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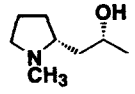
New synthesis of all the four isomers of 2-(2-hydroxypropyl)pyrrolidines via iterative asymmetric dihydroxylation to cause enantiomeric enhancement

Hiroki Takahata*,* Minoru Kubota and Takefumi Momose*

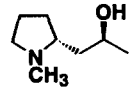
Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930–01, Japan

Abstract: Both enantiomers of 2-(2-propenyl)pyrrolidine **7** (75–84% ee), prepared via the asymmetric dihydroxylation (AD) of terminal olefin **5**, underwent the second AD to provide all of the four stereoisomeric 2-(2-hydroxypropyl)pyrrolidines **8** with enantiomeric enhancement (>98% ee). An asymmetric synthesis, starting from **8**, of several 2-(2-hydroxypropyl)pyrrolidine alkaloids is demonstrated. © 1997 Elsevier Science Ltd

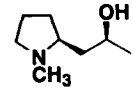
The widespread occurrence and intriguing biological activity of pyrrolidine alkaloids make them attractive to synthetic chemists, especially in view of the short supply of many of them from natural sources.[1] Among these alkaloids, three 2-(2-hydroxypropyl)-1-methylpyrrolidines **1**, **2**, and **3** are isolated from *Erythroxylon coca*,[2] *Schizanthus hookeri*,[3] and *Carallia brachiata*,[4] respectively. Although the synthesis of (+)-hygroline **1**[5] and (−)-hygroline **3**[6] has been reported, the synthesis of both enantiomers (**2** and **4**) of pseudohygroline has never been reported.[7] Accordingly, we were stimulated to the development of a comprehensive synthetic program for these alkaloids. Our interest in this field has been focused on the potential strategies based on the enantiomeric enhancement[8] caused by the twofold or more application of the Sharpless asymmetric dihydroxylation (AD) reactions.[9] In this report, we describe a new synthesis of all the four 2-(2-hydroxypropyl)pyrrolidines **1–4** of high enantiomeric purity via iterative AD.



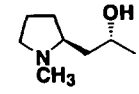
1, (+)-hygroline



2, (+)-pseudohygroline



3, (-)-hygroline

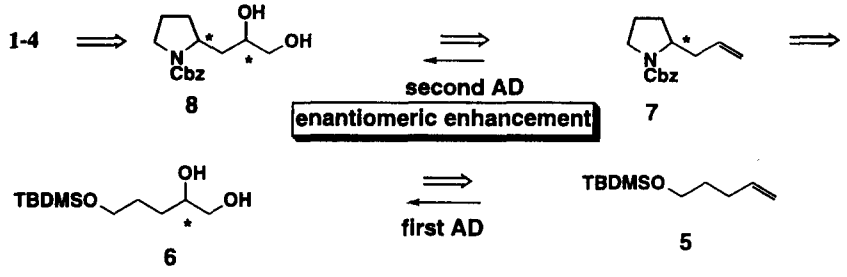


4, (-)-pseudohygroline

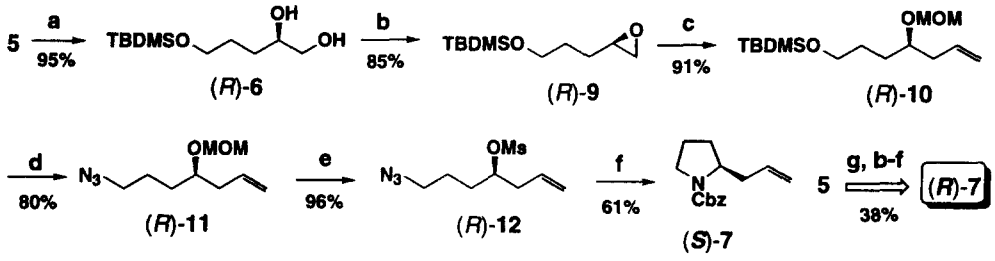
As shown in Scheme 1, we considered that the two stereogenic centers in **1–4** would be installed with high enantio-enhancement via a sequence of twofold AD reactions starting with olefins **5** and **7**. Our synthetic approach to 2-substituted pyrrolidine **7** began with the AD reaction at the terminal olefin in **5**. The $(DHQD)_2$-PYR[10] ligand-derived AD reaction of **5** provided the diol (*R*)-**6** (95%), whose enantiomeric excess (ee) was conveniently determined by ^1H NMR analysis ($CDCl_3$, 500 MHz) of the corresponding bis-Mosher ester (2.3 equiv of (*R*)-MTPA-Cl, 3 equiv of DMAP, THF, 25°C, 6 h), to be 84%. The diol (*R*)-**6** was converted to the epoxide (*R*)-**9** (Scheme 2) by the Sharpless one-pot procedure[11] (1: $CH_3C(OCH_3)_3$/PPTS; 2: CH_3COBr/Et_3N; 3: Amberlite IRA 410) in 85% yield. The regioselective cleavage of the epoxide ring in (*R*)-**9** with vinylmagnesium bromide in combination with a cuprous bromide–dimethyl sulfide complex followed by protection (MOMCl/i-Pr_2EtN) of the resulting secondary hydroxyl yielded (*R*)-**10** in 91% overall yield. Compound (*R*)-**10** was converted to the azide (*R*)-**11** in a three-step sequence (1: desilylation; 2: mesylation; 3: azidation) in 80% overall yield. Deprotection of (*R*)-**11** followed by mesylation afforded (*R*)-**12** in 96% overall yield. The Staudinger reaction[12] of the azide and subsequent benzyloxycarbonylation of the resulting pyrrolidine

* Corresponding author. Email: takahata@ms.toyama-mpu.ac.jp

provided (*R*)-**7** in 61% yield. In a similar sequence of reactions, the $(DHQ)_2$-PYR ligand-derived diol (*R*)-**6** (75% ee) was transformed into (*S*)-**7** in 38% overall yield.



Scheme 1.



Scheme 2. (a) AD-mix-β [$(DHQD)_2$-PYR ligand]; (b) 1) $(CH_2O)_3CCH_3$/PPTS; 2) CH_3COBr; 3) Amberlite IRA410; (c) 1) vinylmagnesium bromide/$(CH_3)_2S$–CuBr; 2) MOMCl/iPr_2NEt; (d) 1) TBAF; 2) MsCl/pyridine; 3) NaN_3; (e) 1) NCl; 2) MsCl/pyridine; (f) 1) Ph_3P/H_2O; 2) CbzCl/K_2CO_3; (g) AD-mix-α [$(DHQ)_2$-PYR ligand].

