[Chem. Pharm. Bull. 34(4)1584—1588(1986)]

An Enantioselective Total Synthesis of (−)-Dihydrocorynantheol

Toshio Suzuki,*,[a] Etsuko Sato,[a] Katsuo Unno,[a] and Tetsuji Kametani*,[b]

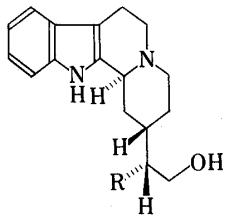
Department of Pharmacy, Akita University Hospital,[a] Hondo, Akita 010, Japan and Institute of Medicinal Chemistry, Hoshi University,[b] Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

(Received September 27, 1985)

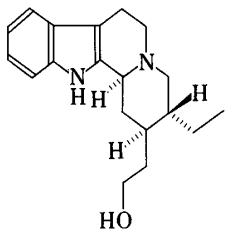
The total synthesis of (−)-dihydrocorynantheol (**3**) has been achieved using a potentially useful chiral synthon, thioketal carboxylic acid (**8**), derived from (*R*)-1,2-isopropylideneglyceraldehyde (**4**) in 7 steps.

Keywords——enantioselective total synthesis; (−)-dihydrocorynantheol; (*R*)-1,2-isopropylideneglyceraldehyde; chiral synthon; Corynanthe-type indole alkaloid

In connection with a project devoted to the total synthesis of natural products, we have been interested in the enantioselective synthesis of Corynanthe-type indole alkaloids using carbohydrates as starting materials. Recently we reported the enantioselective syntheses of (−)-antirhine (**1**)[1] and (+)-dihydroantirhine (**2**),[2] a unique Corynanthe variant indole alkaloid, *via* the β,γ-unsaturated aldehyde (**6**) and the α,β-unsaturated aldehyde (**7**) using a potentially useful chiral synthon, (3*R*)-[3-hydroxy-(*E*)-prop-1-enyl]cyclopentanone (**5**)[3] derived from (*R*)-1,2-isopropylideneglyceraldehyde (**4**).[4] We next studied an application of the chiral synthon (**8**) obtained from the above α,β-unsaturated aldehyde (**7**) to the synthesis of (−)-dihydrocorynantheol (**3**), a Corynanthe-type indole alkaloid, which was firstly isolated from *Aspidosperma marcgravianum* by Gilbert *et al.*[5] (+)-Dihydroantirhine (**2**) was synthesized by linking tryptamine with the thioketal and carboxylic acid groups in **8** as a key intermediate. (−)-Dihydrocorynantheol (**3**) could also be built up by linking tryptamine with the thioketal and *tert*-butyldimethylsilyloxy groups in **8**. Although the total synthesis of racemic forms of **3**[6] was achieved, no enantioselective synthesis of (−)-**3** has previously been accomplished. Here we wish to report the first total synthesis of (−)-dihydrocorynantheol (**3**) from (*R*)-1,2-isopropylideneglyceraldehyde (**4**).



