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Asymmetric synthesis of all stereoisomers of 6-methylpipecolic acids

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Summary. Asymmetric synthesis of all four stereoisomers of 6-methylpipecolic acids with high enantiomeric purity via iterative AD reaction, starting from 1,6-heptadiene, has been described.

Keywords: Asymmetric synthesis – 6-Methypipecolic acid – Asymmetric dihydroxylation – Enantiomeric enhancement

Pipecolic acid is a widespread naturally occurring nonproteinogenic amino acid found in many biologically interesting systems. Recent attention has been focused on unnatural pipecolic acid derivatives substituted on the piperidine ring as building blocks for the synthesis of peptides (Copelend et al., 1990), immunosuppressants (Dragovich et al., 1996), enzyme inhibitors (Gillard et al., 1996) or NMDA antagonists (Skiles et al., 1996). In addition, cyclic amino acids, having both hydrophobic and/ or hydrophilic properties, may serve as a chemical platform required for binding interactions with biological targets, making them ideal building blocks for the preparation of potential nonpeptide therapeutic agents using parallel synthesis or combinatorial chemistry methodologies. Therefore, much attention was turned to asymmetric synthesis of substituted pipecolic acids (Couty, 1999). Out of the four stereoisomeric 6-methylpipecolic acids, the asymmetric synthesis of (2*S*,6*S*)-6-methylpipecolic acid **1** has been reported twice (Berrien et al., 1994; Swarbrick et al., 1999), whereas no other stereoisomers *ent*-**1**, **2**, and *ent*-**2** were described. Therefore, we were stimulated to develop a comprehensive synthesis for these amino acids. Our interest in this field has been directed to the potential strategies based on the the enantiomeric enhancement caused by the twofold or more application of the Sharpless asymmetric dihydroxylation (AD) (Kolb et al., 1994) reactions (Takahata, 2000). In this paper we describe a new entry to the synthesis of all stereoisomers **1**, **2**, *ent*-**1**, and *ent*-**2** of 6-methylpipecolic acids with high enantiomeric purity *via* iterative AD reaction (Fig. 1).

Recently, we developed a general access to *cis*- or *trans*-2,6-disubstituted piperidine *via* sequence of two-fold AD reactions starting from an achiral 1,6-heptadiene (**3**) (Takahata et al., 1998b). According to a similar concept, our retrosynthetic plan is outlined in Fig. 2. Access to to *cis*- or *trans*-2,6-disubstituted piperidine **4** is viewed to be possible by manipulation *via* cyclic amination of *syn*-1,5-diol (*syn*-**5**) or *anti*-1,5-diol (*anti*-**5**) using benzylamine, respectively. This strategy is expected to greatly facilitate the production of the desired stereoisomers because of its two advantages. One advantage is that it provides the different required chiral centers, by using either DHQ-based ligand or DHQD-based ligand respectively. The second advantage is that the transformation of acyclic compounds like **5**, to cyclic derivatives like **4**, involves both rigid conformation and close proximity (1,3-relationship) between two chiral centers that can lead to higher diastereomeric excess and better separation of diastereomers.

Our synthetic approach to **1** began with the single AD of **3**. The $(DHQ)_2$-PYR ligand-derived AD reaction of **3** afforded the diol (*S*)-**7** (85% ee) (Takahata et al., 1998a) in 81% yield. The diol (*S*)-**7** was converted into the epoxide by the Sharpless one-pot procedure (Kolb and Sharpless, 1992) followed by