With both enantiomers of *N*-Cbz-pyrrolidines **7** in hand, we turned our attention to the iterative AD to cause enantiomeric enhancement. The second AD [$(DHQ)_2$-PYR ligand] reaction at the terminal olefin in (*R*)-**7** was carried out to afford a readily separable mixture of the major diastereomer [2*R*-(2*S*)]-**8** (>98% ee) and the minor diastereomer [2*R*-(2*R*)]-**8** (19% ee). These results including another three examples are shown in Table 1. Since the enantioselectivities of all four major diastereomers **8** were found to be more than 98% ee (detected by HPLC on a chiral column using DAICEL CHIRALPAK AS), the enantiomeric enhancement by repeated AD was exemplified.

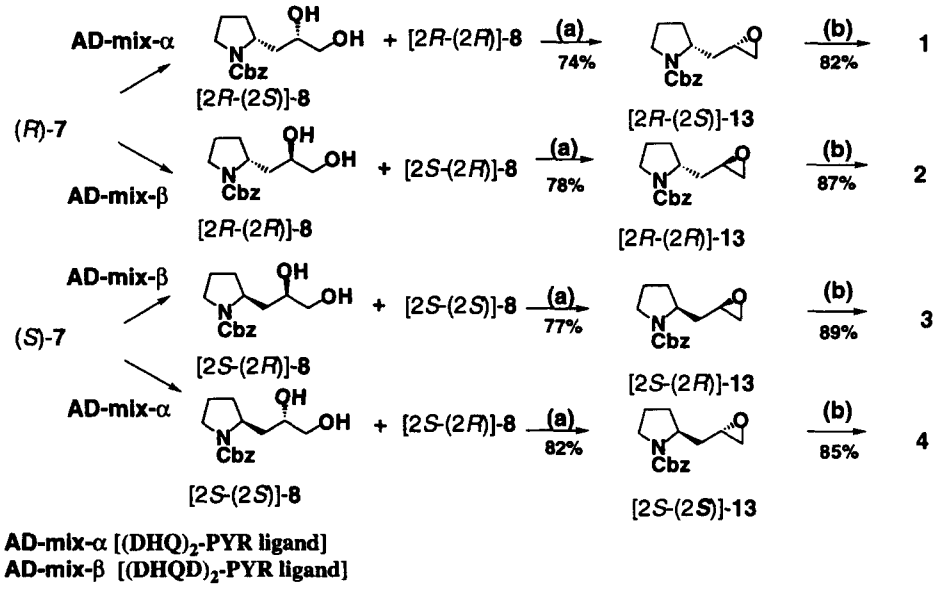
With all the four homochiral 2-(2,3-dihydroxypropyl)pyrrolidines **8** in hand, our attention was directed toward their transformation into biologically active 2-(2-hydroxypropyl)pyrrolidine alkaloids **1**–**4** (Scheme 3). Our synthesis began with the epoxidation of **8**. The four diols **8** were converted into the four epoxides **13** by the Sharpless one-pot procedure in a three-step sequence in good yields, respectively. At the outset, the asymmetric synthesis of (+)-hygroline **1** was undertaken. The simultaneous reduction of the epoxide and the carbamate in [2*R*-(2*S*)]-**13** with lithium aluminum hydride ($LiAlH_4$) was performed to yield the desired **1** {$[\alpha]_D$=+49.6 (EtOH), lit.[2] $[\alpha]_D$=+50 (EtOH)}in

Table 1. The AD reaction of both enantiomers of 7[a]

Substrate **1**	Ligand	major compd. **8**	Yield (ee)	minor compd. **8**	Yield (ee)
(*R*)-**7**	$(DHQ)_2$PYR	[2*R*-(2*S*)]-**8**	64% (>98%)	[2*R*-(2*R*)]-**8**	32% (19%)
(*R*)-**7**	$(DHQD)_2$PYR	[2*R*-(2*R*)]-**8**	75% (>98%)	[2*S*-(2*R*)]-**8**	21% (32%)
(*S*)-**7**	$(DHQD)_2$PYR	[2*S*-(2*R*)]-**8**	75% (>98%)	[2*S*-(2*S*)]-**8**	16% (35%)
(*S*)-**7**	$(DHQ)_2$PYR	[2*S*-(2*S*)]-**8**	78% (>98%)	[2*S*-(2*R*)]-**8**	16% (41%)

a) Ees of [2*S*-(2*R*)]-, [2*R*-(2*S*)]-**8** and [2*R*-(2*R*)]-, [2*S*-(2*S*)]-**8** were determined by DAICEL CHIRALPAK AS and AD, respectively.

82% yield (97% ee).[13] Having this result, the reduction of [2*R*-(2*R*)]-, [2*S*-(2*R*)]-, and [2*S*-(2*S*)]-**13** with $LiAlH_4$ provided **2** (96% ee),[14] ({$[\alpha]_D$=+95.4 (EtOH), lit.[15] $[\alpha]_D$=+84.4 (EtOH)}, **3** (99% ee),[13] {$[\alpha]_D$=−53.1 (EtOH), lit.[6] $[\alpha]_D$=−49 (EtOH)}, and **4** (98% ee),[14] {$[\alpha]_D$=−96.96 (EtOH)} in good yields, respectively.



Scheme 3. (a) (i) $(CH_3O)_3CCH_3$; (ii) CH_3COBr; (iii) K_2CO_3/CH_3OH. (b) $LiAlH_4$.

In summary, we developed a general access to synthetically useful homochiral 2-(2,3-dihydroxypropyl)pyrrolidines **8** starting from an achiral *O*-TBDMS-4-pentenyl ether **5**. The two stereogenic centers in **8** were constructed with high enantio-enhancement via a sequence of twofold AD reactions. In practice, we demonstrated the synthetic utility of **8** as chiral synthons by the asymmetric synthesis of all the four isomers of 2-(2-hydroxypropyl)pyrrolidine alkaloids **1**–**4**.[16] Further application of this methodology (the enantiomeric enhancement via the twofold or more AD reactions) to asymmetric synthesis of other biologically active compounds is under investigation.

