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Intramolecular reductive cyclization strategy to the synthesis of (−)-6-methyl-3-hydroxy-piperidine-2-carboxylic acid, (+)-6-methyl-(2-hydroxymethyl)-piperidine-3-ol and their glycosidase inhibitory activity

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ABSTRACT

The first stereoselective synthesis of (2*S*,3*R*,6*S*)-6-methyl-3-hydroxy-piperidine-2-carboxylic acid (−)-**6** and (2*R*,3*R*,6*S*)-6-methyl-(2-hydroxymethyl)-piperidine-3-ol (+)-**7** was achieved starting from readily available D-glucose in 14 steps with 17% overall yield for both the compounds. The key feature of the present strategy includes the Wittig-olefination for the preparation of required conjugated keto-azide **9** and construction of 2,3,6-trisubstituted piperidine skeleton **11** by applying intramolecular reductive cyclization of conjugated keto-azide intermediate. The glycosidase inhibitory activity of compounds **6** and **7** towards several glycosidases has been evaluated.

1. Introduction

Pipecolic acid **1** (piperidine-2-carboxylic acid)—a conformationally constrained non-proteinogenic amino acid and its alkyl substituted derivatives are naturally occurring and present in a number of biologically active compounds. For example, (2*S*,5*S*,6*S*)-6-methyl-5-hydroxypipecolic acid **2a** (Fig. 1) and (2*S*,5*R*,6*S*)-6-methyl-5-hydroxypipecolic acid **2b** were isolated from the fruits of *Fagus silvatica*.[1] Alkyl pipecolic acid derivatives are known to be thrombin inhibitor,[2] dihydropicolinic acid synthase inhibitors,[3] *N*-methyl-D-aspartic acid receptor agonist,[4] and antagonist.[5] *cis*-6-Alkylpipecolic acids have also attracted the attention of synthetic chemists because of their use as a building block in the synthesis of biologically active molecules.[6] 3-Hydroxy, alkyl substituted pipecolic acid derivatives and their reduced analogs such as prosophylline **3a**, deoxoprosophylline **3b**[7,8] and β-1-*C*-butyl-galactonojirimycin **4**[9] constitute the common structural unit of a wide variety of natural alkaloids and drugs. In fact, **3a**, **3b**, and **4** fall under the category of iminosugars and are known to be potent glycosidase inhibitors,[9] acetylcholinesterase inhibitors,[10a] antibacterial,[10b–e] antimycotic,[10b,d] and DNA binding agents.[10f]

In view of wide-range of biological and synthetic applications of these alkaloids, a number of synthetic methods for alkyl substituted hydroxy piperidines have been developed.[11,12] Recently, Vankar and co-workers[11a] reported the syntheses of deoxoprosophylline (−)-**3b**, (+)-2-epideoxoprosopinine **5**, and (2*R*,3*R*)- and (2*R*,3*S*)-3-hydroxypipecolic acids starting from D-glycal with

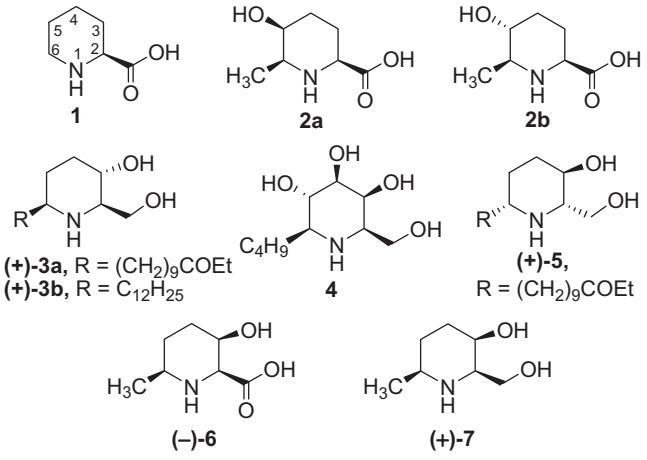

Figure 1. Pipecolic acid and analogs.

