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A New Asymmetric Entry to 2-Substituted Piperidines. A Concise Synthesis of (+)-Coniine, (-)-Pelletierine, (+)-δ-Coniceine, and (+)-Epidihydropinidine

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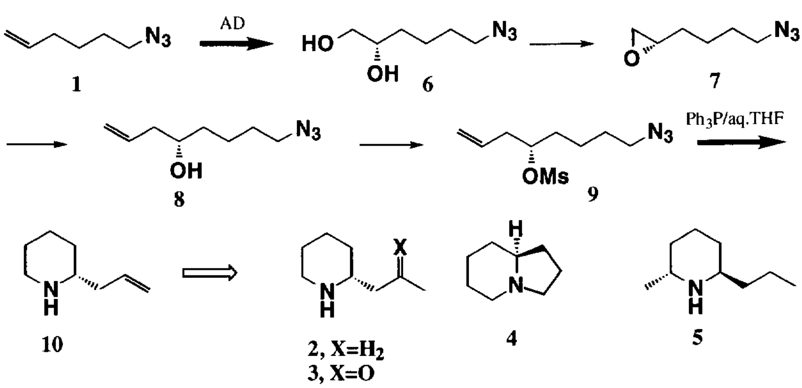
Abstract: A new asymmetric route to 2-substituted piperidines involving the Sharpless asymmetric dihydroxylation (AD) of 5-hexenylazide **1** and an intramolecular aminocyclization as crucial steps and its application to the asymmetric synthesis of four piperidine alkaloids, (+)-coniine **2**, (-)-pelletierine **3**, (+)-δ-coniceine **4**, and (+)-epidihydropinidine **5** is presented.

The development of synthetic methods for the preparation of optically active piperidine derivatives constitutes an area of current interest in view of the frequent occurrence of this heterocyclic system in a large number of ubiquitous natural products of biological importance.[1] Although asymmetric syntheses of 2-substituted piperidines using a variety of chiral auxiliaries derived from phenylglycinol,[2] 2-substituted pyrrolidine,[3] 8-phenylmenthol,[4] α-methylbenzylamine,[5] a sultam,[6] α-amino acids,[7] and *p*-tolyl sulfoxides[8] have extensively been exploited, little attention has been paid to catalytic methods.[9] In this report, we describe a new asymmetric route to 2-substituted piperidines which involves the Sharpless (osmium-catalyzed) asymmetric dihydroxylation (AD)[10] of 5-hexenyl azide **1**[11] and an intramolecular aminocyclization as crucial steps as shown below, and illustrate this process with the enantioselective synthesis of four piperidine related alkaloids, (+)-coniine **2**, (-)-pelletierine **3**, (+)-δ-coniceine **4**, and (+)-epidihydropinidine **5**.



Scheme 1

Our synthetic approach to 2-substituted piperidines **10** or *ent*-**10** began with the AD reaction of **1**. The AD reaction of **1** using three kinds of ligands [1: $(DHQ)_2$- or $(DHQD)_2$-PHAL;[12] 2: $(DHQ)_2$- or $(DHQD)_2$-PYR;[13] 3: $(DHQ)_2$- or $(DHQD)_2$-AQN[14]] afforded the diols **6** or *ent*-**6** shown in Chart 1.[15] Both cases with the PYR and AQN ligands showed better ees than did the one with the PHAL ligand. However, this time we chose the commercially available PYR ligand.[16]

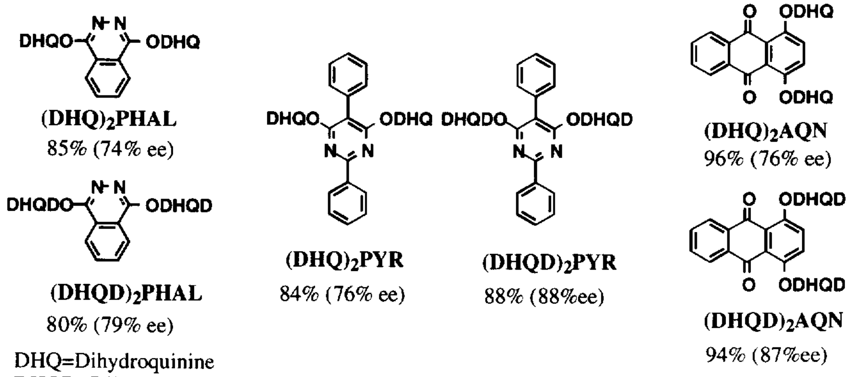
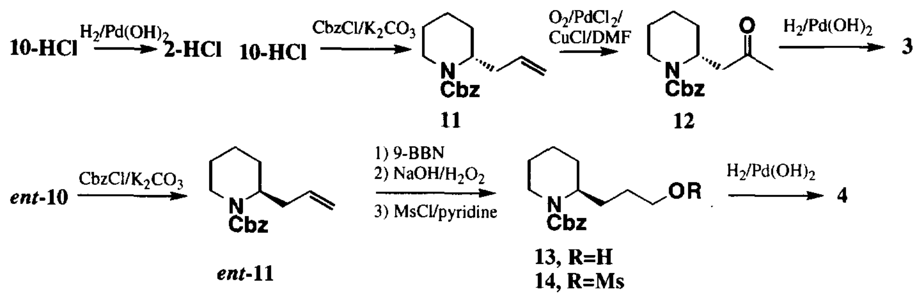


