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Synthesis of γ-Hydroxyalkyl Substituted Piperidine Iminosugars from D-Glucose

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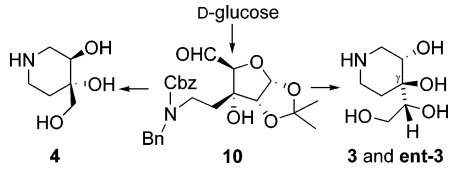

D-Glucose was converted to synthetic equivalent of *meso*-pentodialdose, namely 3-*C*-(1′-aminoethyl)-α-D-*ribo*-pentodialdo-1,4-furanose **10** that gives an easy access to manipulate the aldehyde functionalities on either sides to get enantiomeric pair of **3**. Thus, reduction of C5-aldehyde followed by hydrolysis of 1,2-acetonide functionality and reductive aminocyclization with C1-aldehyde afforded γ-1,2-dihydroxyethyl piperidine iminosugar **3**. On the other hand, first reductive aminocyclization with C5-aldehyde gave piperidine ring skeleton **12** that on removal of 1,2-acetonide and reduction of C1-aldehyde gave **ent-3** while chopping of C1-aldehyde in **12** and reduction afforded γ-hydroxymethyl piperidine iminosugar **4**.

Among six membered iminosugars, the nojirimycin **1a** was the first to be recognized as a glycosidase inhibitor;[1] however, it was noticed that **1a** was highly unstable to the mild acidic/basic conditions. This led to the discovery of a more stable and promising glycosidase inhibitor, namely 1-deoxynojirimycin **1b**, that was synthesized first[2a] and then isolated.[2b,c] Later on, 1,2-dideoxynojirimycin, commonly known as fagomine **1c**, was isolated and evaluated for biological studies.[3] A common feature in **1** is the presence of hydroxymethyl substituent at the α-position with respect to the ring nitrogen atom. In an attempt to find a classical variation in the position of hydroxymethyl substituent in **1**, Bols et al. synthesized β-hydroxymethyl substituted hydroxylated piperidine iminosugars in which nitrogen atom was shifted to the anomeric position of **1** and labeled these compounds as isofagomine **2a**.[4] The structure activity relationship data indicates that the bioactivity of **1** and **2** is reliant on the position and orientation of the hydroxyalkyl group in the piperidine iminosugars.[5] For example, isofagomine **2a** is stronger and more selective inhibitor of β-glucosidases; however, its 5(*S*)-hydroxy (C5-hydrogen replaced by −OH) substituted analogue **2b** is a better inhibitor toward both α and β-glucosidases[6] whereas 5(*R*)-hydroxy isofagomine **2c** is a mild β-mannosidase inhibitor.[4i,7d] The *N*-alkyl derivatives of **2b** inhibit glycolipid biosynthesis[6] with little inhibitory activity against glycosidases. Although α/β-hydroxyalkyl substituted piperidine iminosugars are known in the literature, the existence of γ-hydroxyalkyl substituted pattern is not known. As a part of our continuing efforts in this area,[7] we are now reporting hitherto unknown γ-1,2-dihydroxyethyl and hydroxymethyl

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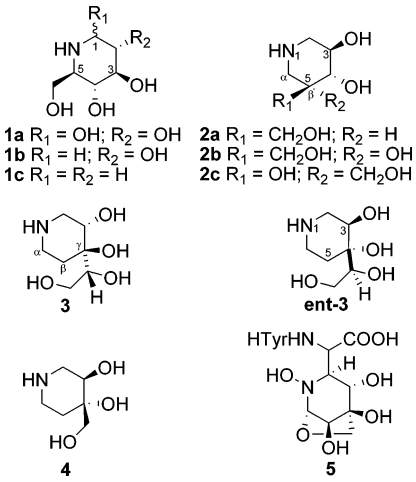
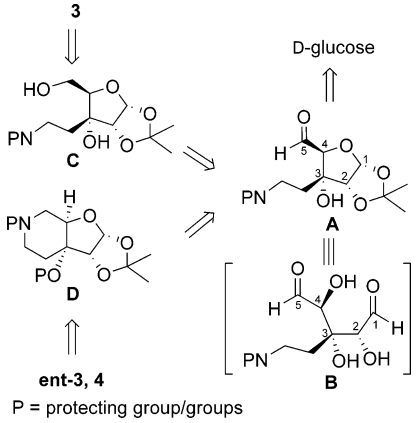


FIGURE 1. Piperidine iminosugars.