Experimental section

Melting points are determined using a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a Perkin–Elmer 1600 series FTIR spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were recorded either at 300 MHz on a Varian Gemini-300, or 500 MHz on a Varian Unity-500 with $CHCl_3$ (7.26 ppm) as internal standards. Carbon-13 NMR spectra were recorded at 75 or 125 MHz with $CDCl_3$ (77.2 ppm) as an internal standard unless otherwise specified. Fluorine-19 NMR spectra were recorded at 254 MHz on a JEOL 270 GX with $CFCl_3$ (0 ppm) as an internal standard unless otherwise specified. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No 9385) with a medium pressure apparatus and a mixture of ethyl acetate/hexane was used as eluant unless otherwise specified. HPLC was performed with a JASCO Intelligent HPLC pump PU-980 using Daicel Chiralpac AD or AS. The extracts were dried over Na_2SO_4 unless otherwise specified.

*(R)-5-[(*tert*-Butyldimethylsilyl)oxy]pentane-1,2-diol (R)-6*

5-[(*tert*-Butyldimethylsilyl)oxy]-1-pentene **5** (3.5 g, 17.5 mmol) was added to a mixture of AD-mix (22 g), prepared from $K_2OsO_4 \cdot 2H_2O$ (11 mg), $(DHQD)_2$-PYR (0.138 g), $K_3Fe(CN)_6$ (15.1 g), and K_2CO_3 (6.35 g) by a known procedure,[10] *tert*-BuOH (82 mL), and H_2O (82 mL) at 0°C. After the reaction mixture was stirred for 24 h at the same temperature, sodium sulfite (25 g) was added to the mixture. After stirring for 30 min, the mixture was filtered through a Celite pad. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed using 50% ethyl acetate–hexane as eluant to yield (*R*)-**6** (3.9 g, 95%) as an oil, which was of 84% ee as determined on its bis-(*R*)-Mosher ester described below: $[\alpha]^{25}_D$ +6.94 (c 1.795, MeOH); IR (neat) 3356, 2929, 2857, 1255, 1098, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6 H, s), 0.88 (9 H, s), 1.42–1.69 (4 H, m), 2.74 (1 H, br s), 3.39–3.47 (1 H, m), 3.56–3.76 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.25, 18.44, 26.04, 29.18, 30.57, 63.58, 66.90, 72.13; HRMS calcd for $C_{11}H_{26}O_3Si$ (M^+) 234.1651, found 234.1618.

bis-Mosher ester of (R)-6

A solution of (*R*)-**6** (11 mg, 47 μmol) and DMAP (17 mg, 141 μmol) in THF (0.24 mL) was treated with (*R*)-Mosher's chloride {(*R*)-MTPA-Cl, 18 μL, 108 μmol)} at 25°C, and the reaction mixture was stirred for 15 h. After filtration of the mixture, the filtrate was evaporated to afford the bis-Mosher ester of (*R*)-**6**; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (6 H, s), 0.88 (9 H, s), 1.40–1.46 (2 H, m), 1.67–1.72 (2 H, m), 3.41 (3 H, d, *J*=1.07 Hz), 3.50 (3 H, d, *J*=0.86 Hz), 3.52–3.55 (2 H, m), 4.34 (1 H, dd, *J*=6.41, 12.2 Hz), 4.60 (0.08 H, dd, *J*=2.78, 12.3 Hz), 4.66 (0.92 H, dd, *J*=2.78, 12.3 Hz), 5.36–5.40 (1 H, m), 7.34–7.42 (6 H, m), 7.42–7.51 (4 H, m).

*(S)-5-[(*tert*-Butyldimethylsilyl)oxy]pentane-1,2-diol (S)-6*

By a procedure similar to that for the preparation of (*R*)-**6**, the reaction of **5** (300 mg, 1.5 mmol) with AD-mix (1.8 g), prepared from $K_2OsO_4 \cdot 2H_2O$ (0.93 mg), $(DHQ)_2$-PYR (12 mg), $K_3Fe(CN)_6$ (1.29 g), and K_2CO_3 (0.54 g), *tert*-BuOH (7 mL), and H_2O (7 mL), gave (*S*)-**6** (334 mg, 95%), which was of 75% ee as determined on its bis-(*R*)-Mosher ester described below: $[\alpha]^{25}_D$ −5.80 (c 1.690, MeOH).

bis-Mosher ester of (S)-6.

By a procedure similar to that for the preparation of bis-Mosher ester of (*R*)-**6**, the reaction of (*S*)-**6** (11 mg, 47 μmol) with (*R*)-Mosher's chloride {(*R*)-MTPA-Cl, 18 μL, 108 μmol}, DMAP (17 mg, 141 μmol) afforded the bis-Mosher ester of (*S*)-**6**; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.44 (6 H, s), 0.88 (9 H, s), 1.50–1.61 (2 H, m), 1.75–1.83 (2 H, m), 3.44 (3 H, d, *J*=0.64 Hz), 3.45 (3 H, d, *J*=0.64 Hz), 3.59 (3 H, t, *J*=5.98 Hz), 4.30 (1 H, dd, *J*=5.23, 12.3 Hz), 4.60 (0.875 H, dd, *J*=2.78, 12.3 Hz), 4.66 (0.125 H, dd, *J*=2.78, 12.3 Hz), 5.34–5.42 (1 H, m), 7.33–7.41 (6 H, m), 7.41–7.51 (4 H, m).

*(R)-5-[(*tert*-Butyldimethylsilyl)oxy]-1,2-epoxypentane (R)-9*

A mixture of (*R*)-**6** (3.5 g, 14.9 mmol), pyridinium *p*-toluenesulfonate (PPTS) (38 mg, 0.15 mmol), and trimethyl orthoacetate (2.5 mL, 19.4 mmol) in CH_2Cl_2 (23 mL) was stirred for 20 min at room temperature. After the solvent was removed by rotary evaporation, CH_2Cl_2 (30 mL) and acetyl bromide (1.32 mL, 17.9 mmol) were successively added to the resulting residue. After stirring for 45 min, sat. $NaHCO_3$ (14.9 mL) was added to the mixture with ice cooling. After vigorous stirring, the mixture was diluted with sat. $NaHCO_3$ (149 mL) and extracted with CH_2Cl_2 three times. The extracts were dried and evaporated. Methanol (18.6 mL) and Amberlite [IRA410] OH^- form (11 g) were successively added to the resulting residue. After stirring for 3 h, the mixture was filtered through a Celite pad, and then the filtrate was evaporated. The residue was chromatographed using 2% ethyl acetate–hexane as eluant to yield (*R*)-**9** (2.7 g, 85%) as an oil; $[\alpha]^{25}_D$ +5.06 (*c* 1.275, $CHCl_3$); IR (neat) 2954, 2930, 2889, 2857, 1254, 1101, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6 H, s), 0.87 (9 H, s), 1.55–1.69 (4 H, m), 2.46 (1 H, dd, *J*=2.75 Hz, 2.47 Hz), 2.73 (1 H, t, *J*=4.67Hz), 2.91–2.93 (1 H, m),

3.60–3.66 (2 H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.21, 18.42, 26.06, 29.15, 29.26, 47.24, 52.30, 62.74; HRMS calcd for $C_{11}H_{24}O_2Si$ (M^+) 216.1546, found 216.1574.