Chart 1

Of the diols **6** and *ent*-**6** in hand, "PYR-derived diols" were converted into the epoxides **7** and *ent*-**7** by the Sharpless's one-pot procedure[17] (1: $CH_3C(OCH_3)_3$/PPTS; 2: CH_3COBr; 3: K_2CO_3) in 85% and 86% yields, respectively. The regioselective cleavage of the epoxide ring in **7** and *ent*-**7** with vinylmagnesium bromide in combination with a cuprous bromide-dimethyl sulfide complex was performed to yield the alcohols **8** and *ent*-**8** in good yields (75% and 86%), respectively. The treatment of **8** and *ent*-**8** with mesyl chloride in the presence of pyridine provided the mesylate **9** (82%) and *ent*-**9** (89%), respectively. The Staudinger reaction[18] of the azides in **9** and *ent*-**9** with triphenylphosphine followed by hydrolysis of the resulting iminophosphoranes in aqueous tetrahydrofuran at 50 °C released the free amines, which immediately cyclized under inversion of configuration into the desired 2-propenylpiperidines **10** and *ent*-**10** as their hydrochloride salts[19] in 86% and 87% yields, respectively. Exposure of **10** to an atmosphere of hydrogen in the presence of palladium hydroxide in methanol furnished (+)-coniine **2**[20] as its hydrochloride salt (mp. 218-21 °C, lit.[3b] 217 °C; $[\alpha]_D^{25}$ + 5.2 (EtOH), lit.[3b] $[\alpha]_D^{28}$ +5.8 (EtOH) in 98% yield. Spectral and physical data are identical with those reported.[2a]

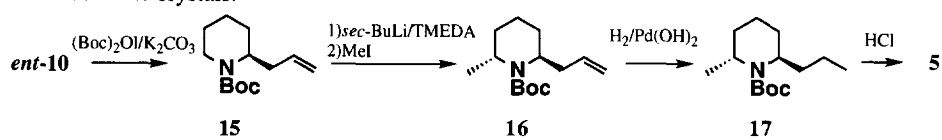
Next, *N*-Cbz-protection of **10** and *ent*-**10** gave **11** and *ent*-**11** in 96% and 88% yield, respectively. With the *N*-Cbz-piperidines in hand, we turned our attention to the synthesis of (-)-pelletierine **3**[21] and (+)-δ-coniceine **4** by starting from **11** and *ent*-**11**, respectively. The Wacker oxidation of **11** furnished the ketone **12** in 94% yield, which was converted *via* hydrogenolysis to **3**[22] {$[\alpha]_D^{25}$ - 22.1 (EtOH), lit.[23] $[\alpha]_D^{23}$ -18.1 (EtOH)} in quantitative yield. As a step to construct an indolizidine skeleton, the hydroboration of *ent*-**11** with 9-BBN followed by oxidation afforded the alcohol **13** (96%). After the hydroxyl in **13** was transformed with mesyl chloride in the presence of pyridine into the mesylate, hydrogenolysis of the resulting system resulted in simultaneous deprotection and cyclization to provide **4** [24] in quantitative yield. Spectral and physical data for the picrate of **4** are identical with those reported.[2a]

As a further illustration of the scope of the method, the preparation of a *trans*-2,6-dialkylpiperidine using Beak's *N*-Boc-piperidine α-lithiation/alkylation methodology[25] was examined. To this end, an asymmetric synthesis of (+)-epidihydropinidine **5**, isolated from the extract of *Picea engelmannii*, was investigated.[26] To date, the asymmetric synthesis of **5** has been performed only once in a multistep and less stereoselective fashion starting from D-alanine by us.[27] *N*-Protection of *ent*-**10** with $(Boc)_2O$ in the presence K_2CO_3 in aqueous



Scheme 2

THF afforded the *N*-Boc-piperidine **15** in 95% yield. Lithiation of **15** using Beak's condition (*sec*-BuLi/TMEDA/ether) and subsequent methylation with methyl iodide gave the *trans*-piperidine **16** in 66% yield. Hydrogenation of **16** furnished **17**, which on treatment with HCl/ethyl acetate at 50 °C provided an 86% yield of the **5**-HCl as white crystals.