SCHEME 1. Retrosynthesis of 3, ent-3, and 4

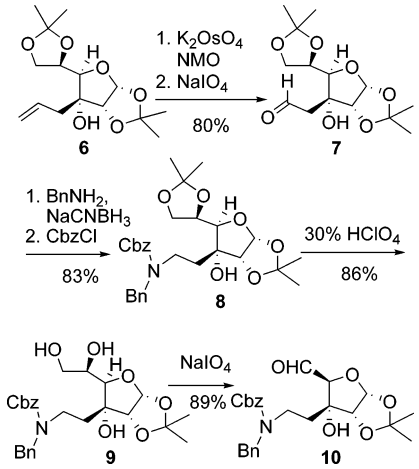


substituted piperidine iminosugars **3**, **ent-3**, and **4**. It is interesting to note that such type of piperidine system (as in **3)** is present in the microbial metabolite **5**, which is a potent and selective inhibitor of bacterial tyrosyl tRNA synthetases (YRS) (see Figure 1).[8]

In general, introduction of hydroxyalkyl moiety at the carbon atom of the piperidine ring skeleton is difficult; however, we thought of utilizing carbon skeleton of D-glucose to get the required substituents while building the piperidine ring. Thus, the common intermediate to the target molecules is the synthetic equivalent of the *meso*-pentodialdose **B**, namely 3-*C*-(1′-aminoethyl)-α-D-*ribo*-pentodialdo-1,4-furanose **A**, that could be easily obtained from the D-glucose (Scheme 1).

Attractive features of chiral template **A** are (i) the presence of two differentially protected and stereochemically defined hydroxylated C2 and C4 carbon atoms, (ii) the presence of one free (C5) and other protected aldehyde (C1) functionalities, and (iii) the suitably placed ethylamine side chain at C3, required for building the piperidine ring skeleton. The masked symmetry of **A** is apparent in the *meso*-open structure of the 1,2-acetonide cleavage product **B** wherein the C3 is achirotopic and stereogenic. The aldehyde functionalities on either side afford inherent flexibility and could be manipulated elegantly to get the enantiomeric pair of **3**. For example, first reduction of C5-aldehyde functionality in **A** will afford **C** that on 1,2-acetonide removal and reductive aminocyclization with C1-aldehyde will give **3**. On the other hand, first reductive aminocyclization in **A** with C5-aldehyde functionality to get piperidine ring skeleton **D** and 1,2-acetonide removal following reduction of C1-aldehyde will give an access to **ent-3**, whereas protection of tertiary hydroxyl in **D** followed by acetonide removal, chopping of the anomeric C1, and reduction will give **4**. Our results in this direction are reported herein.

SCHEME 2. Synthesis of 10



As shown in Scheme 2, D-glucose was converted to the known alcohol **6** as reported earlier.[9] Dihydroxylation of **6** using catalytic amount of $K_2OsO_4 \cdot 2H_2O$ (5 mol %) and NMO as a cooxidant afforded triol which was directly subjected to oxidative cleavage using sodium metaperiodate to give aldehyde **7**.[10] Reductive amination of **7** using benzylamine and sodium cyanoborohydride in methanol followed by treatment with benzyloxycarbonyl chloride and sodium bicarbonate in methanol-water afforded *N*-Cbz protected amino alcohol **8**.[11] Selective 5,6-acetonide deprotection in **8** using 30% $HClO_4$ in THF under controlled conditions gave triol **9** that on treatment with sodium metaperiodate afforded *N*-protected aminoaldehyde **10** in good yield.

