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Synthesis of Amaryllidaceae Alkaloids, (±)-Cherylline and (±)-Latifine

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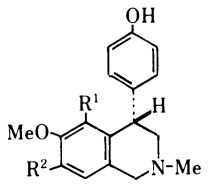
Synthesis of the alkaloids, (±)-cherylline (**1**) and (±)-latifine (**2**), was accomplished by application of an isocyanate cyclization reaction according to Tsuda's two step procedure for constructing 1,2,3,4-tetrahydroisoquinol-1-one and a regioselective cleavage reaction of aromatic methyl ethers with dimethyl sulfide in methanesulfonic acid.

Keywords——Amaryllidaceae alkaloid; cherylline; latifine; Grignard reaction; lactam cyclization; regioselective demethylation; rearrangement; oxazoline

There have been several reports[1] concerning the synthesis of the alkaloids, cherylline (**1**)[2] and latifine (**2**)[3] isolated form Amaryllidaceae plants. We have also reported a synthesis of (±)-cherylline (**1**) by application of Tsuda's two-step procedure for cyclization of β-phenylethyl isocyanate to 3,4-dihydroisoquinol-1-one[4] and regioselective cleavage reaction of aromatic methyl ether using methionine in methanesulfonic acid.[5] We report here in detail the synthesis of (±)-cherylline (**1**) and (±)-latifine (**2**).

Treatment of veratraldehyde (**3**) with dimethyl malonate in the presence of a catalytic amount of benzoic acid and piperidine with removal of water (Dean–Stark) gave the benzylidenemalonate (**4**) in 90% yield. Grignard 1,4-addition of *p*-methoxybenzene magnesium bromide to the malonate (**4**) was accomplished by addition of the malonate to a solution of *p*-methoxybenzenemagnesium bromide and a small amount of copper iodide in ether, giving the diphenylmethylmalonate (**5**) in 88% yield. Alkaline hydolysis of **5** followed by decarboxylation gave the acid (**7**). The requisite material (**7**) thus obtained for cyclization was subjected to Tsuda's two-step procedure, the first key point in our synthesis. The acid chloride derived from the acid (**7**) by treatment with oxalyl chloride was transformed into the acid azide by reaction with sodium azide in good yield. Heating (Curtius rearrangement) of the acid azide gave the corresponding isocyanate which was, without isolation, heated with phosphorus oxychloride at 90—95 °C (bath temperature). After removal of the reagent, the resulting residue was treated with stannic chloride in methylene chloride, furnishing the tetrahydroisoquinolone (**8**) in 67% yield. In this case, the pretreatment of the isocyanate with phosphorus oxychloride was indispensable; otherwise the isoquinolone (**8**) was obtained in low yield. Methylation of **8** gave the *N*-methyl-lactam (**9**), which was subjected to the second key reaction, a regioselective aromatic methoxyl group cleavage. Treatment of the *N*-methyl-lactam (**9**) with methyl sulfide[6] in methanesulfonic acid at 60—65 °C (bath temperature) gave the phenolic lactam (**10**) as a result of regioselective cleavage of methoxyl groups except for the methoxyl group at the *para*-position to the lactam carbonyl, in 50% yield. Confirmation of

the positions of the phenolic hydroxyl groups was ultimately provided by the synthesis of (±)-cherylline (**1**). Lithium aluminium hydride reduction of the phenolic lactam (**10**) gave (±)-cherylline (**1**), the ^{1}H-NMR spectrum of which was identical with that of an authentic sample provided by Professor Fukumoto (Tohoku University).