Scheme 3

In summary, a simple procedure has been devised for the asymmetric synthesis of chiral 2-substituted piperidines. The utility of this methodology has been demonstrated by its application to the expeditious synthesis of the piperidine alkaloids (+)-coniine **2**, (-)-pelletierine **3**, (+)-δ-coniceine **4**, and (+)-epidihydropinidine **5**. Additionally, a practical and efficient method for the assembly of piperidines with a functionalized appendage at C2 should be provided by application of the reaction of the epoxide **7** with cuprates. Further studies are in progress.

Experimental Section

Melting points are determined using a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by 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 determined on a Varian Gemini-300, or 500 MHz on a Varian Unity-500instrument with $CDCl_3$ (77.2 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.

(*S*)-6-Azido-2-hydroxy-1-hexanol 6. 5-Hexenylazide **1** (2.8 g, 22.4 mmol) was added to a mixture of AD-mix (29.3 g), prepared by a mixture of $K_2OsO_4 \cdot 2H_2O$ (15 mg), $(DHQ)_2PYR$ (0.187 g), $K_3Fe(CN)_6$ (20.50 g), and K_2CO_3 (8.6 g) according to the method described in the literature[13], in *tert*-BuOH (111 mL) and H_2O (111 mL) at 0 °C. After the mixture was stirred for 24 h at the same temperature, sodium sulfite (33.0 g) was added to the mixture. After being stirred for 30 min, the mixture was filtered through Celite. The organic solvent was separated, and the aqueous solution was extracted with ethyl acetate three times. The combined organic solvents were washed with brine and dried, and the solvent was removed by rotary evaporation. The residue was purified by chromatography using hexane-ethyl acetate (1:2) as eluant to yield **6** (3.04 g, 84%) as an oil: $[\alpha]^{25}_{D}$ -13.3 (*c* 1.82, MeOH) (76% ee by HPLC as dinitrobenzoate of **6** using DAICEL CHIRALPAC AS: 40 °C, hexane-n-propanol = 9:1; flow 1 mL/min); IR (neat) 3384, 2938, 2867, 2097 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43-1.70 (6 H, m), 2.06 (1 H, br s), 2.29 (1 H, br s), 3.30 (2 H, t, *J* = 6.8 Hz), 3.44-3.48 (1H, m), 3.67-3.73 (2 H, m). HRMS calcd for $C_6H_{13}N_3O_2$ 159.1007, found 159.1012.

(*R*)-6-Azido-2-hydroxy-1-hexanol *ent*-6. By means of a procedure similar to that described for the preparation of **(*S*)-6**, a mixture of **1** (5.0 g, 39.95 mmol), $(DHQD)_2PYR$ (0.335 g)-based AD-mix (52.3 g) in *tert*-BuOH (193 mL) and H_2O (193 mL) gave ***ent*-6** (5.61 g, 88%) as an oil: $[\alpha]^{25}_{D}$ +15.0 (*c* 5.6, MeOH); (88% ee by HPLC as dinitrobenzoate of ***ent*-6** using DAICEL CHIRALPAC AS: 40 °C, hexane-n-propanol = 9:1; flow 1 mL/min).

(*S*)-1-Azido-5,6-epoxyhexane 7. A mixture of **6** (6.02 g, 37.82 mmol), pyridinium *p*-toluenesulfonate (PPTS) (76.0 mg, 0.303 mmol), and trimethyl orthoacetate (5.78 mL, 45.42 mmol) in CH_2Cl_2 (57.7 mL) was stirred for 20 min at room temperature. After the solvent was removed by rotary evaporation, CH_2Cl_2 (57.7 mL) was added to the residue. To the mixture was added acetyl bromide (3.40 mL, 45.77 mmol). After being stirred for 30 min, the solvent was removed by rotary evaporation. To the residue were added methanol (128.8 mL) and potassium carbonate (7.12 g, 49.12 mmol), and the mixture was stirred for 2 h. The reaction was quenched with sat. NH_4Cl, then extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried and evaporated. The residue was distilled under reduced pressure to yield **7** (4.52 g, 85%): bp 105 °C/2 mmHg; $[\alpha]^{25}_{D}$ -10.0 (*c* 3.5, $CHCl_3$); IR (neat) 3447, 3048, 2940, 2864, 2095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51-1.71 (6 H, m), 2.49 (1 H, dd, *J* = 4.9, 2.8 Hz), 2.77 (1 H, dd, *J* = 4.9, 4.1 Hz), 2.91-2.95 (1 H, m), 3.29 (2 H, m). Anal. Calcd for $C_6H_{11}N_3O$: C, 51.04; H, 7.85; N, 29.77. Found: C, 50.70; H, 7.87; N, 30.02.