While targeting the synthesis of **3** (Scheme 3), the C5-aldehyde group in **10** was first reduced with sodium borohydride to give *N*-protected aminoalcohol **11**. Removal of 1,2-acetonide group with TFA-water (to free the C1-aldehyde) and subsequent reductive aminocyclization using ammonium formate and 10%

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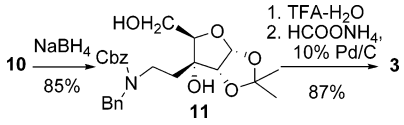
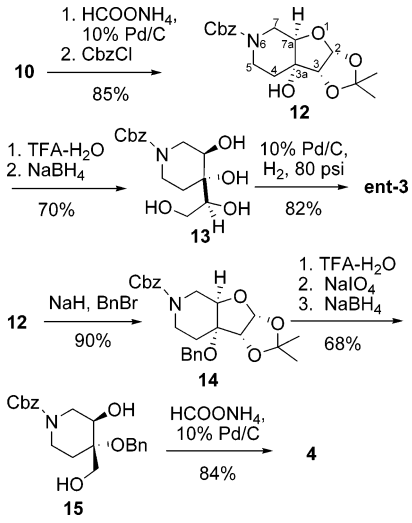
(10) Compound **7** is reported using different methodology, see: Pinheiro, J. M.; Ismael, M. I.; Figueiredo, J. A.; Silva, A. M. S. *J. Heterocycl. Chem.* **2004**, *41*, 877−882.

(11) The ^{1}H and ^{13}C NMR spectra of compounds **8**, **9**, **10**, **11**, **12**, **13**, **14**, and **15** in which a *N*-Cbz group is present, showed doubling of signals. This was due to restricted rotation around the N−C═O bond, see: (a) *Applications of NMR Spectroscopy in Organic Chemistry*; Jackman, L. M., Sternhell, S., Eds.; Pergamon Press: Elmsford, NY, 1978; p 361.

SCHEME 3. Synthesis of 3



SCHEME 4. Synthesis of ent-3 and 4



Pd/C in methanol at reflux afforded (3*S*, 4*S*)-3,4-dihydroxy-4-((*R*)-1,2-dihydroxyethyl)piperidine (**3**) as a thick liquid. This one-pot three-steps process involves hydrogenolysis of *N*-benzyl and *N*-Cbz groups to give insitu formation of primary amine that concomitantly undergoes reductive aminocyclization with C1-aldehyde (equilibrium with hemiacetal) to give **3**.

To achieve the synthesis of **ent-3**, another strategy as described in Scheme 1 was adopted. Thus as shown in Scheme 4, *N*-protected aminoaldehyde **10** was first subjected to reductive aminocyclization (ammonium formate, 10% Pd/C, methanol at reflux) to afford piperidine ring skeleton that on selective *N*-Cbz protection gave bicyclic oxapiperidine **12** (85% yield over two steps).[12] In the next step, hydrolysis of 1,2-acetonide functionality in **12** with TFA-water and reduction of C1-aldehyde with sodium borohydride in THF-water yielded *N*-Cbz protected piperidine **13**. In the final step, hydrogenolysis of **13** using 10% Pd/C in methanol at 80 psi afforded (3*R*, 4*R*)-3,4-dihydroxy-4-((*S*)-1,2-dihydroxyethyl)piperidine (**ent-3**) as a thick liquid.

For the synthesis of γ-hydroxymethyl substituted piperidine **4**, it was necessary to protect the tertiary hydroxyl functionality. Thus, treatment of **12** with sodium hydride and benzyl bromide in THF afforded benzylated product **14** (Scheme 4). In the next step, removal of 1,2-*O*-isopropylidene functionality in **14** with TFA-water followed by oxidative cleavage of the resultant hemiacetal with $NaIO_4$ and subsequent reduction using sodium borohydride gave *N*-Cbz protected hydroxymethyl piperidine **15**. Finally, hydrogenolysis of **15** (ammonium formate and 10% Pd/C, methanol reflux) afforded (3*R*, 4*S*)-3,4-Dihydroxy-4-hydroxymethyl piperidine (**4**) as a thick liquid.

