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The Chemistry of Indoles. XXVII.[1] A Practical Synthesis of the 1-Methoxy Analog of an Ergot Alkaloid, (±)-1-Methoxy-6,7-secoagroclavine

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The first syntheses of 1-methoxy analogs of ergot alkaloids, (±)-1-methoxy-6,7-secoagroclavine and (±)-1-methoxy-6-nor-6,7-secoagroclavine, were achieved with good overall yield in only nine steps from 2-nitrotoluene.

Keywords——2-nitrotoluene; 1-methoxyindole; thallation; 4-iodo-1-methoxy-3-indolecarbaldehyde; ergot alkaloid; (±)-1-methoxy-6-nor-6,7-secoagroclavine; (±)-1-methoxy-6,7-secoagroclavine; 4,5-*trans*-1-methoxy-5-(2-methyl-1-propenyl)-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole

As a part of our synthetic studies on 1-hydroxy- and 1-methoxy-indoles,[2] we have disclosed that although 1-methoxyindoles are generally unstable compounds, they are much more stable than the corresponding 1-hydroxyindoles. Therefore, it is not surprising that many 1-methoxyindole derivatives have been isolated from plants and microorganisms.[3] The existence of 1-methoxyindoles as natural products clearly suggests that the corresponding unstable 1-hydroxyindoles are probably present and might play an important role *in vivo*. Thus, we are interested in the synthesis of 1-hydroxy or 1-methoxy analogs of biologically active indole alkaloids.[4] Now, we have succeeded in the first synthesis of (±)-1-methoxy-6,7-secoagroclavine (**15a**) by a practical route from 2-nitrotoluene (**1**) in only nine steps with an overall yield of 20%. In this paper, we describe these results in detail.

1-Methoxyindole (**4**) is readily available from **1** according to our one-step synthetic method[2b] which consists of the following sequential operations: 1) preparation of the enamine (**2**) with dimethylformamide dimethyl acetal, 2) formation of 1-hydroxyindole (**3**), and 3) methylation of **3**. However, in a large-scale preparation, the yield of **4** depended significantly on the reaction conditions. After considerable research, it turned out that the yield of **4** was governed by the yield of the enamine (**2**), and addition of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) in the first operation increased the yield. As a result of this improvement, the yield of **4** became reproducible in the range of 69%—62% irrespective of the scale (100 mg—14 g).

Conventional Vilsmeier–Haack reaction of **4** with absolute *N*,*N*-dimethylformamide (DMF) and phosphorus oxychloride readily afforded 1-methoxy-3-indolecarbaldehyde[5] (**5**) in 91% yield. Treatment of **5** with 1.5 mol eq of thallium tristrifluoroacetate (TTFA) in trifluoroacetic acid[6] (TFA) and subsequent evaporation of the solvent afforded a residue containing (3-formyl-1-methoxyindole-4-yl)thallium bistrifluoroacetate (**6**). Without isolation of **6**, the residue was immediately treated with aqueous potassium iodide to afford the desired 4-iodo-1-methoxy-3-indolecarbaldehyde (**7**) in 91% yield.

Introduction of the C-5 unit into the 4-position was successfully carried out by applying the Heck reaction.[7,8] Thus, **7** was reacted at 90 °C with 2-methyl-3-buten-2-ol in the presence of triethylamine and a catalytic amount of palladium acetate to afford 4-(3-hydroxy-3-methyl-1-butenyl)-1-methoxy-3-indolecarbaldehyde (**8**) in 93% yield. When this reaction was carried