(*R*)-1-Azido-5,6-epoxyhexane *ent*-7. By means of a procedure similar to that described for the preparation of **7**, reaction using ***ent*-6** (8.61g, 54.09 mmol), PPTS (108.8 mg, 0.414 mmol), CH_2Cl_2 (82.5 mL x 2), trimethyl orthoacetate (8.25 mL, 64.92 mmol), acetyl bromide (4.79 mL, 64.92 mmol), methanol (181.1 mL), and potassium carbonate (9.73 g, 70.33 mmol) gave ***ent*-7** (6.53 g, 86%): $[\alpha]^{25}_{D}$ +11.2 (*c* 3.0, $CHCl_3$).

(*S*)-1-(4-Azidobutyl)-2-propen-1-ol 8. To a slurry of CuBr-Me_2S (582 mg, 2.83 mmol) in THF (61.6 mL) was added a 1 M vinylmagnesium bromide-THF solution (42.6 mL, 42.6 mmol) at -78 °C with stirring. After being stirred for 30 min, a solution of **7** (4.0 g, 28.34 mmol) in THF (10 mL) was slowly added. 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 to give **8** (3.6 g, 75%) as an oil: $[\alpha]^{25}_{D}$ -7.82 (*c* 3.44, $CHCl_3$); IR (neat) 3384,3076, 2937, 2865, 2096 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40-1.65 (6 H, m), 1.88 (1 H, br s), 2.11-2.17 (1 H, m), 2.27-2.32 (1 H, m), 3.26-3.28 (2 H, m), 3.62-3.65 (1 H, m), 5.12-5.15 (2 H, m), 5.77-5.85 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 22.968, 28.914, 36.230, 42.080, 51.453, 70.427, 118.332, 134.742. Anal. Calcd for $C_8H_{15}N_3O$: C, 56.78; H, 8.94; N, 24.83. Found: C, 56.85; H, 8.94; N, 24.57.

(*R*)-1-(4-Azidobutyl)-2-propen-1-ol *ent*-8. By means of a procedure similar to that described for the preparation of **8**, reaction using ***ent*-7** (5.6 g, 39.7 mmol) in THF (22.4 mL), CuBr-Me_2S (816 mg, 3.97

mmol) in THF (86.2 mL), 1M vinylmagnesium bromide-THF (59.6 mL), and gave ***ent*-8** (5.73 g, 86%): $[\alpha]^{25}_{D}$ +9.72 (*c* 3.85, $CHCl_3$).

(*R*)-2-(2-Propenyl)piperidine 10. To a mixture of **8** (3.6 g, 21.27 mmol) and DMAP (390 mg, 3.2 mmol) in pyridine (36 mL) was added methanesulfonyl chloride (2.47 mL, 31.9 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was diluted with ether. The mixture was acidified with 20% $KHSO_4$. The organic solvent was successively washed with H_2O and brine, dried, and evaporated. The residue was purified by chromatography to yield **9** (4.3 g, 82%) as an oil. A mixture of **9**, Ph_3P (5.0 g, 19.1 mmol), and H_2O (2.0 mL) in THF (212 mL) was stirred for 15 h at 50 °C. After the organic solvent was removed by rotary evaporation, 5% HCl was added to the residue. The mixture was washed with ether and then the aqueous layer was basified with 2N NaOH. After the basic solvent was extracted with ether, conc. HCl was added to the extract. Evaporation of the solvent gave the hydrochloride salt of **10** (2.4 g, 86%) as a white solid: mp 175-8 °C (2-propanol-ethyl acetate); $[\alpha]^{25}_{D}$ +2.1 (*c* 1.3, EtOH); IR (neat) 2924, 1643, 1581, 1453 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39-2.05 (6 H, m), 2.47-2.53 (1 H, m), 2.80-2.87 (2 H, m), 2.96-3.49 (1 H, m), 5.20 (2 H, dd, *J* = 25.8, 10.0 Hz), 5.73-5.81 (1 H, m), 9.26 (1 H, br s), 9.55 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 22.400, 22.537, 28.152, 37.880, 45.043, 57.001, 120.056, 131.894. Anal. Calcd for $C_8H_{16}NCl$: C, 59.43; H, 9.98; N, 8.66. Found: C, 59.13; H, 9.87; N, 8.40.