1 : R=CH=CH$_2$
2 : R=Et



3

Chart 1

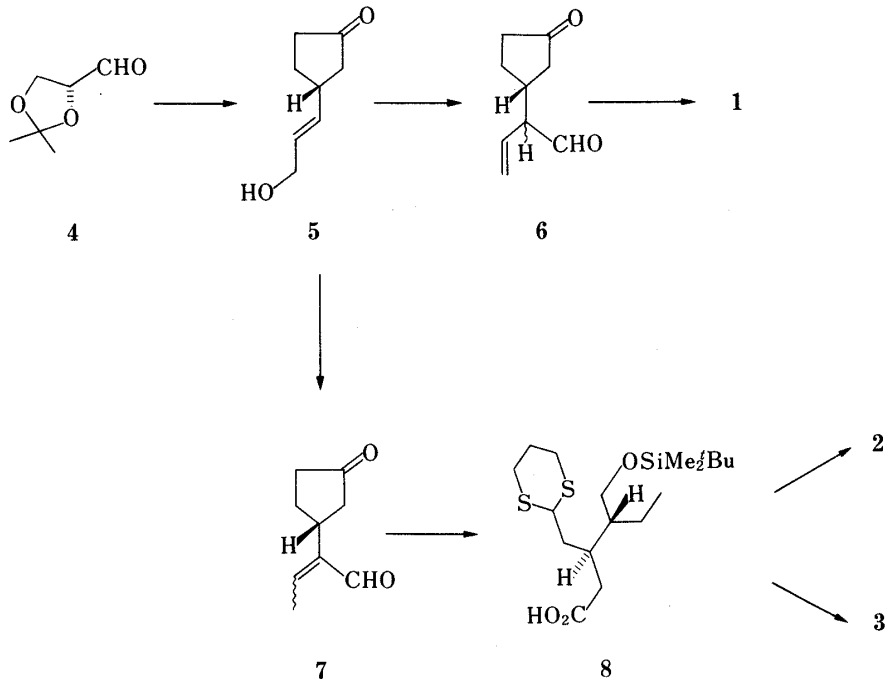


Chart 2

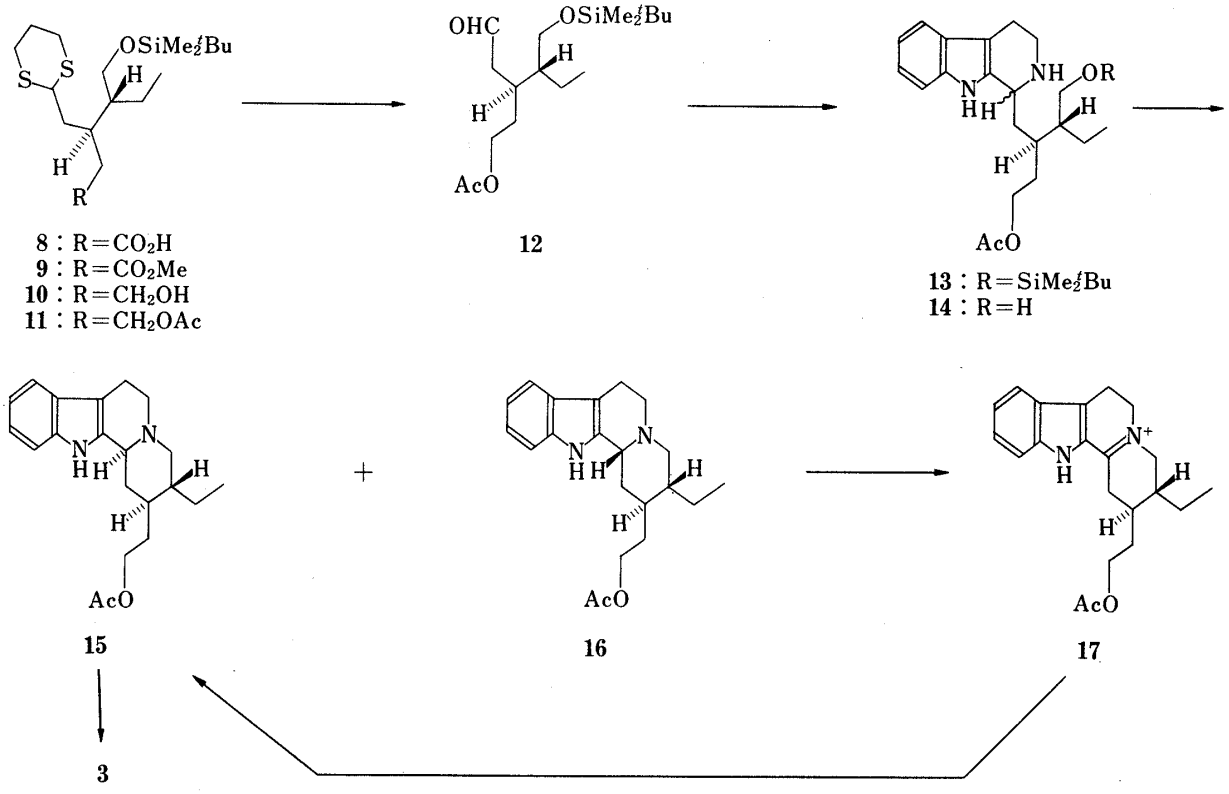


Chart 3

Esterification of the known carboxylic acid (**8**), prepared in 9 steps from **5**,[2] with diazomethane gave the methyl ester (**9**). Reduction of **9** with diisobutylaluminum hydride in tetrahydrofuran at $-70\,^{\circ}C$, followed by acetylation of the alcohol (**10**) with acetic anhydride in pyridine, provided the acetate (**11**) in 92.8% overall yield from **9**.

