Total Synthesis of Optically Active Costaclavine (Synthetic Studies of Indoles and Related Compounds Part 48.)[1)]

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The first total synthesis of optically active costaclavine (18), an ergot alkaloid, was accomplished starting from methyl [4*R*-(*Z*)]-[4-[[(1,1-dimethylethoxy)carbonyl]methylamino]-3,4-dihydro-1-[(4-methylphenyl)sulfonyl]-benz[*cd*]indol-5(1*H*)-ylidene]acetate (8), which was prepared by intramolecular cyclization of 1,1-dimethylethyl [1*R*-(*E*)]-[1-[[4-bromo-1-[(4-methylphenyl)-sulfonyl]-1*H*-indol-3-yl]methyl]-4-carbomethoxy-2-propenyl]methyl-carbamate (7) according to the method we developed earlier during the course of the total synthesis of chanoclavine-I (9).

Key words costaclavine; ergot alkaloid; total synthesis; optically active *N*-methyl-4-bromotryptophan

As the ergot alkaloids such as lysergic acid (**3**) have a variety of pharmacological effects, the study of those biological activities and the structure–activity relationship have been extensively studied. Since those ergot alkaloids are biosynthesized from L-tryptophan (**1**) through a common intermediate, 4-(γ,γ-dimethylallyl)tryptophan (DMAT, **2**)[2)] (Chart 1), commercially available **1** seems to be a good starting material for their total syntheses.

In spite of a number of efforts for regioselective introduction of various substituents at C_4-position of tryptophan,[3—8)] there have so far been only limited successes in the total synthesis of the optically active ergot alkaloids using **1**. The main reason for the difficulty is a poorer reactivity of the C_4-position of **1**. However, if a halogen atom were present at this position of tryptophan, many strategies for selective introduction of carbon side chain would be possible. In order to construct the ergoline skeleton, Harrington and Hegedus[9)] attempted the palladium(0)-catalyzed intramolecular cyclization of 3-allyl-4-bromo-*N*-tosylindole. Recently, Rapoport and his colleagues[10)] also reported that organo-metallic cyclization of C_4-lithiated tryptophan derived from D-4-bromotryptophan afforded (*R*)-4-amino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole, which is the tricyclic core of many tetracyclic ergot alkaloids. We have also succeeded[11)] in a total synthesis of optically active chanoclavine-I (**9**) starting from *N*-methyl-4-bromotryptophan derivative (**6**)[12)] through tricyclic compound (**8**) as a key intermediate, this was obtained by palladium(0)-catalyzed intramolecular cyclization of conjugate ester (**7**). The compound (**5**) was synthesized from 4-bromoindole (**4**) utilizing the selective activation of the indolic C_3-carbon–hydrogen bond with the aid of Pd(II) complex[13)] (Chart 2). In this paper, we describe the first total synthesis of optically active costaclavine (**18**) utilizing the same tricyclic intermediate (**8**).

Costaclavine (**18**), an ergot alkaloid having *cis*-juncture of the C/D ring, has been isolated from cultures of *Agropyrum* or *Penicillium* type fungi[14)] (Fig. 1). Costaclavine (**18**) has been synthesized by several groups[11d,15)] involving the conversion from agroclavine or elymoclavine.[16)] Although formal total synthesis of optically active **18** through optically active agroclavine has been done by Somei's group,[17)] there is no report of direct optically active total synthesis.