(*S*)-2-(2-Propenyl)piperidine (*ent*-10). By means of a procedure similar to that described for the preparation of **10**, a mixture of ***ent*-9** (5.2 g, 21.0 mmol), Ph_3P (6.1 g, 23.1 mmol), and H_2O (2.5 mL) in THF (256 mL) gave the hydrochloride salt of ***ent*-10** (2.95 g, 87%): $[\alpha]^{25}_{D}$ -3.01° (*c* 1.4, EtOH).

(+)-Coniine 2. A suspension of the **10-HCl** (200 mg, 1.24 mmol)) and palladium hydroxide (20 mg) in methanol (6.5 mL) was stirred under a hydrogen atmosphere for 15 h. The insoluble materials were removed by filtration, and the filtrate was evaporated to yield the hydrochloride of **2** (203 mg, 98%): mp 218-21 °C (ethyl acetate-2-propanol), lit.[3b], mp 216-8 °C; $[\alpha]^{25}_{D}$ +5.20 (*c* 0.35, EtOH), lit. [3b], $[\alpha]^{25}_{D}$ +5.8 (EtOH); ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, *J* = 7.3 Hz), 1.38-2.01 (10 H, m), 2.78-2.86 (1 H, m), 2.93 (1 H, m), 3.45 (1 H, br d, *J* = 12.4 Hz), 9.15 (1 H, br s), 9.44 (1 H, br s). Anal. Calcd for $C_8H_{18}NCl$: C, 58.70; H, 11.08; N, 8.56. Found: C, 58.38; H, 11.04; N, 8.44.

(*R*)-1-Benzyloxycarbonyl-2-(2-propenyl)piperidine 11. 2N Potassium carbonate (3.3 mL) was added to a mixture of **10-HCl** salt (500 mg, 3.09 mmol) in THF (4.25 mL) with ice cooling. To the mixture was added benzyloxycarbonyl chloride (0.49 mL, 3.4 mmol) at 0 °C. After the reaction mixture was stirred for 4 h at room temperature, the solvent was removed by rotary evaporation. The residue was 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 purified by chromatography to yield **11** (766 mg, 96%) as an oil: $[\alpha]^{25}_{D}$ +31.42 (*c* 3.08, $CHCl_3$); IR (neat) 2938, 1700, 1639, 1498 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42-1.46 (1 H, m), 1.55-1.63 (5 H, m), 2.26-2.28 (1 H, m), 2.41-2.48 (1 H, m), 2.87 (1 H, t, *J* = 12.8 Hz), 4.07 (1 H, br s),4.39 (1 H, br s), 5.04 (2 H, dd, *J* = 16.9, 10.0 Hz), 5.14 (2 H, ABq, *J* = 19.2, 12.4 Hz), 5.73 (1 H, br s), 7.28-7.39 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 18.875, 25.582, 27.757, 34.553, 39.371, 50.472, 66.985, 117.013, 127.895, 127.976, 128.554, 135.371, 137.158, 155.699. HRMS calcd for $C_{16}H_{21}NO_2$: 259.1573. found 259.1550.

(*S*)-1-Benzyloxycarbonyl-2-(2-propenyl)piperidine *ent*-11. By means of a procedure similar to that described for the preparation of **11**, a mixture of ***ent*-10**-HCl (100 mg, 0.62 mmol), benzyoxycarbonyl chloride (97 μL, 0.68 mmol), and 2N potassium carbonate (0.65 mL) in THF (0.85 mL) gave ***ent*-11** (141 mg, 88%) as an oil: $[\alpha]^{25}_{D}$ -42.97 (*c* 4.1, $CHCl_3$).

(*R*)-1-Benzyloxycarbonyl-2-(2-oxopropyl)piperidine 12. After a mixture of palladium chloride (44 mg, 0.25 mmol), copper(I) chloride (248 mg, 2.51 mmol) in a mixture of dimethylformamide and H_2O (1:7) (2.6 mL) was stirred under oxygen atmosphere for 1 h, a solution of **11** (650 mg, 2.51 mmol) of DMF and H_2O (1:7) (0.62 mL) was added to the mixture. After being stirred under oxygen for 24 h at 50 °C, the reaction was quenched with 10% $KHSO_4$. After the mixture was extracted with ether three times, the extracts were successively washed with sat. $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by chromatography using hexane-ethyl acetate (7:1) as eluant to yield **12** (650 mg, 94%) as an oil: $[\alpha]^{25}_D$ +10.18 (*c* 2.5, $CHCl_3$); IR (neat) 2938, 2361, 2343, 1700, 1654, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38-1.71 (6 H, m), 2.15 (3 H, br s), 2.70 (2 H, d, *J* = 7.9 Hz), 2.86 (1 H, br s), 4.06 (1 H, br s), 4.82 (1 H, s), 5.13 (2 H, AB q, *J* = 17.1, 12.4 Hz), 7.28-7.39 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 18.955, 22.141, 25.377, 28.402, 30.181, 39.920, 44.409, 47.609, 50.296, 67.241, 127.983, 128.107, 128.613, 136.858, 155.406. HRMS calcd for $C_{16}H_{21}NO_3$ 275.1521. found 275.1507.