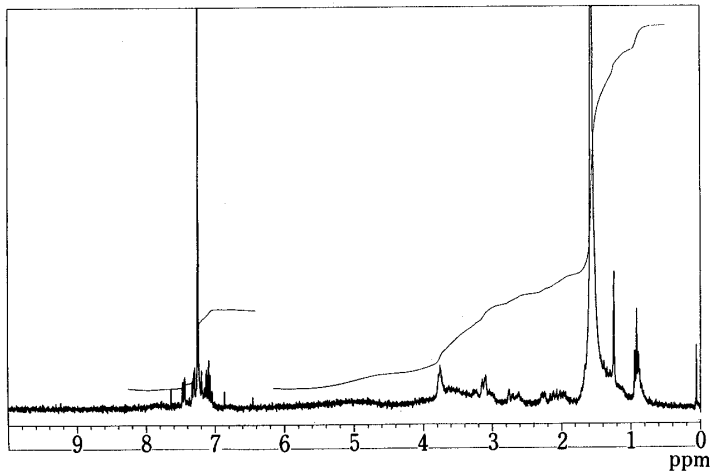


Fig. 1. The NMR Spectrum of Authentic (±)-Dihydrocorynantheol

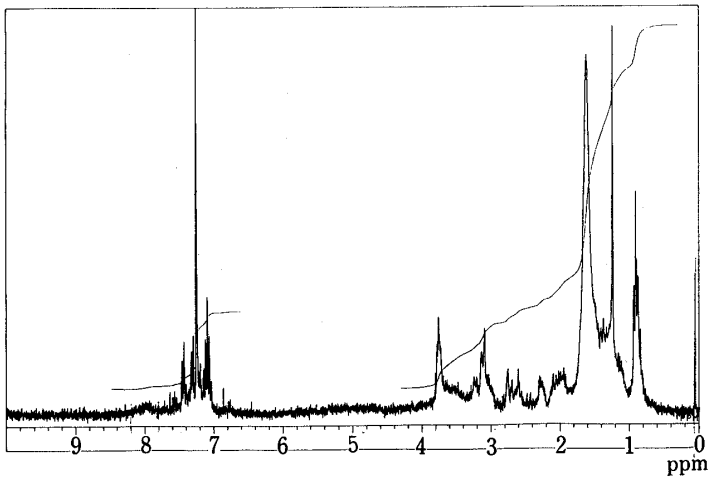


Fig. 2. The NMR Spectrum of Synthetic (−)-Dihydrocorynantheol

Hydrolysis[7] of the dithiane group in **11** with methyl iodide in aqueous acetonitrile in the presence of sodium carbonate, followed by condensation with tryptamine in acetic acid, afforded the secondary amine (**13**) *via* the aldehyde (**12**), which in turn was deprotected with tetrabutylammonium fluoride in tetrahydrofuran (THF) to give the alcohol (**14**) in almost quantitative yield from **11**. Treatment of **14** with methanesulfonyl chloride in pyridine resulted in cyclization to give a separable mixture of **15** and **16** in 29.5 and 26.1% yields, respectively. In order to confirm the relationship between **15** and **16**, transformation of **16** to **15** was examined. Dehydrogenation of **16** with mercuric acetate,[7d,8] followed by reduction with sodium borohydride[7d,8,9] proceeded smoothly to give **15** in addition to the starting material **16** *via* the iminium base (**17**). These conversions indicated that these compounds are C(3) epimers.

Finally, deacetylation of **15** with potassium carbonate in methanol afforded (−)-dihydrocorynantheol (**3**) {$[\alpha]_D$ −20.0° (c=0.03, $CHCl_3$)} {lit.[5] $[\alpha]_D$ −19° (c=1.02, $CHCl_3$)} in quantitative yield.

This synthetic substance had identical thin layer chromatographic behavior, and infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR) and mass spectra (MS) with those of authentic dihydrocorynantheol. Thus, the transformation of (*R*)-1,2-isopropylideneglyceraldehyde *via* the thioketal carboxylic acid (**8**) into (−)-dihydrocorynantheol (**3**) has been achieved.

