JOC*Note*

Chiron Approach to the Synthesis of (2*S*,3*R*)-3-Hydroxypipecolic Acid and (2*R*,3*R*)-3-Hydroxy-2-hydroxymethylpiperidine from D-Glucose

Navnath B. Kalamkar, Vijay M. Kasture, and Dilip D. Dhavale*

Department of Chemistry, Garware Research Centre, University of Pune, Pune - 411 007, India

ddd@chem.unipune.ernet.in

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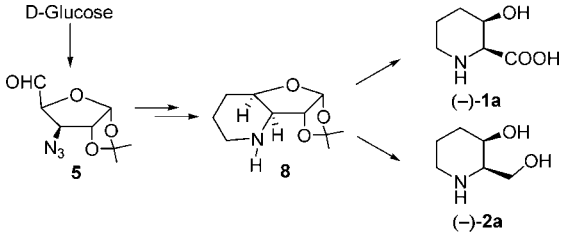

The first chiron approach from D-glucose for the total synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid (−)-**1a** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine (−)-**2a** is reported. The synthetic pathway involves conversion of D-glucose into 3-azidopentodialdose (**5**) followed by the Wittig olefination and reduction to give the piperidine ring skeleton (**8**) with a sugar appendage that on cleavage of an anomeric carbon followed by oxidation gives (−)-**1a** which on reduction affords (−)-**2a**.

The six membered cyclic α-amino-β-hydroxy acids, namely 3-hydroxypipecolic acids **1a** and **1b** (Figure 1), and their stereoisomers are attractive chiral building blocks for the synthesis of various biologically active natural products.[1] For example, cis isomer **1a** is an important constituent of a naturally occurring antitumor antibiotic tetrazomine **3**,[2] while the trans-configured acid **1b** is a precursor for potent α-D-mannosidase inhibitor (−)-swainsonine.[3] In an addition, α-amino-β-hydroxy acid unit embedded in **1** considered as a ring-expanded homologue of hydroxyproline or constrained analogue of serine and permits their use in conformational and ligand-binding studies involving bioactive peptides and peptidomimetics.[4] The carboxyl group reduced analogues of **1**, namely 3-hydroxy-2-hydroxymethylpiperidine **2**, are known as fagomine congeners[5a] due to their resemblance to the piperidine iminosugars which

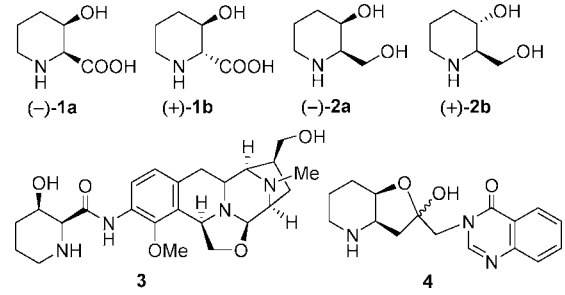

FIGURE 1. 3-Hydroxypipecolic acid analogues.

are promising glycosyltransferases and glycosidase inhibitors.[6] The (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **2a** is also found in the structure of the antimalarial isofebrifugine **4**.[7]

A number of asymmetric as well as chiron approaches for the synthesis of both **1** and **2** and their stereoisomers are known in the literature. In general, the asymmetric methodologies for trans-configured **1** and **2** are prevalent probably due to the easy outcome of the relative trans stereochemistry, on the adjacent carbon atoms, in the asymmetric pathways[8] that involve either dihydroxylation or epoxidation followed by attack of the nitrogen nucleophile. As an alternative, chiron approaches[3,5,9]

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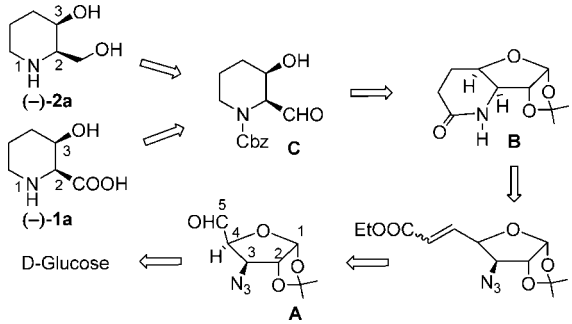
SCHEME 1. Retrosynthetic Analysis