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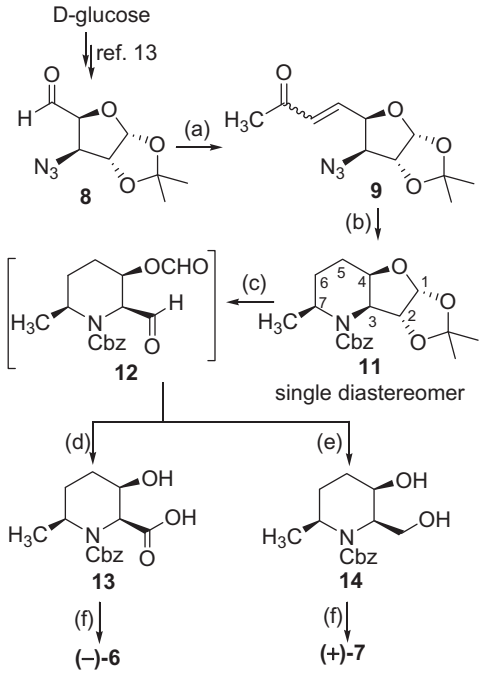
chemoselective saturation of olefins and reductive aminations as key steps. Purkayastha et al.[12e,12f] developed a novel, acid catalyzed cascade of reactions for the synthesis of all-*cis* 6-*tert*-butyl-4-oxo-pipecolic acid derivatives.

Most of the synthetic methods for pipecolic acid derivatives starts from chiral amino acids, carbohydrates and also includes asymmetric syntheses using expensive chiral ligands and transition metals. However, only one group reported the synthesis of methyl substituted hydroxy pipecolic acids from protected threose derivative.[12g] To the best of our knowledge, the syntheses of all-*cis*-6-methyl-3-hydroxy-pipecolic acid **6** and its reduced analog **7** starting from carbohydrate precursor, are not available in the literature. In present work, we utilized D-glucose for the synthesis of all-*cis* configured (2*S*,3*R*,6*S*)-6-methyl-3-hydroxy-piperidine-2-carboxylic acid **6** and (2*R*,3*R*,6*S*)-6-methyl-(2-hydroxymethyl)-piperidine-3-ol **7** using intramolecular reductive aminocyclization of azido-ketone **9** as a key step. The glycosidase inhibitory activity of **6** and **7** was evaluated.

2. Results and discussion

2.1. Synthesis of (−)-6 and (+)-7

As shown in Scheme 1, our synthetic strategy begins with known azido-aldehyde **8** that was easily obtained from D-glucose according to known procedure.[13] Treatment of **8** with the 1-(triphenylphosphoranylidene)-2-propanone[14] in THF at 0 °C afforded α,β-unsaturated methyl ketone **9** as a mixture of *E* and *Z* isomers in the ratio 09:91 as evident from the ^{1}H NMR of crude product.[15] In the next step, hydrogenation of **9** in the presence of 10% Pd/C in MeOH for 12 h at variety of pressure conditions (80, 150, and 200 psi) afforded a complex mixture of products. However, at 260 psi we observed a single product (as evident from the TLC) that on treatment with CbzCl and $NaHCO_3$ gave **11**.



Scheme 1. Reagents and conditions: (a) $CH_3COCH{=}PPh_3$, THF, 0 °C, 2 h, 87%. (b) (i) H_2, Pd/C, MeOH, rt, 12 h, 260 psi, (ii) CbzCl, $NaHCO_3$, MeOH/H_2O (9:1), rt, 6 h, 91%. (c) TFA/H_2O (3:2), 0 °C to rt, 1 h then $NaIO_4$, acetone/water (8:2), 0 °C to rt, 1.5 h. (d) $NaClO_2$, NaH_2PO_4, 30% H_2O_2, aq MeCN, 0 °C to rt, 10 h, 87%. (e) $NaBH_4$, MeOH, 0 °C, 1 h, 89%. (f) H_2, Pd/C, MeOH, rt, 80 psi, 12 h, 97% for (−)-**6**, 93% for (+)-**7**.

The conversion of **9** to piperidine ring skeleton is a one pot four step sequence that probably involves reduction of carbon–carbon double bond and azide functionality to get amine. Subsequently, intramolecular aminocyclization gave cyclic imine **10** which undergoes concomitant imine reduction to give piperidine analog as a single diastereomer (based on the ^{1}H NMR of crude sample) which was isolated as *N*-Cbz protected derivative **11**.