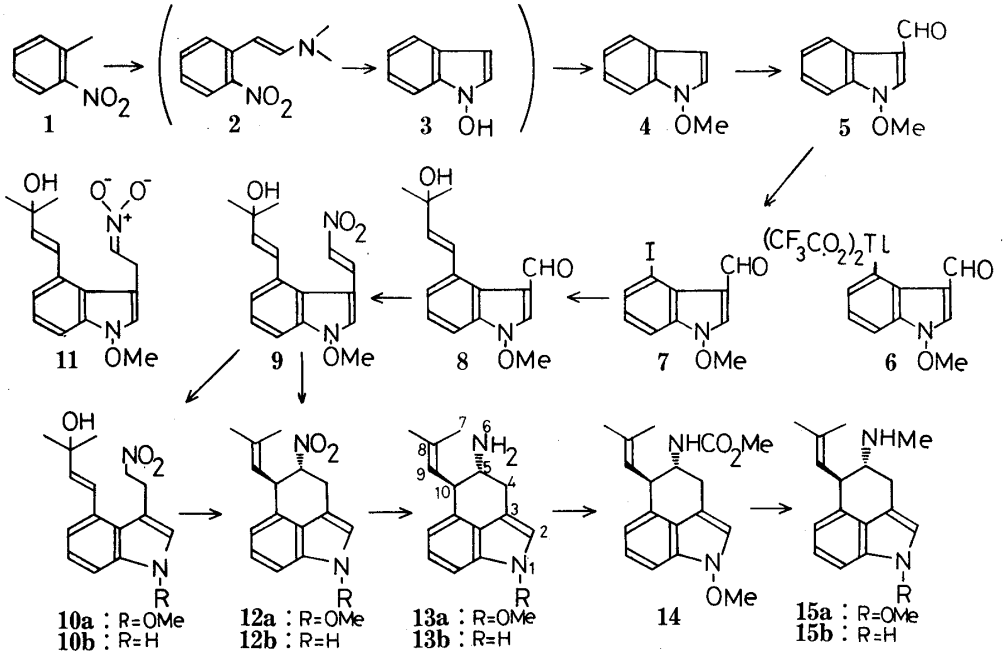

Chart 1

out at a higher reaction temperature, the yield of **8** decreased significantly.

This compound (**8**) underwent aldol condensation reaction with nitromethane to give 4-(3-hydroxy-3-methyl-1-butenyl)-1-methoxy-3-(2-nitrovinyl)indole (**9**) in 97% yield. Subsequent reduction of **9** with sodium borohydride ($NaBH_4$) in methanol (MeOH) afforded 4-(3-hydroxy-3-methyl-1-butenyl)-1-methoxy-3-(2-nitroethyl)indole (**10a**) in 79% yield. Intramolecular cyclization of **10a** was successfully carried out under conditions essentially identical to those required for **10b**[8] without any demethoxylation. Thus, hydrochloric acid (HCl)-catalyzed cyclization of the nitronate anion (**11**), prepared by the reaction of **10a** with $NaBH_4$ in MeOH, gave the desired 4,5-*trans*-1-methoxy-5-(2-methyl-1-propenyl)-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**12a**) in 64% yield as a sole product. The relative stereochemistry of the nitro and 2-methyl-1-propenyl groups was supposed to be the thermodynamically stable *trans* form based on the similarity of its proton nuclear magnetic resonance (^{1}H-NMR) spectrum to that of **12b**[8] and was finally determined by converting it to (±)-6,7-secoagroclavine (**15b**). As expected, the compound (**12a**) could also be prepared directly from **9** in 64% yield by the reaction with $NaBH_4$ in MeOH and subsequent treatment of the resulting solution containing **11** with 2 N HCl.

Reduction of **12a** with zinc amalgam in refluxing methanolic HCl for 10 min afforded 1-methoxy-6-nor-6,7-secoagroclavine (**13a**) and the corresponding demethoxy compound (**13b**) in 86% and 14% yields, respectively. Due to the inherent instability of 1-methoxyindole derivatives, the yield of **13b** increased in proportion to the length of the reaction time. Compound **13b** was identical with an authentic sample of 6-nor-6,7-secoagroclavine prepared according to our previous procedure.[8]

Methoxycarbonylation of **13a** was readily achieved by the reaction with methyl chloroformate to give 1-methoxy-6-methoxycarbonyl-6-nor-6,7-secoagroclavine (**14**) in 93% yield. Reduction of **14** with lithium aluminum hydride ($LiAlH_4$) in refluxing tetrahydrofuran (THF) for 35 min afforded the desired 1-methoxy-6,7-secoagroclavine (**15a**) and 6,7-secoagroclavine (**15b**) in 77% and 20% yields, respectively. When **15a** was reacted with $LiAlH_4$ in refluxing THF for 6.5 h, **15b** was produced in 82% yield. This compound (**15b**) was identical with the authentic (±)-6,7-secoagroclavine prepared in our previous work.[8]