make use of amino acids, in particular D- or L-serine, in enantioselective synthesis of **1** and **2**. We were particularly interested in the synthesis of cis-configured (−)-**1a** and (−)-**2a** because of the fact that (i) the literature scrutiny indicates only a few methods for cis isomers **1a/2a** and (ii) no chiron approach starting from the carbohydrate precursor, to the best of our knowledge, is reported for the synthesis of either **1** or **2**. The first enantioselective synthesis of (−)-**1a**, accomplished by Corey et al., involves an aldol condensation of silyl ketene acetal of *tert*-butylglycinate with different achiral aldehydes using cinchonidine alkaloid derived catalyst as a key step to get good stereoselectivity.[8a] Drummond et al.[8k] as well as Marshall and Makara[8l] reported the synthesis of racemic (±)-**1a** from 3-hydroxypicolinic acid that was later enzymatically resolved by Williams and co-workers using lipase PS.[8m] Recently, Liang and Datta used D-serine as a chiral template, wherein addition of the homoallyl Grignard reagent to D-serinal afforded high diastereoselectivity in favor of *syn*-amino alcohol that was elaborated to (−)-**1a**.[9a] In the case of **2a**, Takahata and co-workers have reported different approaches for **2a** and its stereoisomers starting from Garner aldehyde and by exploiting the ring-closing metathesis approach.[5] In another synthesis, O'Doherty and co-workers[10] utilized the Sharpless asymmetric aminohydroxylation strategy with 2-vinylfurans to give β-hydroxyfurfurylamine in high enantioexcess in the synthesis of tosyl salt of **2a**.

As a part of our continuous interest in the synthesis of iminosugars by using carbohydrate as precursors,[11] we have devised an altogether different strategy for the synthesis of **1a** and **2a** using D-glucose as a chiral template. We envisioned that the D-glucose type of symmetry is hidden in the target molecules wherein the required relative cis stereochemistry at C2 and C3 of the vicinal amino acid/alcohol functionalities in **1a** and **2a** is found to be embedded at C3 and C4, respectively, of 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose **A**, easily prepared from D-glucose (Scheme 1). Thus, as shown in the retrosynthetic analysis, the two-carbon Wittig homologation of **A** with $Ph_3PCHCOOEt$ followed by hydrogenation will give access to sugar-substituted δ-lactam **B**. Reduction of the lactam functionality, removal of 1,2-acetonide protection, and cleavage of an anomeric carbon atom by oxidative cleavage will provide N-protected α-amino-β-hydroxy aldehyde **C**, an immediate precursor with required functionalities and chirality, that on oxidation will afford (−)-**1a**, while reduction will give (−)-**2b**. Our synthetic efforts in this direction are described herein.

The required 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose **5** was prepared from D-glucose as reported earlier.[12] The Wittig olefination of **5** using (carbethoxymethylene)triphenylphosphorane afforded α,β-unsaturated ester **6** as a diastereomeric mixture[13] of *E* and *Z* isomer in a ratio 6:4 as an evident from ^{1}H NMR of crude product (Scheme 2). Hydrogenation of α,β-unsaturated ester **6** using 10% Pd/C in methanol at 80 psi afforded a tricyclic δ-lactam **7** as a white solid.[14] This one-pot three-step process involves reduction of the double bond, conversion of an azide to amine functionality, and concomitant lactamization to give **7** in high yield. The relative cis sterochemistry at the 6/5-ring junction in **7** is established by a NOESY 1D experiment wherein irradiation of H-3 at δ 3.85 showed 2.9% NOE with H-4 at δ 4.57. In the next step, reduction of the δ-lactam functionality in **7** with LAH in THF afforded piperidine ring skeleton **8** which on reaction with benzyl chloroformate and sodium bicarbonate in ethanol–water gave *N*-Cbz-protected amine **9**.