*(S)-5-[(*tert*-Butyldimethylsilyl)oxy]-1,2-epoxypentane (S)-**9***

By a procedure similar to that for the preparation of (*R*)-**9**, (*R*)-**6** (4.7 g, 19.9 mmol) was coverted in a three-step sequence [1) PPTS (51 mg, 0.20 mmol), CH_2Cl_2 (31 mL × 2), trimethyl orthoacetate (0.26 mL, 1.99 mmol); 2) acetyl bromide (1.8 mL, 23.9 mmol); 3) methanol (25 mL) and Amberlite [IRA410] OH^- form (14.7 g)] to (*S*)-**9** (3.7 g, 75%): $[\alpha]^{25}_D$ −4.64 (c 0.500, $CHCl_3$).

*(R)-7-[(*tert*-Butyldimethylsilyl)oxy]-4-[(methoxymethyl)oxy]-1-heptene (R)-**10***

To a slurry of CuBr–Me_2S (276 mg, 1.34 mmol) in THF (26.4 mL) was added a 1 M vinylmagnesium bromide–THF solution (20.1 mL, 20.1 mmol) at −78°C with stirring. After stirring for 30 min, a solution of (*R*)-**9** (2.9 g, 13.4 mmol) in THF (14.5 mL) was slowly added to the reaction mixture. The mixture was gradually warmed to −30°C, stirred for 1.5 h, and quenched with sat. NH_4Cl. The mixture was diluted with ether, washed with brine, dried, and evaporated. The residue was chromatographed using 13% EtOAc–hexane as eluant to give (*R*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-hepten-4-ol (3.0 g, 94%) as an oil: $[\alpha]^{25}_D$ +5.19 (c 1.210, $CHCl_3$); IR (neat) 3383, 2929, 2858, 1472, 1256, 1099, 913, 835, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (6 H, s), 0.89 (9 H, s), 1.42–1.54 (1 H, m), 1.61–1.67 (3 H, m), 2.14–2.32 (2 H, m), 2.66 (1 H, d, *J*=3.85 Hz), 3.64–3.68 (3 H, m), 5.08–5.14 (2 H, m), 5.75–5.92 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.21, 18.50, 26.10, 29.34, 34.15, 42.10, 63.65, 70.77, 117.74, 135.32; Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.55. Found: C, 63.17; H, 11.57. 4-Dimethylaminopyridine (DMAP) (140 mg, 1.1 mmol), *N*-ethyldiisopropylamine (1.2 mL, 6.9 mmol), and chloromethyl methyl ether (MOMCl) (0.34 mL, 4.6 mmol) were added successively to a stirred solution of the alcohol (556 mg, 2.3 mmol) in CH_2Cl_2 (16 mL) at 0°C. The mixture was stirred for 4 h at 65°C. After 0.5 N $KHSO_4$ was added to the reaction mixture at 0°C, the organic layer was separated, and then the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed using 10% EtOAc–hexane as eluant to give (*R*)-**10** (637 mg, 97%) as an oil; $[\alpha]^{25}_D$ +9.98 (c 1.260, $CHCl_3$); IR (neat) 2928, 1098, 1041, 836, 774 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.88 (9 H, s), 1.49–1.65 (4 H, m), 2.27–2.32 (2 H, m), 3.38 (3 H, m), 3.59–3.65 (3 H, m), 4.62–4.69 (2 H, m), 5.04–5.11 (2 H, m), 5.77–5.86 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.19, 18.44, 26.06, 28.70, 30.47, 39.05, 55.58, 63.21, 76.76, 95.47, 117.20, 134.84; HRMS calcd for $C_{15}H_{32}O_3Si$ (M^+) 288.2120, found 288.2137.

*(S)-7-[(*tert*-Butyldimethylsilyl)oxy]-4-[(methoxymethyl)oxy]-1-heptene (S)-**10***

By a procedure similar to that for the preparation of (*R*)-**10**, the reaction of (*S*)-**9** (4.0 g, 18.5 mmol) with CuBr–Me_2S (380 mg, 1.85 mmol) and 1 M vinylmagnesium bromide–THF (27.7 mL, 27.7 mmol) gave (*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-hepten-4-ol (3.9 g, 87%): $[\alpha]^{25}_D$ −4.11 (c 1.335, $CHCl_3$). The reaction of the alcohol (3.8 g, 15.5 mmol) with DMAP (952 mg, 7.8 mmol), *N*-ethyldiisopropylamine (8.1 mL, 46.6 mmol), and MOMCl (2.4 mL, 31.1 mmol) afforded (*S*)-**10** (4.1 g, 93%); $[\alpha]^{25}_D$ −9.24 (c 1.185, $CHCl_3$).