Thus, the 1-methoxy analog of an ergot alkaloid, 1-methoxy-6,7-secoagroclavine, was produced in nine steps with an overall yield of 20% starting from **1**. This synthetic route is suitable for large-scale production. Biological evaluation of the compounds obtained in this work is in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with a JEOL JNM-PMX 60 or FX-100 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 spectrometer. Preparative thin-layer chromatography (pTLC) was performed on Merck Kiesel-gel GF_{254} (Type 60) (SiO_2). Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

1-Methoxyindole (4) from 2-Nitrotoluene (1)——A mixture of 2-nitrotoluene (13.908 g), dimethylformamide dimethyl acetal (25.479 g), DBU (1.546 g), and absolute DMF (110 ml) was refluxed for 35 h with stirring. After evaporation of the solvent *in vacuo*, the red-colored residue (crude enamine, **2**) was dissolved in ether (650 ml). To this ether solution, zinc powder (63.080 g) and a solution of NH_4Cl (20.038 g) in H_2O (140 ml) were added with vigorous stirring. After additional stirring of the mixture for 3 h at room temperature, insoluble zinc was filtered off through silica gel and the filtrate was washed with sat. aq. $NaHCO_3$. To the ether solution containing 1-hydroxyindole (**3**), MeI (32.9 ml), 10% aq. NaOH (700 ml), and tri(*n*-octyl)methylammonium chloride (4.619 g) were added. The whole was stirred for 21 h at room temperature, then the organic layer was separated. The aqueous layer was extracted with ether and the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil. Purification by column chromatography on SiO_2 with hexane–CH_2Cl_2 (7:3, v/v) as an eluent gave **4** (10.230 g, 68.6%) as a colorless oil.[2b]

1-Methoxy-3-indolecarbaldehyde (5) from 4——Phosphorus oxychloride (8.4 ml) was added to ice-cooled absolute DMF (31.0 ml) with stirring. A solution of **4** (12.341 g) in absolute DMF (10.0 ml) was added to the resultant viscous solution and stirring was continued for 2 h at room temperature. Then, crushed ice and 16% aq. NaOH (100 ml) were added to the reaction mixture and the whole was extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a crystalline solid. Repeated recrystallization from ether–hexane afforded **5** (13.411 g, 91.3%) as colorless prisms. mp 50.0—51.0 °C. IR (KBr): 2810, 1660—1650, 1375, 1240 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 3.98 (3H, s), 6.81—7.31 (3H, m), 7.52 (1H, s), 7.80—8.16 (1H, m), 9.57 (1H, s). MS *m/e*: 175 (M^+). *Anal.* Calcd for $C_{10}H_9NO_2 \cdot 1/2H_2O$: C, 66.84; H, 5.33; N, 7.80. Found: C, 67.04; H, 5.11; N, 7.89.

4-Iodo-1-methoxy-3-indolecarbaldehyde (7) from 5——A solution of 0.88 mol of TTFA in TFA[6] (20.6 ml) was added to a solution of **5** (2.115 g) in TFA (65 ml), and the mixture was stirred for 19 h at 45—50 °C. After evaporation of the solvent under reduced pressure, the residue was suspended in H_2O (60 ml) and then a solution of KI (13.311 g) in H_2O (50 ml) was added with vigorous stirring. After stirring of the mixture for 6 h at room temperature, CH_2Cl_2–MeOH (95:5, v/v, 100 ml) was added and insoluble precipitates were filtered off through silica gel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2–MeOH (95:5, v/v). The combined organic layer was washed successively with aq. sodium thiosulfate and brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by column chromatography on SiO_2 with MeOH–CH_2Cl_2 (1:99, v/v) as an eluent. From the early part of the eluate, **7** (3.328 g, 91.2%) was obtained. From the later part, **5** (70.6 mg, 3.3%) was recovered. **7**: mp 175.0—177.5 °C (colorless needles from hexane–CH_2Cl_2). IR (KBr): 1638, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.10 (3H, s), 6.94 (1H, dd, J=8.0, 7.5 Hz), 7.43 (1H, dd, J=8.0, 1.0 Hz), 7.72 (1H, dd, J=7.5, 1.0 Hz), 8.01 (1H, s), 11.01 (1H, s). MS *m/e*: 301 (M^+). *Anal.* Calcd for $C_{10}H_8INO_2 \cdot 1/4H_2O$: C, 39.30; H, 2.80; N, 4.58. Found: C, 38.99; H, 2.51; N, 4.30.