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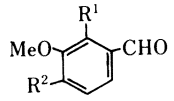
2 : R^1=OH, R^2=H



3 : R^1=H, R^2=OMe
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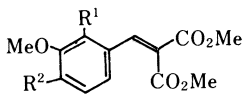
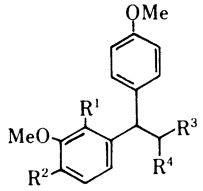
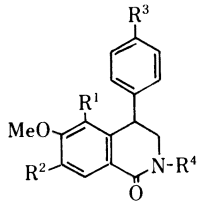


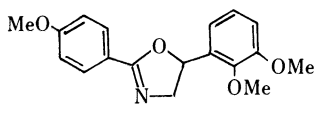
4 : R^1=H, R^2=OMe
12 : R^1=OMe, R^2=H



5 : R^1=H, R^2=OMe, R^3=R^4=CO_2Me
13 : R^1=OMe, R^2=H, R^3=R^4=CO_2Me
6 : R^1=H, R^2=OMe, R^3=R^4=CO_2H
7 : R^1=R^3=H, R^2=OMe, R^4=CO_2H
14 : R^1=OMe, R^2=R^3=H, R^4=CO_2H



8 : R^1=R^4=H, R^2=R^3=OMe
15 : R^2=R^4=H, R^1=R^3=OMe
9 : R^1=H, R^2=R^3=OMe, R^4=Me
16 : R^1=R^3=OMe, R^2=H, R^4=Me
10 : R^1=H, R^2=R^3=OH, R^4=Me
17 : R^1=R^3=OH, R^2=H, R^4=Me



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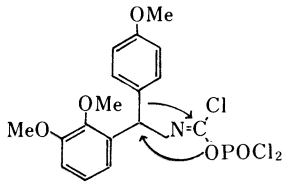

By starting from 2,3-dimethoxybenzaldehyde (**11**) and following the same reaction sequence, the acid (**14**) was obtained in 44% over-all yield. An attempt was made to synthesize the lactam (**15**) from the acid (**14**) by the same reaction sequence as mentioned above. However, the yield of the required lactam (**15**) was only 14%, and instead the oxazine (**18**) was obtained in 47% yield. The structure of the latter was proposed on the basis of its spectroscopic properties. Thus, its mass spectrum (MS) (M^+ *m/z* 313) and elemental analysis were consistent with the molecular formula, $C_{18}H_{19}NO_4$. Its infrared (IR) spectrum showed no band in the OH and NH region but a strong band at 1650 cm^{-1}. Furthermore, its proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed a doublet signal corresponding to two protons at δ 8.00 as a part of an A_2B_2 pattern. The chemical shift was at considerably lower field than that of the *para*-substituted benzene ring of the starting material (**14**) or the normally cyclized compound (**15**), indicating that the *p*-methoxybenzene ring is conjugated with a carbonyl group or a double bond containing a heteroatom(s). Its carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum ($CDCl_3$) showed sixteen signals (see Experimental) corresponding to eleven sp^2 carbons, one secondary carbon assigned to a carbon bearing ether oxygen (76.38 ppm), a methylene carbon (62.77 ppm), and three methoxyl carbons (60.74, 55.78, and 55.29 ppm). No signal at lower field than 163.49 ppm and no signal assignable to a formyl proton were seen, suggesting that the compound has no carbonyl group in the molecule. Based on these findings, we proposed the structure of the compound to be the oxazoline (**18**) as indicated in the chart. The mechanism for formation of the compound is not clear, but 2,3-dimethoxybenzene ring might react sluggishly in the cyclization reaction to the isoquinolone. As a result, the *p*-methoxybenzene ring migrates to the isocyanate carbon

followed by concomitant cyclization to the oxazoline by participation of isocyanate oxygen, as depicted in the chart. On the other hand, the use of boron trifluoride etherate in place of stannic chloride for cyclization afforded the normally cyclized compound (**15**) in 85% yield. Methylation of **15** gave the *N*-methyl-lactam (**16**). Application of the demethylation reaction to **16** gave the phenolic lactam (**17**) in 55% yield. Lithium aluminium hydride reduction of **17** gave a good yield of (±)-latifine (**2**) which exhibited IR (KBr) and ^{1}H-NMR ($CDCl_3$) spectra identical with those of an authentic sample provided from Professor S. Kobayashi (Tokushima University), accomplishing a synthesis of (±)-latifine (**2**).

