Pergamon

Tetrahedron 54 (1998) 13505–13516

TETRAHEDRON

A General Asymmetric Route to *trans*- or *cis*-2,6-Disubstituted Piperidine. First Total Synthesis of (+)-9-Epi-6-epipinidinol and (-)-Pinidinol

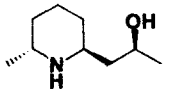
Hiroki Takahata,* Yasuhito Yotsui, and Takefumi Momose

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University
2630 Sugitani, Toyama 930-0194, Japan

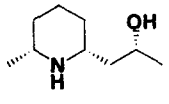
Received 23 July 1998; accepted 1 September 1998

Abstract: Starting from 1,6-heptadiene, two AD reactions in a stepwise manner lead to the *anti*-1,5-diol and *syn*-1,5-diol stereodivergently, which have been converted by aminocyclization into *trans*- and *cis*-2,6-disubstituted piperidines (*trans*- and *cis*-**12**), respectively. The first total synthesis of (+)-9-epi-6-epipinidinol (**2**) and (-)-pinidinol (**3**) has been achieved from *trans*- and *cis*-**12**.

The abundance of biologically active compounds containing the 2,6-disubstituted piperidine ring has resulted in considerable synthetic efforts to reach these systems.[1] Recent attention is turned to their asymmetric synthesis, most of which have been achieved by chiral auxiliaries-mediated methods[2] and chiral pools-derived procedures.[3] Our interest in this field has been focused on the synthetic application of the double or iterative Sharpless asymmetric dihydroxylation (AD)[4] to cause enantiomeric enhancement (or amplification of ee).[5] In this report, we describe an asymmetric avenue to *trans*- or *cis*-2,6-disubstituted piperidine *via* 1,5-diol using two AD reactions starting from symmetrical 1,6-heptadiene (**1**) and according to this process demonstrate the first total synthesis of two toxic piperidine alkaloids, (+)-9-epi-6-epipinidinol (**2**)[6] and (-)-pinidinol (**3**)[7], isolated from pine (*Pinus*) and spruce (*Picea*).



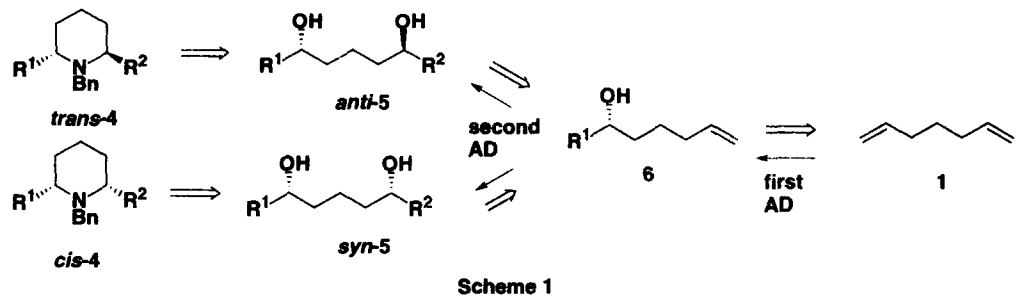
2



3

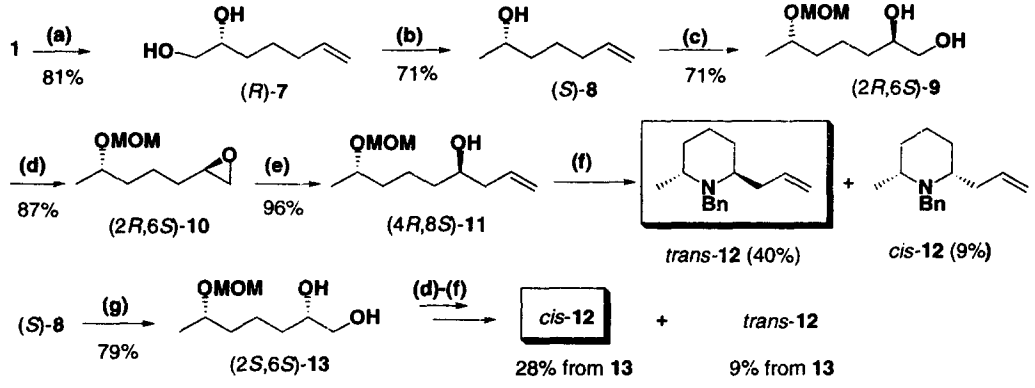
Our reterosynthetic plan that we have employed for the construction for 2,6-disubstituted piperidines (*trans*-**4** and *cis*-**4**) is outlined in Scheme 1. Access to 2,6-disubstituted piperidines is viewed to be possible by cyclic amination of *anti*-1,5-diol (*anti*-**5**) or *syn*-1,5-diol (*syn*-**5**) using benzylamine, respectively. A key aspect of this strategy is the installation of the selective hydroxylation of olefins with two AD reactions. That is to say, the repeated AD reactions using same ligand (DHQD-based ligand) provide the *anti*-diol (**1** → **6** → *anti*-**5**). On the other hand, the *syn*-diol can be obtained when DHQD-based ligand and DHQ-based one are used alternately in the iterative AD reactions (**1** → **6** → *syn*-**5**).

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00831-X



Scheme 1

Our synthetic approach to *anti*-**5** began with the single AD of **1**. The (DHQD)2-PYR ligand-derived AD reaction of **1** afforded the diol (*R*)-**7** (88% ee)[5a] in 81% yield. The diol (*R*)-**7** was converted into the epoxide by the Sharpless one-pot procedure,[8] followed by the regioselective reduction with Super-Hydride® provided the secondary alcohol (*S*)-**8** in 71 % overall yield. Methoxymethylation of (*S*)-**8** gave methoxymethyl ether which was then subjected to the second (DHQD)2-PYR ligand-derived AD reaction to give **9** as an inseparable diastereoisomeric mixture.[9] The treatment of the diol **9** with a three-step sequence (1. cyclic stannoxanation, 2. primary tosylation, 3. epoxidation) gave the epoxide **10**,[9] which was cleavaged with vinylmagnesium bromide in the presence of CuBr-Me2S to provide the hydroxyl **11**.[9] The compound **11** was successively subjected to deprotection, ditosylation, and cyclic amination with benzylamine to give enantiomerically enriched *trans*-piperidine *trans*-**12** (> 98% ee) as major product together with *cis*-piperidine *cis*-**12** in 40% and 9% three-step yields, respectively. On the other hand, the (DHQ)2-PYR ligand-based AD reaction of **8** gave a diastereomeric mixture of **13**,[9] followed by the similar sequence described above (**9** → *trans*-**12**) to give *cis*-**12** (97% ee) and *trans*-**12** in the ratio of about 3:1.