4-(3-Hydroxy-3-methyl-1-butenyl)-1-methoxy-3-indolecarbaldehyde (8) from 7——A mixture of **7** (162.8 mg), freshly distilled 2-methyl-3-buten-2-ol (540.1 mg), NEt_3 (0.5 ml), DMF (1.0 ml) and $Pd(OAc)_2$ (6.4 mg) was heated in a sealed tube at 90—93 °C. After stirring of the mixture for 1.5 h, 1.3 mg of $Pd(OAc)_2$ was added and stirring was continued for an additional 2.5 h. The whole was cooled and ethyl acetate (50 ml) was added, then insoluble precipitates were filtered off through silica gel. The filtrate was washed successively with aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated to leave an oil, which was subjected to pTLC on SiO_2 with hexane–ether (1:4, v/v) as a developing solvent. Under a ultraviolet (UV) lamp, three dark bands were detected on the whole luminescent plate. Extraction of the upper band with CH_2Cl_2–MeOH (95:5, v/v) afforded **7** (1.7 mg, 1.0%). Extraction of the middle band with the same solvent gave **5** (2.4 mg, 2.5%). Extraction of the lower band with the same solvent afforded **8** (130.5 mg, 93.2%). **8**: mp 96.0—97.0 °C (pale yellow prisms from ether–hexane). IR (KBr): 3490, 3100, 2970, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (6H, s), 2.30 (1H, s, OH), 4.10 (3H, s), 6.20 (1H, d, J=16.0 Hz), 7.03—7.40 (3H, m), 7.69 (1H, d, J=16.0 Hz), 7.79 (1H, s), 9.74 (1H, s). MS *m/e*: 259(M^+). *Anal.* Calcd for $C_{15}H_{17}NO_3 \cdot 1/2H_2O$: C, 67.15; H, 6.76; N, 5.22. Found: C, 67.57; H, 6.54; N, 5.06.

4-(3-Hydroxy-3-methyl-1-butenyl)-1-methoxy-3-(2-nitrovinyl)indole (9) from 8——NH_4OAc (29.2 mg) was added to a solution of **8** (70.0 mg) in nitromethane (2.0 ml) and the whole was heated at 90 °C and stirred for 3 h. Then CH_2Cl_2–MeOH (95 : 5, v/v) and brine were added and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2–MeOH (95 : 5, v/v) and the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to leave a crystalline solid. Recrystallization from CH_2Cl_2–hexane afforded **9** (57.4 mg) as red prisms. The mother liquor was purified by pTLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give a further crop of **9** (22.8 mg). Total yield of **9** was 80.2 mg (97.6%). mp 103.8—108.0 °C. IR (KBr): 3380, 2970, 1615, 1565 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (6H, s), 1.68 (1H, br s), 4.12 (3H, s), 6.17 (1H, d, J=15.5 Hz), 7.03—7.39 (3H, m), 7.08 (1H, d, J=15.5 Hz), 7.39 (1H, d, J=13.5 Hz), 7.62 (1H, s), 8.48 (1H, d, J=13.5 Hz). MS *m/e*: 302 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_4 \cdot H_2O$: C, 59.99; H, 6.29; N, 8.75. Found: C, 60.36; H, 6.14; N, 8.55.

4-(3-Hydroxy-3-methyl-1-butenyl)-1-methoxy-3-(2-nitroethyl)indole (10a) from 9——$NaBH_4$ (9.3 mg) was added to a solution of **9** (18.7 mg) in MeOH (1.0 ml) and stirring was continued for 15 min at 0 °C. The mixture was diluted with H_2O and the whole was made neutral (pH 7—8) by adding 0.2 N HCl carefully at 0 °C, then extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil which was subjected to pTLC on SiO_2 with ether–hexane (4 : 1, v/v) as a developing solvent to give **10a** (14.9 mg, 79.3%). Pale yellow oil. IR (film): 3360, 2960, 1545, 1375 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, s), 1.77 (1H, br s), 3.49 (2H, t, J=7.5 Hz), 3.97 (3H, s), 4.55 (2H, t, J=7.5 Hz), 6.15 (1H, d, J=15.5 Hz), 6.87—7.33 (5H, m). High-resolution MS *m/e*: Calcd for $C_{16}H_{20}N_2O_4$: 304.1421. Found: 304.1421.

