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Diversity-Oriented Synthesis of *cis*-3,4-Dihydroxylated Piperidine and Its Higher Saturated and Unsaturated Homologues from D-Ribose and Their Glycosidase-Inhibition Study[1]

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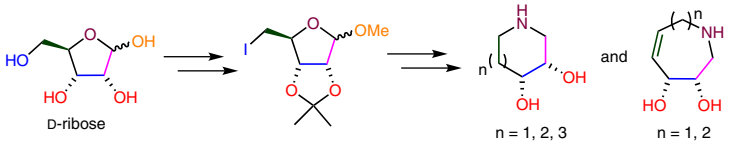

synthesis of six-, seven- and eight-membered saturated and unsaturated dihydroxylated piperidine homologues

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Abstract The synthesis of six-, seven-, and eight-membered *cis*-dihydroxy azacycles has been accomplished from D-ribose using Vasella reductive amination as a key step and utilization of hydroboration–oxidation, Mitsunobu reaction, and ring-closing metathesis (RCM) reactions in a facile manner. These homologous dihydroxylated heterocyclic scaffolds were subjected to the glycosidase inhibition assays. However, only a moderate inhibitory activity for three out of five compounds was observed against α-glucosidases with a high degree of selectivity.

Key words *cis*-dihydroxy azacycles, Vasella reductive amination, hydroboration–oxidation, Mitsunobu reaction, ring-closing metathesis, glycosidase inhibition.

Diversity-oriented synthesis (DOS) is a strategy for quick access to molecule libraries. The concept of DOS was introduced by Stuart Schreiber in the beginning of this millennium and has gained much success.[2] DOS aims to produce chemical libraries that are representative of a large portion of chemical space by applying a variety of reaction conditions to starting materials with multiple functional groups. DOS approaches have widely been used in drug discovery and chemical biology to develop a library of molecules. Due to their stereochemical variation and multiple polar functionalities, carbohydrates are attractive building blocks and possess a great potential for the synthesis of structurally diverse molecules. DOS can be used to bring about variation in appending functionalities, stereochemistry, or skeletal frameworks.[3] In this context, the skeletal diversity can be achieved either by a reagent-based approach (using different reagents on the same substrate) or a substrate-based approach (subjecting different starting materials to similar reaction conditions). This report describes a carbohydrate-based DOS strategy employing a reagent-based approach to obtain skeletal diversity in azacycles by reactions involving anomeric carbon atom of D-ribose.

Iminosugars can be considered as analogues of pyranoses/furanoses in which the ring oxygen is replaced by nitrogen.[4] Being one of the most important class of glycosidase inhibitors[5] their medicinal significance is because of their ability to act as transition-state analogues of carbohydrate-processing enzymes.[6] Iminosugars have many favourable qualities to act as drug molecules. These include water solubility, absorption, blood–brain barrier penetration, chemical and biological stability, and oral bioavailability. Iminosugar therapeutics have attracted interest as anticancer,[7a] antidiabetic,[7b] and antiviral agents.[7c,d] They are also active against tuberculosis,[7e] lysosomal storage disorder,[7f–i] and cystic fibriosis.[7j] Two of the iminosugar-derived drugs Glyset (**1**) and Zavesca (**2**, Figure 1) are being marketed for type II diabetes and Gaucher's disease, respectively, many other iminosugar-based drugs are presently under clinical trials.[8]