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-408 infrared spectrophotometer. ^{1}H-NMR were taken on Hitachi R-600, Varian EM360, JEOL FX-90Q, and JEOL FX400 spectrometer with tetramethylsilane as an internal standard in $CDCl_3$ and DMSO-d_6. The following abbreviation are used; s = singlet, d = doublet, t = triplet, q = quartet and br = broad. Column chromatography was carried out with silica gel (Merck 7734).

Since the experimental procedures for synthesis of latifine were similar to those of synthesis of cherylline, all the intermediates are described as the 2,3-dimethoxy congeners.

Dimethyl 3,4-Dimethoxybenzalmalonate (4)——A solution of veratraldehyde (15 g), dimethyl malonate (17.3 g), benzoic acid (1.85 g), and piperidine (1.5 ml) in benzene (300 ml) was heated under reflux with a water separator (Dean–Starck) overnight. After cooling, the solution was washed with diluted HCl, aqueous Na_2CO_3 and water, and dried. Removal of the solvent gave the diester (**4**) (22.5 g), mp 129—132 °C. *Anal.* Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.69; H, 5.83.

The 2,3-dimethoxy congener (**12**) was obtained in 85% yield from 2,3-dimethoxybenzaldehyde (**11**). mp 67—68 °C. *Anal.* Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.83; H, 5.69.

Grignard 1,4-Addition to the Diester (4)——*p*-Methoxyphenylmagnesium bromide was prepared in the usual manner from magnesium, (4.7 g) and *p*-bromoanisole (25 ml) in tetrahydrofuran (413 ml). Copper iodide (30 mg) was added to the solution of the reagent under ice-salt cooling. To this solution was added a solution of the diester (**4**) (30 g) in tetrahydrofuran (100 ml) under ice-salt cooling with stirring, and the whole was stirred at room temperature overnight. After addition of an aqueous solution of NH_4Cl, the mixture was diluted with ether. The ethereal solution was washed with diluted HCl, aqueous Na_2CO_3, and water, and dried. Removal of the solvent left an oily residue which was chromatographed on silica gel in CH_2Cl_2. Elution with the same solvent gave *p*-methoxybiphenyl (7.8 g). mp 179—182 °C. *Anal.* Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.18; H, 6.46. Subsequent elution with the same solvent gave the diphenylmethyl-malonate (**5**) (37.3 g), which crystallized from EtOH–Et_2O, mp 150—153 °C. *Anal.* Calcd for $C_{21}H_{24}O_7$: C, 64.93; H, 6.23. Found: C, 64.90; H, 6.34. The 2,3-dimethoxy congener (**13**) was obtained in the same way as an oil, MS, M^+ Calcd for $C_{21}H_{24}O_7$ *m/z* 388.1522, Found: 388.1525.

Hydrolysis of the Diphenylmethylmalonate (5)——A solution of the diphenylmethylmalonate (**5**) (27.5 g) and K_2CO_3 (32 g) in EtOH (300 ml) and water (250 ml) was heated under reflux with stirring overnight and concentrated under reduced pressure. The resulting residue was dissolved in water. The aqueous solution was washed with ether, acidified with concentrated HCl and extracted with ethyl acetate. The extract was washed with salin, dried and concentrated under reduced pressure to give the diacid (**6**) (21.2 g) which was crystallized from ether–*n*-hexane, mp 167—170 °C. *Anal.* Calcd for $C_{19}H_{20}O_7 \cdot 3/2H_2O$: C, 58.91; H, 5.98. Found: C, 59.48; H, 6.05.