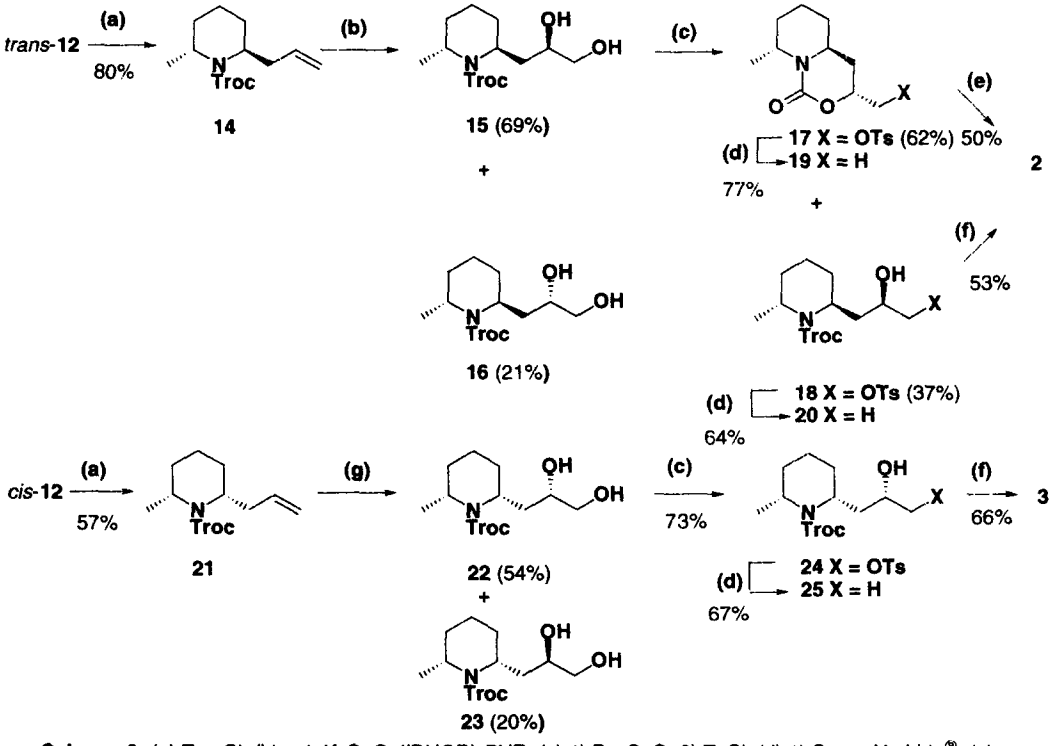


Scheme 2: (a) cat. K_2OsO_4, $(DHQD)_2PYR$; (b) 1) $(MeO)_3CMe$/PPTS; 2) MeCOBr; 3) K_2CO_3/MeOH; 4) Super-Hydride®; (c) 1) MOMCl/i-Pr_2EtN; 2) cat. K_2OsO_4, $(DHQD)_2PYR$; (d) 1) Bu_2SnO; 2) TsCl; 3) K_2CO_3; (e) vinylmagnesium bromide/CuBr-Me_2S; (f) 1) c. HCl; 2) TsCl/Et_3N; 3) $BnNH_2$; (g) cat. K_2OsO_4, $(DHQ)_2PYR$

With both optically active *trans*- and *cis*-**12** in hand, we next turned our attention to the asymmetric synthesis of **2** and **3**.[10] Carbamation of *trans*-**12** with 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) in refluxing toluene gave the urethane **14**,[12] which was subjected to the $(DHQD)_2$-PYR ligand-derived AD reaction

to afford a diastereomeric mixture of **15** (69%) and **16** (21%). Selective monotosylation of **15** was performed with a two-step sequence (1. Bu_2SnO 2. *p*-TsCl) to give the bicyclic carbamate **17** and the carbamate **18** in 62% and 37% yields, respectively. Both the tosylates **17** and **18** were reduced with Super-Hydride® to provide **19** and **20**, respectively. Hydrolysis of **19** with 2M KOH in ethanol at 140 °C in a sealed tube gave **2** {$[\alpha]^{26}_D$ +4.7 ($CHCl_3$), lit.[6] $[\alpha]^{25}_D$ +4.2 ($CHCl_3$)} in 50% yield. Deprotection of **20** with 10% Cd-Pb[13] also gave **2** in 53% yield. Spectral data of both **2** prepared from **19** and **20** were identical with those reported.[6]

Our synthesis of **3** was initiated with the carbamation of *cis*-**12** obtained from **13**. The reaction afforded the carbamate **21**, which was subjected to the $(DHQ)_2$-PYR ligand-derived AD reaction to afford a diastereomeric mixture of **22** (54%) and **23** (20%). Monotosylation of **22** followed by the reduction of the resulting tosylate **24**[14] gave **25**, which was then deprotected to afford the desired **3** {mp 76-7° C $[\alpha]^{26}_D$ -15 ($CHCl_3$); lit.[7b] 70.5-72 °C, $[\alpha]^{26}_D$ -17 ($CHCl_3$)}. Spectral data of **3** were consistent with those reported.[7b]



Scheme 3: (a) TrocCl; (b) cat. K_2OsO_4/$(DHQD)_2PYR$; (c) 1) Bu_2SnO; 2) TsCl; (d) 1) Super-Hydride®; (e) KOH/EtOH; (f) Pb-Cd/NH_4OAc; (g) cat. K_2OsO_4/$(DHQ)_2PYR$

In summary, we have developed a general method for the stereodivergent preparation of the *trans* and the *cis* diastereomers of 2,6-disubstituted piperidine (**4**) with highly enantiomeric enhancement in a sequence of the two AD reactions from 1,6-heptadiene as a symmetrical educt.[15] In addition, we demonstrated the synthetic utility of *trans*- and *cis*-**12** as chiral synthons by the first asymmetric synthesis of **2** and **3**. This methodology should permit the construction of all four stereoisomers of the 2,6-disubstituted piperidines **4** with functionalized appendages and our work along this line is in progress.

Experimental

Melting points were 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 (^{1}H 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. 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/*n*-hexane or acetone/*n*-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 $MgSO_4$ unless otherwise specified.

(S)-Hept-6-en-2-ol (8). A mixture of (S)-**7**[5a] (556 mg, 1.81 mmol), pyridinium *p*-toluenesulfonate (PPTS) (36 mg, 14.5 mmol), and trimethyl orthoacetate (276 μL, 2.17 mmol) in CH_2Cl_2 (2.8 mL) was stirred for 1.5 h at room temperature. After the solvent was removed by rotary evaporation, CH_2Cl_2 (2.8 mL) and acetyl bromide (161 μL, 2.17 mmol) were successively added to the resulting residue. After vigorous stirring, the mixture was evaporated. Methanol (6.1 mL) and K_2CO_3 (325 mg) were successively added to the resulting residue. After stirring for 2.5 h, the mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The extracts were washed with brine, dried, and evaporated to yield the crude epoxide. To a solution of the crude epoxide (500 mg) in THF (2 mL) was injected Super-Hydride® (1M in THF, 15 mL, 15 mmol) at 0 °C. After being stirred for 15 min, a few pieces of ice were added to the reaction mixture. After being stirred for 15 min at room temperature, water (12 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (30 mL) three times. The extracts were dried and evaporated. The residue was chromatographed using *n*-hexane:acetone (80:1) as eluant to yield (*S*)-**8** (345 mg, 71%) as an oil; $[\alpha]^{26}_D$ +10.4 (*c* 0.79, $CHCl_3$); IR cm^{-1} (neat): 3354, 2968, 2931, 2860, 1641, 1458, 1373, 1321, 1121; ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.19 (d, *J* = 6.0 Hz, 3 H), 1.36-1.55 (m, 4 H), 2.04-2.10 (m, 2 H), 3.80 (sixtet-like, *J* = 6.0 Hz, 1 H), 4.93-5.04 (m, 2 H), 5.75-5.87 (m, 1 H); ^{13}C NMR (75.5 MHz) δ: 23.8, 25.3, 33.9, 39.0, 68.2, 114.7, 138.8. HRMS Calcd. for C7H14O (M+) 114.1045. Found 114.1033.

(2R, 6S)-6-Methoxymethoxyheptane-1,2-diol (9). A mixture of (*S*)-**8** (700 mg, 6.14 mmol), *N,N*-diisopropylethylamine (2.36 mL, 13.5 mmol), chloromethyl methyl ether (0.93 mL, 12.3 mmol) in $CHCl_3$ (40 mL) was refluxed for 5 h. The mixture was diluted with Et_2O (100 mL) and filtered through a Celite pad. The filtrate was evaporated and the residue was chromatographed using *n*-hexane: acetone (100:1) as eluant to give (*S*)-6-(methoxymethoxy)-hept-1-ene (808 mg, 83 %) as an oil; $[\alpha]^{26}_D$ +18.1 (*c* 1.33, $CHCl_3$); IR cm^{-1} (neat): 3077, 2971, 2932, 1640, 1376, 1146, 1101; ^{1}H NMR (300MHz $CDCl_3$) δ 1.16 (d, *J* = 6.0 Hz, 3H), 1.36-1.61 (m, 4 H), 2.06 (q, *J* = 6.6 Hz, 2 H), 3.37 (s, 3 H), 3.68 (sixtet, *J* = 3.3 Hz, 1 H), 4.62, 4.69 (ABq, *J* = 6.6 Hz, 2 H), 4.93-5.05 (m, 2 H), 5.81 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 25.1, 34.0, 36.7, 55.5, 73.1, 94.9, 114.6, 138.8. The olefin (155 mg, 0.98 mmol) was added to a mixture of AD-mix (1.42 g), prepared from $K_2OsO_4 \cdot 2H_2O$ (5.6 mg), $(DHQD)_2PYR$ (0.071 g), $K_3Fe(CN)_6$ (7.74 g), and

K_2CO_3 (3.25 g) in *tert*-BuOH (4.9 mL), and H_2O (4.9 mL) at 0 °C . After the reaction mixture was stirred for 14 h at the same temperature, sodium sulfite (1.65 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 (10 mL) five times. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed using *n*-hexane: acetone (5:1) as eluant to yield a diasteromeric mixture of (2R,6*S*)-**9** as a major product (159 mg, 85%) as an oil; ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.14 (d, *J* = 6.6 Hz, 3 H), 1.40-1.57 (m, 6 H), 3.34 (s, 3 H), 3.33-3.42 (m, 3 H), 3.55-3.68 (m, 3 H), 4.59, 4.65(ABq, *J* = 7.1 Hz, 2 H); ^{13}C NMR (75.5MHz) δ: 20.6, 21.8, 33.2, 37.1, 55.5, 66.9, 72.2, 73.3, 95.0; MS 131 (M^+-MOM); HRMS Calcd. for $C_7H_{14}O_2$ (M^+-MOM) 130.0994, Found 130.098.