The stereochemical outcome in **11** was unambiguously assigned on the basis of ^{1}H–^{1}H COSY (Supplementary Fig. 5-S7) and 2D-NOESY (Supplementary Fig. 6-S8) correlation studies. The chemical shift assignments and coupling constant values were obtained from decoupling as well as ^{1}H–^{1}H COSY and ^{1}H NMR, respectively, and are given in Table 1.

In the 2D-NOESY spectrum, C-7 methyl showed cross peaks with the H-1, H-2 and each one of the proton from H-5/H-6 indicating their close spatial proximity.

The formation of compound **11** could be explained from the cyclic imine **10** as shown in Figure 2. The attack from the β-face is hindered due to bulky furanose ring, hence hydrogen approaches from less hindered α-face to make C-7 methyl β-orientated with '7*S*' absolute configuration. To achieve the synthesis of target molecules, 1,2-acetonide group in **11** was hydrolyzed with TFA/H_2O (3:2) to afford anomeric mixture of hemiacetals that on oxidative cleavage using $NaIO_4$ afforded α-aminal **12** which was noticed to be unstable and directly used it for further reactions. Thus, compound **12** on treatment with sodium chlorite and hydrogen peroxide gave *N*-Cbz protected pipecolic acid **13**. In the final step, hydrogenolysis in presence of catalytic amount of 10% Pd/C at 80 psi in methanol afforded 6-methyl-3-hydroxy-piperidine-2-carboxylic acid **6**.

Targeting the synthesis of hydroxymethyl derivative **7**, α-aminal **12** was reduced with sodium borohydride in methanol to afford *N*-Cbz protected diol **14** in good yield. Finally hydrogenolysis with 10% Pd/C in MeOH at 80 psi afforded the 6-methyl-(2-hydroxymethyl)-piperidine-3-ol **7** as a white solid. All the compounds were characterized by spectral and analytical techniques, and the data were found to be in good agreement with the assigned structures.

2.2. Glycosidase inhibitory activity

After the successful synthesis of **6** and **7**, the inhibitory activities of these compounds were studied against various glycosidases viz. α-galactosidase, β-galactosidase, β-glucosidase, α-mannosidase, *N*-acetyl-β-D-glucosaminidase (isolated from almond seeds), α-galactosidase (isolated from *Geobacillus toebii* BK 1) and α-glucosidase from Baker's yeast (Sigma Chemical Co.). The results are summarized in Table 2.

Compound **6** exhibited strong competitive inhibition of α-glucosidase from Baker's yeast with K_i = 71 μM and IC_{50} = 1150 μM. On the other hand compound **6** showed non-competitive inhibitory activity against α-Galactosidase (*G. toebii* BK 1) with K_i = 26 μM and IC_{50} = 180 μM. However, compound **6** showed no inhibition against remaining five enzymes and also compound **7** showed no inhibition against any of the glycosidases screened. Substitution of carboxylic acid group by hydroxymethyl group

Table 1
δ and J values from ^{1}H NMR spectrum of **11**

Proton	δ	J (Hz)
H-1	5.89 (d)	3.9 ($J_{1,2}$)
H-2	4.56 (d)	3.9 ($J_{2,1}$)
H-3	4.46 (d)	7.2 ($J_{3,4}$), 0 ($J_{3,2}$)
H-4	4.63–4.68 (m)	—
H-7	4.08–4.12 (m)	—
C-7-methyl	1.16 (d)	6.3 ($J_{vicinal}$)

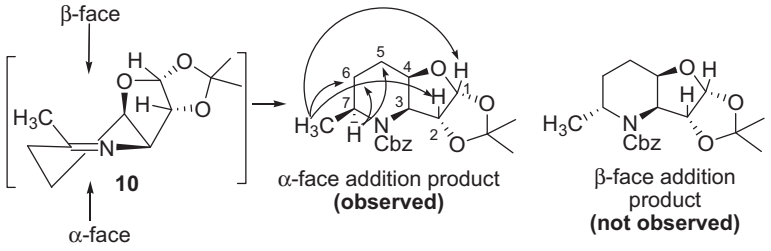


Figure 2. Facial selectivity and observed NOESY of **11**.