3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)propionic Acid (7)——The diphenylmethyl-malonic acid (**6**) (2.88 g) was heated at 160—200 °C (bath temperature) for 1 h. After heating, the residue was taken up in methylene chloride. The methylene chloride solution was washed with aqueous Na_2CO_3 solution. The aqueous washing was acidified with concentrated HCl and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to dryness to leave the acid (**7**) (2 g), which was crystallized from EtOH–Et_2O, mp 82—85 °C. *Anal.* Calcd for $C_{18}H_{20}O_5 \cdot 1/5H_2O$: C, 67.57; H, 6.36. Found: C, 67.78; H, 6.42. The 2,3-dimethoxy congener (**14**) was obtained from the diester (**13**) (3.24 g) by a hydrolysis with K_2CO_3 followed by heating in 71% yield without isolation of the corresponding diacid. mp 110—111 °C (from EtOH–Et_2O). IR ν_{max} ($CHCl_3$): 3430—2600, 1714 cm^{-1}(COOH). *Anal.* Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found; C, 68.24; H, 6.33.

6,7-Dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinol-1-one (8)——A mixture of the acid (**7**) (1.15 g), oxalyl chloride (3 ml), and benzene (30 ml) was stirred overnight and concentrated under reduced pressure to leave an oily residue which was taken up in dry acetone (12 ml). The acetone solution was added dropwise to a saturated solution of sodium azide (6 g) in water under cooling (ice-salt) with stirring. After 1 h of stirring, the solution was extracted with benzene. The benzene solution was washed with water, dried, refluxed for 1 h, and concentrated under reduced pressure to leave an oil. The oily residue was heated in phosphorus oxychloride (13 ml) at 90 °C (bath temperature) for 1 h. After removal of the reagent, the residue was dissolve in methylene chloride (16 ml). To this

solution was added a solution of stannic chloride (360 mg) in methylene chloride (2.6 ml) with stirring at room temperature. After 2 h of stirring, the solution was diluted with methylene chloride, washed with diluted HCl, aqueous Na_2CO_3, and water, and dried. Removal of the solvent gave a residue, which was chromatographed on silica gel in chloroform. Elution with the same solvent gave the lactam (**8**) (779 mg), which was crystallized from acetone–Et_2O, mp 177—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.63 (1H, s), 7.09 and 6.82 (2H each, d, J=8.5 Hz), 6.71 (1H, br s, NH), 6.43 (1H, s), 4.18 (1H, dd, J=4.5, 7 Hz), 3.93, 3.78, and 3.74 (3H each, s). IR ν_{max} (KBr): 3150 (NH), 1660 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.07; H, 6.37; N, 4.23.

Cyclization of the Dimethoxy Congener (14) with Stannic Chloride——The dimethoxy congener (**14**) (3.22 g) was treated in the same manner as described for the preparation of the lactam (**8**) using stannic chloride as a catalyst, and the same work-up gave a mixture which was chromatographed on silica gel in $CHCl_3$. Elution with $CHCl_3$ gave the rearranged product (**18**) (1.52 g) (47% yield), mp 109—110 °C. MS m/z: 313 (M^+). IR ν_{max} (KBr):1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.97 and 6.94 (2H each, d, J=9.2 Hz), 7.04 (1H, t, J=7.0 Hz), 6.94 and 6.88 (1H each, dd, J=7.0, 1.5 Hz), 5.90 (1H, dd, J=7.9 and 10.1 Hz), 4.47 (1H, dd, J=10.1, 14.3 Hz), 3.88 (1H, dd, J=7.9 and 14.3 Hz), 3.88, 3.87 and 3.85 (3H each, s). ^{13}C-NMR ($CDCl_3$, ppm): 163.49 (s), 162.08 (s), 152.57 (s), 146.04 (s), 135.13 (s), 129.93 (d), 124.21 (d), 120.39 (s), 117.73 (d), 113.72 (d), 112.23 (d), 76.58 (d), 62.77 (t), 60.74 (q), 55.78 (q), 55.29 (q). *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.98; H, 6.07; N, 4.42. Subsequent elution with the same solvent gave the lactam (**15**) (430 mg), which was crystallized from acetone–Et_2O, mp 168—170 °C. IR ν_{max} (KBr): 3400, 3180 (NH), 1670 cm^{-1} ($CHCl_3$), 3400, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.97 (1H, d, J=8.8 Hz), 7.04 and 6.78 (2H each, d, J=8.8 Hz), 6.98 (1H, d, J=8.8 Hz), 5.68 (1H, br d, J=5.1 Hz, NH), 4.55 (1H, dd, J=4.8, 1.5 Hz), 3.89 (1H, dd, J=12.5, 4.8 Hz), 3.91, 3.75, and 3.46 (3H each, s), 3.47 (1H, ddd, J=12.5, 5.1, 1.5 Hz). When boron trifluoride etherate was used as the cyclization catalyst in place of stannic chloride, the lactam (**15**) was obtained as a sole product in 87% yield.