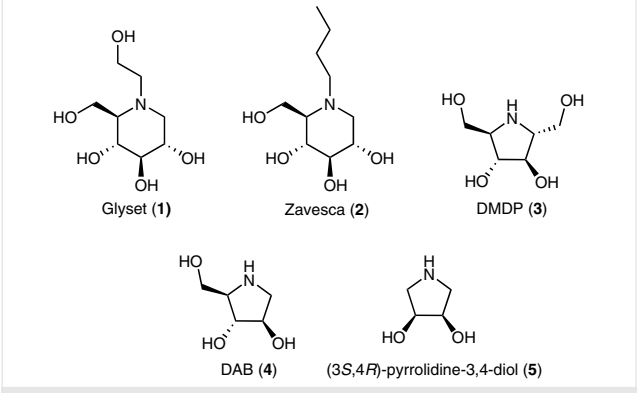
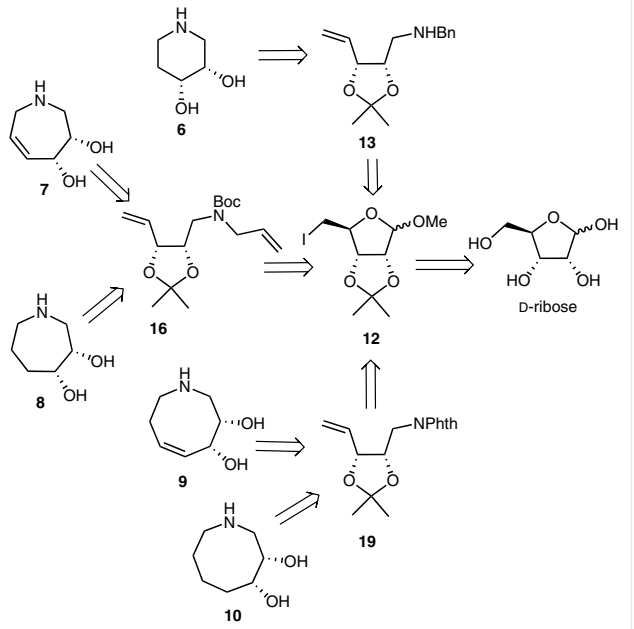


Figure 1 Examples of some biologically active iminosugars

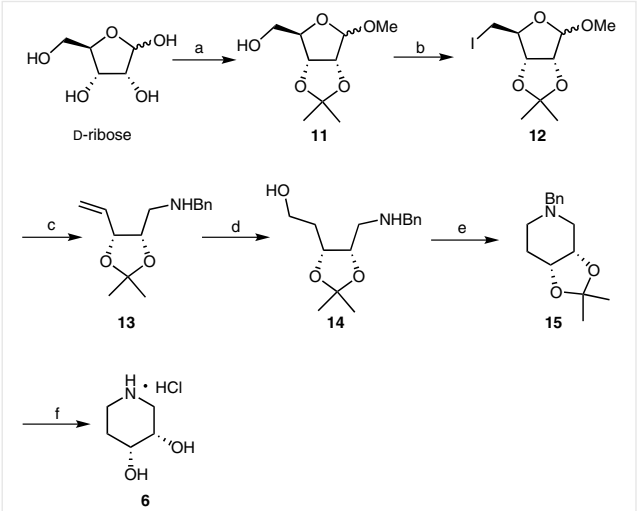
(2*R*,3*R*,4*R*,5*R*)-2,5-Dihydroxy methyl-3,4-dihydroxy pyrrolidine (DMDP, **3**) and 1,4-dideoxy-1,4-imino-D-arabinitol (DAB, **4**) represent pyrrolidine iminosugars exhibiting β- and α-glucosidase inhibition, respectively.[9] Amongst various monocyclic iminosugar scaffolds, dihydroxylated azacycles without any hydroxymethyl substituent have scarcely been explored for their glycosidase inhibition properties. *cis*-3,4-Dihydroxylated pyrrolidine **5** shows 70% inhibition of jack bean α-mannosidase with IC_{50} = 400 μM and is supposed to be a potent anticancer agent[5a] but is a nonselective inhibitor.[10] Glycosidase inhibition studies of its other ring analogues, that is, six-, seven-, or eight-membered dihydroxylated azacycles have not yet been explored although various synthetic routes to *trans*- and *cis*-dihydroxylated piperidines have been reported.[11] In continuation of our search for selective glycosidase inhibitors, earlier we have explored the activity of conformationally restricted[12a,b] and C-alkylated[12c] iminosugars as glycosidase inhibitors. Herein we describe the synthesis of various *cis*-3,4-dihydroxylated piperidine homologues **6**–**10** (Scheme 1) all of which are easily accessible from a single D-ribose-derived template, and these sugar analogues have further been explored to study their effect on inhibition of carbohydrate-processing enzymes. A divergent approach to the synthesis of various polyhydroxylated iminocyclitols starting from D-ribose using asymmetric catalysis has been recently described.[13]