*(R)-7-Azido-4-[(methoxymethyl)oxy]-1-heptene (R)-**11***

Tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 1.0 mL, 1.0 mmol) was added to a solution of (*R*)-**10** (200 mg, 0.7 mmol) in THF (2.1 mL). After stirring for 1 h, the mixture was diluted with EtOAc and washed successively with H_2O and brine. The organic layer was dried and evaporated. The residue was chromatographed (20% EtOAc–hexane) to give (*R*)-4-[(methoxymethyl)oxy]-6-hepten-1-ol (114 mg, 94%) as an oil; $[\alpha]^{25}_D$ +31.73 (c 1.175, $CHCl_3$); IR (neat) 3411, 2939, 1442, 1150, 1100, 1038, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51–1.71 (4 H, m), 1.89 (1 H, br s), 2.25–2.36 (2 H, m), 3.37 (3 H, s), 3.64–3.69 (3 H, m), 4.66 (2 H, ABq, *J*=10.58 Hz, 6.87 Hz), 5.04–5.11 (2 H, m), 5.73–5.87 (1 H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 28.61, 30.67, 38.99, 55.83, 63.13, 76.87,

95.62, 117.51, 134.69; HRMS calcd for $C_7H_{13}O_2$ ($M^+-CH_2CH_2OH$) 129.0916, found 129.0937. To a mixture of the alcohol (110 mg, 0.63 mmol) and DMAP (11.6 mg, 0.095 mmol) in pyridine (1.0 mL) was added methanesulfonyl chloride (MsCl) (74 μL, 0.95 mmol) at 0°C. After stirring for 2 h at the same temperature, the reaction mixture was diluted with ether and acidified with 20% $KHSO_4$. After separation of the layers, the organic layer was washed successively with H_2O and brine, dried, and evaporated. The residue was chromatographed (10% EtOAc–hexane) to yield 7-[(methanesulfonyl)oxy]-4-[(methoxymethyl)oxy]-1-heptene (144 mg, 91%) as an oil; $[\alpha]^{25}_D$ +27.53 (c 1.430, $CHCl_3$); IR (neat) 2935, 1354, 1174, 1037, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54–1.69 (2 H, m), 1.74–1.95 (2 H, m), 2.24–2.35 (2 H, m), 2.99 (3 H, s), 3.36 (3 H, s), 3.63 (1 H, qui, *J*=6.04 Hz), 4.24 (2 H, t, *J*=6.59 Hz), 4.64 (2 H, ABq, *J*=10.58 Hz, 6.87 Hz), 5.05–5.11 (2 H, m), 5.71–5.85 (1 H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.27, 30.06, 37.50, 38.94, 55.82, 70.19, 76.17, 95.61, 117.77, 134.29; HRMS calcd for $C_{10}H_{20}O_5S$ (M^+) 252.1031, found 252.0988. A mixture of the mesylate (2.3 g, 9.1 mmol) and NaN_3 (889 mg, 13.7 mmol) in DMF (14 mL) was stirred at 45°C for 1 h. After H_2O (39 mL) was added to the reaction mixture, the whole mixture was extracted with ether three times. The extracts were washed successively with sat. $KHSO_4$ and brine, dried, and evaporated. The residue was chromatographed (7% EtOAc–hexane) to yield (*R*)-**11** (1.7 g, 94%) as an oil; $[\alpha]^{25}_D$ +28.35 (c 1.11, $CHCl_3$); IR (neat) 2934, 2096, 1458, 1258, 1151, 1098, 1037, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51–1.76 (4 H, m), 2.24–2.32 (2 H, m), 3.28 (2 H, t, *J*=6.59 Hz), 3.37 (3 H, s), 3.62 (1H, qui, *J*=6.04 Hz), 4.65 (2 H, ABq, *J*=10.17 Hz, 7.14 Hz), 5.05–5.11 (2 H, m), 5.72–5.86 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.94, 31.28, 38.99, 51.61, 55.77, 76.32, 95.56, 117.63, 134.43; HRMS calcd for $C_9H_{17}N_2O_2$ (M^+-N) 185.1290, found 185.1267.

*(S)-7-Azido-4-[(methoxymethyl)oxy]-1-heptene (S)-**11***

By a procedure similar to that for the preparation of (*R*)-**11**, reaction of (*S*)-**10** (4.0 g, 13.9 mmol) with TBAF (1.0 M in THF) (20.9 mL, 20.9 mmol) gave (*S*)-4-[(methoxymethyl)oxy]-6-hepten-1-ol (2.3 g, 96%); $[\alpha]^{25}_D$ −24.04 (c 1.460, $CHCl_3$). Subsequently, mesylation of desilylated compound (2.2 g, 12.6 mmol) with DMAP (231 mg, 1.89 mmol), pyridine (20 mL), and MsCl (1.46 mL, 18.9 mmol) afforded the mesylate (2.9 g, 91%); $[\alpha]^{25}_D$ −21.91 (c 1.280, $CHCl_3$). Finally, azidation of the mesylate (2.8 g, 11.1 mmol) with NaN_3 (1.1 g, 16.6 mmol) in DMF (17 mL) provided (*S*)-**11** (2.11 g, 96%); $[\alpha]^{25}_D$ −25.73 (c 1.305, $CHCl_3$).

*(R)-7-Azido-4-[(methanesulfonyl)oxy]-1-heptene (R)-**12***

To a solution of (*R*)-**11** (1.7 g, 8.5 mmol) in MeOH (18 mL) was added conc. HCl (10 drops), and the reaction mixture was heated at 60°C for 1 h. After removal of the solvent, the resulting residue was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed (12% EtOAc–hexane) to yield (*R*)-7-azido-1-hepten-4-ol (1.29 g, 99%); $[\alpha]^{25}_D$ +12.16 (c 1.265, $CHCl_3$); IR (neat) 3384, 3077, 2933, 2098, 1350, 1256, 996, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44–1.84 (5 H, m), 2.10–2.34 (2 H, m), 3.31 (2 H, t, *J*=6.59 Hz), 3.62–3.70 (1 H, m), 5.11–5.17 (2 H, m), 5.74–5.88 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.38, 33.84, 42.27, 51.60, 70.19, 118.74, 134.55; HRMS calcd for $C_7H_{13}ON_3$ (M^+) 155.1059, found 155.0994. To a mixture of the alcohol (1.3 g, 8.4 mmol)) and DMAP (153 mg, 1.26 mmol) in pyridine (14.7 mL) was added MsCl (0.97 mL, 12.6 mmol) at 0°C. After stirring for 2 h at the same temperature, the reaction mixture was diluted with ether and acidified with 20% $KHSO_4$. After separation of the layers, the organic layer was washed successively with H_2O and brine, dried, and evaporated. The residue was chromatographed (10% EtOAc–hexane) to yield (*R*)-**12** (1.94 g, 97%) as an oil; $[\alpha]^{25}_D$ +17.58 (c 1.15, $CHCl_3$); IR (neat) 2924, 2096, 1458, 1341, 1171, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64–1.82 (4 H, m), 2.46–2.51 (2 H, m), 3.01 (3 H, s), 3.33 (2 H, t, *J*=6.04 Hz), 4.72–4.78 (1 H, m), 5.14–5.21 (2 H, m), 5.71–5.83 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.66, 31.46, 38.97, 39.29, 51.08, 81.75, 119.54, 132.29; HRMS calcd for $C_8H_{15}N_3O_3S$ (M^+) 233.0834, found 233.0785.