Treatment of **9** with TFA−water (3:2) at room temperature afforded an anomeric mixture of hemiacetals (as an evident from the ^{1}H NMR of crude product) that was directly subjected to oxidative cleavage using sodium metaperiodate in acetone–water (to cleave the anomeric carbon) to give α-aminal **10** as a thick oil. The *N*-Cbz-protected α-aminal **10** was found to be relatively unstable and therefore was immediately reacted with sodium chlorite and 30% H_2O_2 using sodium dihydrogen phosphate as a buffer in acetonitrile−water to afford *N*-Cbz-protected (2*S*,3*R*)-3-hydroxypipecolic acid derivative **11** as a sticky gum. In the final step, hydrogenolysis of **11** using 10% Pd/C in methanol at 80 psi afforded (−)-**1a** as a solid in high yield. The spectral and analytical data for (−)-**1a** was found to be in consonance with that reported: $[\alpha]^{25}_D$ −73.8 (*c* 0.10, 1 M HC1) [lit.[2] $[\alpha]^{20}_D$ −72.3 (*c* 0.10, 1 M HCl)], $[\alpha]^{25}_D$ −54.1 (*c* 0.6, H_2O) [lit.[8a] $[\alpha]_D$ −52.8 (*c* 0.6, H_2O)].

While targeting to the synthesis of (−)-**2a**, the *N*-Cbz-protected α-aminal **10** was treated with sodium borohydride in methanol–water that afforded *N*-Cbz-protected piperidine diol **12** as a white solid. Finally, hydrogenolysis of **12** using 10% Pd/C in methanol gave (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine (−)-**2a**. The spectral and analytical data of (−)-**2a** was found to be in good agreement with that reported: $[\alpha]^{25}_D$ −13.2 (*c* 2.51, H_2O) [lit.[10] $[\alpha]^{21}_D$ −12.4 (*c* 2.51, H_2O)].

In conclusion, we have demonstrated the first chiron approach from D-glucose for the total synthesis of (−)-**1a** and (−)-**2a** in 15 linear steps with 27% and 25% overall yield, respectively. The sequence involves simple reagents and minimum column purification, high yielding steps that can be elaborated for large scale preparation. The methodology could be readily extended

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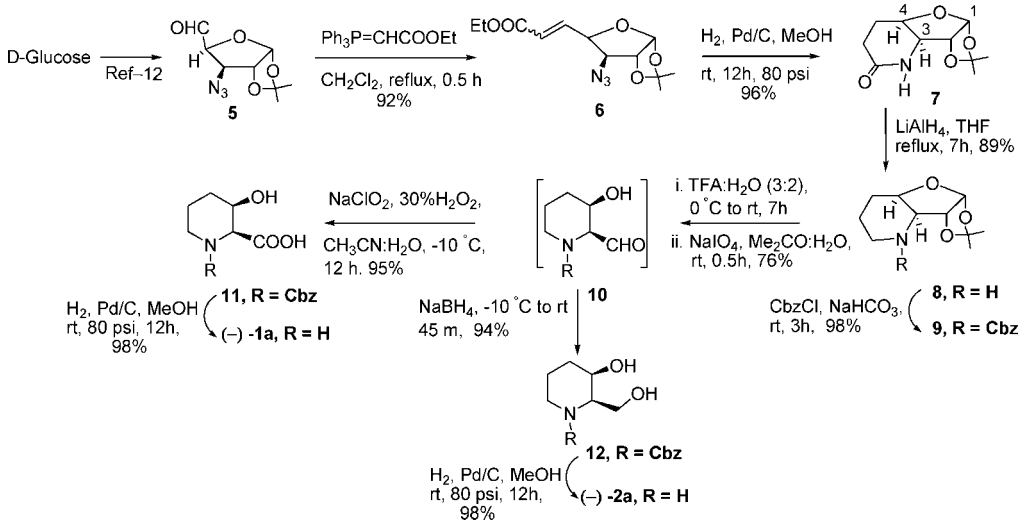
(13) Our attempts to separate the diastereomeric mixture of **6** by flash chromatography were unsuccessful due to the close R_f values; however, we have isolated the *E*-isomer in a small quantity, and its data are given in the Experimental Section. Compound **6** (*E*-isomer) is known; however, no data are reported to be the same. See: Chanderasekhar, S.; Samala, J. P.; Chennamaneni, L. R. *J. Org. Chem.* **2006**, *71*, 2196.

(14) Compound **7** is prepared by a different method in which the nature of the compound and specific rotation is not given; see ref 13. We have isolated compound **7** as a white solid and characterized it independently. The data are given in the Experimental Section.

SCHEME 2. Synthesis of (−)-1a and (−)-2a



for the synthesis of naturally occurring (2*S*,3*R*)-β-hydroxylysine and *cis*-3-hydroxyproline, and work in this direction is in progress.