(-)-Pelletierine (3). A suspension of **12** (655 mg, 2.38 mmol) and palladium hydroxide (65.5 mg) in ethyl acetate (25.2 mL) was stirred under a hydrogen atmosphere for 15 h. The insoluble materials were removed through Celite by filtration. The filtrate was evaporated to yield **3** (100%): $[\alpha]^{25}_D$ -22.1 (*c* 4.1, EtOH), lit. [23] $[\alpha]^{23}_D$ -18.1° (EtOH); mp 218-21 °C as a hydrochloride salt; IR (neat) 3404, 2950, 2806, 2579, 2514, 2436, 2401, 1712, 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48-1.56 (1 H, m), 1.65-1.73 (1 H, m), 1.81-1.97 (4 H, m), 2.19 (3 H, s), 2.88 (1 H, t, *J* = 12.2 Hz), 2.95-3.01 (1 H, m), 3.27-3.33 (1 H, m), 3.48 (2 H, br d, *J* = 12.2 Hz), 9.25 (1 H, br s), 9.46 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 22.191, 22.338, 28.408, 30.678, 45.031, 46.049, 53.064, 204.946. Anal. Calcd for $C_8H_{16}NOCl$: C, 54.08; H, 9.08; N, 7.88. Found: C, 54.12; H, 9.07; N, 7.85.

(*S*)-1-Benzyloxycarbonyl-2-(3-hydroxypropyl)piperidine 13. To a solution of ***ent*-12** (730 mg, 2.81 mmol) in THF (4.11 mL) was added 0.5 M 9-BBN in THF (16.86 mL, 8.43 mmol) at 0 °C. After being stirred for 15 h at room temperature, 6M NaOH (7.64 mL) and 30% H_2O_2 (7.64 mL) were successively added to the mixture with ice cooling. After being stirred for 1 h at the same temperature, the organic solvent was separated. The aqueous layer was extracted with ether four times and the combined organic solvents were washed with brine, dried, and evaporated. The residue was purified by chromatography using hexane-ethyl acetate (1:1) as eluant to yield **13** (751 mg, 96%): $[\alpha]^{25}_D$ -27.99 (*c* 4.2, $CHCl_3$); IR (neat) 3426, 2935, 2864, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26-1.73 (10 H, m), 1.75-2.06 (2 H, m), 2.85 (1H, t, *J* = 12.6 Hz), 3.65 (1 H, br s), 4.07 (1 H, br s), 4.35 (1 H, br s), 5.13 (2 H, AB q, *J* = 14,8, 12.4 Hz), 7.31-7.42 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 19.021, 25.700, 26.183, 29.288, 39.268, 50.597, 62.818, 67.139, 128.019, 128.093,128.627, 137.092, 155.882. HRMS calcd for $C_{16}H_{23}NO_3$ 277.1678. found 277.1659.

(+)-δ-Coniceine 4. To a mixture of **13** (745 mg, 2.69 mmol) and DMAP (49.6 mg, 0.4 mmol) in pyridine (4.5 mL) was added methanesulfonyl chloride (0.31 mL, 4.04 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was diluted with ether. The mixture was acidified with 20% $KHSO_4$. The organic solvent was successively washed with H_2O and brine, dried, and evaporated. The residue was purified by chromatography to yield **14** (830 mg, 87%) as an oil. A suspension of **14** (830 mg, 2.34 mmol) and palladium hydroxide (83 mg) in methanol (12.3 mL) was stirred under a hydrogen atmosphere for 15 h. The insoluble materials were removed through Celite by filtration. After conc. HCl (0.47 mL) was added to the filtrate, the organic solvent was evaporated to yield a hydrochloride salt of **4** (375 mg, 100%) as a white solid. After the salt was treated with 10% K_2CO_3, the mixture was extracted with ether. The extract was washed with brine, dried over anhyd. K_2CO_3. After the solvent was removed under an atmosphere, sat. picric acid in EtOH was added to the residue. After being warmed, the mixture was cooled to room temperature. The solid was precipitated to yield the picrate of **4**: mp 226-8 °C, lit. [2a], 227-31 °C; $[\alpha]^{25}_D$ +2.75 (*c* 0.35, EtOH), lit. [2a] $[\alpha]_D$ -2.0 (EtOH) for its enantiomer; IR (neat) 2756, 1659, 1650, 1643, 1632, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47-2.27 (10 H, m), 2.67-2.81 (2 H, m), 3.84-3.95 (3 H, m), 10.24 (2H br s), 10.93 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 19.833, 22.960, 23.114, 27.317, 28.115, 53.650, 68.566, 126.849, 128.284, 141.809, 162.071. Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.29; H, 5.12; N, 15.71.