In conclusion, we have adroitly exploited the carbon skeleton of D-glucose to introduce otherwise difficult 1,2-dihydroxyethyl and hydroxymethyl functionalities at the γ-position of the piperidine ring nitrogen to get new piperidine iminosugars **3**, **ent-3**, and **4**. Another interesting aspect of present route is that we have converted D-glucose to enantiomeric pair **3**. Thus, a single starting compound obtained from D-glucose has been used to synthesize two enantiomers having several stereo-centers. The new molecules are being studied for their inhibitory activity, and the results will be published in due course.

Experimental Section

1,2:5,6-Di-*O*-isopropylidene-3-*C*-(1′-(*N*-benzyl-*N*-benzyloxycarbonyl)aminoethyl)-α-D-*allo*-1,4-furanose (8). To a solution of benzyl amine (0.79 mL, 7.28 mmol) and glacial acetic acid (0.02 mL) in dry methanol (20 mL) was added a solution of **7** (2.00 g, 6.62 mmol) in methanol (15 mL) over a period of 30 min at −20 °C and stirred for 1 h. Sodium cyanoborohydride (1.04 g, 16.55 mmol) was added in three portions (10 min), and the solution was warmed to 0 °C and stirred for 2 h. Reaction mixture was quenched by adding saturated aq $NaHCO_3$ solution. Methanol was removed under reduced pressure, and the residue was extracted with chloroform (25 mL × 3) and concentrated to afford crude amine. To a solution of crude amine (2.60 g, 6.61 mmol) in methanol−water (25 mL, 9:1) at 0 °C was added sodium bicarbonate (1.66 g, 19.84 mmol) and benzyloxycarbonyl chloride (1.40 mL, 9.92 mmol). The reaction mixture was allowed to attain room temperature and stirred for 3 h. Methanol was evaporated under reduced pressure, and the residue was extracted with chloroform (25 mL × 3) and concentrated. Purification by column chromatography (*n*-hexane/ethyl acetate = 4/1) gave **8** (2.90 g, 83% over two steps) as a thick liquid: R_f 0.50 (*n*-hexane/ethyl acetate = 2/3); $[\alpha]_D^{25}$ +11 (*c* 1.06, $CHCl_3$); IR ($CDCl_3$) 3525 (br), 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10−2.10 (m, 14H), 2.67 (br s, 1H), 3.20−4.70 (m, 9H), 5.05−5.75 (m, 3H), 7.10−7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.4, 26.6 (s), 30.0, 42.3, 51.1, 67.2, 67.7, 73.0, 78.3, 80.4, 82.1, 103.5, 109.4, 112.4, 127.3 (s), 127.6, 127.8 (s), 128.1, 128.4 (s), 128.5 (s), 137.5 (s), 156.2. Anal. calcd for $C_{29}H_{37}NO_8$: C, 66.02; H, 7.07; Found: C, 65.95; H, 7.00.

(3*S*,4*S*)-3,4-Dihydroxy-4-((*R*)-1,2-dihydroxyethyl)piperidine (3). A solution of **11** (0.10 g, 0.21 mmol) in TFA−water (2 mL, 3:1) was stirred for 3 h at 0 °C. TFA was coevaporated with toluene at reduced pressure to furnish a hemiacetal as a thick liquid. To a solution of hemiacetal (0.09 g, 0.21 mmol) in dry methanol (5 mL) was added 10% Pd/C (0.05 g) and ammonium formate (0.07 g, 1.09 mmol), and the reaction mixture was refluxed for 1 h. On cooling, the reaction mixture was filtered through celite, washed with methanol, and the solvent was evaporated at reduced pressure. Purification by column chromatography (methanol) gave **3** (0.03 g, 87% over two steps) as a thick liquid: R_f 0.18 (25% aq NH_4OH/MeOH = 1/9); $[\alpha]_D^{25}$ +12 (*c* 0.65, MeOH); IR (neat) 3600−2900 (br) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.68−1.89 (m, 2H), 2.75−3.00 (m, 3H), 3.05 (dd, *J* = 14.1, 1.8 Hz, 1H), 3.61 (br s, 1H), 3.62 (dd, *J* = 11.1, 7.8 Hz, 1H), 3.72 (dd, *J* = 7.8, 2.7 Hz, 1H), 3.85 (dd, *J* = 11.1, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 28.5, 39.7, 46.7, 61.2, 67.4, 72.3, 75.4. Anal. calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; Found: C, 47.70; H, 8.85.