(2R, 6S)-1, 2-Epoxy-6-methoxymethoxyheptane (10). n-Bu_2SnO (247 mg, 0.99 mmol) was added to a solution of (2R,6*S*)-**9** (159 mg, 0.83 mmol) in dry toluene (20.5 mL) and THF (2 mL). This solution was heated to reflux for 6 h using a Dean-Stark trap for water removal. The reaction was cooled, and triethylamine (57.7 μL, 0.41 mmol) and *p*-toluenesulfonyl chloride (*p*-TsCl) (189 mg, 0.99 mmol) were added to the reaction mixture. The reaction was stirred for 16 h at room temperature and brine (10 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried and evaporated. The residue was chromatographed using *n*-hexane: acetone (12:1) as eluant to yield (2*R*, 6*S*)-6-(methoxymethoxy)-1-(*p*-toluenesulfonyloxy)heptan-2-ol (274 mg, 96%) as an oil; ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.14 (d, *J* = 6.0 Hz, 3H), 1.34-1.58 (m, 6H), 2.17 (d, *J* = 4.4 Hz, 1 H), 2.45 (s, 3 H), 3.35 (s, 3 H), 3.62-3.69 (m, 1 H), 3.82-3.91 (m, 2 H), 4.01 (d, *J* = 1.6 Hz, 1 H), 4.59, 4.67 (ABq, *J* = 7.1 Hz, 2 H), 7.36 (d, *J* = 7.7 Hz, 2 H), 7.80 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 20.6, 21.6, 20.0, 32.8, 36.9, 37.0, 55.6, 69.6, 73.1, 74.1, 95.1, 128.1, 130.1, 145.2; MS 285 (M^+-MOM); HRMS Calcd. for $C_{14}H_{21}O_4S$ (M^+-MOM) 285.1160, Found 285.1147. To a solution of the tosylate 274 mg, 0.79 mmol) in MeOH (3.0 mL) was added K_2CO_3 (164 mg, 1.19 mmol) at 0 °C. The reaction was stirred for 40 min at room temperature and sat. NH_4Cl (10 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 (10 mL) five times. The extracts were dried and evaporated. The residue was chromatographed using *n*-hexane: acetone (60:1) as eluant to yield (2*R*, 6*S*)-**10** (125 mg, 91%) as an oil; ^{1}H NMR (300 MHz $CDCl_3$) δ; 1.15 (d, *J* = 6.0 Hz, 3 H), 1.44-1.61 (m, 6 H), 2.46 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.74 (t, *J* = 4.4 Hz, 1 H), 2.90 (br, 1 H), 3.35 (s, 3 H), 3.67 (sixtet-like, *J* = 6.0 Hz, 1 H), 4.60, 4.67 (ABq, *J* = 6.6 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 20.5, 22.4, 32.8, 37.1, 47.3, 52.5, 55.5, 73.1, 95.0; MS 113 (M^+-MOM); HRMS Calcd. for $C_7H_{14}O$ (M^+-MOM) 114.1045, Found 114.1027.

(4R, 8S)-8-Methoxymethoxynon-1-en-2-ol (11). To a slurry of CuBr-SMe$_2$ (61.4 mg, 0.30 mmol) in THF (12 mL) was added vinylmagnesium bromide (1 M in THF, 5.38 mL, 5.38 mmol) at -78 °C with stirring. After being stirred for 1 h at -45 °C, a solution of **10** (520 mg, 2.99 mmol) in THF (3 mL) was slowly added. The mixture was gradually warmed to -30 °C, stirred for 4 h, and quenched with sat. NH_4Cl. The mixture was diluted with ether, washed with brine, dried, and evaporated. The residue was chromatographed using *n*-hexane: acetone (30:1) as eluant to give (4*R*, 8*S*)-**11** (578 mg, 96 %) as an oil; IR cm^{-1} (neat): 3423, 2933, 1686, 1641, 1560, 1508, 1439, 1377, 1217, 1148, 1102; ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.15 (d, *J* = 6.0 Hz, 3 H), 1.39-1.61 (m, 6 H), 1.71-1.80 (m, 1 H), 2.08-2.18 (m, 1 H), 2.25-2.33 (m ,1 H), 3.36 (s, 3 H), 3.59-3.71 (m, 1 H), 4.61, 4.68 (ABq, *J* = 7.1 Hz, 2 H), 5.09-5.15 (m, 2 H), 5.74-5.88 (m, 1 H); ^{13}C NMR (75.5 MHz) δ:

20.6, 22.0, 37.2, 42.2, 55.5, 70.7, 73.3, 95.0, 118.2, 134.9; MS 141 (M^+-MOM); HRMS Calcd. for $C_9H_{17}O$ (M^+-MOM) 141.1279, Found 141.1265.