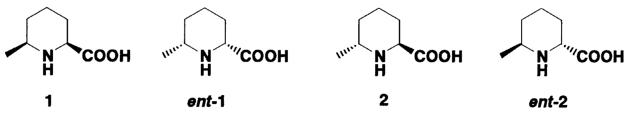

Fig. 1

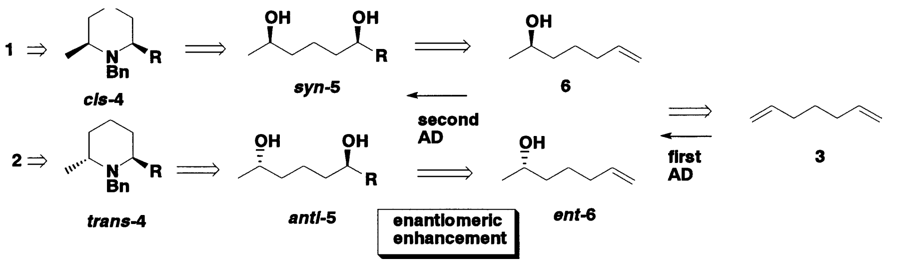

Fig. 2

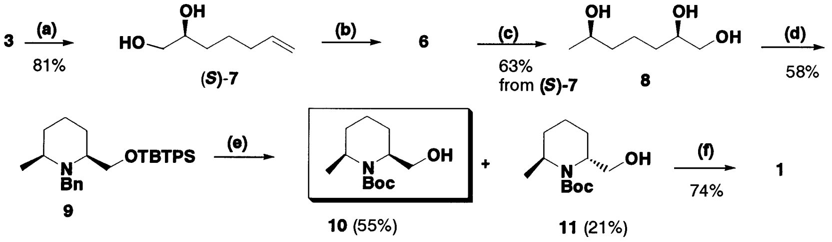

Fig. 3. (**a**) cat. K_2OsO_4, $(DHQ)_2PYR$; (**b**) 1) $(MeO)_3CMe$/PPTS; 2) MeCOBr; 3) K_2CO_3/MeOH; 4) Super-Hydride®; (**c**) cat. K_2OsO_4, $(DHQD)_2PYR$; (**d**) 1) TBDPSCl/imidazole; 2) $TsCl/Et_3N$; 3) $BnNH_2$; B(**e**) 1) H_2/cat. $Pd(OH)_2$; 2) Boc_2O/K_2CO_3; 3) TBAF; (**f**) 1) cat. $RuCl_3/NaIO_4$; 2) CF_3COOH

the regioselective reduction with Super-Hydride® that provided the secondary alcohol **6**. Without further purification due to low boiling point of **6**, this olefin **6** was then subjected to the second $(DHQD)_2$-PYR ligand-derived AD reaction to give **8*** as an inseparable diastereoisomeric mixture in 63% yield from (*S*)-**7**. The triol **8*** was successively subjected to selective monoprotection of primary hydroxyl, ditosylation of secondary hydroxyls, and cyclic amination with benzylamine to give enantiomerically enriched *cis*-piperidine **9*** contaminated with a small amount of *trans*-piperidine in 58% three-step yields. In this stage a separation of a mixture of the diastereomers is impossible. However, a three-step sequence (1. deprotection of *N*-benzyl group; 2. *N*-protection with Boc_2O; 3. desilylation) provided the piperidinols, which were readily separated to provide *cis* product **10** in 55% overall yield and *trans* product **11**** in 21%. With a single diastereomer in hand, **10** was transformed into **1** in two steps (i; oxidation (Calsen et al., 1981); ii deprotection) in 74% yield (Fig. 3). Spectral data of **1** were consistent with the reported values (Berrien et al., 1994).

With the above result in hand, our attention was centered on synthesis of *trans* isomer **2**. At the outset, the $(DHQD)_2$-PYR ligand-derived AD reaction of **3** afforded the diol (*R*)-**7** (88% ee) (Takahata et al., 1998a) in 66% yield. According to the above procedure, the diol (*R*)-**7** was converted into the secondary alcohol *ent*-**6**, which was then subjected to the second $(DHQD)_2$-PYR ligand-derived AD reaction to give **12*** as an inseparable diastereoisomeric mixture in 68% overall yield from (*R*)-**7**. Next, similar six-step sequence described for the synthesis of **10** and **11** provided *trans* piperidinol **13** (60%) and its *cis* isomer **14**** (11%). Finally, the first synthesis of **2** was performed from **13** in 68% two-step yield. In line of similar procedure, the synthesis of *ent*-**1** and *ent*-**2** was accomplished in 15% and 19% overall yields from *ent*-**6** and **6**, respectively (Fig. 4).

Although the ees of the four stereoisomers were not confirmed directly, they were determined by ^1H-NMR analysis of the corresponding Mosher esters (**15**–**18** [obtained by esterification of **10**, **13**, and their enantiomers with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) followed by de-*tert*-butoxycarbonylation of the

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*The stereo-configurations of **8** and **9** in Fig. 3 and **12** in Fig. 4 show only major isomers.

The absolute configurations of **11 and **14** remain unknown.