(2*R*,3*R*,3a*R*,7a*R*)-2,3-*O*-Isopropylidene-3a-hydroxy-6-(benzyloxycarbonyl) octahydrofuro[2,3-*c*]pyridine (12). Reductive aminocyclization of **10** (0.10 g, 0.21 mmol), 10% Pd/C (0.05 g), and ammonium formate (0.07 g, 1.09 mmol) in dry methanol (5 mL) as described for **3** afforded crude amine as a thick liquid: R_f 0.30 (chloroform/methanol = 1/1). Selective *N*-Cbz protection of amine as described for **8** and purification by column chromatography (*n*-hexane/ethyl acetate = 9/1) gave **12** (0.065 g, 85% over two steps) as a thick liquid: R_f 0.40 (*n*-hexane/ethyl acetate = 1/1); $[\alpha]_D^{25}$ +1 (*c* 10.0, $CHCl_3$); IR (neat) 3421, 1693 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.40−1.78 (m, 2H), 1.55 (s, 3H), 1.80−2.60 (br s, 1H), 2.83−3.21 (m, 2H), 3.58−3.68 (m, 1H), 3.86−

(12) While our work was in progress, Hanessian et al. have reported the synthesis of 3a-methoxy-*N*-Bus bicyclic oxapiperidine, analogous to compound **12**, using different methodology, see: Loiseleur, O.; Ritson, D.; Nina, M.; Crowley, P.; Wagner, T.; Hanessian, S. *J. Org. Chem.* **2007**, *72*, 6353−6363.

4.20 (br s, 2H), 4.34−4.56 (m, 1H), 5.00−5.23 (m, 2H), 5.72 (br s, 1H), 7.30−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2 (s), 29.8, 38.6, 42.0, 66.8, 73.6, 74.4, 82.3, 103.2, 112.1, 127.2, 127.4 (s), 128.0 (s), 136.2, 155.3. Anal. calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; Found: C, 62.04; H, 6.90.

(3*R*,4*R*)-3,4-Dihydroxy-4-((*S*)-1,2-dihydroxyethyl)-*N*-benzyloxycarbonyl Piperidine (13). A solution of **12** (0.10 g, 0.28 mmol) in TFA−water (2 mL, 3:1) was stirred for 3 h at 0 °C. TFA was coevaporated with toluene to furnish a thick liquid. To an ice-cooled solution of hemiacetal (0.08 g, 0.28 mmol) in THF−water (4 mL, 4:1) was added sodium borohydride (0.01 g, 0.34 mmol) in two portions and stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated aq NH_4Cl solution. THF was evaporated under reduced pressure, extracted with ethyl acetate (10 mL × 3), and concentrated. Purification by column chromatography (*n*-hexane/ethyl acetate = 3/7) gave **13** (0.06 g, 70% over two steps) as a thick liquid: R_f 0.25 (*n*-hexane/ethyl acetate = 0/10); $[\alpha]_D^{25}$ −24 (*c* 0.50, MeOH); IR (neat) 3600−2900 (br), 1691 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 1.82 (br s, 2H), 2.97−3.20 (m, 1H), 3.24−3.42 (m, 1H), 3.60−3.80 (m, 3H), 3.82−4.15 (m, 3H), 5.16 (br s, 2H), 7.45 (br s, 5H); ^{13}C NMR (75 MHz, D_2O) δ 28.5, 39.3, 46.3, 61.3, 67.7, 68.0, 72.6, 75.2, 127.9 (s), 128.5, 128.9 (s), 136.5, 157.4. Anal. calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; Found: C, 58.16; H, 7.04.