Preparation of 4,5-*trans*-1-Methoxy-5-(2-methyl-1-propenyl)-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (12a)——i) From **10a**: $NaBH_4$ (81.3 mg) was added to a solution of **10a** (53.4 mg) in MeOH (5.0 ml) at 0 °C with stirring and the mixture was allowed to stand for 15 min at room temperature. After removal of the solvent under reduced pressure, the residue was dissolved in H_2O (6.0 ml). The resultant solution was added dropwise to 2 N HCl (8.0 ml) with vigorous stirring at room temperature. After being stirred for 15 min, the whole was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and evaporated to leave a crude product. Subsequent purification by pTLC on SiO_2 with hexane–ether (1 : 1, v/v) as a developing solvent afforded **12a** (32.7 mg, 65.1%). mp 95.0—96.0 °C (colorless prisms from hexane–CH_2Cl_2). IR (KBr): 2900, 1545, 1435, 1360 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.73 (3H, d, J=1.5 Hz), 1.83 (3H, d, J=1.5 Hz), 3.33 (2H, d, J=6.5 Hz), 3.95 (3H, s), 4.13—4.80 (2H, m), 5.03 (1H, br d, J=9.0 Hz), 6.50—7.13 (4H, m). MS *m/e*: 286 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.07; H, 6.34; N, 9.51.

ii) Direct Preparation from **9**: $NaBH_4$ (2.008 g) was added to a solution of **9** (2.011 g) in MeOH (280 ml) at room temperature. After stirring for 15 min, the mixture was diluted with H_2O (280 ml). The resultant solution was added dropwise to 2 N HCl (560 ml) during 20 min with vigorous stirring at room temperature. After being stirred for an additional 10 min, the whole was extracted with CH_2Cl_2 (800 ml), washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was purified by column chromatography on SiO_2 with hexane–CH_2Cl_2 (1 : 1, v/v) as an eluent to give **12a** (1.214 g, 63.7%) as colorless prisms.

1-Methoxy-6-nor-6,7-secoagroclavine (13a) and 6-Nor-6,7-secoagroclavine (13b) from 12a——A mixture of zinc (303.0 mg), mercuric chloride (31.4 mg), and 2 N HCl (1.0 ml) was stirred for 5 min and the supernatant solution was decanted. A solution of **12a** (33.1 mg) in MeOH (4.0 ml) and 2 N HCl (2.0 ml) were added to the resultant zinc amalgam and the whole was heated under reflux for 10 min with stirring. Insoluble precipitates were filtered off and the filtrate was concentrated under reduced pressure, then brine was added. The whole was made alkaline by adding 2 N NaOH, and extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to pTLC on SiO_2 with $CHCl_3$–MeOH–NH_4OH–hexane (90 : 10 : 1 : 25, v/v) as a developing solvent. Under a UV lamp, two dark bands were detected on the whole luminescent plate. Extraction of the upper band with $CHCl_3$–MeOH–NH_4OH (90 : 10 : 1, v/v) afforded **13a** (25.5 mg, 86.1%). Extraction from the lower band with the same solvent gave **13b** (3.4 mg, 13.5%). **13a**: Colorless oil. IR (film): 3340, 2960, 1600, 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CCl_4, 1 : 1, v/v) δ: 1.70 (2H, br s), 1.84 (3H, d, J=1.2 Hz), 1.89 (3H, d, J=1.2 Hz), 2.63 (1H, ddd, J=16.0, 10.4, 1.2 Hz), 2.90—3.22 (2H, m), 3.60 (1H, br t, J=9.8 Hz), 4.03 (3H, s), 5.12 (1H, d septet, J=9.8, 1.2 Hz), 6.64 (1H, t, J=4.0 Hz), 6.88 (1H, s), 6.95—7.15 (2H, m). High-resolution MS *m/e*: Calcd for $C_{16}H_{20}N_2O$: 256.1574. Found: 256.1574. **13b**: mp 121.5—123.0 °C. All spectral data were identical with those of an authentic sample, prepared according to our previous paper.[8]