Table 2
Inhibitory potencies of piperidines **6** and **7**

Enzyme	**6**		**7**	
	IC_{50}[a] (μM)	K_i[b] (μM)	IC_{50}[a] (μM)	K_i[b] (μM)
α-Galactosidase	NI	NI	NI	NI
β-Galactosidase	NI	NI	NI	NI
β-Glucosidase	NI	NI	NI	NI
α-Manosidase	NI	NI	NI	NI
N-Acetyl-β-D-glucosaminidase	NI	NI	NI	NI
α-Glucosidase (Baker's yeast)	1150	71	NI	NI
α-Galactosidase (*Geobacillus toebii* BK 1)	180	26	NI	NI

NI: no inhibition.
[a] Less than 50% inhibition at 1 mM concentration of inhibitor.
[b] No inhibition at 1 mM concentration of inhibitor. Data is average of three sets of assay performed.

(as in **7**) led to complete loss in inhibitory activity against the given enzymes.

3. Conclusion

In conclusion, starting from readily available D-glucose and following a practical sequence of reactions, efficient synthetic route to enantiopure and new compounds **6** and **7** have been developed. This method is expected to be attractive alternative to the existing methods for the synthesis of the similar piperidine alkaloids (e.g., alkaloids from *Cassia* and *Prosopis* species) having all *syn* configurations by simply changing the Wittig reagent. Our work in this direction is in progress. Among the title compounds, pipecolic acid derivative (−)-**6** showed a significant inhibitory activity against α-glucosidase (Baker's yeast) and α-galactosidase (*G. toebii* BK 1). This finding could be a potential lead to further chemotherapeutic applications.

4. Experimental

4.1. General

Melting points were recorded with Thomas Hoover Capillary melting point apparatus and are uncorrected. IR spectra were recorded with Shimadzu FTIR-8400 as a thin film or using KBr pellets and are expressed in cm^{-1}. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with Varian Mercury instrument using $CDCl_3$ or D_2O as the solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are given in hertz. ^1H–^1H COSY and decoupling experiments confirmed the assignments of the signals wherever required. Elemental analyzes were carried out with Thermo-Electron Corporation CHNS analyzer Flash-EA 1112. Optical rotations were measured using Jasco P1020 polarimeter with sodium light (589.3 nm) at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F254). Visualization was made by absorption of UV light or by thermal development after spraying with 3.5% solution of 2,4-dinitrophenylhydrazine in ethanol/H_2SO_4 or with basic aqueous potassium permanganate solution.

4.1.1. 3-Azido-1,2-*O*-isopropylidene-3,5,6,8-tetradeoxy-α-D-xylo-oct-5-(*E*:*Z*)-ene-furanos-7-ulose (9)

To a stirred solution of azido aldehyde **8** (3.2 g, 15 mmol) in dry THF (40 mL) was added the Wittig reagent (5.26 g, 16 mmol) at 0 °C. The reaction mixture was stirred for 2 h at the same temperature. After completion of reaction (monitored by TLC), THF was vacuum evaporated. ^1H NMR of crude product showed *Z* as a major isomer in 91:09 ratio. Column purification afforded mixture **9** (3.24 g, 85%) from which we have isolated the pure *Z*-isomer as thick liquid and used for characterization. Data of the *Z*-isomer is given below: R_f = 0.48 (ethyl acetate/hexane, 1.5:8.5); IR (thin film) 2109, 1693, 1622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.53 (s, 3H), 2.28 (s, 3H), 4.46 (d, *J* = 3.3 Hz, 1H), 4.64 (d, *J* = 3.6 Hz, 1H), 5.48–5.51 (m, 1H), 5.94 (d, *J* = 3.9 Hz, 1H), 6.17 (dd, *J* = 6.0, 11.7 Hz, 1H), 6.40 (dd, *J* = 1.8, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.7, 31.1, 68.1, 78.4, 84.0, 104.7, 112.2, 128.3, 142.2, 198.4; Elem. Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 53.52; H, 7.11; N, 16.59. Found: C, 53.61; H, 7.19; N, 16.73.