(S)-7-Azido-4-[(methanesulfonyl)oxy]-1-heptene (S)-12

By a procedure similar to that for the preparation of (*R*)-**12**, the reaction of (*S*)-**11** (2.1 g, 10.5 mmol) with conc. HCl (1.2 mL) gave (*S*)-7-azido-1-hepten-4-ol (1.57 g, 98%); $[\alpha]^{25}_D$ −10.99 (c 1.230, $CHCl_3$). Mesylation of the alcohol obtained above (1.5 g, 9.7 mmol) with DMAP (178 mg, 1.46 mmol), pyridine (17 mL), and MsCl (1.13 mL, 14.6 mmol) afforded (*S*)-**12** (2.18 g, 95%); $[\alpha]^{25}_D$ −16.07 (c 1.360, $CHCl_3$).

(S)-1-Benzyloxycarbonyl-2-(2-propenyl)pyrrolidine (S)-7

A mixture of (*R*)-**12** (75 mg, 0.32 mmol), Ph_3P (92 mg, 0.35 mmol), and H_2O (0.05 mL, 0.03 mmol) in THF (4 mL) was stirred for 15 h at 45°C. After the volatiles were removed by rotary evaporation, 5% HCl (0.3 mL) was added to the resulting residue. The resulting mixture was washed with ether, and then the aqueous layer was basified with 2 N NaOH and extracted with ether. After conc. HCl (0.04 mL) was added to the extract, removal of the solvent by evaporation gave the hydrochloride salt (33 mg, 70%). Potassium carbonate (62.2 mg, 0.45 mmol) was added to the resulting salt in THF (0.29 mL) with ice cooling. After benzyloxycarbonyl chloride (33 μL, 0.23 mmol) was added to the mixture at 0°C, the reaction mixture was stirred for 4 h at room temperature, acidified with 10% $KHSO_4$, and extracted with ethyl acetate three times. The extracts were successively washed with sat. $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed (10% EtOAc–hexane) to yield (*S*)-**7** (45 mg, 87%, 2 steps 61%) as an oil; $[\alpha]^{25}_D$ −38.71 (c 1.13, $CHCl_3$); IR (neat) 2955, 1700, 1411, 1358, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56–1.78 (4 H, m), 2.00–2.09 (1 H, m), 2.30–2.51 (1 H, m), 3.28–3.37 (2 H, m), 3.79–3.81 (1 H, m), 4.87–5.09 (4 H, m), 5.55–5.67 (1 H, m), 7.15–7.28 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.10, 23.86, 29.37, 30.17, 38.21, 39.11, 46.68, 46.77, 47.02, 56.85, 57.35, 57.43, 66.58, 66.67, 66.81, 117.28, 117.34, 127.83, 127.86, 128.01, 128.25, 128.45, 134.87, 134.87, 135.04, 136.98, 137.11, 154.73, 154.90; HRMS calcd for $C_{12}H_{14}NO_2$ ($M^+ - CH_2CH{=}CH_2$) 204.1024, found 204.1002.

(R)-1-Benzyloxycarbonyl-2-(2-propenyl)pyrrolidine (R)-7

By a procedure similar to that for the preparation of (*S*)-**7**, reaction of (*R*)-**12** (2.15 g, 9.2 mmol) with PPh_3 (2.6 g, 10.1 mmol), H_2O (1.7 mL, 0.092 mmol) and THF (114 mL) gave the hydrochloride salt of a pyrrolidine (1.2 g, 88%). The *N*-protection of the pyrrolidine with CbzCl (1.27 mL, 8.9 mmol) and K_2CO_3 (2.4 g, 17.1 mmol) afforded (*R*)-**7** (1.75 g, 88%, 2 steps 77%) as an oil; $[\alpha]^{25}_D$ +33.52 (c 0.875, $CHCl_3$).

[2R-(2S)]- and [2R-(2R)]-1-Benzyloxycarbonyl-2-(2,3-dihydroxypropyl)pyrrolidine [2R-(2S)]- and [2R-(2R)]-8

A solution of (*R*)-**7** (600 mg, 2.4 mmol) in *tert*-BuOH (2 mL) was added to a suspension of AD-mix-α {$(DHQ)_2$-PYR ligand} (3.1 g) [prepared from $K_2OsO_4 \cdot 2H_2O$ (1.55 mg), $(DHQD)_2$-PYR (19.4 mg), $K_3Fe(CN)_6$ (2.13 g), and K_2CO_3 (895 mg)] in *tert*-BuOH (10 mL) and H_2O (12 mL) at 0°C. After the reaction mixture was stirred for 24 h at the same temperature, sodium sulfite (3.6 g) was added to the mixture. After stirring for 30 min, the mixture was filtered through a Celite pad. The organic layer of the filtrate was separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried, and evaporated by rotary evaporation. The residue was chromatographed using 50% ethyl acetate–hexane as eluant to yield [2*R*-(2*S*)]-**8** (427 mg, 64%) and [2*R*-(2*R*)]-**8** (215 mg, 32%) as oils.

[2*R*-(2*S*)]-**8**; $[\alpha]^{25}_D$ +0.83 (c 2.055, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.40–1.45 (1 H, m), 1.56–2.01 (5 H, m), 2.51–2.65 (1 H, m), 3.22–3.43 (3 H, m), 3.45–3.62 (1 H, m), 3.68–3.74 (1 H, m), 3.92–4.02 (2 H, m), 5.03 (2 H, ABq, *J*=16.48 Hz, 3.85 Hz)), 7.20–7.32 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.86, 31.19, 38.24, 46.48, 55.48, 67.00, 67.25, 70.49, 127.87, 127.96, 128.46, 136.60, 155.33.

[2*R*-(2*R*)]-**8**; $[\alpha]^{25}_D$ +7.83 (c 1.515, $CHCl_3$), IR (neat) 3406, 2954, 1675, 1419, 1356, 1104 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28–1.41 (2 H, m), 1.52–1.56 (1 H, m), 1.77–1.95 (3 H, m), 2.38 (1 H, br s), 3.33 (2 H, t, *J*=6.59 Hz), 3.38–3.50 (2 H, m), 3.54–3.62 (1 H, m), 4.13–4.20 (1 H, m), 4.96–5.09 (3 H, m), 7.20–7.27 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.77, 31.37, 39.37, 46.62, 54.54, 66.64, 67.46, 68.70, 127.87, 128.16, 128.59, 136.48, 157.03; HRMS calcd for $C_{15}H_{21}NO_4$ (M^+) 279.1470, found 279.1433.