***N*-Methylation of the Lactam (8)**——A suspension of the lactam (**8**) (770 mg) and sodium hydride (880 mg in mineral oil-coated state) in benzene (90 ml) was heated under reflux for 1 h. After cooling of the mixture, methyl iodide (9 ml) was added, and the whole was refluxed with stirring overnight. The excess reagent was decomposed by addition of acetic acid and the solution was diluted with benzene. The benzene solution was washed with diluted HCl, aqueous Na_2CO_3, and water, and dried. Removal of the solvent left a residue which was chromatographed on silica gel in $CHCl_3$. Elution with the same solvent gave the *N*-methyl-lactam (**9**) (440 mg) which was crystallized from benzene–Et_2O, mp 127—130 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.63 (1H, s), 7.06 and 6.80 (2H each, d, J=9.0 Hz), 6.36 (1H, s), 4.16 (1H, dd, J=5.0, 7.5 Hz), 3.92, 3.76, and 3.72 (3H each, s), 3.03 (3H, s). IR ν_{max} (Nujol): 1640 cm^{-1}. *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.91; H, 6.55; N, 4.13.

The 2,3-dimethoxy congener (**16**) was obtained in the same way in 81% yield, mp 135—136 °C. *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.70; H, 6.46, N, 4.28. Found: C, 69.52; H, 6.44; N, 4.26. ^{1}H-NMR ($CDCl_3$) δ: 7.96 (1H, d, J= 8.8 Hz), 7.02 and 6.77 (2H each, d, J=8.8 Hz), 6.95 (1H, d, J=8.8 Hz), 4.47 (1H, dd, J=4.6, 1.5 Hz), 4.06 (1H, dd, J=12.5, 4.6 Hz), 3.38 (1H, dd, J=12.5, 1.5 Hz), 3.89, 3.75, and 3.46 (3H each, s), 2.97 (3H, s). IR ν_{max} (KBr): 1645 cm^{-1}.

Demethylation of the *N*-Methyl-lactam (9)——A solution of the *N*-methyl-lactam (**9**) (327 mg) and methyl sulfide[6] (186 mg) in methanesulfonic acid (2 ml) was heated with stirring at 50 °C (bath temperature) overnight, diluted with ice-water, neutralized with Na_2CO_3 to a slightly acidic state, and extracted with ethyl acetate. The organic extract was washed with water and dried. Removal of the solvent left a residue which was chromatographed on silica gel in $CHCl_3$. Elution with the same solvent gave the phenol-lactam (**10**) (143 mg), mp 223—226 °C (from EtOH–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 9.67—8.33 (2H, br), 7.36 (1H, s), 6.97 and 6.69 (2H each, d, J=8.3 Hz), 6.52 (1H, s), 4.05 (1H, dd, J=4.5, 5.9 Hz), 3.67 (3H, s), 2.90 (3H, s). IR ν_{max} (Nujol): 3415, 3300 (OH), 1635 cm^{-1}. *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.44; H, 5.72; N, 4.42. The 2,3-dimethoxy congener (**17**), mp 285—286 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.16 and 8.80 (1H each, br s), 7.46 (1H, d, J=8.6 Hz), 6.99 (1H, d, J= 8.6 Hz), 6.84 and 6.61 (2H each, d, J=8.6 Hz), 4.31 (1H, dd, J=4.4, 1.4 Hz), 3.94 (1H, dd, J=12.5, 4.4 Hz), 3.84 (3H, s), 3.44 (1H, dd, J=12.5, 1.4 Hz), 2.83 (3H, s). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 67.97; H, 5.72; N, 4.67.