1-Methoxy-6-methoxycarbonyl-6-nor-6,7-secoagroclavine (14) from 13a——Triethylamine (0.06 ml) was added to a mixture of methyl chloroformate (153.7 mg) and **13a** (104.1 mg) in CH_2Cl_2 (5.0 ml) and stirring was continued for 1.5 h at room temperature. Brine (10 ml) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2–MeOH (95 : 5, v/v) and the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid. Purification by pTLC on SiO_2 with CH_2Cl_2 as a developing solvent afforded **14** (119.0 mg, 93.2%). mp 157.0—159.0 °C (colorless needles from hexane–CH_2Cl_2). IR (KBr): 3290, 2910, 1685, 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, d, J=1.1 Hz), 1.88 (3H, d, J=1.3 Hz), 2.75 (1H, dd, J=15.7, 5.4 Hz), 3.20 (1H, ddd, J=15.7, 4.0, 1.2 Hz), 3.61 (3H, s), 3.87 (1H, dd, J=9.4, 5.6 Hz), 4.06 (3H, s), 3.96—4.22 (1H, m), 4.63 (1H, br d, J=8.4 Hz), 5.04 (1H, d septet, J=9.4, 1.3 Hz), 6.75 (1H, dd, J=4.7, 2.7 Hz), 6.94 (1H, br s), 7.12—7.21 (2H, m). MS *m/e*: 314 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C, 68.57; H,

7.16; N, 8.78. Found: C, 68.77; H, 7.05; N, 8.91.

(±)-1-Methoxy-6,7-secoagroclavine (15a) and (±)-6,7-Secoagroclavine (15b) from 14——A solution of **14** (102.3 mg) in dry THF (2.5 ml) was added with stirring to a suspension of $LiAlH_4$ (154.7 mg) in dry THF (2.0 ml) under an argon atmosphere. The whole was heated under reflux for 35 min, then cooled, and wet ether was added to destroy excess $LiAlH_4$. A solution of Rochelle salt and brine was added and the whole was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to pTLC on SiO_2 with $CHCl_3$–MeOH–NH_4OH–hexane (90 : 10 : 1 : 25) as a developing solvent. Under a UV lamp, two dark bands were detected on the whole luminescent plate. Extraction of the upper band with $CHCl_3$–MeOH–NH_4OH (90 : 10 : 1, v/v) afforded **15a** (68.1 mg, 77.4%). Extraction of the lower band with the same solvent gave **15b** (16.9 mg, 20.2%). **15a**: mp 76.0—78.0 °C (colorless prisms from hexane–CH_2Cl_2). IR (KBr): 3400, 2940, 1603, 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CCl_4, 1 : 1) δ: 1.84 (3H, d, J = 1.2 Hz), 1.88 (3H, d, J = 1.0 Hz), 2.00 (1H, br s), 2.50 (3H, s), 2.54—2.90 (2H, m), 3.22 (1H, br d, J = 13.4 Hz), 3.80 (1H, br t, J = 9.5 Hz), 4.03 (3H, s), 5.09 (1H, br d, J = 9.5 Hz), 6.60—6.74 (1H, m), 6.89 (1H, s), 7.04—7.16 (2H, m). MS *m/e*: 270 (M^+). *Anal.* Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.35; H, 8.37; N, 10.24. **15b**: mp 204.0—205.0 °C (colorless prisms from MeOH). All spectral data were identical with those of an authentic sample, prepared according to our previous procedure.[8]

15b from 15a——$LiAlH_4$ (35.3 mg) was added to a solution of **15a** (20.9 mg) in dry THF (1.5 ml) and the whole was heated under reflux for 6.5 h under an argon atmosphere. The reaction mixture was cooled, then wet ether was added to destroy excess $LiAlH_4$, and a solution of Rochelle salt and brine were added. The whole was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and evaporated to leave a crystalline solid. Purification by pTLC on SiO_2 with $CHCl_3$–MeOH–NH_4OH–hexane (90 : 10 : 1 : 25, v/v) afforded **15b** (15.3 mg, 82.3%) as colorless prisms. All spectral data were identical with those of an authentic sample.[8]

References and Notes

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