[2R-(2R)]- and [2S-(2R)]-1-Benzyloxycarbonyl-2-(2,3-dihydroxypropyl)pyrrolidine [2R-(2R)]- and [2S-(2R)]-8

By a procedure similar to that for the preparation of [2*R*-(2*S*)]- and [2*R*-(2*R*)]-**8**, the reaction of (*R*)-**7** (500 mg, 2.0 mmol) with AD-mix-β {$(DHQD)_2$-PYR} (2.6 g) gave [2*R*-(2*R*)]-**8** (418 mg, 75%) and [2*S*-(2*R*)]-**8** (118 mg, 21%) as oils. [2*R*-(2*R*)]-**8**; $[\alpha]^{25}_D$ +44.0 (c 1.175, $CHCl_3$). [2*S*-(2*R*)]-**8**, $[\alpha]^{25}_D$ −0.202 (c 3.055, $CHCl_3$).

[2S-(2R)]- and [2S-(2S)]-1-Benzyloxycarbonyl-2-(2,3-dihydroxypropyl)pyrrolidine [2S-(2R)]- and [2S-(2S)]-8

By a procedure similar to that for the preparation of [2*R*-(2*S*)]- and [2*R*-(2*R*)]-**8**, the reaction of (*S*)-**7** (500 mg, 2.0 mmol) with AD-mix-β {$(DHQD)_2$-PYR}(2.6 g) yielded [2*S*-(2*R*)]-**8** (420 mg, 75%) and [2*S*-(2*S*)]-**8** (91 mg, 16%) as oils. [2*S*-(2*R*)]-**8**; $[\alpha]^{25}_D$ −0.95 (c 0.99, $CHCl_3$). [2*S*-(2*S*)]-**8**, $[\alpha]^{25}_D$ −12.17 (c 3.185, $CHCl_3$).

[2S-(2S)]- and [2S-(2R)]-1-Benzyloxycarbonyl-2-(2,3-dihydroxypropyl)pyrrolidine [2S-(2S)]- and [2S-(2R)]-8

By means of a procedure similar to that for the preparation of [2*R*-(2*S*)]- and [2*R*-(2*R*)]-**8**, the reaction of (*S*)-**7** (500 mg, 2.0 mmol) with AD-mix-α {$(DHQ)_2$-PYR}(2.6 g) yielded [2*S*-(2*S*)]-**8** (437 mg, 78%) and [2*S*-(2*R*)]-**8** (88 mg, 16%) as oils. [2*S*-(2*S*)]-**8**; $[\alpha]^{25}_D$ −41.19 (c 1.225, $CHCl_3$). [2*S*-(2*R*)]-**8**, $[\alpha]^{25}_D$ −0.237 (c 2.645, $CHCl_3$).

[2R-(2S)]-1-Benzyloxycarbonyl-2-(2,3-epoxypropyl)pyrrolidine [2R-(2S)]-13

Trimethyl orthoacetate (0.22 mL, 1.71 mmol) was added to a solution of [2*R*-(2*S*)]-**8** (394 mg, 1.41 mmol) and PPTS (2.8 mg, 0.011 mmol) in CH_2Cl_2 (2.1 mL). After stirring for 20 min, the reaction mixture was evaporated, and then CH_2Cl_2 (30 mL) and acetyl bromide (0.13 mL, 1.71 mmol) were successively added to the resulting residue. After stirring for 45 min, the mixture was evaporated. To a solution of the resulting residue in methanol (4.7 mL) was added K_2CO_3 (253 mg, 1.83 mmol), and the reaction mixture was stirred for 2 h. The reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated. The residue was chromatographed using 20% EtOAc–n-hexane as eluant to yield [2*R*-(2*S*)]-**13** (272 mg, 74%) as an oil; $[\alpha]^{25}_D$ +33.31 (c 1.050, $CHCl_3$); IR (neat) 2955, 1700, 1410, 1356, 1103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27–1.44 (1 H, m), 1.75–2.11 (5 H, m), 2.26–2.35 (1 H, m), 2.55–2.64 (1 H, m), 2.76–2.89 (1 H, m), 3.32–3.38 (2 H, m), 3.98 (1 H, br s), 4.99–5.09 (2 H, m), 7.21–7.28 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.13, 23.98, 30.49, 31.29, 37.42, 38.14, 46.38, 46.47, 46.58, 46.68, 50.35, 50.60, 55.74, 55.79, 56.52, 66.68, 66.76, 67.02, 127.84,127.93, 128.05, 128.49, 137.02, 154.85; HRMS calcd for $C_{15}H_{19}O_3N$ (M^+) 261.1365, found 261.1376.

[2R-(2R)]-1-Benzyloxycarbonyl-2-(2,3-epoxypropyl)pyrrolidine [2R-(2R)]-13

By a procedure similar to that for the preparation of [2*R*-(2*S*)]-**13**, [2*R*-(2*R*)]-**8** (390 mg, 1.39 mmol) was converted in a three-step sequence [1) PPTS (2.8 mg, 0.011 mmol), trimethyl orthoacetate (0.21 mL, 1.68 mmol), CH_2Cl_2 (2.1 mL); 2) acetyl bromide (0.12 mL, 1.68 mmol); 3) K_2CO_3 (252 mg, 1.82 mmol), MeOH (4.6 mL)] to [2*R*-(2*R*)]-**13** (284 mg, 78%) as an oil; $[\alpha]^{25}_D$ +51.53 (c 1.035, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57–1.96 (6 H, m), 2.30–2.39 (1 H, m), 2.59–2.66 (1 H, m), 2.78–2.88 (1 H, m), 3.36–3.43 (2 H, m), 3.97–3.98 (1 H, m), 5.04 (2 H, ABq, *J*=14.84 Hz, 14.84 Hz)), 7.20–7.27 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.27, 24.02, 30.49, 31.07, 36.68, 37.50, 46.74, 46.88, 47.00, 49.58, 49.69, 55.01, 55.62, 66.62, 66.73, 68.87, 127.781, 127.86, 128.42, 136.95, 154.81.