Results and Discussion

Chart 3 shows the synthetic route of **18**. The catalytic reduction of **8** gave selectively the *cis* ester (**10**) quantitatively. The conversion of ester (**10**) to methyl ketone (**12**) was carried out by the treatment with Tebbe reagent® ($Cp_2TiCH_2AlClMe_2$)[18)] followed by hydrolysis of the resulted vinyl ether (**11**). The methyl ketone (**12**) was treated again with Tebbe reagent® to give *exo*-olefin (**13**) in 84% yield. Treatment of **12** with either Wittig reagent ($Ph_3P{=}CH_2$) or Petasis reagent

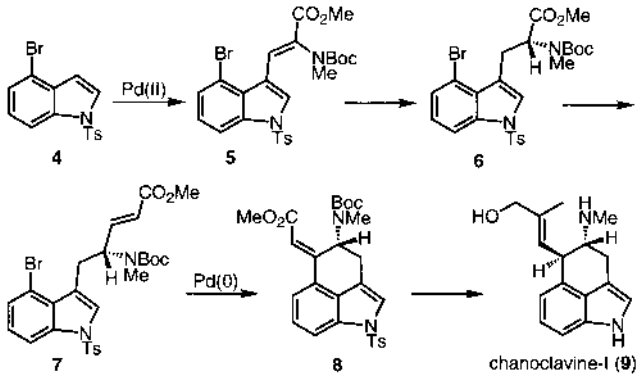

Chart 2. Total Synthesis of Optically Active **9**

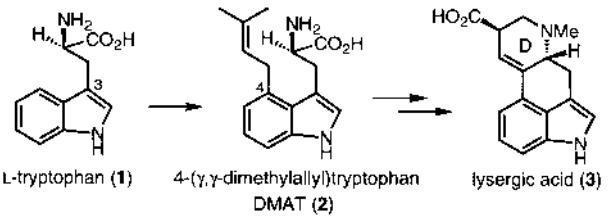

Chart 1. Biosynthesis of Ergot Alkaloids

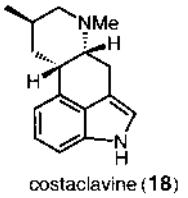

Fig. 1

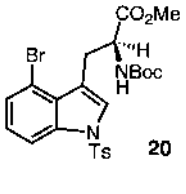

Fig. 2

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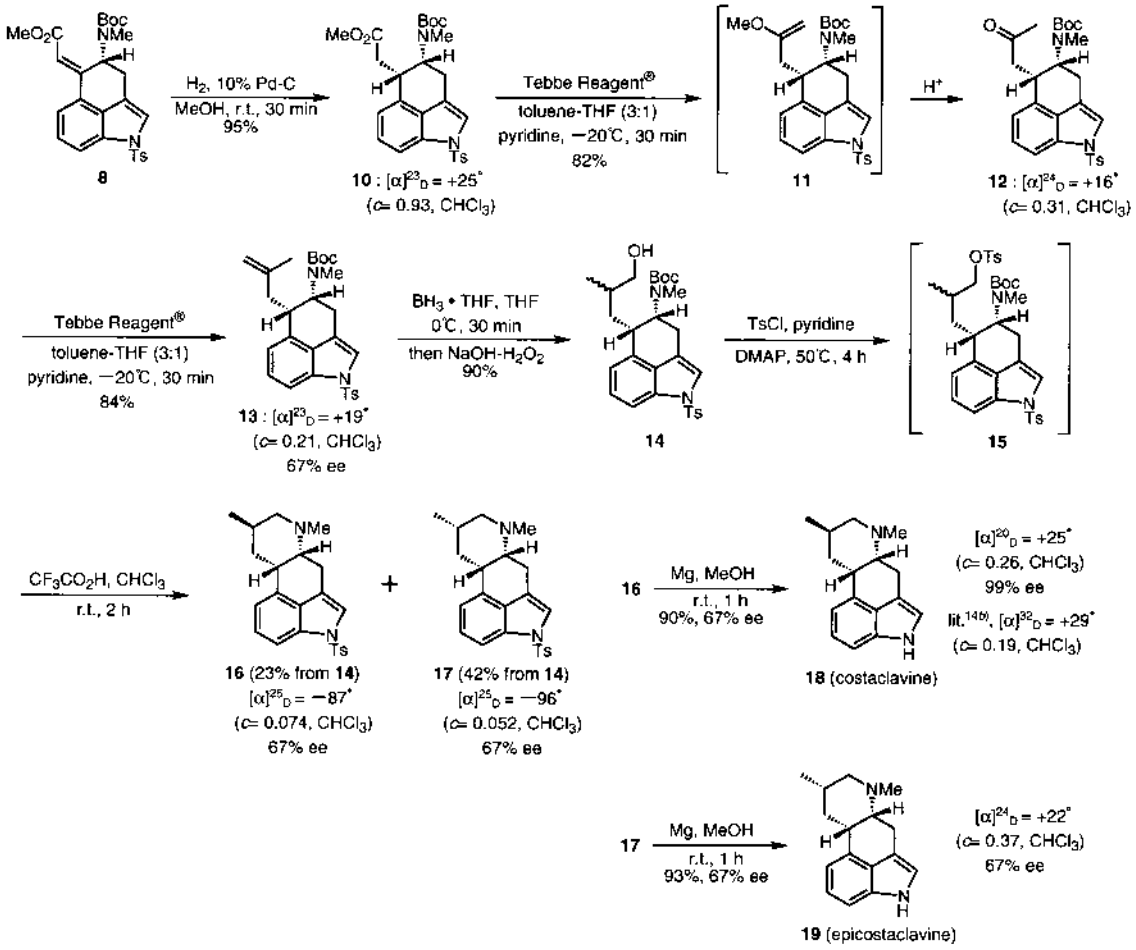