Scheme 1 Retrosynthetic analysis

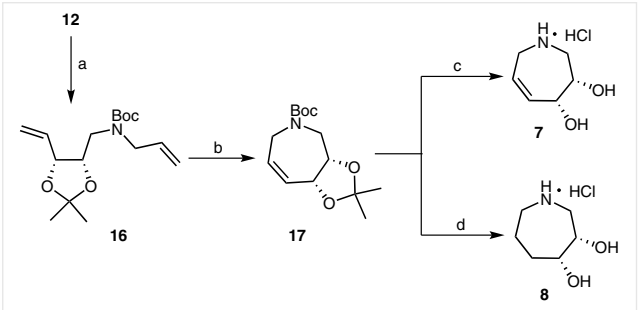
The retrosynthetic strategy for the divergent synthesis of six-, seven-, and eight-,membered dihydroxylated azacycles is depicted in Scheme 1. We envisaged that *cis*-3,4-dihydroxypiperidine (**6**) could be synthesized by hydroboration–oxidation of protected amino-alkene **13** followed by cyclization of the resulting amino alcohol and subsequent global deprotection. This amino-alkene **13** would arise from iodide **12**, which in turn could easily be prepared from D-ribose. Dihydroxy azepine (**7**) and its corresponding azepane **8** can be synthesized from diene **16** by ring-closing metathesis (RCM) followed by its selective deprotection (for **7**) or global deprotection (for **8**). The synthesis of diene **16** in turn is conceivable from Vasella reductive amination of common intermediate **12** obtainable from D-ribose. Azocine/Azaoctene **9** and its corresponding saturated analogue **10** could be obtained from phthalyl-protected amino-alkene **19** by its consecutive homoallylation and RCM followed by subsequent deprotection. Terminal alkene **19** could in turn be obtained by Vasella reduction of iodide **12** followed by Mitsunobu amination of the resulting alcohol.

As per above discussions, we started our synthesis from acetonide-protected iodinated methyl furanoside **12** which was obtained from D-ribose in two steps following the literature precedence[14] (Scheme 2). The Vasella reductive amination of iodide **12** with zinc, benzyl amine, and $NaCNBH_4$ at 110 °C for three hours yielded secondary amine **13** with 79% yield.[15] The amine upon hydroboration–oxidation reaction sequence provided primary alcohol **14** with good yield (up to 82% yield).[16] It was esterified with MsCl/Et_3N, and the resulting mesylate was immediately treated with K_2CO_3 to furnish the fully protected piperidine **15** (75% yield for two steps).[17] Its hydrogenation with H_2, Pd/C in 6 N methanolic HCl[18] at room temperature for three hours afforded *cis*-3,4-dihydroxypiperidine hydrochloride salt (**6**) with 91% yield.[19]



Scheme 2 Synthesis of *cis*-3,4-dihydroxypiperidine **6**. *Reagents and conditions*: (a) HCl, MeOH–acetone, r.t., 8 h, 85%; (b) I_2, Ph_3P, imidazole, toluene, 70 °C, 2 h, 92%; (c) Zn, $BnNH_2$, $NaCNBH_4$, 1-PrOH–H_2O (9:1), 110 °C, 3 h, 79%; (d) BH_3·SMe_2, dry THF, 0 °C to r.t., 1.5 h; then H_2O_2, 3 N NaOH, 0 °C to r.t., 2 h, 82%; (e) i. MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 30 min.; ii. K_2CO_3, DMF, r.t., 6 h, 75% for 2 steps; (f) H_2, Pd/C, 6 N methanolic HCl, r.t., 3 h, 91%.