4.1.2. 2,2-Dimethylperhydro[1,3]dioxolo-*N*-benzyloxycarbonyl-[4′,5′:4,5]furo[3,2-*b*]-7-methyl-pyridine (11)

A solution of **9** (1.6 g, 6.3 mmol) in dry MeOH (20 mL) and 10% Pd/C (0.05 g) was hydrogenated at 260 psi for 12 h at 25 °C. After completion of the reaction, it was filtered through a Celite pad, washed with MeOH, and concentrated on a rotavapor to give amine as a single diastereomer (determined by ^1H NMR of crude sample), (crude wt 1.5 g). This crude amine was dissolved in MeOH/H_2O (41 mL; 9:1) and cooled to 0 °C. To this $NaHCO_3$ (1.1 g, 12.7 mmol) was added followed by dropwise addition of CbzCl (50% solution in toluene; 2.7 mL, 9.5 mmol). Reaction mixture was stirred for 6 h at rt. Solvent was evaporated under reduced pressure and thick residue thus obtained was extracted in ethyl acetate. Evaporation of solvent and column purification (ethyl acetate/hexane, 1:9) afforded Cbz protected piperidine **11**

as a thick liquid (1.99 g, yield 91%): R_f = 0.38 (ethyl acetate/hexane, 2:8); $[\alpha]_D^{25}$ +9 (*c* 1.23, $CHCl_3$); IR (thin film) 1704, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.3 Hz, 3H), 1.32 (s, 3H), 1.52–1.58 (m, 5H), 1.82–1.90 (m, 2H), 4.08–4.12 (m, 1H), 4.46 (d, *J* = 7.2 Hz, 1H), 4.56 (d, *J* = 3.9 Hz, 1H), 4.63–4.68 (m, 1H), 5.19 (s, 2H), 5.89 (d, *J* = 3.9 Hz, 1H), 7.28–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 22.9, 23.5, 26.5, 27.1, 46.4, 60.5, 67.1, 73.5, 87.7, 104.8, 111.7, 126.8, 127.7, 127.8, 128.3, 136.5, 141.1, 156.1; Elem. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.89; H, 7.31; N, 4.16.

4.1.3. (2*S*,3*R*,6*S*)-*N*-Benzyloxycarbonyl-6-methyl-3-hydroxypiperidine-2-carboxylic acid (13)

An ice-cold solution of **11** (0.53 g, 1.5 mmol) in TFA-H_2O (5.0 mL, 3:2) was stirred for 1 h. Trifluoroacetic acid was co-evaporated with toluene using high vacuum to afford hemiacetal as a thick liquid (crude wt 0.46 g) that was dissolved in acetone/water (10 mL, 9:1), cooled to 0 °C. Sodium metaperiodate (0.48 g, 2.2 mmol) was added and reaction mixture was stirred for 1.5 h at 25 °C. After completion of reaction, ethylene glycol (0.2 mL) was added and solvent was evaporated. The residue thus obtained was extracted with chloroform (3 × 10 mL) to get α-aminal **12** as a thick liquid (crude wt 0.415 g). To a stirred solution of **12** (0.24 g, 0.87 mmol) in acetonitrile (6 mL) was added the solution of sodium dihydrogen phosphate (0.03 g, 0.17 mmol) in water (2 mL) and 30% H_2O_2 (0.13 mL, 0.95 mmol). The mixture was cooled to 0 °C, and $NaClO_2$ (0.12 g, 1.4 mmol) in water (3.5 mL) was added dropwise over 30 min. The reaction mixture was stirred at 15 °C and 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_4 (0.10 g) and extracted with ethyl acetate (3 × 10 mL). Evaporation of solvent and column purification with methanol/chloroform (0.5:9.5) gave **13** as a sticky gum (0.23 g, 67% from **11**): R_f = 0.41 (methanol/chloroform, 2:8); $[\alpha]_D^{25}$ −36 (*c* 3.2, $CHCl_3$); IR (thin film) 1708, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J* = 7.2 Hz, 3H), 1.58–1.63 (m, 1H), 1.69–1.90 (m, 3H), 3.77–3.84 (m, 1H), 4.38 (m, 1H), 5.00 (d, *J* = 5.9 Hz, 1H), 5.18 (s, 2H), 5.82–6.23 (br s, 2H, D_2O Ex.), 7.31–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 24.9, 28.8, 46.5, 54.8, 68.1, 68.5, 127.83–136.01, 156.7, 174.2; Elem. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.53; H, 6.65; N, 4.86.

