with CH_3I in the presence of NaH in DME resulted in the formation of **10** and **11** in 59 and 12% yields, respectively. These results show that it is hard to achieve selective *N*-methylation on the lactam NH. Therefore, we then tried to convert **9** into **8**. Thus, reaction of **9** with phenylselenenyl chloride in the presence of NaH in DME gave **12** in 26% yield. Oxidative elimination of the phenylselenenyl group of **12** with 30% H_2O_2 in water–methylene chloride proceeded successfully to give **8** in 32% yield, and **8** can be transformed into **1** as above.

In summary, **1** was synthesized starting from the Michael addition of **2** to **3** in five steps, involving the

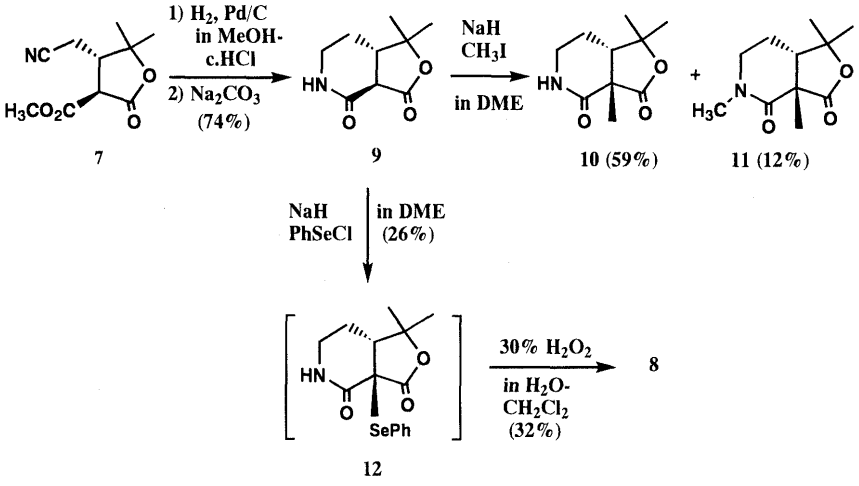

Chart 2

catalytic reduction of the nitrile group in the presence of the conjugated carbon–carbon double bond.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were measured with a JEOL JMS-HX100 instrument at 70 eV.

Michael Addition of 2 to 3 A solution of **2** (13.29 g, 89 mmol) in dry THF (35 ml) was added dropwise to a stirred solution of LDA [prepared from diisopropylamine (21 ml, 150 mmol) and *n*-BuLi (67 ml, 1.6 M hexane solution, 107 mmol) in dry THF (70 ml)] at −76 °C under an N_2 atmosphere. After 30 min, a solution of **3** (15.00 g, 88 mmol) in dry THF (45 ml) was added to the above solution and the mixture was stirred at −76 °C for 5 min, then warmed to room temperature and stirred at that temperature for 3 h. It was acidified with 10% HCl (pH 2) and extracted three times with $CHCl_3$. After drying over anhydrous Na_2SO_4, the combined extracts were concentrated *in vacuo* to give the residue, which was crystallized from a mixture of 2-propanol–hexane to furnish **4** (26.07 g, 93%) as colorless needles. As a TLC check and ^{1}H-NMR inspection of the product showed it was a mixture of two diastereomers, **4** (68 mg) was separated into the less polar isomer (35 mg) and the more polar isomer (26 mg) by SiO_2 preparative TLC (developed with a mixture of diethyl ether : hexane = 2 : 1). Less polar isomer: colorless needles from a mixture of 2-propanol–hexane, mp 145—147 °C. IR ($CHCl_3$): 1775, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.49, 1.71 (each 3H, s, CH_3), 3.30 (1H, dd, J = 11.5, 11.0 Hz, CC<u>H</u>CHCN), 3.68 (1H, d, J = 11.5 Hz, COCHCO$_2$Me), 3.70 (1H, d, J = 11.0 Hz, CCHC<u>H</u>CN), 3.90 (3H, s, CO_2Me), 7.39—7.68 (5H, m, ArH). More polar isomer: mp 138.5—140.5 °C (2-propanol–hexane). IR ($CHCl_3$): 1775, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50, 1.66 (each 3H, s, CH_3), 3.26 (1H, dd, J = 11.5, 7.0 Hz, CC<u>H</u>CHCN), 3.86 (3H, s, CO_2Me), 3.87 (1H, d, J = 7.0 Hz, CCHC<u>H</u>CN), 3.88 (1H, d, J = 11.5 Hz, COC<u>H</u>CO$_2$Me), 7.39—7.65 (5H, m, ArH). *Anal.* Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.39. Found: C, 60.24; H, 5.47; N, 4.40.