Experimental

IR spectra were recorded on Shimadzu IR-400 and JASCO IR-810 spectrophotometers. MS were obtained with a JEOL-JMS-01-SG-2 spectrometer. ^{1}H-NMR spectra were taken for solutions in deuteriochloroform with tetramethylsilane as an internal standard on JEOL JNM-PMX-60 and JNM-GX270 instruments. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.

Methyl [(4*R*)-*tert*-Butyldimethylsilyloxymethyl-(3*S*)-(2-trimethylenedithio)ethyl]hexanoate (9)——The carboxylic acid (**8**) (186 mg, 0.477 mmol) in ether was treated with an excess of diazomethane. After usual work-up, the residue was subjected to chromatography on silica gel. Elution with chloroform afforded the methyl ester (**9**) (135 mg, 69.8%) as a pale yellow syrup: $[\alpha]_D$ +0.6° (c=0.130, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1731 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s, $SiMe_2$), 0.90 (9H, s, Si^{t}Bu), 2.67—3.00 (4H, m, $SC\underline{H}_2CH_2C\underline{H}_2S$), 3.52 (2H, d, J=5 Hz, CH_2OSi), 3.63 (3H, s, CO_2CH_3). MS m/z: 349 ($M^+ - {}^t$Bu).

[(4*R*)-*tert*-Butyldimethylsilyloxymethyl-(3*S*)-(2-trimethylenedithio)ethyl]hexyl Acetate (11)——Diisobutylaluminum hydride (1.76 mol in hexane) (0.66 ml, 1.16 mmol) was added dropwise to a solution of **9** (118 mg, 0.291 mmol) in THF (3.2 ml) at −70 °C under nitrogen, and the mixture was stirred for 2.5 h at the same temperature. The reaction was quenched with saturated ammonium chloride solution and the mixture was extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate and then concentrated to yield the practically pure alcohol (**10**) (106 mg) as a pale yellow syrup, which was used in the next reaction without further purification.

A mixture of **10** and acetic anhydride (0.4 ml) in pyridine (0.4 ml) was stirred for 12 h at room temperature. Water was added to the mixture and the solvent was evaporated to leave a residue, which was extracted with ether. The extract was washed with brine, dried over magnesium sulfate and then evaporated. The resultant residue was subjected to column chromatography on silica gel with 5% ethyl acetate–hexane as an eluent to provide the acetate (**11**) (114 mg, overall 92.8% from **9**) as a colorless syrup: $[\alpha]_D$ −2.6° (c=0.156, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s, $SiMe_2$), 0.90 (9H, s, Si^{t}Bu), 2.02 (3H, s, $COCH_3$), 2.68—3.00 (4H, m, $SC\underline{H}_2CH_2C\underline{H}_2S$), 3.50 (2H, d, J=5 Hz, CH_2OSi), 4.03 (2H, t, J=6 Hz, $C\underline{H}_2COCH_3$), 4.10 (1H, t, J=7 Hz, SCHS). MS m/z: 363 ($M^+ - {}^t$Bu).

[(2*R*)-(2-Acetoxyethyl)-(3*R*)-*tert*-butyldimethylsilyloxymethylpentyl]-1,2,3,4-tetrahydro-β-carboline (13)——A mixture of methyl iodide (1.92 g, 13.5 mmol), water (0.5 ml) and sodium bicarbonate (715 mg, 6.75 mmol) was added to a stirred solution of **11** (114 mg, 0.270 mmol) in acetonitrile (4.4 ml). After being stirred for 14 h at room temperature, the reaction mixture was diluted with chloroform. The organic layer was separated, washed with brine and then dried over magnesium sulfate. The solvent was removed to give the aldehyde (**12**) (94.7 mg) as a pale yellow syrup: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, $SiMe_2$), 0.87 (9H, s, Si^{t}Bu), 2.02 (3H, s, $COCH_3$), 3.53 (2H, d, J=5 Hz, CH_2OSi), 4.05 (2H, t, J=6 Hz, $C\underline{H}_2OCOCH_3$), 9.87 (1H, d, J=2 Hz, CHO). This syrup was used in the next reaction without further purification because of the lability of the compound.