(3*R*,4*R*)-3,4-Dihydroxy-4-((*S*)-1,2-dihydroxyethyl)piperidine (ent-3). To a solution of **13** (0.08 g, 0.25 mmol) in dry methanol (5 mL) was added 10% Pd/C (0.04 g), and the solution was hydrogenated at 80 psi for 12 h. The catalyst was filtered, washed with methanol, and the filtrate was concentrated. Purification by column chromatography (methanol) gave **ent-3** (0.03 g, 82%) as a thick liquid: R_f 0.14 (25% aq NH_4OH/MeOH = 1/9); $[\alpha]_D^{25}$ −11 (*c* 0.65, MeOH); IR (Neat) 3600−2900 (br) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 1.58−1.78 (m, 2H), 2.66−2.88 (m, 3H), 2.95 (br d, *J* = 14.1 Hz, 1H), 3.51 (br s, 1H), 3.52 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.59 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.73 (dd, *J* = 10.8, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 28.4, 39.8, 46.7, 61.2, 67.3, 72.3, 75.4. Anal. calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; Found: C, 47.75; H, 8.82.

(3*R*,4*S*)-3,4-Dihydroxy-4-hydroxymethyl-*N*-benzyloxycarbonyl Piperidine (15). Reaction of **14** (0.40 g, 0. 91 mmol) with TFA−water (5 mL, 3:1) as described for **3** gave hemiacetal as a thick oil. Treatment of hemiacetal with sodium metaperiodate as described for **10** afforded an aldehyde as a thick liquid: R_f = 0.35 (*n*-hexane/ethyl acetate = 4/1), which on subsequent sodium borohydride reduction as describe for **13** and purification by column chromatography (*n*-hexane/ethyl acetate = 4/1) gave **15** (0.23 g, 68% over three steps) as a thick liquid: R_f 0.25 (*n*-hexane/ethyl acetate = 1/1); $[\alpha]_D^{25}$ −14 (*c* 2.30, CH_2Cl_2); IR (CH_2Cl_2) 3580−2900 (br), 1691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.51−1.92 (m, 2H), 3.00−4.20 (m, 7H), 4.32−4.55 (m, 2H), 5.18 (br s, 2H), 7.18−7.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$ + D_2O) δ 24.7, 39.2, 62.5, 63.2, 67.1, 71.2, 76.2, 127.0, 127.5 (s), 127.7, 128.2 (s), 136.3, 138.1, 156. Anal. calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; Found: C, 68.10; H, 6.80.

(3*R*,4*S*)-3,4-Dihydroxy-4-hydroxymethyl Piperidine (4). Reaction of **15** (0.10 g, 0.26 mmol) with 10% Pd/C (0.05 g) and ammonium formate (0.05 g, 0.80 mmol) in dry methanol (5 mL) as described for **3** and purification by column chromatography (methanol) gave **4** (0.03 g, 84%) as a thick liquid: R_f 0.20 (25% aq NH_4OH/MeOH = 1/9); $[\alpha]_D^{25}$ −19 (*c* 0.50, MeOH); IR (neat) 3590−2900 (br) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 1.42−1.53 (br d, *J* = 14.4 Hz, 1H), 1.80 (ddd, *J* = 14.4, 9.3, 5.7 Hz, 1H), 2.74−2.90 (m, 3H), 3.07 (dd, *J* = 13.8, 2.1 Hz, 1H), 3.52 (d, *J* = 12.0 Hz, 1H), 3.65(br s, 1H), 3.68 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 28.9, 40.1, 46.9, 65.4, 68.3, 72.0. Anal. calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; Found: C, 49.17; H, 9.11.

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Supporting Information Available: General experimental methods, experimental procedure, spectral and analytical data for compounds **7**, **9**, **10**, **11**, and **14**, and copies of ^{1}H and ^{13}C NMR spectra of compounds **7**, **8**, **9**, **10**, **11**, **3**, **12**, **13**, **ent-3**, **14**, **15**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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