MCPBA Oxidation of 4 A solution of MCPBA (154 mg, 0.63 mmol) in dry CH_2Cl_2 (12 ml) was added to a solution of **4** (diastereomeric mixture: 199 mg, 0.62 mmol) in dry CH_2Cl_2 (14 ml) under stirring and ice-cooling within 10 min. After 5 min, the cool reaction mixture was poured into a mixture of ether (42 ml) and 10% aqueous Na_2SO_3 solution (42 ml), and the organic layer was separated. The organic layer was washed with saturated $NaHCO_3$ solution and brine successively, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the residue. Crystallization of the residue from a mixture of 2-propanol–hexane gave **5** (168 mg, 80%) as a single isomer, colorless needles, mp 166.5—168 °C. IR (Nujol): 1770, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.49, 1.77 (each 3H, s, CH_3), 3.50 (1H, d, J = 10.5 Hz, COC<u>H</u>CO$_2$Me), 3.59 (1H, t, J = 10.5 Hz, CC<u>H</u>CHCN), 3.86 (1H, d, J = 10.5 Hz, CCHC<u>H</u>CN), 3.91 (3H, s, CO_2Me), 7.60—7.80 (5H, m, ArH). *Anal.* Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18. Found: C, 57.04; H, 5.19; N, 4.12.

Preparation of 6 A solution of **5** (301 mg, 0.9 mmol) in benzene (10 ml) was refluxed with stirring for 7 h. The reaction mixture was washed with water and brine successively. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the residue. Crystallization of the residue from a mixture of 2-propanol–hexane furnished **6** (106 mg, 57%) as colorless plates, mp 100—102 °C. IR (Nujol): 2900, 1765, 1720, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (6H, s, CH_3 × 2), 3.94 (3H, s, CO_2Me), 3.99 (2H, s, CH_2CN). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.34; H, 5.26; N, 6.70.

Catalytic Hydrogenation of 6 in the Absence of Concentrated HCl A solution of **6** (200 mg, 1.0 mmol) in acetic acid (10 ml) containing 10% Pd–C (100 mg) was stirred under a hydrogen atmosphere (1.6 atm) at room temperature for 2 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the residue. Crystallization of the residue from a mixture of 2-propanol–haxane gave **7** (160 mg, 79%) as colorless plates, mp 127—129 °C. IR (Nujol): 2870, 1765, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41, 1.64 (each 3H, s, CH_3), 2.535 (1H, dd, J = 17.0, 8.7 Hz, CH_2CN), 2.625 (1H, dd, J = 17.0, 6.0 Hz, CH_2CN), 3.07 (1H, ddd, J = 12.0, 8.5, 6.0 Hz, C<u>H</u>CH$_2$CN), 3.525 (1H, d, J = 12.0 Hz, COCHCO), 3.865 (3H, s, CO_2Me). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.75; H, 6.17; N, 6.65.

Catalytic Hydrogenation of 6 in the Presence of Concentrated HCl Concentrated HCl (0.2 ml, 2.4 mmol) was added to a suspension of **6** (500 mg, 2.4 mmol) and 10% Pd–C (250 mg) in MeOH (25 ml) just before starting the hydrogenation reaction. During the reaction, the pressure of hydrogen was kept at 1.0 atm. After 3 h at room temperature, the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* to give the residue, which was taken up in 10% aqueous Na_2CO_3 solution and adjusted to pH 9. After saturation with solid NaCl, the solution was extracted with $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the residue. Crystallization of the residue from MeOH furnished **8** (189 mg, 44%) as a colorless crystalline powder, mp 226—229 °C. IR (Nujol): 3200, 1770, 1685, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (6H, s, CH_3 × 2), 2.67 (2H, t, J = 7.0 Hz, CC<u>H</u>$_2$CH$_2$N), 3.65 (2H, dt, J = 7.0, 2.5 Hz, CCH$_2$C<u>H</u>$_2$N), 7.21 (1H, br s, NH). HRMS *m/z*: Calcd for $C_9H_{11}NO_3$ (M^+): 181.0739. Found: 181.0712.