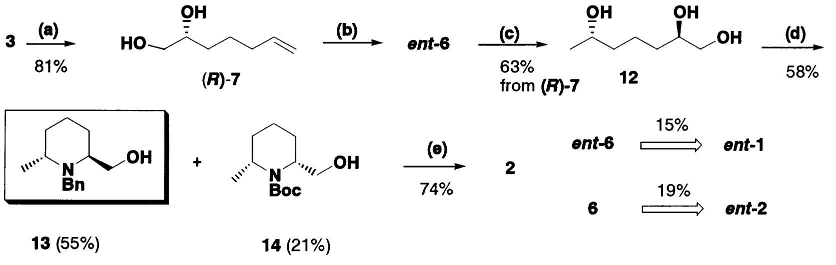

Fig. 4. (**a**) cat. K_2OsO_4, $(DHQD)_2PYR$; (**b**) 1) $(MeO)_3CMe$/PPTS; 2) MeCOBr; 3) K_2CO_3/MeOH; 4) Super-Hydride®; (**c**) cat. K_2OsO_4, $(DHQD)_2PYR$; (**d**) 1) TBDPSCl/imidazole; 2) TsCl/Et_3N; 3) $BnNH_2$; H_2/cat. $Pd(OH)_2$; 5) Boc_2O/K_2CO_3; 6) TBAF; (**f**) 4) cat. $RuCl_3$/$NaIO_4$; 2) CF_3COOH

Fig. 5

resulting MTPA ester], resulting in 94%, 96%, 94%, and 92%, respectively (Fig. 5). Since ees of single AD products (*S*)- and (*R*)-**7** were 85% and 88%, respectively, the enantiomeric enhancement by the iterative AD reaction was confirmed.

In conclusion, we have demonstrated a straightforward route to the synthesis of all four stereoisomers **1**, **2**, *ent*-**1**, and *ent*-**2** (the first synthesis except for **1**) of 6-methylpipecolic acids with high enantiomeric purity in a sequence of iterative AD reaction. This methodology should permit the construction of all four stereoisomers of 6-substituted pipecolic acids 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 (^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. 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. The extracts were dried over Na_2SO_4 unless otherwise specified.

*(2R,6R)-1,2,6-Heptanetriol (**8**)*

A mixture of (S)-**7** (Takahata and Takahashi et al., 1998) (891 mg, 6.84 mmol), pyridinium *p*-toluenesulfonate (PPTS) (17.6 mg, 0.07 mmol), and trimethyl orthoacetate (1.13 mL, 8.90 mmol) in CH_2Cl_2 (8.65 mL) was stirred for 1 h at room temperature. After the solvent was removed by rotary evaporation, triethylamine (0.095 mL, 0.68 mmol), CH_2Cl_2 (8.65 mL) and acetyl bromide (0.7 mL, 10.3 mmol) were successively added to the resulting residue. After vigorous stirring for 45 min, the reaction mixture was added to 1M HCl solution (13.6 mL). The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. A mixture of ether (16.7 mL) and methanol (0.4 mL) was added to the residue and pulverized NaOH (604 mg, 15.1 mmol)) were successively added to the resulting residue. After stirring for 2.5 h, the mixture was filtered through on K_2CO_3-packed glass-filter. The filtrate was removed at an atmosphere to yield the crude epoxide. To a solution of the crude epoxide in THF (18.2 mL) was injected Super-Hydride (1M in THF, 13.7 mL, 13.7 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 (30 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (80 mL) three times. The extracts were dried and evaporated to yield crude **6**. The olefin **6** was added to a mixture of AD-mix (9.72 g), prepared from $K_2OsO_4 \cdot 2H_2O$ (38 mg), $(DHQD)_2PYR$ (0.49 g), $K_3Fe(CN)_6$ (53 g), and K_2CO_3 (22 g) in *tert*-BuOH (34.2 mL), and H_2O (34.2 mL) at 0°C. After the reaction mixture was stirred for 14 h at the same temperature, sodium sulfite (10.3 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 (60 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 (2*R*,6*R*)-**8** as a major product (565 mg, 56%) as an oil; IR (neat) 3382, 2935, 1458, 1375, 1068 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 1.20 (3 H, d, J = 6.6 Hz), 1.38–1.62 (7 H, m), 2.00 (1 H, br s), 2.26 (1 H, br s), 3.39–3.48 (1 H, m), 3.65–3.84 (3 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.87, 23.87, 33.22, 39.23, 66.96, 68.14, 72.34; MS (m/z) 158 (M^+).