A mixture of **12** and tryptamine (127 mg, 0.297 mmol) in acetic acid (2 ml) was stirred for 1 h at room temperature under nitrogen. The mixture was basified with 10% ammonium hydroxide solution and then extracted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to leave a residue, which was chromatographed on silica gel with 40% acetone–benzene as an eluent to give the secondary amine (**13**) (127 mg, quantitative yield) as a pale yellow syrup: $[\alpha]_D$ +4.18° (c=0.670, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (ArNH), 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.02 (6H, s, $SiMe_2$), 0.93 (9H, s, Si^{t}Bu), 2.02 (3H, s, $COCH_3$), 4.10 (2H, t, J=6 Hz, CH_2OCOCH_3), 6.77—7.60 (4H, m, ArH), 8.37—8.57 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{27}H_{44}N_2O_3Si$ (M^+): Calcd m/z 472.3122; Found 472.3139.

[(2*R*)-(2-Acetoxyethyl)-(3*R*)-hydroxymethylpentyl]-1,2,3,4-tetrahydro-β-carboline (14)——A solution of tetrabutylammonium fluoride (1 mol in THF) (55 μl, 0.0556 mmol) was added dropwise to a stirred solution of **13** (13.1 mg, 0.0278 mmol) in THF (0.1 ml) and the mixture was stirred for 1 h at room temperature. The mixture was extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate and then evaporated to leave a residue, which was subjected to chromatography on silica gel with 2% methanol–chloroform to afford the alcohol (**14**) (10 mg, quantitative yield) as a pale brown syrup: $[\alpha]_D$ +28.0° (c=0.314, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (ArNH), 3400—3100 (OH), 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s, $COCH_3$), 4.03 (2H, t, J=6 Hz, $C\underline{H}_2OCOCH_3$), 6.67—7.35 (4H, m, ArH), 8.10—8.53 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{21}H_{30}N_2O_3$ (M^+): Calcd m/z 358.2255; Found 358.2210.

Dihydrocorynantheol Acetate (15) and 3-*epi*-Dihydrocorynantheol Acetate (16)——A solution of methanesulfonyl chloride (19.2 mg, 0.168 mmol) in dichloromethane (0.4 ml) was added to a solution of **14** (40 mg, 0.112 mmol) in pyridine (1 ml) and the mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of water and the solvent was evaporated off to leave a residue, which was basified with 10% ammonium hydroxide solution, and extracted with chloroform. The extract was washed with brine and then dried over magnesium sulfate. The solvent was removed to leave a residue, which was purified by preparative thin-layer chromatography (TLC) on silica gel developed with benzene–acetone (2:1, v/v) to yield dihydrocorynantheol acetate (**15**) (11.2 mg, 29.5%) as a pale yellow syrup: Rf=0.68 (benzene–acetone (2:1, v/v)). $[\alpha]_D$ +46.2° (c=0.026, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3474

(ArNH), 1731 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.02 (3H, s, $COCH_3$), 4.05 (2H, t, J=6 Hz, CH_2OCOCH_3), 6.77—7.42 (4H, m, ArH), 7.50—7.90 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{21}H_{28}N_2O_2$ (M^+): Calcd m/z 340.2149; Found 340.2144 and 3-*epi*-dihydrocorynantheol acetate (**16**) (9.9 mg, 26.1%) as a pale yellow syrup: Rf= 0.58 (benzene–acetone (2:1, v/v)). $[\alpha]_D$ +27.8° (c=0.036, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3474 (ArNH), 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.02 (3H, s, $COCH_3$), 4.13 (2H, t, J=6 Hz, CH_2OCOCH_3), 6.97—7.55 (4H, m, ArH), 7.80—8.20 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{21}H_{28}N_2O_2$ (M^+): Calcd m/z 340.2149; Found 340.2122.

Epimerization of 3-*epi*-Dihydrocorynantheol Acetate (16) to Dihydrocorynantheol Acetate (15)——A mixture of **16** (1.2 mg, 0.00353 mmol) and mercuric acetate (2.8 mg, 0.00883 mmol) in acetic acid (0.1 ml) was stirred for 16 h at room temperature. The solvent was evaporated off to give the iminium base (**17**), which was used in the next reaction without further purification.