Experimental Section

(*E*:*Z*)-Ethyl-1,2-*O*-isopropylidene-3-azido-3,5,6-trideoxy-α-D-*xylo*-hept-5-enofuranuronate-pentodialdo-1,4-furanose (6). To a stirred solution of 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose **5** (5 g, 23.47 mmol) in dry dichloromethane (80 mL) was added (carbethoxymethylene)triphenylphosphorane (11.55 g, 35.21 mmol). The reaction mixture was refluxed for 30 min and cooled to 26 °C. Solvent was evaporated under reduced pressure, and the residue on flash column chromatography (*n*-hexane/ethyl acetate = 97/3) afforded the *E*-isomer (0.2 g, 03%) and a diastereomeric mixture of *E*:*Z*, α,β unsaturated ester **6** as an oil (5.9 g, 89%). Data for *E*-isomer: R_f 0.6 (*n*-hexane/ethyl acetate = 9/1); $[\alpha]_D$ −1.09 (*c* 0.95, $CHCl_3$); IR (neat) 2108, 1717, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.34 (s, 3H), 1.51 (s, 3H), 3.95 (d, *J* = 3.3 Hz, 1H), 4.2 (q, *J* = 7.2 Hz, 2H), 4.70 (d, *J* = 3.6 Hz, 1H), 4.84–4.92 (m, 1H), 5.96 (d, *J* = 3.6 Hz, 1H), 6.22 (dd, *J* = 15.6, 4.5 Hz, 1H), 6.91 (dd, *J* = 15.6, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.6, 26.5, 60.6, 67.2, 78.5, 83.4, 104.4, 112.2, 124.1, 139.6, 165.4. Anal. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05. Found: C, 50.96; H, 6.28.

2,2-Dimethylperhydro[1,3]dioxolo[4′,5′:4,5]furo[3,2-*b*]pyridin-7-one (7). The azido ester **6** (5.8 g, 20.49 mmol) and 10% Pd/C (0.1 g) in methanol (25 mL) was subjected to hydrogenation at room temperature (25 °C) at 80 psi. After 12 h, the solution was filtered through Celite and the residue washed with methanol. Evaporation of solvent on a rotary evaporator and crystallization with *n*-hexane/ethyl acetate = 3/7 gave tricyclic sugar appended δ-lactam **7** (4.18 g, 96%) as a white solid: mp 185–187 °C; R_f 0.3 (ethyl acetate); $[\alpha]_D$ −92.85 (*c* 0.75, CH_2Cl_2); IR (KBr) 1668, 1411, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.49 (s, 3H), 1.83–1.98 (m, 1H), 2.20–2.32 (m, 2H), 2.52 (ddd, *J* = 17.6, 12.9, 6.3 Hz, 1H), 3.81 (d, *J* = 3.7 Hz, 1H), 4.48 (d, *J* = 3.7 Hz, 1H), 4.58 (bs, 1H), 5.87 (d, *J* = 3.7 Hz, 1H), 6.88 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 25.6, 26.3, 26.8, 60.4, 71.8, 85.3, 104.8, 112.0, 172.0. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09. Found: C, 56.62; H, 7.29.

2,2-Dimethylperhydro[1,3]dioxolo[4′,5′:4,5]furo[3,2-*b*]pyridine (8). To a stirred, ice-cold suspension of lithium aluminum hydride (2.14 g, 56.33 mmol) in dry THF (20 mL) was added δ-lactam **7** (4 g, 18.77 mmol) in dry THF (25 mL) over a period of 10 min. The reaction mixture was then stirred for 15 min at 0 °C, allowed to attain at room temperature (25 °C), and then refluxed at 80 °C. After 7 h, reaction mixture was cooled to 25 °C and quenched by slow addition of ethyl acetate (50 mL) followed by saturated solution of aq ammonium chloride (15 mL) and stirred for 2 h. The solution was filtered through Celite, the residue was washed with ethyl acetate, and the filtrate was evaporated under vacuum with column chromatography purification using *n*-hexane/ethyl acetate = 3/7 to give amine **8** (3.32 g, 89%) as a pale yellow oil: R_f 0.3 ($CHCl_3$/MeOH = 8/2); $[\alpha]_D$ + 1.5 (*c* 1.25, CH_2Cl_2); IR (neat) 3439, 1087 and 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.45 (s, 3H), 1.53–1.80 (m, 2H), 1.82–2.10 (m, 1H), 2.25 (bd, *J* = 14.3 Hz, 1H), 2.70 (bt, *J* = 12.3 Hz, 1H), 3.30 (bd, *J* = 12.3 Hz, 1H), 3.40 (d, *J* = 1.5 Hz, 1H), 4.30 (d, *J* = 1.5 Hz, 1H), 4.7 (d, *J* = 3.6 Hz, 1H), 6.15 (d, *J* = 3.6 Hz, 1H), 6.75 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 23.7, 26.1, 26.3, 43.2, 59.3, 71.2, 82.5, 104.6, 111.8. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.09; H, 8.55.