(2R, 6S)-1-Benzyl-2-methyl-6-(2-propenyl)piperidine (12). A mixture of (4*R*, 8*S*)-**11** (578 mg, 2.86 mmol) and conc. HCl (0.3 mL) in MeOH (20 mL) was heated at 62 °C for 30 min. The reaction was diluted with $CHCl_3$ (50 mL) and sat. $NaHCO_3$ (4 mL) was added to the dilute solution solution at 0 ° C. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (20 mL) four times. The combined organic solvents were dried and evaporated. The residue was chromatographed using *n*-hexane: acetone (7:1) as eluant to give (2*S*, 6*R*)-8-heptene-2, 6-diol (466 mg, 99%) as an oil; IR cm^{-1} (neat): 3346, 3076, 2933, 1641, 1560, 1458, 1436, 1374, 1330, 1124, 996; ^1H NMR (300 MHz $CDCl_3$) δ: 1.16 (δ, *J* = 6.6 Hz, 3 H), 1.34-1.57 (m, 6 H), 2.09-2.30 (m, 2 H), 2.35 (br s, 1 H), 2.50(br s, 1 H),3.62 (br s, 1 H), 3.77 (br s, 1 H), 5.07 (s, 1 H), 5.11-5.12 (m, 2 H), 5.73-5.87 (m, 1 H); ^{13}C NMR (75.5 MHz) δ: 22.0, 23.8, 36.6, 39.1, 42.1, 67.8, 70.6, 117.9, 135.0; MS 159 (M^++1), 157(M^+ -1), HRMS Calcd. for $C_9H_{17}O_2$ 157.1229, Found 157.1240. *p*-Toluenesulfonyl chloride (1.57 g, 8.26 mmol), Et_3N (1.15 mL, 8.26 mmol), and DMAP (67.3 mg, 0.55 mmol)were successively added to a solution of the diol (432 mg, 2.75 mmol) in CH_2Cl_2 (3.65 mL) at 0 °C. The reaction was stirred for 48 h at room temperature and then diluted with Et_2O (40 mL). The dilute solution solution was filtered through a Celite pad. The filtrate was washed with brine (8 mL), dried, and evaporated. The residue was chromatographed using n-hexane:acetone (12:1) as eluant to give (2*S*,6*R*)-2,6-bis(*p*-toluenesulfonyl)non-8-ene (1.11 g, 87%) as an oil; IR cm^{-1} (neat): 2953, 2872, 1924, 1643, 1598, 1496, 1455, 1360, 1306, 1292, 1175; ^1H NMR (300 MHz $CDCl_3$) δ: 1.15 (d, *J* = 6.6 Hz, 3 H), 1.30-1.54 (m, 6 H), 2.24 (t-like, *J* = 6.0 Hz, 2 H), 2.41 (s, 6 H), 4.40-4.52 (m, 2 H), 4.93-5.00 (m, 2 H), 5.47-5.61 (m, 1 H), 7.31 (d, *J* = 8.2 Hz, 4 H), 7.74 (d, *J* = 8.2 Hz, 4 H); ^{13}C NMR (75.5 MHz) δ: 20.1, 20.8, 21.8, 33.3, 36.0, 38.7, 80.0, 82.4, 118.8, 127.6, 127.7, 129.8, 132.0, 132.0, 134.1, 144.6; MS 124 (M^+-2xTsO); HRMS Calcd. for C_9H_{16} (M^+-2xTsO) 124.1252, Found 124.1250. A mixture of the ditosylate (1.03 g, 2.21 mmol) and $BnNH_2$ (7.24 mL, 66.3 mmol) was heated at 70 °C for 2 days. The reaction was diluted with *n*-pentane (50 mL) at 0 °C and 2N NaOH (160 mL) was added to the dilute solution. The organic layer was separated and the aqueous layer was extracted with n-pentane (30 mL) four times. The combined organic layers were dried with K_2CO_3 and evaporated. The residue was chromatographed using n-hexane: ethyl acetate (60:1) as eluant to give a mixture of piperidines, which were rechromatographed using *n*-hexane: ethyl acetate (60:1) as eluant to yield (2*R*, 6*S*)-**12** (233 mg, 46 %) and (2*S*, 6*S*)-**12** (44 mg, 10 %) as oils; (2*R*, 6*S*)-**12**; $[\alpha]^{26}_D$ -35.8 (*c* 1.30, $CHCl_3$); IR cm^{-1} (neat): 3025, 2929, 2802, 1639, 1494, 1452, 1376; ^1H NMR (300 MHz $CDCl_3$) δ: 1.06 (d, *J* = 6.6 Hz, 3 H), 1.30-1.68 (m, 6 H), 2.22-2.42 (m, 2 H), 2.78-2.86 (m, br m, 1 H), 2.87-2.94 (m, 2 H), 3.57, 3.93 (ABq, *J* = 14.3 Hz, 2 H), 4.98-5.06 (m, 2 H), 5.68-5.82 (m, 1 H), 7.21-7.42 (m, 5 H); ^{13}C NMR (75.5 MHz) δ: 18.1, 19.7, 27.7, 32.0, 33.4, 50.1, 52.7, 54.8, 115.8, 126.4, 128.4, 137.1, 141.5; MS 229 (M^+), 91 (100); Anal. Calcd. for $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found C, 83.28; H, 10.48; N, 5.79.
(2*S*, 6*S*)-**12**; $[\alpha]^{26}_D$ +1.32 (*c* 0.65, $CHCl_3$).

(2S, 6S)-6-Methoxymethoxyheptane-1,2-diol (13). By a procedure similar to that for the preparation of (2*R*, 6*S*)-**9**, the reaction of (*S*)-6-(methoxymethoxy)-hept-1-ene (180 mg, 1.14 mmol) with AD mix-α (DHQ-PYR ligand) (1.65 g) in *t*-BuOH (5.7 mL) and H_2O (5.7 mL) to yield (*n*-hexane:acetone = 5:1 as eluant) (2*S*,6*S*)-**13** (major diastereomer) (173 mg, 79 %) as an oil; IR cm^{-1} (neat): 3410, 2933, 1686, 1459, 1378,

1216, 1036, 918; ^{1}H NMR (300MHz $CDCl_3$) δ: 1.14 (d, J = 6.6 Hz, 3 H), 1.32-1.56 (m, 6 H), 3.22 (br s, 2 H), 3.34 (s, 3 H), 3.36-3.43 (m, 1 H), 3.56-3.69 (m, 3 H), 4.59, 4.66 (ABq, J = 7.1 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 20.6, 21.7, 33.2, 37.1, 55.5, 66.8, 72.3, 73.2, 94.9; MS 131 (M^+-MOM); HRMS Calcd. for $C_7H_{14}O_2$(M^+-MOM) 130.0994, Found 130.1041.

(2S, 6S)-1, 2-Epoxy-6-methoxymethoxyheptane (10). By a procedure similar to that for the preparation of (2*R*, 6*S*)-6-(methoxymethoxy)-1-(*p*-toluenesulfonyloxy)heptan-2-ol , the reaction of (2*S*,6*S*)-**13** (170 mg, 0.89 mmol) with n-Bu_2SnO (264 mg, 1.06 mmol) in toluene (21.8 mL) and THF (2.2 mL) give the cyclic stannane, which was tosylated with *p*-TsCl(203 mg, 1.06 mmol) in the presence of Et_3N (61.0 mL, 0.44 mmol) to yield (*n*-hexane:acetone = 12:1 as eluant) (2*S*,6*S*)-6-(methoxymethoxy)-1-(*p*-toluenesulfonyloxy)heptan-2-ol (288 mg, 94%) as an oil; IR cm^{-1} (neat): 3445, 2934, 1700, 1653, 1598, 1457, 1361, 1177, 1140, 1098; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13 (d, J = 6.0 Hz, 3 H), 1.29-1.52 (m, 6 H), 2.43 (s, 3 H), 3.33 (s, 3 H), 3.63 (q, J = 6.0 Hz, 1 H), 3.80-3.89 (m, 2 H), 4.00 (d-like, J = 7.1 Hz, 1 H), 4.57, 4.65 (ABq, J = 6.6 Hz, 2 H), 7.36 (d, J = 8.2 Hz, 2 H), 7.80 (d, J = 8.2 Hz, 2 H); ^{13}C NMR 75.5 MHz) δ: 20.4, 21.4, 21.9, 32.8, 36.8, 55.5, 69.4, 73.1, 74.1, 94.9, 128.0, 130.0, 132.6, 145.1; MS 285 (M^+-MOM); HRMS Calcd. for $C_{14}H_{21}O_4S$ (M^+-MOM) 285.1160, Found 285.1133.

By a procedure similar to that for the preparation of (2*R*, 6*S*)-**10**, the reaction of the tosylate (288 mg, 0.83 mmol) with K_2CO_3 (173 mg, 1.25 mmol) in MeOH (3.1 mL) gave (*n*-hexane:acetone = 60:1 as eluant) (2*S*,6*S*)-**10** (132 mg, 91%) as an oil; IR cm^{-1} (neat): 2933, 1460, 1450, 1411, 1377, 1260, 1217, 1144, 1097, 1039, 918; ^{1}H NMR(300 MHz $CDCl_3$) δ: 1.14 (d, J = 6.0 Hz, 3 H), 1.44-1.58 (m, 6 H), 2.45 (dd, J = 4.9, 2.7 Hz, 1 H), 2.72 (t, J = 4.4 Hz, 1 H), 2.88 (m, 1 H), 3.34 (s, 3 H), 3.66 (sixtet-like, J = 6.0 Hz, 1 H), 4.58, 4.66 (ABq, J = 6.6 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 20.4, 22.2, 32.6, 36.9, 47.2, 52.4, 55.5, 73.0, 94.9; MS 113 (M^+-MOM); HRMS Calcd. for $C_7H_{14}O$ (M^+-MOM) 114.1045, Found 114.1012.