*(2S,6S)-N-Benzyl-1,2[(tert-butyldiphenylsilyloxy)methyl-6-methylpiperidine (**9**)*

A mixture of (2*R*,6*R*)-**8** (565 mg, 3.81 mmol), imidazole (311 mg, 4.57 mmol), and *tert*-butyldiphenylsilyl chloride (1.06 mL, 4.00 mmol) in DMF (3.30 mL) was stirred at room temperature for 5 h. A large amount of water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 three times. The extracts were successively washed with 20% $KHSO_4$, saturated $NaHCO_3$, and brine. The solvent was dried and evaporated to leave the residue, which was chromatographed to yield a diasteromeric mixture of diol (1.094 g, 74%) as an oil. IR (neat) 3385, 2931, 1427, 1113, 824, 740, 701 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 1.08 (9 H, s), 1.17 (3 H, d, J = 6.0 Hz), 1.22–1.55 (6 H, m), 1.70 (1 H, br s), 1.94 (1 H, br s), 3.50 (1H, dd, $J = 9.9, 7.7$ Hz), 3.66 (1H, dd, $J = 9.9, 3.3$ Hz), 7.34–7.47 (6H, m), 7.66–7.71 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.53, 21.92, 23.75, 27.12, 32.84, 39.43, 68.16, 72.01, 127.87, 129.92, 133.18, 135.61; MS (m/z) 386 (M^+). To a solution of the diol (1.094 g) in CH_2Cl_2 (4.83 mL) was successively added *p*-toluenesulfonyl chloride (*p*-TsCl) (2.15 g, 10.8 mmol), triethylamine (1.57 mL, 11.3 mmol), and 4-N,N-dimethylaminopyridine (138 mg, 1.13 mmol) with ice cooling. The reaction was stirred for 2 days at room temperature and then diluted with a large amount of ether. The solvent was filtered through Celite. The filtrate was washed with brine, dried, and evaporated. The residue was chromatographed to yield a pale yellow oil (1.511 g, 11.3 mmol) IR (neat) 2931, 1598, 1363, 1189, 1176, 1113, 905, 816, 758, 704, 664 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (9H, s), 1.19 (3H, d, $J = 6.6$ Hz), 1.36–1.66 (6H, m), 2.41 (6H, s), 3.52–3.64 (2H, m), 4.40–4.53 (2H, m), 7.23–7.35 (4H, m), 7.37–7.47 (6H, m), 7.55–7.59 (4H, m), 7.61–7.77 (4H, m); ^{13}C-NMR (75 MHz, CDCl3) δ 19.47, 20.40, 20.91, 21.88, 27.01, 30.94, 36.32, 64.54, 80.10, 82.50, 127.75, 127.84, 129.81, 129.85, 129.92, 132.88, 133.06, 134.28, 134.49, 135.57, 144.57, 144.60.

A mixture of the ditosylate (1.51 g, 2.17 mmol) and $BnNH_2$ (7.12 mL, 65.2 mmol) was heated at 70°C for 2 days. The reaction was diluted with *n*-pentane (50 mL) at 0°C and 2N NaOH (130 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 4% ethyl acetate/n-hexane as eluant to yield **9** (779 mg, 78%) as a diastereomeric mixture. IR (neat) 2930, 1428, 1113, 824, 727, 701 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95–1.02 (15H, m), 1.20–1.41 (3.8H, m), 1.54–1.69 (2H, m), 1.92–1.93 (1H, m), 2.49–2.61 (2H, m), 2.82–2.90 (0.57H, m), 3.35 (1H, dd, $J = 9.9$ Hz, 7.1 Hz), 3.55–3.91 (4.2H, m), 7.12–7.42 (10H, m), 7.53–7.65 (5H, m); ^{13}C-NMR (68 MHz, CDCl3) δ 19.49, 22.08, 23.34, 27.12, 29.38, 34.31, 55.26, 57.52, 64.59, 67.67, 126.00, 127.63, 127.93, 128.08, 128.19, 129.53, 133.82, 135.64, 135.67, 142.47; MS (m/z) 458(M^+); HRMS: calcd for $C_{30}H_{39}NOSi$ (M^+) 457.2801, found 457.2869.