(*S*)-1-*ert*-Butoxycarbonyl-2-(2-propenyl)piperidine 15. 2N Potassium carbonate (8.32 mL) was added to a mixture of ***ent*-10-HCl** salt (1.28 g, 7.92 mmol) in THF (11 mL) with ice cooling. To the mixture was added di-*tert*-butyl dicarbonate (200 μL, 8.71 mmol) at 0 °C. After the reaction mixture was stirred for 4 h at room temperature, the solvent was removed by rotary evaporation. The residue was 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 purified by chromatography to yield **15** (1.69 g, 95%) as an oil: $[\alpha]^{25}_D$ -39.96 (*c* 1.23, $CHCl_3$); IR (neat) 2934, 2362, 1690, 1411, 1364 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (9 H, s), 1.41-1.62 (6 H, m), 2.23 (1 H, m), 2.35-2.41 (1 H, m), 2.75 (1 H, t, *J* = 12.0 Hz), 3.95 (1 H, br d, *J* =10.3 Hz), 4.26 (1H, br s), 4.97-5.05 (2 H, m), 5.69-5.77 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 18.948, 25.612, 27.735, 28.577, 28.724, 34.575, 38.990, 50.047, 79.206, 116.699, 135.723, 155.216. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.27; H, 10.30; N, 6.22.

(2*S*,6*R*)-1-*tert*-Butoxycarbonyl-6-methyl-2-(2-propenyl)piperidine 16. To a solution of **15** (726 mg, 3.37 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.662 mL, 4.38 mmol) in ether (11.2 mL) was added *sec*-BuLi (3.89 mL, 4.38 mmol) at -60 °C. The reaction mixture was slowly warmed to -20 °C. After being stirred for 30 min, methyl iodide (0.43 mL, 6.73 mmol) was added to the mixture at -78 °C. The reaction mixture was slowly warmed to room temperature and quenched with H_2O (20 mL) with ice cooling. The mixture was extracted with ether three times. The extracts were dried over anhyd. K_2CO_3 and evaporated. The residue was purified by chromatography using hexane-ethyl acetate (40:1) as eluant to yield **16** (424 mg, 66%): $[\alpha]^{25}_D$ -24.67 (*c* 3.1, $CHCl_3$); IR (neat) 2972, 2361, 1688, 1458, 1393, 1364 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3 H, d, *J* = 6.6 Hz), 1.44 (9H, s), 1.48-1.91 (6 H, m), 2.13-2.20 (1 H, m), 2.40-2.45 (1 H, m), 3.82-3.84 (1 H, m), 3.94-3.97 (1 H, m), 4.98-5.06 (2 H, m), 5.71-5.79 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 13.090, 20.998, 22.338, 26.622, 28.655, 39.298, 46.957, 51.124, 79.016, 116.574, 136.279, 155.209. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.10; H, 10.54; N, 5.55.

(2*R*,6*R*)-1-*tert*-Butoxycarbonyl-6-methyl-2-propylpiperidine 17. A suspension of **16** (255 mg, 1.07 mmol) and palladium hydroxide (25.5 mg) in methanol (5.6 mL) was stirred under a hydrogen atmosphere for 15 h. The insoluble materials were removed through Celite by filtration. After the filtrate was evaporated, the residue was purified by chromatography using hexane-ethyl acetate (60:1) as eluant to yield **17** (222 mg, 86%): $[\alpha]^{25}_D$ -35.15 (*c* 3.0, CHCl3); IR (KBr) 2956, 2361, 2343, 1686, 1458, 1394 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89-0.92 (3 H, d, J = 6.8 Hz), 1.22 (3 H, t, *J* = 6.6 Hz), 1.24-1.43 (3 H, m), 1.44 (9 H, s), 1.47-1.67 (5 H, m), 1.73-1.88 (2 H, m), 3.78-3.81 (1 H, m), 3.88-3.93 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 13.881, 14.254, 20.398, 20.991, 23.320, 27.018, 28.716, 36.691, 47.089, 51.497, 78.848, 155.428. HRMS calcd for $C_{14}H_{27}NO_2$ 241.2041. found 241.2022.