Chart 3. Total Synthesis of **18**

(Cp_2TiMe_2)[19] gave **13** in low yield (20—40%). The next hydroboration–oxidation reaction of **13** at 0 °C non-stereoselectively gave a diastereomeric mixture of the alcohols (**14**) (2 : 1), whose stereochemistries were not determined at this stage. This reaction at higher temperature (60—70 °C) did not change the diastereoselectivity of the products (**14**). Although a more sterically hindered borane reagent such as bis(3-methyl-2-butyl)borane (Sia_2BH) or 3-methyl-2-butylborane ($SiaBH_2$) was expected to increase the regioselectivity, the former did not react at all and the latter showed low stereoselectivity (2.3 : 1). Since the mixture could not be separated into each component, the cyclization was accomplished by *p*-toluenesulfonylation of primary alcohols of **14** followed by the deprotection of *tert*-butoxycarbonyl (Boc) group to give the tetracyclic products as a mixture of stereoisomers. This mixture could be separated by column chromatography and the pure isomers **16** and **17** were obtained in 23% and 42% yield, respectively. Treatment of the minor isomer (**16**) with magnesium/methanol[20] gave desired **18**, whose optical purity was over 99% after recrystallization from methanol. Since the synthetic **18** has the same optical rotation as the natural product, the first total synthesis of naturally occurring costaclavine was achieved successfully. The same treatment of the major isomer (**17**) afforded epicostaclavine (**19**) which has been isolated from *Penicillium gorlenkoanum* by Kozlovskii and other workers.[14a,21]

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Optical rotations were recorded on a JASCO DIP-1000 instrument. Infrared (IR) spectra were performed with a JASCO FT/IR-230 spectrometer. Optical rotatory dispersions (ORD) were obtained with a JASCO J-720 CD spectrometer. Nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a JEOL EX-400 spectrometer in chloroform-*d* ($CDCl_3$). Chemical shifts of protons are reported in δ and referenced to tetramethylsilane as an internal standard, or the residual chloroform (7.26 ppm) was used as the internal reference when measured in $CDCl_3$. Mass spectra were measured on a JEOL JMS-AM II 50. Thin-layer chromatography (TLC) was performed on Merck 25 DC-Platten 20×20 cm Kieselgel 60 F_{254} (Art 5715) and Fuji Silysia Chemical, Ltd. NH TLC plate (aminopropylated silica gel) 20×20 cm 60 Å F_{254}. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned. Extra pure reagents were used in commercially available solvents or pure solvents were distilled before use.