*(2S,6S)-N-tert-Butoxycarbonyl-2-hydroxymethyl-6-methylpiperidine (**10**)*

A suspension of a mixture of **9** and diastereomer (779 mg, 1.70 mmol) and $Pd(OH)_2$ (170 mg) in MeOH (12.9 mL) under a hydrogen atmosphere was stirred for 1 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated. To the residue in a mixture of THF (12.5 mL) and H_2O (12.5 mL) was successively added K_2CO_3 (305 mg, 221 mmol) and di-*tert*-butyl dicarbonate (Boc_2O) (0.78 mL, 3.40 mmol) at 0°C. After being stirred at room temperature for 5 h, the organic solvent was removed *in vacuo*. After the residue was acidified with 20% $KHSO_4$, the mixture was extracted with ethyl acetate. The extract was dried and evaporated. The residue was chromatographed using 3% ethyl acetate-hexane as eluant to give *N*-Boc compound (624 mg, 79%). IR (neat) 2933, 1690, 1364, 1113, 702 cm^{-1}; 1H-NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, d, $J = 6.6$ Hz), 1.05 (9H, s), 1.06 (2.6H, s), 1.20 (3H, d, $J = 6.6$ Hz), 1.38 (2.6H, s), 1.4 2 (9H, s), 1.32–1.63 (7H, m), 1.84–1.87 (0.25H, m), 2.02–2.06 (1H, m), 3.47–3.64 (2.3H, m), 3.72 (0.27H, dd, $J = 9.3$, 4.4 Hz), 3.90–4.00 (0.54H, m), 4.16–4.29 (1.73H, m), 7.34–7.46 (7.1H, m), 7.60–7.70 (5.1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.04, 19.52, 20.72, 20.81, 24.50, 27.07, 27.12, 28.70, 30.23, 45.47, 51.90, 63.57, 64.82, 79.31, 127.74, 129.69, 133.61, 135.66, 155.22; MS (m/z) 470(M^+). To a mixture of *N*-Boc compound (624 mg, 1.33 mmol) in THF (15.2 mL) was added 1M tetra-*n*-butylammonium fluoride (1.6 mL, 1.6 mmol) THF solution with ice cooling. The reaction mixture was stirred for 2 h at room temperature and then sat. $NaHCO_3$ was added to the reaction mixture with ice cooling. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to leave the residue, which was chromatographed using 15% ethyl acetate-hexane as eluant to yield **11** (80 mg, 26%) and **10** (209 mg, 69%) as oils. **10**: $[\alpha]^{27}_D - 11.6°$ (*c* 0.61, $CHCl_3$); IR (neat) 3447, 2937, 1666, 1458, 1366, 1328, 1256, 1176, 1083, 1053 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl3) δ 1.14 (3H, d, $J = 7.1$ Hz), 1.46 (9H, s), 1.43–1.84 (6H, m), 2.48 (1H, br s), 3.61–3.69 (2H, m), 4.21–4.31 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.16, 20.72, 25.07, 28.68, 30.20, 46.00, 51.86, 65.30, 79.90, 156.55; MS (m/z) 229(M^+); HRMS: calcd for $C_{12}H_{33}NO_3$ (M^+) 229.1678, found 229.1644; Anal. calcd for $C_{12}H_{33}NO_3$: C, 62.85, H, 10.11, N, 6.11, found C, 62.66, H, 10.25, N, 6.40.

*(2S,6S)-6-Methylpipecolic acid (**1**)*

To a solution **10** (85 mg, 0.37 mmol) in carbon tetrachloride (2.2 mL), acetonitrile (1.5 mL), and water (2.2 mL) was added $NaIO_4$ (235 mg, 1.11 mmol). After the mixture was stirred for 3 min, $RuCl_3$-nH2O (3.0 mg, 2,2 mol%) was added to the reaction mixture. The mixture was vigorously stirred for 3 h. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. Et_2O was added to the residue. The mixteure was filtrated through Celite. The filtrate was evaporated to leave the residue. CH_2Cl_2 (0.11 mL) and trifluoroacetic acid (0.11 mL) were added to the residue. The mixture was stirred for 1h and evaporated. The residue was purified through ion exchange resin (50W-X8) using 20% aq. NH_3 as eluant to yield **1** (39 mg, 74%) as a white solid. Mp >250°C. $[\alpha]^{27}_D - 24.0°$ (*c* 0.78, H_2O): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.46 (3H, d, $J = 6.8$ Hz), 1.48–1.94 (4H, m), 2.20–2.30 (2H, br d), 3.10–3.25 (1H, br s), 3.40–3.48 (1H, br d); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.71, 23.57, 27.00, 30.70, 52.98, 60.73, 173.10.