(+)-Epidihydropinidine 5. A solution of **17** (113 mg, 0.47 mmol) and conc. HCl (0.1 mL) in ethyl acetate (0.24 mL) was heated for 1 h at 60 °C. Evaporation of the solvent gave the hydrochloride salt of **5** (130 mg, 100%) as a white solid: mp 171-3 °C (2-propanol-ethyl acetate), lit.[26] 164.5-165.5 °C; $[\alpha]^{25}_D$ +3.8 (*c*

0.75, EtOH), lit.[26] $[\alpha]^{23}_D$ +4.7 (EtOH); IR (KBr) 2958, 2845, 2544, 1556, 1538 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.5 Hz), 1.34-1.46 (2 H, m), 1.48 (3 H, d, J = 6.8 Hz), 1.65-1.79 (5 H, m), 1.91-2.02 (3 H, m), 3.30 (1 H, m), 3.56 (1 H, m), 0.96 (2 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.932, 17.013, 17.559, 19.229, 26.513, 29.078, 33.008, 48.123, 51.690. Anal. Calcd for $C_9H_{20}NCl$: C, 60.83; H, 11.34; N, 7.88. Found: C, 60.33; H, 11.13; N, 7.65.

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References and notes

1. (a) Strunzand, G. M.; Findlay, J. A. In *The Alkaloids*, ed. by Brossi, A. Academic Press, San Diego, 1986, Vol 26, p. 89. (b) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; ed. by Pelletier, S. W. Wiley, New York, 1986, Vol 3, p. 1.
2. (a) Munchhof, J. M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084. (b) Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron:Asymmetry* **1995**, *6*, 2651. (c) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223.
3. (a) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 6119. (b) Ender, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173.
4. Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *Tetrahedron Lett.* **1992**, *33*, 7635.
5. (a) Marx, E.; Bouz, M. E.; Célérier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1992**, *33*, 4307. (b) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525.
6. Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015.
7. Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444.
8. Louis, C.; Mill, S.; Mancuso, V.; Hootele, C. *Can. J. Chem.* **1994**, *72*, 1347.
9. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.
10. For an excellent review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
11. Compoud **1** was prepared by the tosylation of 5-hexenol followed by the azidation with sodium azide in DMF (69%, 2 steps).
12. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
13. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.
14. Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448. These ligands were provided by Prof. K. B. Sharpless and Dr. H. Becker (Scripps Research Institute).
15. Enantiomeric excess of **6** and *ent*-**6** was determined as their dinitorobenzoates by HPLC using Daicel CHIRALPAC AS.
16. After this work has been done, $(DHQ)_2$- and $(DHQD)_2$-AQN ligands were very recently commercially available from Aldrich Chemical Co., Inc.
17. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
18. For a review, see: Gololobov, Y. G.; Kasukhin, L.F. *Tetrahdron* **1992**, *48*, 1353.
19. The hydrochloride salts (mp 175-8 °C) of **10** and *ent*-**10** were recrystallized from of ethyl acetate containing a small of 2-propanol. Accordingly, their ees would have been improved, but their values remain undetermined.
20. Recent syntheses of (+)-coniine: (a) refs. 2a,b,3a,b. (b) Royer, J.; Husson, H. P. *Janssen Chim. Acta* **1993**, *11*, 3.
21. Hess, K.; Eichel, A. *Ber.* **1917**, *50*, 1192.
22. To our knowledge, a chiral synthesis of **3** has been reported only once. ref. 8. ^1H NMR spectrum is identical with that reported.[8]
23. Galinovsky, F.; Bianchetti, Vogel, O. *Monatsch. Chem.* **1953**, *84*, 1221.
24. Recent asymmetric synthesis of δ-coniceine: (a) ref.[2a,7]. (b) Arai, Y.; Kontani, T. Koizumi, T. *J. Chem. Soc. Perkin Trans 1*, **1994**, 15. (c) Sibi, M. P.; Christensen, J. M. *Tetrahedron Lett.* **1990**, *31*, 5689.
25. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
26. Tawara, J. N.; Blokhin, A.; Foderano, T.A.; Stermitz, F. R. *J. Org. Chem.* **1993**, *58*, 4813.
27. Takahata, H.; Inose, K.; Araya, N.; Momose, T. *Heterocycles* **1994**, *38*, 1961.

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