2,2-Dimethylperhydro[1,3]dioxolo-*N*-benzyloxycarbonyl[4′,5′:4,5]furo[3,2-*b*]pyridine (9). To an ice-cooled solution of **8** (3.2 g, 16.08 mmol) and sodium bicarbonate (5.4 g, 64.32 mmol) in ethanol–water (3:1, 40 mL) was added benzyloxycarbonyl chloride (4.1 g, 24.12 mmol) in ethanol (10 mL). After 3 h, ethanol was removed on a rotary evaporator, and the residue was extracted with dichloromethane (3 × 20 mL). Usual workup and purification by column chromatography (*n*-hexane/ethyl acetate = 97/3) gave **9** (5.2 g, 98%) as a colorless thick liquid: R_f 0.5 (*n*-hexane/ethyl acetate = 8/2); $[\alpha]_D$ −54.8 (*c* 0.75, CH_2Cl_2); IR (neat) 1705, 1419, 1269, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.50 (s, 3H), 1.54–1.86 (m, 3H), 2.0–2.12 (m, 1H), 3.20–3.35 (m, 1H), 3.50–3.64 (m, 1H), 4.08 (d, *J* = 4.9 Hz, 1H), 4.48–4.58 (m, 1H), 4.67 (bd, *J* = 3.0 Hz, 1H), 5.16 (AB quartet, *J* = 12.4 Hz, 2H), 5.81 (d, *J* = 3.8 Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 21.9, 26.3, 26.8, 40.1, 60.7, 67.2, 73.4, 86.2, 104.3, 111.1, 127.8, 127.93, 128.4, 136.4, 156.3. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95. Found: C, 65.03; H, 7.16.

(2*S*,3*R*)-*N*-Benzyloxycarbonyl-3-hydroxypiperidine-2-carboxylic Acid (11). An ice-cold solution of **9** (4.9 g, 14.71 mmol) in TFA−H_2O (40 mL, 3:2) was stirred for 15 min and at 25 °C for 7 h. Trifluoroacetic acid was coevaporated with toluene at rotary evaporator using high vacuum to furnish hemiacetal as a thick liquid (crude wt = 3.6 g). To an ice-cooled solution of hemiacetal (2 g, 6.8 mmol) in acetone/water (10 mL, 5:1) was added sodium metaperiodate (2.19 g, 10.23 mmol), and the solution was stirred for 30 min at 25 °C. Ethylene glycol (0.2 mL) was added, solvent was evaporated on rotary evaporator, and the residue was extracted with chloroform (3 × 15 mL). Usual workup afforded α-aminal **10** as a thick liquid (1.5 g). To a stirred solution of **10** (0.46 g,