Methyl (4*R*,5*R*)-4-[[(1,1-Dimethylethoxy)carbonyl]methylamino]-1,3,4,5-tetrahydro-1-[(4-methylphenyl)sulfonyl]benz[*cd*]indol-5-acetate (10) To a solution of methyl [4*R*-(*Z*)]-[4-[[(1,1-dimethylethoxy)carbonyl]methylamino]-3,4-dihydro-1-[(4-methylphenyl)sulfonyl]benz[*cd*]indol-5(1*H*)-ylidene]acetate (**8**) (751 mg, 1.47 mmol) in methanol (MeOH, 30.0 ml) was added 10% palladium on activated carbon (Pd-C, 752 mg), and the resulting mixture was stirred under a hydrogen atmosphere for 30 min. The catalyst was then filtered and the filtrate was concentrated. The resultant residue was purified by silica gel column chromatography [benzene : ethyl acetate (EtOAc)=20 : 1] to give **10** (721 mg, 95%) as a colorless viscous oil. $[\alpha]_D^{23}$ +25° (*c*=0.93, chloroform ($CHCl_3$)). IR (neat) cm^{-1}: 1735, 1684, 1362, 1175. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.33 (3H, s), 2.52—2.69 (5H, m), 2.94—3.08 (2H, m), 3.67 (3H, s), 3.83—3.90 (1H, m), 4.59 (1H, br s), 6.97 (1H, d, *J*=7.3 Hz), 7.19—7.26 (4H, m), 7.72—7.77 (3H, m). EI-MS *m/z*: 512 (M^+), 381, 308 (bp), 257, 226, 57. *Anal*. Calcd for $C_{27}H_{32}N_2O_6S$: C, 63.26; H, 6.29; N, 5.46. Found: C, 63.24; H, 6.48; N, 5.37.

1,1-Dimethylethyl (4*R*,5*R*)-[1,3,4,5-Tetrahydro-5-(2-oxopropyl)-1-[(4-methylphenyl)sulfonyl]benz[*cd*]indol-4-yl]-*N*-methylcarbamate (12) To a stirred solution of **10** (376 mg, 0.733 mmol) in a mixture (3 : 1 : 0.1) of toluene, tetrahydrofuran (THF) and pyridine (30 ml) was added 0.5 M toluene solution of $(\eta^5\text{-}C_5H_5)_2TiCH_2AlClMe_2$ (Tebbe reagent®, 6.00 ml, 3.00 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 30 min and quenched by the addition of water. The mixture was extracted with EtOAc and the combined organic layer was vigorously mixed with 10% aqueous hydrochloric acid (HCl) to complete the hydrolysis of vinyl ether. After checking the complete formation of the desired compound (**12**) by TLC, the organic layer was washed with saturated aqueous sodium bicarbonate ($NaHCO_3$) and brine, and dried over sodium sulfate (Na_2SO_4). After evaporation of the solvent, the resultant residue was purified by silica gel column chromatography [benzene : EtOAc = 10 : 1] to give **12** (297 mg, 82%) as a colorless viscous oil. $[\alpha]_D^{24}$ +16° (c=0.31, $CHCl_3$). IR (neat) cm^{-1}: 1716, 1683, 1363, 1175. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.13 (3H, s), 2.34 (3H, s), 2.51 (3H, s), 2.75 (2H, d, J=6.8 Hz), 3.01—3.07 (2H, m), 3.92 (1H, dt, J=6.1, 4.6 Hz), 4.53—4.59 (1H, m), 6.91 (1H, d, J=7.3 Hz), 7.19 (1H, s), 7.21 (2H, d, J=8.3 Hz), 7.22 (1H, dd, J=7.3, 7.3 Hz), 7.70—7.75 (3H, m). EI-MS m/z: 496 (M^+), 365, 308 (bp), 241, 210, 57. *Anal*. Calcd for $C_{27}H_{32}N_2O_5S$: C, 65.30; H, 6.49; N, 5.64. Found: C, 65.05; H, 6.53; N, 5.56.