(4S, 8S)-8-Methoxymethoxynon-1-en-2-ol (11). By a procedure similar to that for the preparation of (4*R*, 6*S*)-**11**, the reaction of (2*S*,6*S*)-**10** (132 mg, 0.76 mmol) with vinylmagnesium bromide (1.37 mL, 1.37 mmol, 1 M in THF) in the presence of CuBr-SMe_2 (15.6 mg, 0.076 mmol) in THF (2 mL) gave (*n*-hexane: acetone (30:1) as eluant) (4*S*, 8*S*)-**11** (123 mg, 80 %) as an oil; IR cm^{-1} (neat): 3421, 2933, 1654, 1458, 1377, 1217, 1145, 1102, 1039; ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.13 (d, J = 6.0 Hz, 3 H), 1.34-1.55 (m, 6 H), 1.90 (br s, 1 H), 2.11(dt, J = 13.7, 7.7 Hz, 1 H), 2.22-2.30 (m, 1 H), 3.33 (s, 3 H), 3.57-3.68 (m, 1 H), 4.58, 4.65 (ABq, J = 7.1 Hz, 2 H), 5.07-5.12 (m, 2 H), 5.72-5.85 (m, 1 H); ^{13}C NMR (75.5 MHz) δ: 20.5, 21.8, 36.9, 42.1, 55.4, 70.6, 73.3, 94.9, 118.0, 134.9; MS 141 (M^+-MOM); HRMS Calcd. for $C_9H_{17}O$ (M^+-MOM) 141.1280, Found 141.1246.

(2S, 6S)-1-Benzyl-2-methyl-6-(2-propenyl)piperidine (12). By a procedure similar to that for the preparation of (2*R*, 6*S*)-8-heptene-2, 6-diol, the reaction of (4*S*, 8*S*)-**11** (800 mg, 3.96 mmol) with conc. HCl (0.2 mL) in MeOH (28 mL) gave (*n*-hexane: acetone (7:1) as eluant) (2*S* ,6*S*)-8-heptene-2, 6-diol (625 mg, 99%) as an oil; IR cm^{-1} (neat): 3366, 1641, 1560, 1458, 1374, 1331, 1131, 995; ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.17 (d, J = 6.0 Hz, 3 H), 1.32-1.58 (m, 6 H), 2.09-2.34 (m, 4 H), 3.64 (br s, 1 H), 3.78 (br s, 1 H), 5.08 (br s, 1 H), 5.11-5.13 (m, 2 H), 5.73-5.88 (m, 1 H); ^{13}C NMR (75.5 MHz) δ: 21.5, 23.3, 36.4, 38.8, 41.8,

67.6, 70.3, 117.6, 134.5; MS 159 (M^++1), 157 (M^+-1); MS 131 (M^+-MOM); HRMS Calcd. for $C_9H_{17}O_2$ (M^+-MOM) 157.1228, Found 157.1235.

By a procedure similar to that for the preparation of (2*R*, 6*S*)-2,6-bis(*p*-toluenesulfonyloxy)non-8-ene, the reaction of the diol (625 mg, 3.96 mmol) with *p*-TsCl (2.26 g, 11.9 mmol) in the presence of Et_3N (1.65 mL, 11.9 mmol) and DMAP (96.7 mg, 0.79 mmol) in CH_2Cl_2 (5.28 mL) gave (*n*-hexane: acetone (15:1) as eluant) (2*S*, 6*S*)-2,6-bis(*p*-toluenesulfonyloxy)non-8-ene (1.47 g, 80%) as an oil; IR cm^{-1} (neat): 3069, 2952, 2872, 1924, 1643, 1598, 1496, 1456, 1360, 1307, 1292; ^1H NMR (300 MHz $CDCl_3$) δ: 1.02-1.12 (m, 1 H), 1.17 (d, *J* = 6.0 Hz, 3 H), 1.21-1.31 (m, 1 H), 1.33-1.51 (m, 4 H), 2.24 (t-like, *J* = 6.0 Hz, 2 H), 2.43 (s, 6 H), 4.41-4.54 (m, 2 H), 4.93-5.02 (m, 2 H), 5.55 (ddt, *J* = 17.0, 11.0, 6.6 Hz, 1 H), 7.32 (m, 4 H), 7.76 (dd-like, *J* = 8.2, 1.1 Hz, 4 H); ^{13}C NMR (75.5 MHz) δ: 20.4, 20.9, 21.9, 33.4, 36.2, 38.8, 80.1, 82.4, 118.9, 127.7, 127.8, 129.8, 129.8, 132.0, 132.0, 134.2, 144.6; MS 124 (M^+-2xTsO); HRMS Calcd. for C_9H_{16} (M^+-2xTsO) 124.1252, Found 124.1214.

By a procedure similar to that for the preparation of (2*R*, 6*S*)-**12**, the reaction of the ditosylate (1.47 g, 3.15 mmol) with $BnNH_2$ (10.3 mL, 94.6 mmol) gave (*n*-hexane: ethyl acetate (60:1) as eluant) (2*R*, 6*S*)-**12** (121 mg, 17 %) and (2*S*, 6*S*)-**12** (375 mg, 52 %) as oils; (2*S*, 6*S*)-**12**; $[\alpha]^{26}_D$ +13.1 (*c* 0.84, $CHCl_3$); IR cm^{-1} (neat): 3025, 2929, 2802, 1639, 1494, 1452, 1376; ^1H NMR (300 MHz $CDCl_3$) δ: 1.06 (d, *J* = 6.0 Hz, 3 H), 1.26-1.42 (m, 3 H), 1.52-1.59 (m, 1 H), 1.65-1.74 (m, 2 H), 2.02 (dt, *J* = 14.3, 8.2 Hz, 1H), 2.36-2.44 (m, 1 H), 2.46-2.55 (m, 1 H), 2.58-2.65 (m, 1 H), 3.81 (s, 2 H), 4.92-4.95 (m, 1 H), 4.99 (br s, 1 H), 5.67-5.81 (m, 1 H), 7.18-7.33 (m, 3 H), 7.41 (d, *J* = 7.7 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 22.2, 24.0, 30.2, 33.6, 40.0, 53.6, 58.1, 62.3, 116.2, 126.1, 127.8, 128.0, 136.6, 142.6; MS 229 (M^+), 228 (M^+-1), 91(100); Anal. Calcd. for $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found C, 83.33; H, 10.43; N, 5.74.

(2*R*, 6*S*)-**12**; $[\alpha]^{26}_D$ -8.8 (*c* 1.12, $CHCl_3$).

2,2,2-Trichloroethyl (2R,6S)-2-methyl-6-(2-propenyl)-1-piperidinecarboxylate (14). A mixture of (2*R*, 6*S*)-**12** (558 mg, 2.44 mmol) and 2,2,2-trichloroethyl chloroformate (TrocCl) (1.0 mL, 7.31 mmol) in benzene (10.5 mL) was refluxed for 2 days. The reaction was cooled and diluted with Et_2O (50 mL). The dilute solution was successively washed with 10% HCl and H_2O, dried, and evaporated. The residue was chromatographed using *n*-hexane:ethyl acetate (100:1) as eluant to give (2*R*,6*S*)-**14** (611 mg, 80%) as an oil; $[\alpha]^{26}_D$ -27.1 (*c* 1.32, $CHCl_3$); IR cm^{-1} (neat): 2950, 1712, 1640, 1406, 1377, 1346, 1317, 1125; ^1H NMR (300 MHz $CDCl_3$) δ: 1.31 (d, *J* = 6.6 Hz, 3 H), 1.61-1.99 (m, 6 H), 2.24 (dt, *J* = 14.0, 8.8 Hz, 1 H), 2.54 (dt, *J* = 3.7, 4.9 Hz, 1 H), 3.93-4.01 (m, 1 H), 4.06 (br s, 1 H), 4.68, 4.82 (ABq, *J* = 12.1 Hz, 2 H), 5.02-5.12 (m, 2 H), 5.70-5.84 (m, 1 H); ^{13}C NMR (75.5 MHz) δ: 13.3, 21.0, 22.4, 26.7, 39.0, 48.0, 52.0, 75.0, 96.0, 117.2, 135.5, 153.7; MS 314 (M^+), 276(100); HRMS Calcd. for $C_{12}H_{18}Cl_3NO_2$ 313.0404, Found 313.0424.