1.74 mmol) in acetonitrile (10 mL) was added the solution of sodium dihydrogen phosphate (0.05 g, 0.31 mmol) in water (3 mL) and 30% H_2O_2 (0.15 mL, 1.92 mmol). The mixture was stirred and cooled at −10 °C, $NaClO_2$ (0.25 g, 2.72 mmol) in water (3.5 mL) was added dropwise over 30 min, the reaction mixture was then stirred at 15 °C, and the reaction was monitored by the evolution of oxygen with a bubbler connected to the apparatus. After 10 h, the reaction was decomposed by addition of a small amount of Na_2SO_3 (0.1 g) and acidified with 10% aq HC1 (5 mL). The organic layer was separated, aqueous layer was extracted with ethyl acetate (4 × 5 mL), the combined organic layer was evaporated, and the residue was dissolved in 10% $NaHCO_3$ solution (25 mL). The bicarbonate layer was washed with ethyl acetate (15 mL) and then made acidic to pH 2 and extracted with ethyl acetate (3 × 15 mL). Usual workup gave **11** (0.46 g, 95%) as a sticky gum: R_f 0.5 ($CHCl_3$/MeOH = 8/2); $[\alpha]_D$ −13.9 (*c* 0.42, CH_2Cl_2); IR (KBr) 3600–2870 (br), 1708, 1676, cm^{-1}; ^1H NMR (300 MHz, CDClδ 1.40–1.60 (m, 2H), 1.62–1.80 (m, 1H), 1.92– 2.12 (m, 1H), 2.75–3.05 (m, 1H), 3.80–4.10 (m, 2H), 4.95–5.20 (m, 3H), 6.80–8.20 (br, 2H, exchangeable with D_2O), 7.30 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 29.6, 40.9, 57.6, 68.1, 68.5, 127.6, 127.9, 128.4, 135.7, 156.5, 172.1. The ^1H NMR showed broadening of the signals and ^{13}C NMR showed doubling of signals. This could be attributed to the presence of *N*-Cbz functionality resulting into the rotamers. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14. Found: C, 60.50; H, 6.38.

(2*S*,3*R*)-3-hydroxypiperidine-2-carboxylic Acid (−)-1a. A solution of **11** (0.19 g, 0.68 mmol) and 10% Pd/C (0.025 g) in methanol (5 mL) was hydrogenolized at 80 psi for 12 h at 25 °C. The catalyst was filtered through Celite. Evaporation of solvent afforded (−)-**1a** (96 mg, 98%) as a solid: R_f 0.21 ($CHCl_3$/MeOH/30% NH_4OH = 3/5/2); $[\alpha]^{25}_D$ −73.8 (*c* 0.10, 1 M HC1) [lit.[2] $[\alpha]^{20}_D$ −72.3 (*c* 0.10, 1 M HCl)], $[\alpha]^{25}_D$ −54.1 (*c* 0.6, H_2O) [lit.[8a] $[\alpha]_D$ −52.8 (*c* 0.6, H_2O)].

(2*R*,3*R*)-*N*-Benzyloxycarbonyl-3-hydroxy-2-hydroxymethylpiperidine (12). To a stirred solution of **10** (0.5 g, 1.9 mmol) in methanol/water (5 mL, 3:1), maintained at −10 °C, was added sodium borohydride (0.1 g, 2.85 mmol) in portions during 20 min. The resulting solution was stirred for 30 min and allowed to attain room temperature (25 °C). Solvent was evaporated, and the residue was extracted with chloroform (3 × 5 mL). Evaporation of solvent and column purification using *n*-hexane/ethyl acetate = 6.5/3.5 gave **12** (0.47 g, 94%) as a white solid: mp 105–107 °C; R_f 0.5 (*n*-hexane/ethyl acetate = 2/8); $[\alpha]_D$ +6.24 (*c* 0.25, CH_2Cl_2); IR (KBr) 3429, 1670, 1435, 1251, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + drop of D_2O), δ 1.35–1.90 (m, 4H), 2.9 (bs, 1H), 3.75 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.80–3.98 (m, 2H), 4.10 (dd, *J* = 11.2, 6.1 Hz, 1H), 4. 38– 4.52 (bm, 1H), 5.12 (s, 2H), 7.30 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 28.3, 40.0, 56.6, 59.1, 67.5, 69.1, 127.7, 128.0, 128.4, 136.3, 156.0. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.68; H, 7.33.

(2*R*,3*R*)-2-(Hydroxymethyl)piperidin-3-ol (−)-2a. A solution of **12** (0.3 g, 1.13 mmol) and 10% Pd/C (0.03 g) in methanol (7 mL) was hydrogenolized as described for (−)-**1a**. Column chromatography purification using $CHCl_3$/MeOH = 7/3 afforded (−)-**2a** (0.14 g, 98%) as a thick liquid: R_f 0.25 ($CHCl_3$/MeOH/30% NH_4OH = 3/4/3); $[\alpha]^{25}_D$ −13.2 (*c* 2.51, H_2O); [lit.[10] $[\alpha]^{21}_D$ −12.4 (*c* 2.51, H_2O)].

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Supporting Information Available: General experimental methods and the copies of ^1H and ^{13}C NMR spectra of compounds **6**−**11**, (−)-**1a**, **12**, and (−)-**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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