*(2R,6S)-1,2,6-Heptanetriol (**12**)*

By a procedure similar to that for the preparation of **8**, the reaction of (*R*)-**7** (1.543 g, 11.85 mmol) with three-step sequence {1. PPTS (30.2 mg, 0.12 mmol), trimethyl orthoacetate (81.93 mL, 15.2 mmol), CH_2Cl_2 (15.0 mL); 2. triethylamine (0.165 mL, 1.19 mmol), acetyl bromide (1.31 mL, 17.8 mmol), CH_2Cl_2 (15.0 mL); 3.K_2CO_3 (1.01 g, 25.7 mmol), methanol (0.7 mL), ether (29.0 mL)} provided the crude epoxide, which was converted with Super hydride® (23.7 mL, 23.7 mmol) in THF (31.5 mL) into *ent*-**6**. Reaction of *ent*-**6** with AD-mix[(DHQD)2PYR ligand] (19.5 g) in *tert*-BuOH (59 mL) and H_20 (59 mL) gave **12** (1.19 g, 68%) as a diasteromeric mixture; IR (neat) 3354, 2934, 1458, 1067 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.15 (1H, brs), 1.20 (3H, d, $J = 6.1$ Hz), 1.42–1.66 (6H, m), 2.14 (1H, br s), 2.51 (1H, br s), 3.42–3.82 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.99, 23.96, 33.08, 39.09, 67.03, 68.11, 72.24; MS (m/z) 150 (M^++1).