2,2,2-Trichloroethyl [2R,6S-(2R)]-2-methyl-6-(2,3-dihydroxypropyl)-1-piperidinecarboxylate (15) and 2,2,2-Trichloroethyl [2R,6S-(2S)]-2-methyl-6-(2,3-dihydroxypropyl)-1-piperidinecarboxylate (16). By a procedure similar to that for the preparation of (2*R*, 6*S*)-**9**, the reaction of (2*R*,6*S*)-**14** (455 mg, 1.45 mmol) with AD mix-β (DHQD-PYR ligand) (1.86 g) in *t*-BuOH (7.3 mL) and H_2O (7.3 mL) to yield (*n*-hexane:ethyl acetate = 2:1 as eluant) [2*R*,6*S*-(2*R*)]-**15** (350 mg, 69%) and [2*R*,6*S*-(2*S*)]-**16** (105 mg, 21%) as oils.

[2*R*,6*S*-(2*R*)]-**15**; $[\alpha]^{26}_{D}$ -24.1 (*c* 0.75, $CHCl_3$); IR cm^{-1} (neat): 3419, 2951, 1682, 1559, 1410, 1378, 1317, 1116; ^1H NMR (300 MHz $CDCl_3$) δ: 1.34 (d, *J* = 6.6 Hz, 3 H), 1.47-1.77 (m, 6 H), 1.86-2.05 (m, 2 H), 2.70 (br s, 1 H), 3.45-3.63 (m, 3 H), 4.04 (m, 2 H), 4.73, 4.82 (ABq, *J* = 11.5 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 12.9, 21.2, 25.2, 25.8, 39.4, 48.2, 48.9, 66.6, 68.8, 75.4, 95.6; MS 348 (M^+), 272 (100); HRMS Calcd. for $C_{12}H_{20}Cl_3NO_4$ 347.0458, Found 347.0468. Anal. Calcd for $C_{12}H_{20}Cl_3NO_4 \cdot 0.5H_2O$: C, 40.28; H, 5.87; N, 3.91. Found C, 40.22; H, 5.64; N, 3.58

[2*R*,6*S*-(2*S*)]-**16**; $[\alpha]^{26}_{D}$ -28.6 (*c* 1.16, $CHCl_3$); IR cm^{-1} (neat): 34121, 2949, 1684, 1411, 1318, 1317, 1114; ^1H NMR (300 MHz $CDCl_3$) δ: 1.32 (d, *J* = 6.6 Hz, 3 H), 1.60-2.07 (m, 8 H), 2.62 (br s, 1 H), 3.47 (m, 1 H), 3.60 (br s, 2 H), 3.72 (br s, 1 H), 4/70, 4.82 (ABq, *J* = 12.1 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 12.9, 20.8, 24.1, 26.5, 39.4, 48.0, 49.7, 67.1, 70.4, 75.2, 95.7, 154.4; MS 348 (M^+), 272 (100); HRMS Calcd. for $C_{12}H_{20}Cl_3NO_4$ 347.0458, Found 347.0463.

(4R,6S,10R)-1-Aza-4-(p-tosyloxymethyl)-10-methyl-3-oxabicyclo[4.4.0]decan-2-one (17) and 2,2,2-Trichloroethyl [2S,6R-(2R)]-2-(2-hydroxy-3-tosyloxy)-6-methyl-1-piperidinecarboxylate (18). n-Bu_2SnO (159 mg, 0.64 mmol) was added to a solution of [2*R*,6*S*-(2*R*)]-**15** (185 mg, 0.53 mmol) in dry toluene (13.0 mL) and THF (1.3 mL). This reaction was heated to reflux for 6 h using a Dean-Stark trap for water removal. The reaction was cooled, and triethylamine (37 μL, 0.27 mmol) and *p*-TsCl (121 mg, 0.64 mmol) were added to the reaction mixture. The reaction was stirred for 9 h at room temperature and brine (8 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (20 mL) four times. The combined organic layers were dried and evaporated. The residue was chromatographed using *n*-hexane: acetone (10:1) as eluant to yield (4*R*,6*S*,10*R*)-**17** (116 mg, 62%) as a solid and [2*S*,6*R*-(2*R*)]-**18** (80 mg, 37%) as an oil.

(4*R*,6*S*,10*R*)-**17**; $[\alpha]^{26}_{D}$ -68.1(*c* 2.04, $CHCl_3$); mp. 146-8 °C; IR cm^{-1} (KBr): 2936, 1684, 1598, 1430, 1364, 1292, 1228, 1176, 1045; ^1H NMR (300 MHz $CDCl_3$) δ: 1.15 (d, *J* = 7.21. Hz, 3 H), 1.27-1.40 (m, 1 H), 1.49-1.72(m, 5 H), 1.79 (dt, *J* = 10.4, 3.3 Hz, 1 H), 2.04 (ddd, *J* = 14.3, 9.3, 7.1 Hz, 1 H), 2.44 (s, 3 H), 3.44-3.54 (m, 1 H), 4.06 (qd, *J* = 10.4, 5.5 Hz, 2 H), 4.33-4.41 (m, 1 H), 4.57 (m, 1 H), 7.35 (d, *J* =8.2 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 16.2, 19.4, 22.3, 30.4, 33.8, 46.8, 48.2, 69.9, 70.6, 128.5, 130.5, 132.5, 145.8, 152.7; MS 353 (M^+), 182(M^+-TsO); HRMS Calcd. for $C_{17}H_{23}NO_5S$ 353.1297, Found 353.1276. Anal. calcd for $C_{17}H_{23}NO_5S$: C, 57.77; H, 6.56; N, 3.96. Found C, 58.01; H, 6.60; N, 3.83.

[2*S*,6*R*-(2*R*)]-**18**; $[\alpha]^{26}_{D}$ -19.6 (*c* 1.18, $CHCl_3$); IR cm^{-1} (neat): 3434, 3061, 2952, 1682, 1598, 1409, 1359, 1189, 1177, ; ^1H NMR (300 MHz $CDCl_3$) δ: 1.34 (d, *J* = 6.6. Hz, 3 H), 1.52-1.93 (m, 6 H), 2.02 (br s, 1 H), 2.44 (s, 3 H), 3.78 (m, 1 H), 3.96 (d *J* = 5.5 Hz, 2 H), 4.04 (m, 1 H), 4.19 (m, 1 H), 4.72, 4.80 (ABq, *J* = 12.1 Hz, 2H0, 7.34 (d, *J* = 7.7 Hz, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 13.1, 21.0, 21.9, 25.3, 25.9, 39.5, 48.3, 48.7, 66.1, 73.3, 75.3, 76.7, 95.6, 128.1, 129.9, 132.7, 145.0; MS 502 (M^+); HRMS Calcd. for $C_{19}H_{26}Cl_3NO_6S$ 503.0546, Found 503.0565.

(4S,6S,10R)-1-Aza-4,10-dimethyl-3-oxabicyclo[4.4.0]decan-2-one (19). To a solution of (4*R*,6*S*,10*R*)-**17** (100 mg, 0.28 mmol) in THF (2.5 mL) was added 1M Super-Hydride® (1.13 mL 1.13 mmol) at 0 °C. The reaction was stirred for 3 h at room temperature and a few pieces of ice were added to the reaction mixture. The mixture was diluted with CH_2Cl_2 (20 mL) and the dilute solution was dried and evaporated. The

combined organic layers were dried and evaporated. The residue was chromatographed using *n*-hexane: acetone (8:1) as eluant to yield (4*S*,6*S*,10*R*)-**19** (40 mg, 77%) as an oil; [α] $^{26}_{D}$ -99.1(*c* 0.74, $CHCl_3$); IR cm^{-1} (neat): 2934, 1683, 1521, 1429, 1293, 1233, 1156, 1121; ^1H NMR (300MHz $CDCl_3$) δ: 1.21 (d, *J* = 6.6 Hz, 3 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.37-1.47 (m, 1 H), 1.50-1.76 (m, 5 H), 1.89 (ddd, *J* = 13.7, 9.3, 7.1 Hz, 1 H), 3.46-3.54 (m, 1 H), 4.28-4.38 (m, 1 H), 4.60-4.67 (m, 1 H); ^{13}C NMR (75.5 MHz) δ: 15.8, 19.3, 20.6, 30.1, 33.6, 35.2, 46.6, 47.5, 69.5, 153.8; MS 183 (M^+), 124 (100); HRMS Calcd. for $C_{10}H_{17}NO_2$ 183.1259, Found 183.1261.