Sodium borohydride (1 mg, 0.0264 mmol) was added to a stirred solution of **17** in methanol (0.3 ml) at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with water and the mixture was concentrated. The resultant residue was basified with 10% ammonium hydroxide solution and then extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate and evaporated to leave a residue, which was purified by preparative TLC on silica gel developed with benzene–acetone (2:1, v/v) to give **15** (0.7 mg, 58%) along with the starting material **16** (0.3 mg, 25%).

(−)-Dihydrocorynantheol (3)——Potassium carbonate (4 mg, 0.0289 mmol) was added to a solution of **15** (2 mg, 0.00588 mmol) in methanol (0.1 ml), and the mixture was stirred for 3 h at room temperature. The solvent was removed to leave a residue, which was extracted with chloroform. The extract was washed with brine and dried over magnesium sulfate. Evaporation of the solvent left a residue, which was purified by preparative TLC on silica gel developed with benzene–acetone (1:3, v/v) to give (−)-dihydrocorynantheol (**3**)[10] (1.8 mg, quantitative yield) $[\alpha]_D$ −20.0° (c=0.03, $CHCl_3$) [lit.[5] $[\alpha]_D$ −19° (c=1.02, $CHCl_3$)]. High-MS for $C_{19}H_{26}N_2O$ (M^+): Calcd m/z 298.2043; Found 298.2041. The IR and ^{1}H-NMR spectra, and TLC behavior of the product were identical with those of authentic (±)-dihydrocorynantheol.

Acknowledgement We thank Nippon Denshi Co., Ltd., for 270 MHz ^{1}H-NMR spectral measurement.

References and Notes

1) T. Suzuki, E. Sato, K. Unno, and T. Kametani, *Heterocycles*, **23**, 839 (1985).
2) T. Kametani, T. Suzuki, E. Sato, M. Nishimura, and K. Unno, *J. Chem. Soc., Chem. Commun.*, **1982**, 1201.
3) T. Kametani, T. Suzuki, E. Sato, M. Nishimura, and K. Unno, *J. Chem. Soc., Chem. Commun.*, **1982**, 123.
4) H. Fischer and E. Baer, *Helv. Chim. Acta*, **17**, 622 (1934); E. Baer and H. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).
5) B. Gilbert, L. D. Autonaccio, and C. Djerrasi, *J. Org. Chem.*, **27**, 4702 (1962).
6) C. Vamvacas, W. V. Philpsborn, E. Schlittler, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **40**, 1793 (1957); F. E. Ziegler and J. G. Sweeny, *Tetrahedron Lett.*, **1969**, 1097; T. Kametani, N. Kanaya, H. Hino, S. Hung, and M. Ihara, *Heterocycles*, **14**, 1771 (1980); S. Takano, K. Shibuya, M. Takahashi, S. Hatakeyama, and K. Ogasawara, *ibid.*, **16**, 1125 (1981); B. Daniele, G. Lesma, G. Palmisano, and S. Tollari, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1237.
7) *a*) M. Fetizon and M. Jurion, *J. Chem. Soc., Chem. Commun.*, **1972**, 382; *b*) S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Am. Chem. Soc.*, **98**, 3022 (1976); *idem, ibid.*, **101**, 6414 (1979); *c*) S. Takano, M. Takahashi, and K. Ogasawara, *ibid.*, **102**, 4282 (1980); *d*) S. Takano, K. Masuda, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1980**, 887.
8) N. J. Dastoor, A. A. Gorman, and J. Schmid, *Helv. Chim. Acta*, **50**, 213 (1967); H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, **1963**, 1461; S. Takano, S. Hatakeyama, and K. Ogasawara, *Tetrahedron Lett.*, **1978**, 2519.
9) E. Wenkert, K. G. Dave, and F. Haglid, *J. Am. Chem. Soc.*, **87**, 5461 (1965).
10) Crystallization of **3** was difficult because of the small amount obtained. (−)-Dihydrocorynantheol (**3**); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (ArNH), 3400—3200 (OH), 2900—2700 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7 Hz, CH_2CH_3), 2.54—2.87 (2H, m, $ArCH_2$), 2.95—3.29 (4H, m, $NCH_2 \times 2$), 3.64—3.80 (2H, m, CH_2OH), 7.00—7.48 (4H, m, ArH), 7.80—8.20 (1H, br s, ArNH).