*(2S,6R)-N-tert-Butoxycarbonyl-2-hydroxymethyl-6-methylpiperidine (**13**)*

By a procedure similar to that for the preparation of **9**, reaction of **12** (1.19 g, 8.02 mmol) with imidazole (655 mg, 9.62 mmol) and *tert*-butyldiphenylsilyl chloride (1.06 mL, 4.00 mmol) in DMF (3.30 mL) yielded silyl compound (1.85 g, 60%) as a diasetreomeric mixture; IR (neat) 3381, 2931, 2858, 1428, 1113, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.17 (3H, d, $J = 6.0$ Hz), 1.35–1.48 (7H, m), 2.56 (1H, br s), 3.45–3.51 (1H, m), 3.63–3.78 (6H, m), 7.36–7.47 (6H, m), 7.64–7.67 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.52, 21.85, 22.01, 23.75, 27.12, 27.29, 32.77, 32.86, 39.35, 67.96, 68.22, 72.04, 127.46, 127.84, 129.88, 133.20, 133.23, 135.58, 135.93; MS (m/z) 386 (M^+). Reaction of the silyl product (1.85 g, 4.78 mmol) with *p*-TsCl (3.65 g, 19.1 mmol), triethylamine (2.66 mL, 19.1 mmol), and 4-*N*,*N*-dimethylaminopyridine (233 mg, 1.91 mmol) in CH_2Cl_2 (8.3 mL) yilded didosyl compound (2.60 g, 78%) as a diasetreomeric mixture; IR (neat) 2931, 1598, 1428, 1361, 1189, 1176, 1113, 906, 815, 758, 704, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (9 H, s), 1.06–1.16 (3 H, m), 1.19 (3 H, d, *J* = 6.6 Hz), 1.13–1.67 (3 H, m), 2.41 (6 H, s), 3.51–3.64 (2 H, m), 4.42–4.55 (2 H, m), 7.23–7.77 (18 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.47, 20.29, 20.87, 21.88, 27.01, 30.94, 36.32, 64.50, 80.02, 82.51, 111.56, 127.75, 127.84, 129.85, 129.92, 132.91, 133.05, 134.29, 134.50, 135.57, 135.63, 135.87, 144.60. Reaction of the ditosyl product (1.85 g, 2.66 mmol) with benzylamine (8.72 mL, 79.8 mmol) yielded (2*S*,6*R*)-*N*-Benzyl-1,2[(*tert*-butyldiphenylsilyloxy)methyl-6-methylpiperidine (1.06 g, 87%) as a diasetreomeric mixture; IR (neat) 2930, 1653, 1427, 1112, 823, 701 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.97 (3 H, d, *J* = 6.6 Hz), 1.02 (9 H, s), 1.26–1.27 (6 H, m), 2.82–2.90 (2 H, m), 3.56–3.70 (2 H, m), 3.79–3.91 (2 H, m), 7.19–7.45 (11 H, m), 7.60–7.65 (4 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.88, 19.50, 19.90, 26.54, 27.15, 31.84, 50.82, 53.36, 57.24, 64.21, 126.32, 127.69, 128.10, 128.19, 129.60, 133.96, 135.70, 141.80; MS (m/z) 458(M$^+$); HRMS:calcd for $C_{30}H_{39}NOSi$(M$^+$) 457.2801, found 457.2784. By a procedure similar to that for the preparation of **10**, reaction of the piperidine (1.15 g, 2.51 mmol) with a two-step sequence of {1. hydrogen using cat. $Pd(OH)_2$ (250 mg) in methanol (19.0 mL); 2. Boc_2O (1.15 mL, 5.02 mmol), K_2CO_3 (451 mg, 3.26 mmol) in THF/H_20 (18.4 mL/18.4 mL)} gave *N*-Boc-piperidine (1.02 g, 87%) as a diasetreomeric mixture; IR (neat) 3932, 1690, 1364, 1178, 1089, 825, 756, 701 cm^{-1}; ^{1}H-NM R (300 MHz, $CDCl_3$) δ 0.90 (1 H, d, *J* = 6.6 Hz), 1.05 (3 H, s), 1.06 (9 H, s), 1.20 (3 H, d, *J* = 6.6 Hz), 1.38(9 H, s), 1.46–1.52 (3 H, m), 1.59–1.62 (3 H, m), 1.85–1.89 (1 H, m), 2.02–2.08 (1 H, m), 3.48–3.61 (1.5 H, m), 3.70–4.00 (2 H, m), 7.34–7.45 (8 H, m), 7.64–7.69 (5.3 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.54, 19.55, 20.81, 21.02, 24.50, 27.14, 27.21, 28.73, 46.91, 52.84, 64.85, 79.20, 127.72, 129.66, 133.73, 133.84, 135.66, 155.08; MS (m/z) 467(M$^+$). Reaction of *N*-Boc-piperidine (277 mg, 0.59 mmol) with TBAF (0.71 mL, 0.71 mmol) in THF (6.9 mL) yielded **13** (79%) and **14** (18%) as oils; **13**; $[\alpha]^{27}_D$ − 47.5° (*c* 1.61, $CHCl_3$); IR (neat) 3447, 2973, 1672, 1400, 1176, 1126, 1092, 1049, 877, 756 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.18 (3 H, d, *J* = 6.6 Hz), 1.45 (9 H, s), 1.47–1.80 (6 H, m), 3.61–3.79 (3 H, m), 4.03 (1 H, br s), 4.14–4.22 (1 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.22, 18.80, 25.57, 28.24, 28.73, 48.62, 54.42, 66.44, 80.08, 156.46; MS (m/z) 229(M$^+$); Anal. calcd for $C_{12}H_{13}NO_3$: C, 62.85, H, 10.11, N, 6.11, found C, 63.05, H, 10.33, N, 6.34.

*6-Methylpipecolic acid (**2**)*

By a procedure similar to that for the preparation of **1**, the reaction of **13** (150 mg, 0.654 mmol) with a two-step sequence of {1. $NaIO_4$ (420 mg, 1.96 mmol), $RuCl_3$-nH2O (3.0 mg, 2.2 mol%) in CCl_4/acetonitrile/H_2O (2.2 mL/1.5 mL/2.2 mL); 2. CF_3COOH (0.2 mL) in CH_2Cl_2 (0.2 mL)} yielded **2** (64 mg, 68%) as a white solid; mp > 250 C (methanol/ether); $[\alpha]^{27}_D$ − 6.8° (*c* 0.08, H_2O); IR (KBr) 3444, 2856, 1578, 1396, 1325, 1128, 524 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3OD) δ 1.36 (3 H, d, *J* = 6.6 Hz), 1.40–1.65 (2 H, m), 1.75–1.92 (3 H, m), 2.18–2.24 (1 H, m), 3.60–3.69 (1 H, m), 3.80 (1 H, t, *J* = 4.8 Hz); ^{13}C-NMR (75 MHz, CD_3OD) δ 16.56, 18.41, 24.56, 28.97, 48.60, 55.26, 170.90; MS (m/z) 143(M+); HRMS : calcd for $C_7H_{12}NO_2$ (M$^+$-1) 142.0868, found 142.0881; Anal. calcd for $C_7H_{12}NO_2$: C, 58.72, H, 9.15, N, 9.78, found : C, 58.64, H, 9.05, N, 9.55.