2,2,2-Trichloroethyl [2S,6R-(2S)]-6-(2-hydroxypropyl)-2-methyl-1-piperidinecarboxylate (20). By a procedure similar to that for the preparation of (2*R*, 6*S*)-**9**, the reaction of [2*S*,6*R*-(2*R*)]-**18** (80 mg, 0.16 mmol) with 1M Super-Hydride® (0.51 mL 0.51 mmol) in THF (1 mL) gave *n*-hexane: ethyl acetate (20:1) as eluant [2*S*,6*R*-(2*S*)]-**20** (34 mg, 64%) as an oil; [α] $^{26}_{D}$ -26.8 (*c* 1.43, $CHCl_3$); IR cm^{-1} (neat): 3460, 2953, 2238, 1682, 1522, 1408, 1377, 1344, 1322, 1123; ^1H NMR (300MHz $CDCl_3$) δ: 1.18 (d, *J* = 6.0 Hz, 3 H), 1.35 (d, *J* = 6.6 Hz, 3 H), 1.42-1.52 (m, 1 H), 1.55-1.76 (m, 4 H), 1.82 (dd, *J* = 13.7, 2.7 Hz, 1 H), 1.88-2.04 (m, 1 H), 3.70 (br s, , 1 H), 4.03 (m, 1 H), 4.22-4.28 (m, 1 H), 4.38 (br s, 1 H), 4.76, 4.81 (ABq, *J* = 11.5, 2 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 13.5, 21.7, 23.6, 25.8, 26.4, 46.0, 48.6, 49.7, 64.2, 75.8, 96.1, 156.2; HRMS Calcd. for $C_{12}H_{20}Cl_3NO_3$ 331.0509, Found 331.0513.

(+)-6-Epi-9-epipinidinol (2). a) A solution of (4*S*,6*S*,10*R*)-**19** (54 mg, 0.30 mmol) in 2 M KOH/EtOH (3.0 mL) in a sealed tube was heated at 140 °C for 2 days. The reaction was diluted with H_2O and the dilute solution was extracted with CH_2Cl_2 four times. The extracts were dried with K_2CO_3 and evaporated. The residue was chromatographed on alumina using $CHCl_3$ as eluant to yield **2** (23 mg, 50%) as an oil; [α] $^{26}_{D}$ +4.7 (*c* 0.39, $CHCl_3$), lit.[6] [α] $^{25}_{D}$ +4.2 (*c* 6.4, $CHCl_3$); IR cm^{-1} (neat): 3300, 2929, 1654, 1458, 1374, 1206, 1182; ^1H NMR (300MHz $CDCl_3$) δ: 1.10 (d, *J* = 6.6 Hz, 3 H), 120 (d, *J* = 6.6 Hz, 3 H), 127 (ddd, *J* = 14.3, 6.6, 3.3 Hz, 2 H), 1.34-1.43 (m, 1 H), 1.51-1.70 (m, 4 H), 1.88 (ddd, *J* = 14.3, 8.8, 3.3 Hz, 1 H), 3.09-3.18 (m, 1 H), 3.29-3.37 (m, 1 H), 4.08 (quintet-d, *J* = 6.0, 3.8 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ: 19.7, 20.4, 23.6, 31.4, 32.5, 40.1, 46.3, 47.8, 66.0; MS 157 (M^+); HRMS Calcd. for $C_9H_{19}NO$ 157.1467, Found 157.1465. Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found C, 68.30; H, 12.39; N, 8.55.
b) 1N NH_4OAc (1.1 mL) and 10% Cd-Pb couple (192 mg, 1.44 mmol) were added to a solution of [2*S*,6*R*-(2*S*)]-**20** (48 mg, 0.14 mmol) in THF (1.1 mL). After being stirred for 12 h, the mixture was diluted with $CHCl_3$ (10 mL). The dilute solution was basified with 2N NaOH and filtered on Celite. The filtrate was extracted with $CHCl_3$ (5 mL) five times. The extracts were dried with K_2CO_3 and evaporated. The residue was chromatographed to give **2** (12 mg, 53%) as an oil.

2,2,2-Trichloroethyl (2R,6R)-2-(2-propenyl)-6-methyl-1-piperidinecarboxylate (21). By a procedure similar to that for the preparation of (2*R*,6*S*)-**14**, the reaction of (2*S*, 6*S*)-**12** (647 mg, 2.83 mmol) with TrocCl (1.17 mL, 8.48 mmol) in benzene (12.2 mL) gave (*n*-hexane:ethyl acetate = 100:1 as eluant) (2*R*,6*R*)-**21** (507 mg, 57%) as an oil; [α]$^{26}_{D}$ -13.2(*c* 1.50, $CHCl_3$); IR cm^{-1} (neat): 2942, 1708, 1411, 1381, 1341, 1313, 1271, 1118; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (d, *J* = 6.6 Hz, 3 H), 1.45-1.79 (m, 6 H), 2.35-2.40 (m, 2 H), 4.24 (q, *J* = 6.6 Hz, 1 H), 4.40 (quintet-d, *J* = 6.6, 1.6 Hz, 1 H), 4.80 (br s, 2 H), 5.01-5.09 (m, 2 H), 5.76 (ddt, *J* = 17.6, 10.5, 6.6 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ: 13.9, 20.8, 26.7, 30.3, 39.5,

46.8, 50.9, 75.2, 96.0, 117.3, 136.0, 154.0; MS 314 (M^+), 98(100); HRMS Calcd. for $C_{12}H_{18}Cl_3NO_2$ 314.0481, Found 314.0458.

2,2,2-Trichloroethyl [2R,6R-(S)]-(2,3-dihydroxypropyl)-6-methyl-1-piperidinecarboxylate (22) and 2,2,2-Trichloroethyl [2R,6R-(2R)]-2-(2,3-dihydroxypropyl)-6-methyl-1-piperidinecarboxylate (23). By a procedure similar to that for the preparation of **15** and **16**, the reaction of (2*R*,6*R*)-**21** (507 mg, 1.61 mmol) with AD-mix-α [(DHQ)$_2$-PYR ligand] (2.07 g) in *t*-BuOH (8.0 mL) and H_2O (8.0 mL) gave [2*R*,6*R*-(2*S*)]-**22** (303 mg, 54%) and [2*R*,6*R*-(2*R*)]-**23** (114 mg, 20%) as oils.

[2*R*,6*R*-(2*S*)]-**22**: $[\alpha]^{26}_D$ -2.15 (*c* 0.88, $CHCl_3$); IR cm^{-1} (neat): 3420, 2938, 1684, 1457, 1116, 1044; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25 (d, *J* = 6.6 Hz, 3 H), 1.39-1.79 (m, 7 H), 1.89 (t, *J* = 13.7 Hz, 1 H), 2.39 (br s, 1H), 3.46-3.60 (m, 3 H), 4.43-4.56 (m, 3 H), 4.63, 4.99 (ABq, *J* = 12.i Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 14.4, 20.9, 29.9, 30.3, 39.0, 46.9, 47.8, 66.6, 68.8, 75.4, 95.7, 155.9; MS 348 (M^+), 347 (M^+-1), 272(100); HRMS Calcd. for $C_{12}H_{20}Cl_3NO_4$ 347.0458, Found 347.0462. Anal. Calcd for $C_{12}H_{20}Cl_3NO_4$: C, 41.34; H, 5.78; N, 4.02. Found C, 40.98; H, 5.90; N, 3.77.

[2*R*,6*R*-(2*R*)]-**23**: $[\alpha]^{26}_D$ +11.8 (*c* 0.97, $CHCl_3$); IR cm^{-1} (neat): 3420, 2938, 2870, 1682, 1417, 1310, 1275, 1112; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 6.6 Hz, 3 H), 1.47-1.75 (m, 7 H), 1.88 (ddd, *J* = 14.3, 9.3, 2.7 Hz, 1 H), 3.09 (br s, 1 H), 3.39-3.47 (m, 1 H), 3.58-3.64 (m, 2 H), 3.77 (br s, 1 H), 4.32 (br, s, 1 H), 4.36-4.44 (m, 1 H), 4.66 (br s, 1 H), 4.84 (d, *J* = 11.5 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ: 13.8, 20.9, 27.8, 30.2, 39.0, 46.9, 48.3, 67.0, 70.2, 75.2, 95.7, 154.3; MS 349(M^++1), 348 (M^+), 347 (M^+-1), 272 (100); HRMS Calcd. for $C_{12}H_{20}Cl_3NO_4$ 347.0458, Found 347.0439.