Preparation of 1 Compound **6** (136 mg, 0.75 mmol) was added to a suspension of NaH (37 mg, 60% in a mineral oil, 0.85 mmol) in dry DME (20 ml) with stirring under an N_2 atmosphere at room temperature, and the resulting reaction mixture was stirred for 30 min. A solution of methyl *p*-toluenesulfonate (195 mg, 1.0 mmol) in dry DME (3 ml) was then added and the whole was refluxed for 1 h. DME (10 ml) was removed *in vacuo*, and the resultant solution was diluted with water, salted out and then extracted with $CHCl_3$ containing a small amount of MeOH. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the residue, which was purified by SiO_2 column chromatography (eluted with a mixture of $CHCl_3$: MeOH = 6 : 1) to afford **1** (117 mg, 81%) as colorless prisms, mp 267—271 °C ($CHCl_3$–MeOH) (lit.[1] 268—270 °C). IR (KBr): 1750, 1655, 1590, 1560, 1545 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (6H, s, CH_3 × 2), 3.64 (3H, s, NCH_3), 6.29 (1H, d, J = 6.9 Hz, CC<u>H</u> = CHN), 7.68 (1H, d, J = 6.9 Hz, CCH = C<u>H</u>N). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found; C, 62.14; H, 5.74; N, 7.27. HRMS *m/z*: Calcd for $C_{10}H_{11}NO_3$ (M^+): 193.0737. Found: 193.0738.

Catalytic Reduction of 7 To a solution of **7** (200 mg, 0.95 mmol) in MeOH (9 ml) were added 10% Pd–C (100 mg) and concentrated HCl–MeOH solution (1 ml) [prepared by dilution of concentrated HCl (0.78 ml) with MeOH until 10 ml]. The reaction mixture was stirred under a hydrogen atmosphere (1.6 atm) at room temperature for 4.5 h. More catalyst (50 mg) was added, and stirring was continued under the same conditions for a further 1 h. Removal of the catalyst and concentration of the filtrate gave the residue, which was treated with 10% aqueous Na_2CO_3 solution to adjust the pH to 10. The mixture was saturated with salt and extracted with $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **9** (128 mg, 74%) as a colorless crystalline powder, mp 251—254 °C (MeOH-2-propanol). IR (Nujol): 3200, 1755, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43, 1.45 (each 3H, s, CH_3), 1.62 (1H, dtd, J = 13.0, 12.5, 5.0 Hz, C<u>H</u>$_2$CH$_2$NH), 1.96 (1H, ddd, J = 13.0, 3.0, 1.3 Hz, C<u>H</u>$_2$CH$_2$NH), 2.53 (1H, ddd, J = 12.5, 7.5, 5.0 Hz, C<u>H</u>CH$_2$CH$_2$), 3.29 (1H, td, J = 12.5, 3.0 Hz, C<u>H</u>$_2$NH), 3.42 (1H, dtd, J = 12.5, 5.0, 3.0 Hz, C<u>H</u>$_2$NH), 3.69 (1H, dd, J = 7.5, 1.3 Hz, COC<u>H</u>CO), 6.77 (1H, br s, NH). HRMS *m/z*: Calcd for $C_9H_{13}NO_3$ (M^+): 183.0896. Found: 183.0907.