1,1-Dimethylethyl (4*R*,5*R*)-[1,3,4,5-Tetrahydro-5-(2-methyl-1-propenyl)-1-[(4-methyl-phenyl)sulfonyl]benz[*cd*]indol-4-yl]-*N*-methylcarbamate (13) To a solution of **12** (52.7 mg, 0.106 mmol) in a mixture (3 : 1 : 0.5) of toluene, THF and pyridine (5.30 ml) was added 0.5 M toluene solution of Tebbe reagent® (0.860 ml, 0.430 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 30 min, and quenched by the addition of water, then extracted with EtOAc. The combined organic extracts were washed with saturated aqueous ammonium chloride (NH_4Cl) and brine, dried over Na_2SO_4 and concentrated. The resultant residue was purified by silica gel column chromatography [hexane : EtOAc = 3 : 1] to give **13** (44.2 mg, 84%) as a colorless viscous oil. The optical purity was 67% ee based on high-performance liquid chromatography (HPLC) using a chiral column (Daicel Chiralcel OD *n*-hexane : ethanol = 80 : 1). $[\alpha]_D^{23}$ +19° (c=0.21, $CHCl_3$). IR (neat) cm^{-1}: 1685, 1362, 1148. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.75 (3H, s), 2.15—2.25 (1H, m), 2.29—2.38 (1H, m), 2.34 (3H, s), 2.66 (3H, s), 2.91 (1H, dd, J=14.3, 4.7 Hz), 3.03 (1H, br dd, J=14.3, 9.0 Hz), 3.43—3.50 (1H, m), 4.50 (2H, s), 4.78 (1H, s), 6.94 (1H, d, J=7.3 Hz), 7.14—7.22 (4H, m), 7.70—7.76 (3H, m). EI-MS m/z: 494 (M^+), 363, 308 (bp), 239, 208. *Anal*. Calcd for $C_{28}H_{34}N_2O_4S$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.81; H, 7.29; N, 5.27.

1,1-Dimethylethyl (4*R*,5*R*)-[1,3,4,5-Tetrahydro-5-[(2*RS*)-2-methyl-1-propanol)-3-yl]-1-[(4-methylphenyl)sulfonyl]benz[*cd*]indol-4-yl]-*N*-methylcarbamate (14) A 1.03 M THF solution of borane–THF complex (BH_3·THF, 11.5 ml, 11.8 mmol) was added to a solution of **13** (725 mg, 1.47 mmol) in THF (44.0 ml) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. To this solution were added 1 N sodium hydroxide (NaOH) and 30% hydrogen peroxide (H_2O_2) at 0 °C, and stirring was continued for 1 h at room temperature. The reaction mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over (Na_2SO_4), and concentrated. Silica gel column chromatography [hexane : EtOAc = 1 : 1] of the residue **14** gave a mixture of diastereomers (682 mg, 90%) as a colorless viscous oil. IR (neat) cm^{-1}: 3439, 1677, 1364, 1175. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (2/3×3H, d, J=6.3 Hz), 1.04 (1/3×3H, d, J=6.3 Hz), 1.18—1.36 (1/3×2H, m), 1.44 (2/3×9H, s), 1.45 (1/3×9H, s), 1.65—1.78 (2/3×2H, 1/3×1H, m), 1.79—1.93 (2/3×1H, m), 2.33 (2/3×3H, s), 2.34 (1/3×3H, s), 2.53 (2/3×1H, br s), 2.81 (1/3×1H, br s), 2.88 (1/3×1H, dd, J=14.6, 4.1 Hz), 2.96 (2/3×1H, dd, J=14.9, 4.9 Hz), 3.01—3.11 (1H, m), 3.30—3.43 (2/3×1H, 1/3×2H, m), 3.52—3.60 (2/3×2H, 1/3×1H, m), 4.44 (1/3×1H, br s), 4.62 (2/3×1H, br s), 6.96 (1/3×1H, d, J=7.0 Hz), 7.02 (2/3×1H, d, J=7.0 Hz), 7.17—7.27 (4H, m), 7.70—7.76 (3H, m). EI-MS m/z: 512 (M^+), 381, 308, 257, 57 (bp). *Anal*. Calcd for $C_{28}H_{36}N_2O_5S$: C, 65.60; H, 7.08; N, 5.46. Found: C, 65.71; H, 7.47; N, 5.25.