2,2,2-Trichloroethyl [2R,6R-(2S)]-2-[2-hydroxy-3-tosyloxy]-6-methyl-1-piperidinecarboxylate (24). By a procedure similar to that for the preparation of **17** and **18**, the reaction of [2*R*,6*R*-(2*S*)]-**22** (127 mg, 0.36 mmol) with Bu_2SnO (109 mg, 0.44 mmol) in toluene (8.9 mL) and THF (0.89 mL) gave the stannane, which was tosylated with *p*-TsCl (83 mg, 0.44 mmol) in the presence of Et_3N (25 mL, 0.18 mmol) to yield (*n*-hexane:ethyl acetate= 5:1 as eluant) [2*R*,6*R*-(2*S*)]-**24** (134 mg, 73%) as an oil; $[\alpha]^{26}_D$ -0.02 (*c* 0.89, $CHCl_3$); IR cm^{-1} (neat): 3446, 2944, 1678, 1598, 1417, 1360, 1342, 1309, 1277, 1190, 1177, 1150, 1119; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 7.1 Hz, 3 H), 1.34-1.1.42 (m, 1 H), 1.58-1.75 (m, 6 H), 1.99 (t, *J* = 12.6 Hz, 1 H), 2.44 (s, 3 H), 3.70 (br s, 1 H), 3.91-4.02 (m, 2 H), 4.40-4.59 (m, 4 H), 4.97 (d, *J* = 12.1 Hz, 1 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ: 14.3, 20.9, 21.9, 29.8, 30.2, 39.1, 46.9, 47.5, 66.2, 73.0, 75.3, 95.7, 128.0, 129.9, 132.9, 144.9, 155.7; MS 503(M^++1), 502 M^+), 501 (M^+-1), 272(100); HRMS Calcd. for $C_{19}H_{26}Cl_3NO_6S$ 501.0547, Found 501.0511.

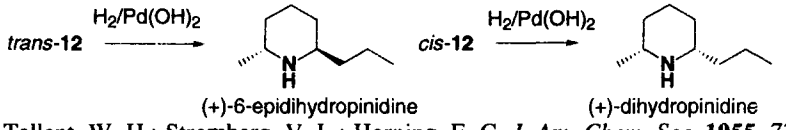
2,2,2-Trichloroethyl [2R,6R-(2R)]-2-(2-hydroxypropyl)-6-methyl-1-piperidinecarboxylate (25). By a procedure similar to that for the preparation of (2*R*, 6*S*)-**9**, the reaction of [2*R*,6*R*-(2*S*)]-**24** (148 mg, 0.29 mmol) with Super-Hydride® (0.88 mL, 0.88 mmol, 1M in THF) in THF (1.85 mL) gave (*n*-hexane:ethyl acetate= 40:1 as eluant) [2*R*,6*R*-(2*R*)]-**25** (66 mg, 67%) as an oil; $[\alpha]^{26}_D$ -0.51 (*c* 2.41, $CHCl_3$); IR cm^{-1} (neat): 3475, 2941, 1683, 1522, 1417, 1386, 1342, 1326, 1314, 1274, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17(d, *J* = 6.0 Hz, 3 H), 1.24 (d, *J* = 7.1 Hz, 3 H), 1.33-1.46(m, 1 H), 1.50-1.78 (m, 6 H), 1.95 (t, *J* = 12.6 Hz, 1 H), 3.65 (br s, 1 H), 4.20 (br s, 1 H), 4.42-4.53 (m, 2 H), 4.60, 4.99 (ABq, *J* = 12.1 Hz, 2

H); ^{13}C NMR (75.5 MHz) δ: 14.4, 20.9, 22.8, 22.9, 30.0, 30.4, 31.8, 45.1, 46.8, 48.1, 63.9, 75.3, 95.8, 155.6; MS 333 (M^++1), 332 (M^+), 331 (M^+-1), 272(100); HRMS Calcd. for $C_{12}H_{20}Cl_3NO_3$ 331.0509, Found 331.0539.

(-)-Pinidinol (3). By a procedure similar to that for the preparation of **2**, the reaction of [2*R*,6*R*-(2*R*)]-**25** (109 mg, 3.28 mmol) with 10% Cd-Pb (436 mg, 32.8 mmol) in THF (2.5 mL) and 1N NH_4OAc (2.5 mL) gave (*n*-hexane:ethyl acetate= 5:1 as eluant) **3** (34 mg, 66%) as a solid; $[\alpha]^{26}_D$ -15.0 (*c* 0.55, $CHCl_3$); mp 76-7 °C, lit.[7b] 70.5-72 °C, $[\alpha]^{26}_D$ -17 ($CHCl_3$); IR cm^{-1} (KBr) 2932, 1450, 1372, 1338, 1274, 1208, 1165, 1149, 1108, 1069, 1045: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.91-1.11 (m, 1 H), 1.02 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3 H), 1.45-1.61 (m, 7 H), 1.74-1.81 (m, 1 H), 2.52-2.62 (m, 1 H), 2.88-2.96 (m, 1 H), 4.05-4.15 (m, 1 H); ^{13}C NMR (75.5 MHz) δ: 23.4, 23.9, 24.9, 30.6, 34.1, 44.0, 52.7, 55.2, 65.2; MS 157 (M^+), 70 (100) Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found C, 69.06; H, 12.28; N, 8.84 .

References and Notes:

1. Schneider; M. J. "Alkaloids: Chemical & Biological Perspectives" Pelletier, S. M. ed; Pergamon; Oxford, 1996; Vol 10; Chapter 2, pp 155.
2. (a) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151. (b) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399. (c) Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015. (d) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851. (e) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475.
3. (a) Leclercq, S.; Thirione' I.; Breders, F.; Daloze, D.; Van der Meer, R.; Braeckman, I. Tetrahedron **1994**, *50*, 8465. (b) Takahata, H.; Inose, K.; Araya, N.; Momose, T. *Heterocycles* **1994**, *38*, 1961. (c) Takahata, H.; Bandoh, H.; Hanayama, M.; Momose, T. *Tetrahedron: Asymmetry* **1992**, *3*, 607. (d) Kotsuki, H.; Kusumi, T.; Inoue, M.; Usho, Y.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4159. (e) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1397.
4. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
5. (a) Takahata, H.; Takahashi, S.; Kouno, S.; Momose, T. *J. Org. Chem.* **1998**, *63*, 2224. (b) Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron Lett.* **1997**, *38*, 3541. (c) Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2801.
6. Tawara, J. N.; Blokhin, A.; Foderaro, T. A.; Stermitz, F. R. *J. Org. Chem.* **1993**, *58*, 4813.
7. (a) Schneider, M. J.; Montali, J. A.; Hazen, D.; Stanton, C. E. *J. Nat. Prod.* **1991**, *54*, 905. (b) Schneider, M. J.; Stermitz, F. R. *Phytochemistry* **1990**, *29*, 1811.
8. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
9. Only the preferred diastereomer is depicted.
10. The piperidines *trans*-**12** and *cis*-**12** were transformed by hydrogenation using palladium hydroxide as a catalyst into (+)-6-epidihydropinidine {$[\alpha]^{26}_D$ +4.6 (EtOH), lit.[6] $[\alpha]^{29}_D$ +4.7 (EtOH)} and (+)-dihydropinidine {$[\alpha]^{26}_D$ +13.4 (EtOH), lit.[11] $[\alpha]_D$ +12.8 (EtOH)} in 68% and 95% yields, respectively.



(+)-6-epidihydropinidine (+)-dihydropinidine

11. Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc.* **1955**, *77*, 631.
12. Kometani, T.; Shiotani, S.; Mitsuhashi, K. *Chem. Pharm. Bull.* **1976**, *24*, 342.
13. Dong, Q.; Anderson, C. E.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 5681.
14. Both substituents at 2,6-positions of **24** would be axial orientation due to 1,3-allylic strain. Accordingly, an intramolecular carbamation between Troc and the hydroxyl would not occur.
15. Ho, T.-L. " Symmetry: A Basis for Synthesis Design" John Wiley & Sons, Inc. New York, 1995.