4.1.4. (2*S*,3*R*,6*S*)-3-Hydroxy-6-methylpiperidine-2-carboxylic acid (−)-6

A solution of **13** (0.20 g, 0.68 mmol) and 10% Pd/C (0.025 g) in methanol (8 mL) was stirred under H_2 atmosphere at 80 psi for 12 h at 25 °C. The catalyst was filtered through pad of Celite. Solvent evaporation afforded (−)-**6** as a thick liquid (0.10 g, 97%): R_f = 0.51 (methanol); $[\alpha]_D^{25}$ −36 (*c* 2, H_2O); IR (thin film); br 3352, 1702 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.39 (d, *J* = 6.4 Hz, 3H), 1.77–1.86 (m, 3H), 2.00–2.05 (m, 1H), 3.27–3.33 (m, 1H), 3.73 (br s, 1H), 4.51 (br s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 18.1, 24.0, 29.1, 52.7, 62.9, 63.5, 172.0; Elem. Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.71; H, 8.33; N, 8.96.

4.1.5. (2*R*,3*R*,6*S*)-*N*-Benzyloxycarbonyl-6-methyl-2-hydroxymethylpiperidine-3-ol (14)

To a stirred solution of aminal **12** (obtained as in the above experiment) (0.41 g, 1.5 mmol) in methanol (8 mL), maintained at 0 °C, sodium borohydride (0.11 g, 2.9 mmol) was added in portions during 20 min. The resulting solution was stirred for 30 min and allowed to attain room temperature (25 °C). Excess of hydride was quenched with satd NH_4Cl, solvent was evaporated and the residue was extracted with chloroform (3 × 10 mL). Evaporation of solvent and column purification using *n*-hexane/ethyl acetate = 6.5/3.5 gave **14** as a thick liquid (0.32 g, 74% from **11**): R_f = 0.49 (ethyl acetate/hexane, 3:7); $[\alpha]_D^{25}$ +16 (*c* 4.8, $CHCl_3$); IR (thin film) br 3352, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3H),[16] 1.54–1.84 (m, 4H), 3.52–3.64 (m, 1H), 3.71–3.81 (br s, 2H, D_2O Ex.), 3.89–4.21 (m, 2H), 4.27–4.31 (m, 1H), 4.53–4.58 (m, 1H), 5.19 (s, 2H), 7.29–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 20.2, 23.2, 28.1, 45.1, 55.4, 62.6, 67.4, 69.7, 127.72–136.44, 156.1; Elem. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.52; H, 7.48; N, 5.13.

4.1.6. (2*R*,3*R*,6*S*)-6-Methyl-2-hydroxymethylpiperidin-3-ol (7)

The same procedure was adopted for the synthesis of **7** as used to obtain **6**. Column purification with methanol/chloroform (1:9) afforded (+)-**7** as a white solid. (0.072 g, 93%): mp 164–166 °C; R_f = 0.46 (methanol/chloroform, 3:7); $[\alpha]_D^{25}$ +3 (*c* 2.1, MeOH); IR (KBr, disk): 3374, 2934, 1048 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.36 (d, *J* = 6.3 Hz, 3H), 1.80 (m, 3H), 1.98 (m, 1H), 3.31 (m, 2H), 3.77 (dd, *J* = 8.7, 12.3 Hz, 1H), 3.86 (dd, *J* = 4.8, 11.8 Hz, 1H), 4.17 (br s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 18.2, 24.5, 28.7, 53.3, 59.8, 60.8, 61.9; Elem. Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.81; H, 10.32; N, 9.77.

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Supplementary data

This material can be found in the online version. Contained in this are general experimental and inhibition assay methods, experimental details for **9** and ^1H and ^{13}C NMR spectra of compounds **9**, **11**, **13**, **14**, (−)-**6**, and (+)-**7**, ^1H–^1H COSY and 2D-NOESY spectrum of compounds **11**, Lineweaver–Burk plot of **6** with α-glucosidase and α-galactosidase. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.09.055.

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16. ^{1}H and ^{13}C NMR of the compound **14** showed a doubling of signals due to restricted rotation around the C–N bond of *N*-Cbz functionality.