Methylation of 9 Compound **9** (30 mg, 0.16 mmol) was added to a suspension of NaH (8 mg, 60% in a mineral oil, 0.18 mmol) in dry DME (5 ml) with stirring under an N_2 atmosphere at room temperature, and the whole was stirred for 30 min. A solution of CH_3I (14 ml, 0.22 mmol) in dry DME (1 ml) was added and the whole was stirred at room temperature for 1 h. After the addition of water and salt, the mixture was extracted with $CHCl_3$, and the combined extracts were dried over anhydrous Na_2SO_4. Concentration of the extracts *in vacuo* gave the residue, which was crystallized from AcOEt to furnish **10** (12 mg, 59%) as colorless needles. The dimethylated compound **11** (4 mg, 12%) was obtained by SiO_2 preparative TLC of the filtrate (developed with a mixture of $CHCl_3$: MeOH = 5 : 1). **10**: mp 155—157.5 °C. IR ($CHCl_3$): 3190, 1760, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39, 1.50 (each 3H, s, CH_3), 1.67 (3H, s, COC(CH_3)CO), 1.84 (1H, m, C<u>H</u>$_2$CH$_2$CN), 2.05 (1H, m, C<u>H</u>$_2$CH$_2$CN), 2.45 (1H, dd, J = 7.5, 6.5 Hz, C<u>H</u>CH$_2$CH$_2$N), 3.30—3.51 (2H, m, CHCH$_2$C<u>H</u>$_2$N), 7.44 (1H, br s, NH). HRMS *m/z*: Calcd for $C_{10}H_{15}NO_3$ (M^+): 197.1051. Found: 197.1074. **11**: mp 96—101 °C. IR ($CHCl_3$): 1760, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36, 1.50 (each 3H, s, CH_3), 1.65 (3H, s, COC(CH_3)CO), 1.90 (1H, ddd,

J=14.0, 13.0, 6.0 Hz, $C\underline{H}_2CH_2N$), 2.08 (1H, dtd, J=14.0, 7.0, 5.5 Hz, $C\underline{H}_2CH_2N$), 2.42 (1H, dd, J=7.0, 6.0 Hz, $C\underline{H}CH_2CH_2N$), 2.99 (3H, s, NCH_3), 3.365 (1H, dd, J=13.0, 5.5 Hz, $CHCH_2C\underline{H}_2N$), 3.46 (1H, dd, J=13.0, 6.0 Hz, $CHCH_2C\underline{H}_2N$). HRMS m/z: Calcd for $C_{11}H_{17}NO_3$ (M^+): 211.1208. Found: 211.1203.

Conversion of 9 to 8 A solution of **9** (100 mg, 0.55 mmol) in dry DME (5 ml) was added to a suspension of NaH (34 mg, 60% in a mineral oil, 0.78 mmol) in dry DME (10 ml) with stirring at room temperature. Stirring was continued for 20 min, then a solution of phenylselenenyl chloride (114 mg, 0.58 mmol) in dry DME (5 ml) was added to the reaction mixture and the whole was stirred at room temperature for 1 h. It was poured into a mixture of $CHCl_3$ (40 ml), 7% aqueous $NaHCO_3$ solution (10 ml) and ice (10 g), and the organic layer was separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the residue, which was purified by SiO_2 column chromatography (eluted with a mixture of acetone : hexane = 3 : 2) to furnish **12** (47 mg, 26%) as an oil. A solution of **12** (35 mg, 0.10 mmol) in CH_2Cl_2 (5 ml) was treated with 30% H_2O_2 (24 mg, 0.21 mmol) in water (1 ml), and the mixture was stirred at room temperature for 2.5 h, then washed with 7% $NaHCO_3$ solution (5 ml) and water, successively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **8** (6 mg, 32%), which was identical with the compound obtained above.

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12) At this stage, it seemed hard to reduce the nitrile group of **6** chemoselectively in the presence of the α,β-unsaturated carbonyl group. Therefore, the following Michael reaction of (i) to **3** was tried, but a complex mixture was generated.

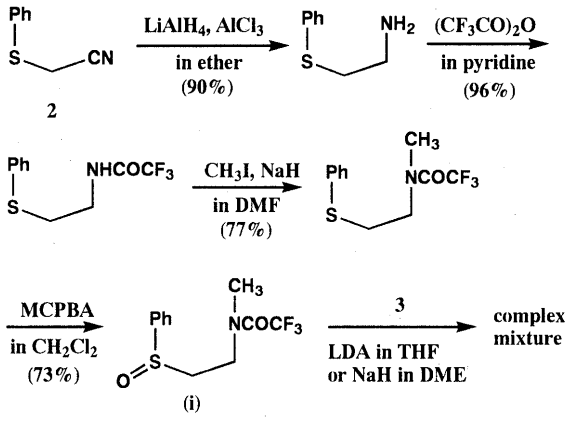

Chart 3