(5*R*,8*R*,10*R*)- and (5*R*,8*S*,10*R*)-1-(4-Methylphenyl)sulfonyl-6,8-dimethylergoline (16, 17) To a solution of **14** (619 mg, 1.21 mmol) in pyridine (25.0 ml) were added 4-dimethylaminopyridine (DMAP) (29.7 mg, 0.243 mmol) and *p*-toluenesulfonyl chloride (TsCl) (1.17 g, 6.14 mmol) at 0 °C. The reaction mixture was stirred at 50 °C for 2.5 h, diluted with water, and extracted with EtOAc. The combined organic extracts were dried over (Na_2SO_4), and evaporated *in vacuo* to give a colorless viscous oil. To a solution of crude tosylate (**15**) in $CHCl_3$ (25.0 ml) was added trifluoroacetic acid (5.00 ml) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and then concentrated *in vacuo*. The resultant residue was purified by silica gel column chromatography [aminopropylated silica gel, hexane : EtOAc = 2 : 1] to give a mixture of diastereomers as a pale yellow viscous oil (381 mg). Further separation by silica gel column chromatography aminopropylated silica gel, hexane : EtOAc = 4 : 1) gave **16** (112 mg, 23%) and **17** (198 mg, 42%) as a colorless viscous oil and the optical purity was 67% ee based on HPLC using a chiral column (Daicel Chiralcel OD *n*-hexane : EtOH = 70 : 1), respectively.

16: $[\alpha]_D^{25}$ −87° (c=0.074, $CHCl_3$). IR (neat) cm^{-1}: 3019, 1215, 929. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=5.0 Hz), 1.42 (1H, ddd, J=12.6, 10.4, 4.3 Hz), 1.70—1.84 (2H, m), 2.19 (3H, s), 2.35 (3H, s), 2.36—2.47 (1H, m), 2.59 (1H, br s), 2.65—2.76 (2H, m), 3.16—3.25 (2H, m), 7.04 (1H, br d, J=7.0 Hz), 7.16 (1H, d, J=1.7 Hz), 7.22 (2H, br d, J=7.8 Hz), 7.25 (1H, dd, J=7.3, 7.3 Hz), 7.68 (1H, d, J=7.3 Hz), 7.80 (2H, d, J=7.8 Hz). EI-MS m/z: 394 (M^+), 239 (bp), 149, 91. *Anal*. Calcd for $C_{23}H_{26}N_2O_2S$: C, 70.02; H, 6.64; N, 7.10. Found: C, 69.92; H, 7.07; N, 6.68.

17: $[\alpha]_D^{25}$ −96° (c=0.052, $CHCl_3$). IR (neat) cm^{-1}: 3019, 1215, 929. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=6.6 Hz), 1.07 (1H, ddd, J=11.8, 11.8, 11.8 Hz), 1.75 (1H, ddd, J=11.8, 3.6, 3.6 Hz), 1.88—2.00 (1H, m), 2.33 (1H, dd, J=11.8, 11.8 Hz), 2.34 (3H, s), 2.50 (3H, s), 2.60 (1H, ddd, J=11.8, 4.1, 1.2 Hz), 2.77—2.89 (2H, m), 3.14 (1H, ddd, J=11.8, 3.6, 3.6 Hz), 3.22—3.29 (1H, m), 6.97 (1H, d, J=7.0 Hz), 7.16—7.26 (4H, m), 7.71 (1H, d, J=7.0 Hz), 7.76 (2H, d, J=8.0 Hz). EI-MS m/z: 395 (M^++1), 394 (M^+), 239 (bp), 149, 91. *Anal*. Calcd for $C_{23}H_{26}N_2O_2S$: C, 70.02; H, 6.64; N, 7.10. Found: C, 69.65; H, 6.76; N, 6.87.