*(2R,6R)-N-tert-Butoxycarbonyl-2-hydroxymethyl-6-methylpiperidine (ent-**10**)*

By a procedure similar to that for the preparation of **10**, a seven-step sequence of *ent*-**6** afforded **11** (6%) and *ent*-**10** (20%) as oils. *ent*-**10**; $[\alpha]^{27}_D$ + 11.0° (c 1.99, $CHCl_3$).

*6-Methylpipecolic acid (ent-**1**)*

By a procedure similar to that for the preparation of **1**, reaction of *ent*-**10** (191 mg, 0.83 mmol) with a two-step sequence of {1. $NaIO_4$ (535 mg, 2.50 mmol), $RuCl_3$-nH_2O (3.8 mg, 2.2 mol%) in CCl_4/acetonitrile/H_2O (2.8 mL/1.9 mL/2.8 mL); 2. CF_3COOH (0.25 mL) in CH_2Cl_2 (0.25 mL)} yielded *ent*-**1** (35 mg, 56%) as a white solid; mp > 250 C (methanol/ether); $[\alpha]^{27}_D$+24.7° (*c* 0.48, H_2O).

*(2R,6S)-N-tert-Butoxycarbonyl-2-hydroxymethyl-6-methylpiperidine (ent-**13**)*

By a procedure similar to that for the preparation of **10**, a seven-step sequence of **6** afforded **13** (25%) and *ent*-**10** (6%) as oils. *ent*-**13**; $[\alpha]^{26}_D$+44.9° (c 1.26, $CHCl_3$).

*6-Methylpipecolic acid (ent-**2**)*

By a procedure similar to that for the preparation of **1**, reaction of *ent*-**10** (382 mg, 1.67 mmol) with a two-step sequence of {1. $NaIO_4$ (1.07 g, 5.01 mmol), $RuCl_3$-nH_2O (7.7 mg, 2.2 mol%) in CCl_4/acetonitrile/H_2O (5.6 mL/3.8 mL/5.6 mL); 2. CF_3COOH (0.5 mL) in CH_2Cl_2 (0.5 mL)} yielded *ent*-**1** (163 mg, 68%) as a white solid; mp > 250°C (methanol/ether); $[\alpha]^{27}_D$+5.3° (c 0.69, H_2O).

*Moscher ester (**15**)*

A solution of **10** (6 mg, 26.2 μmol) and DMAP (4.8 mg, 39.3 μmol) in THF (0.139 μL) was treated with (*S*)-MTPA-Cl (5.4 μL, 28.8 μmol), and the reaction mixture was stirred for 10 h. After dilution with ether, the mixture washed with 20% $KHSO_4$, water, and sat. $NaHCO_3$, dried and evaporated to afford the Moscher ester of *N*-Boc (15 mg). A solution of the Moscher ester (15 mg) and trifluoroacetic acid (0.1 mL) and CH_2Cl_2 (0.1 mL) was stirred at room temperature for 4 h. After addition of sat. $NahCO_3$ to the reaction mixute, the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated to yield **15** (8 mg). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.054 (0.03 H, dd, *J* = 10.5, 8.2 Hz, -C*H*HOMTPA), 4.188 (0.97 H, dd, *J* = 10.5, 8.2 Hz, -C*H*HOMTPA).

*Moscher esters (**16**–**18**)*

By a procedure similar to that for the preparation of **15**, **16**, **17**, and **18** were obtained from **13**, *ent*-**10**, and *ent*-**13**, respectively. **16**; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.392 (0.02 H, dd, *J* = 10.8, 9.3 Hz, -C*H*HOMTPA), 4.572 (0.98 H, dd, *J* = 10.8, 9.3 Hz, -C*H*HOMTPA). **17**; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.054 (0.97 H, dd, *J* = 10.5, 8.2 Hz, -C*H*HOMTPA), 4.188 (0.03 H, dd, *J* = 10.5, 8.2 Hz, -C*H*HOMTPA). **18**; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.392 (0.96 H, dd, *J* = 10.8, 9.3 Hz, -C*H*HOMTPA), 4.572 (0.04 H, dd, *J* = 10.8, 9.3 Hz, -C*H*HOMTPA).

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