[2S-(2R)]-1-Benzyloxycarbonyl-2-(2,3-epoxypropyl)pyrrolidine [2S-(2R)]-13

By a procedure similar to that for the preparation of [2*R*-(2*S*)]-**13**, [2*S*-(2*R*)]-**8** (398 mg, 1.42 mmol) was converted in a three-step sequence [1) PPTS (2.9 mg, 0.01 mmol), trimethyl orthoacetate (0.22 mL, 1.71 mmol), CH_2Cl_2 (2.1 mL); 2) acetyl bromide (0.13 mL, 1.71 mmol); 3) K_2CO_3 (256 mg, 1.85 mmol), MeOH (4.7 mL)] to [2*S*-(2*R*)]-**13** (287 mg, 77%) as an oil; $[\alpha]^{25}_D$ −36.66 (c 1.080, $CHCl_3$).

[2S-(2S)]-1-Benzyloxycarbonyl-2-(2,3-epoxypropyl)pyrrolidine [2S-(2S)]-13

By a procedure similar to that for the preparation of [2*R*-(2*S*)]-**13**, [2*S*-(2*S*)]-**8**, (412 mg, 1.47 mmol) was converted in a three-step sequence [1) PPTS (3.0 mg, 0.012 mmol), trimethyl orthoacetate (0.23 mL, 1.77 mmol), CH_2Cl_2 (2.2 mL); 2) acetyl bromide (0.14 mL, 1.77 mmol); 3) K_2CO_3 (265 mg, 1.92 mmol), MeOH (4.9 mL)] to [2*S*-(2*R*)]-**13** (314 mg, 82%) as an oil; $[\alpha]^{25}_D$ −50.95 (c 1.640, $CHCl_3$).

(+)-Hygroline 1

To a suspension of $LiAlH_4$ (74 mg, 1.96 mmol) in THF (5.7 mL) was added a solution of [2*R*-(2*S*)]-**13** (255 mg, 0.98 mmol) in THF (1.1 mL) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was refluxed for 15 h. To the mixture were successively added H_2O (74 μL), 2 N NaOH (74 μL), H_2O (222 μL), and anhyd. K_2CO_3 with ice cooling, and the resulting mixture was stirred for 30 min at room temperature. The mixture was filtered through a Celite pad, and the filtrate was evaporated at room temperature. The residue was chromatographed using 5% MeOH–CH_2Cl_2 as eluant to yield **1** (114 mg, 82%); mp 29–31°C, lit.[2] mp 29–31°C; $[\alpha]^{25}_D$ +49.64 (c 1.28, EtOH), lit.[2] $[\alpha]^{25}_D$ +50 (c 0.77, EtOH), IR (neat) 3384, 2965, 1458, 1375, 1117, 1036, 951, 901 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3 H, d, *J*=6.04 Hz), 1.36–1.43 (1 H, m), 1.65–1.91 (5 H, m), 2.08–2.16 (1 H, m), 2.31 (3 H, s), 2.51–2.58 (1 H, m), 3.01–3.07 (1 H, m), 4.08–4.18 (1 H, m), 6.59 (1 H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.61, 23.96, 28.50, 37.26, 40.76, 57.26, 64.77, 64.97; HRMS calcd for $C_8H_{17}NO$ (M^+) 143.1310, found 143.1287.

Mosher ester of 1

^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (2.96 H, s), 2.38 (0.04 H, s).

(+)-Pseudohygroline 2

By a procedure similar to that for the preparation of **1**, reaction of [2*R*-(2*R*)]-**13** (275 mg, 1.05 mmol) with $LiAlH_4$ (79 mg, 2.10 mmol) in THF (7.8 mL) gave **2** (130 mg, 87%) as an oil; $[\alpha]^{25}_D$ +95.39 (c 0.940, EtOH), lit.[15] $[\alpha]^{25}_D$ +84.4 (EtOH); IR (neat) 3384, 2963, 2844, 2790, 1456, 1371, 1181, 1133, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3 H, d, *J*=6.04 Hz), 1.30–1.49 (3 H, m), 1.70–1.80 (2 H, m), 1.94–2.07 (1 H, m), 2.30–2.38 (1 H, m), 2.34 (3 H, s), 2.65–2.74 (1 H, m), 2.99–3.07 (1 H, m), 3.86–3.95 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.08, 24.53, 30.73, 43.12, 43.33, 55.61, 65.92, 67.64; HRMS calcd for $C_6H_{12}N$ (M^+-CH_3CHOH) 98.0970, found 98.1007.

Mosher ester of 2

^{19}F NMR (254 MHz, $CDCl_3$) δ 71.06 (0.02 F, s), 71.22 (0.98 F, s).

(−)-Hygroline 3

By a procedure similar to that for the preparation of **1**, reaction of [2*S*-(2*R*)]-**13** (256 mg, 0.98 mmol) with $LiAlH_4$ (74 mg, 1.96 mmol) in THF (6.9 mL) gave **3** (124 mg, 89%); mp 28–30°C, lit.[17] mp 33–34°C; $[\alpha]^{25}_D$ −53.05 (c 1.025, EtOH), lit.[6] $[\alpha]^{22}_D$ −49 (c 0.4, EtOH); IR (neat) 3384, 2965, 2792, 1458, 1374, 1135, 1070, 1036, 951, 901 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (3 H, d, *J*=6.59 Hz), 1.38–1.44 (1 H, m), 1.66–1.91 (5 H, m), 2.09–2.18 (1 H, m), 2.32 (3 H, s), 2.54–2.58 (1 H, m), 3.03–3.09 (1 H, m), 4.11–4.18 (1 H, m), 5.29 (1 H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.66, 23.99, 28.50, 37.21, 40.79, 57.27, 64.82, 64.98.

Mosher ester of 3

^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (2.99 H, s), 2.38 (0.01 H, s).

(−)-Pseudohygroline 4

By a procedure similar to that for the preparation of **1**, reaction of [2*S*-(2*S*)]-**13** (295 mg,1.05 mmol) with $LiAlH_4$ (86 mg, 2.10 mmol) in THF (7.98 mL) gave **4** (133 mg, 85%); $[\alpha]^{25}_D$ −96.96 (c 1.005, EtOH).

Mosher ester of 4

^{19}F NMR (254 MHz, $CDCl_3$) δ 71.06 (0.99 F, s), 71.22 (0.01 F, s).

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