(5*R*,8*R*,10*R*)-6,8-Dimethylergoline; Costaclavine (18) A solution of magnesium turnings (120 mg, 4.94 mmol) in MeOH (7.50 ml) was stirred vigorously at 80 °C for 30 min. To this suspension was added **16** (97.5 mg, 0.247 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min, diluted with 10% aqueous HCl and extracted with $CHCl_3$. The combined organic layer was washed successively with water, saturated aqueous $NaHCO_3$ and brine, dried over (Na_2SO_4) and concentrated. The resultant residue was purified by silica gel column chromatography (aminopropylated silica gel, hexane : EtOAc = 2 : 1) to give **18** (53.7 mg, 90%) as white powders which were recrystallized from isopropanol–hexane to yield colorless sharp needles. The optical purity was 99% ee based on HPLC using a chiral column (Daicel Chiralcel OD *n*-hexane : isopropanol = 50 : 1). mp 192—194 °C. $[\alpha]_D^{20}$ +25° (c=0.26, $CHCl_3$). IR (KBr) cm^{-1}: 3197, 2948, 2853, 2780, 1448. ORD (c=0.01, MeOH) $[M]^{21}$ (nm) +7436° (298), −6.03° (281), −5730° (261).[16] ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=5.5 Hz), 1.44 (1H, ddd, J=12.8, 10.5, 4.2 Hz), 1.78—1.92 (2H, m), 2.25 (3H, s), 2.50 (1H, br d, J=10.5 Hz), 2.64 (1H, br s), 2.70—2.75 (1H, m), 2.88 (1H, ddd, J=15.0, 3.3, 1.8 Hz), 3.28 (1H, dd, J=15.0, 3.6 Hz), 3.33—3.37 (1H, m), 6.83 (1H, dd, J=1.8, 1.8 Hz), 6.89—6.93 (1H, m), 7.10—7.15 (2H, m), 7.76 (1H, br s). EI-MS m/z: 240 (M^+), 149, 83, 43 (bp). *Anal*. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.07; H, 8.47; N, 11.62.

(5*R*,8*S*,10*R*)-6,8-Dimethylergoline; Epicostaclavine (19) This material was synthesized as above from **17** (185 mg, 0.469 mmol) with magnesium turnings (228 mg, 9.38 mmol) in MeOH (15.0 ml). Silica gel column chromatography (aminopropylated silica gel, hexane : EtOAc = 2 : 1) afforded **19** (105 mg, 93%) as a colorless viscous oil. The optical purity was 67% ee based on HPLC using a chiral column (Daicel Chiralcel OD *n*-hexane : isopropanol = 50 : 1). $[\alpha]_D^{24}$ +22° (c=0.37, $CHCl_3$). IR (neat) cm^{-1}: 3019. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J=6.6 Hz), 1.19 (1H, ddd, J=11.6, 11.6, 11.6 Hz), 1.78—1.85 (1H, m), 1.94—2.07 (1H, m), 2.32 (1H, dd, J=11.6, 11.6 Hz), 2.55 (3H, s), 2.64 (1H, br dd, J=11.6, 4.5 Hz), 2.91—3.01 (2H, m), 3.24 (1H, ddd, J=11.6, 11.6, 3.9 Hz), 3.39 (1H, ddd, J=8.3, 7.3, 3.9 Hz), 6.84—6.88 (2H, m), 7.10—7.16 (2H, m), 7.99 (1H, br s). EI-MS m/z: 240 (M^+), 197, 154, 83, 43 (bp).

References and Notes

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