(±)-Cherylline (1)——A solution of the phenol-lactam (**10**) (100 mg) and lithium aluminium hydride (60 mg) in tetrahydrofuran (20 ml) was heated under reflux with stirring for 5 h. After addition of aqueous ammonium chloride, the solution was diluted with $CHCl_3$ and the whole was washed with water and dried. Removal of the solvent gave (±)-cherylline (**1**) (46 mg), which was crystallized from EtOH–Et_2O, mp 214—217 °C. The NMR-spectral data of the synthetic specimen were in accord with the reported values. *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N. 4.91. Found: C, 71.28; H. 6.69; N, 4.85.

(±)-Latifine (2)——A solution of the phenolic lactam (**17**) (200 mg) and lithium aluminium hydride (60 mg) in tetrahydrofuran (20 ml) was heated under reflux for 7 h. After addition of aqueous ammonium chloride, an appropriate amount of EtOAc was added. The solution was washed with a small amount of water and dried. Removal of the solvent left (±)-latifine (**2**) (160 mg) which was crystallized from MeOH, mp 211—214 °C. *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.31; H, 6.71; N, 4.86. The ^{1}H-NMR spectrum of the synthetic (±)-latifine (**2**) was identical with that of an authentic specimen of (±)-latifine (**2**) provided by Professor S.

Kobayashi (Tokushima University).

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References and Notes

1) A. Brossi and S. Teitel, *Tetrahedron Lett.*, **1970**, 417; *idem, J. Org. Chem.*, **35**, 3559 (1970); M. A. Schwartz and S. W. Scott, *ibid.*, **36**, 1827 (1971); T. Kametani, K. Takahashi, and C. V. Loc, *Tetrahedron*, **31**, 235 (1975); P. J. Hart, F. A. Cain, and D. A. Evans, *J. Am. Chem. Soc.*, **100**, 1548 (1978); H. Irie, A. Shiina, T. Fushimi, J. Katakawa, N. Fujii, and H. Yajima, *Chem. Lett.*, **1980**, 875; S. V. Kessar, P. Singh, R. Chawla, and P. Kumar, *J. Chem. Soc., Chem. Commun.*, **1981**, 1074; T. Kametani, K. Higashiyama, T. Honda, and H. Otomasu, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2935; H. Hara, R. Shirai, O. Hoshino, and B. Umezawa, *Heterocycles*, **20**, 1945 (1983); *idem, Chem. Pharm. Bull.*, **33**, 3107 (1985); T. Nomoto, N. Nasui, and H. Takayama, *J. Chem. Soc., Chem. Commun.*, **1984**, 1646; S. Takano, M. Akiyama, and K. Ogasawara, *Chem. Lett.*, **1985**, 505; *idem, J. Chem. Soc., Perkin Trans. 1*, **1985**, 2447; S. Kobayashi, T. Tokumoto, S. Iguchi, M. Kihara, Y. Imakura, and Z. Taira, *J. Chem. Research (S)*, **1986** 280.
2) A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, and D. T. Bailey, *J. Org. Chem.*, **35**, 1100, (1970); V. Toome, J. F. Blount, G. Grethe, and M. Uskokovic, *Tetrahedron Lett.*, **1970**, 49.
3) S. Kobayashi, T. Tokumoto, and Z. Taira, *J. Chem. Soc., Chem. Commun.*, **1984**, 1043.
4) Y. Tsuda, K. Isobe, J. Toda, and J. Taga, *Heterocycles*, **5**, 157 (1976); T. Fushimi, H. Ikuta, H. Irie, K. Nakadachi, and S. Uyeo, *ibid.*, **12**, 1311 (1979); H. Irie, A. Shiina, T. Fushimi, J. Katakawa, N. Fujii, and H. Yajima, *Chem. Lett.*, **1980**, 875.
5) N. Fujii, H. Irie, and H. Yajima, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2288.
6) Though we had previously used methionine as a soft base, methyl sulfide gave better results.