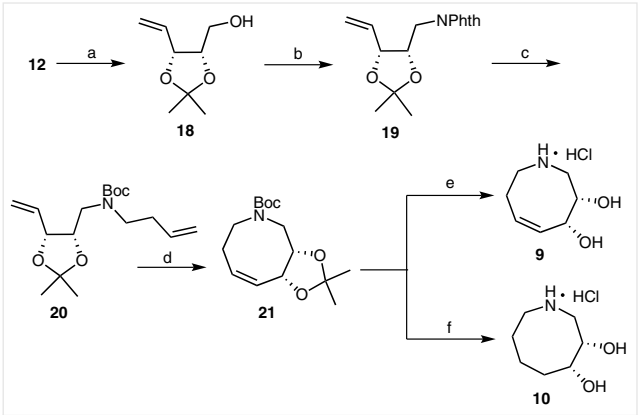
The synthesis of seven-membered azacycles **7** and **8** (Scheme 3) was initiated with the iodide **12** which upon Vasella reductive amination with allylamine at 110 °C for four hours produced an amino-diene intermediate whose free nitrogen was protected with $(Boc)_2O$/dioxane at room temperature to give N-protected diene **16** with 81% yield over two steps.[15] Its RCM with Grubbs first-generation catalyst (10 mol%) in dry CH_2Cl_2 at 50 °C for six hours furnished azepine **17** with 93% yield.[20]



Scheme 3 Synthesis of *cis*-dihydroxy azepine **7** and azepane **8**. *Reagents and conditions*: (a) i. Zn, allylamine, $NaCNBH_4$, 1-PrOH–H_2O (9:1), 110 °C, 4 h; ii. $(Boc)_2O$, 1,4-dioxane, r.t., 3 h, 81% for two steps; (b) Grubbs I catalyst (10 mol%), dry CH_2Cl_2 (0.1 M), reflux, 6 h, 93%; (c) 6 N methanolic HCl, r.t., 2 h, 96%; (d) H_2, Pd/C, 6 N methanolic HCl, r.t., 3 h, 92%.

The unsaturated azacycle, dihydroxy azepine (**7**) was prepared by selectively removing acetonide and Boc functionalities of azepine **17** by treating it with 6 N methanolic HCl[21] at room temperature for two hours to deliver the desired sugar **7** (96% yield).[22] Hydrogenation of azepine **17** with H_2, Pd/C in methanolic HCl (6 N)[18] at room temperature for three hours led to global deprotection to yield the azepane **8** with 92% yield.[23]

Synthesis of eight-membered azacycles **9** and **10**, which has so far not been reported, was accomplished as follows (Scheme 4). Zinc dust mediated ring opening of iodide **12** using Zn/AcOH afforded an intermediate aldehyde, which was further reduced with $NaBH_4$ to give alcohol **18** with 89% yield.[24] Its Mitsunobu reaction with phthalimide, Ph_3P, and DIAD at –20 °C and stirring at room temperature for three hours led to the formation of desired phthalimido compound **19** in 79% yield.[25] The phthalimido functionality in **19** was then hydrolyzed with aqueous $MeNH_2$ to afford a primary amine,[26] which was used for the next step without further purification. Thus the amine was alkylated using 1-butenyl bromide/K_2CO_3 in DMF at 0 °C to room temperature for 12 hours to afford a free secondary amine which was protected with $(Boc)_2O$/dioxane under previously stated conditions at room temperature for three hours to afford diene **20** with an overall yield of 69% for three steps. It was then cyclized to azocine **21** by using Grubbs first-generation catalyst (10 mol%) in refluxing CH_2Cl_2 (90% yield) for six hours. In order to prepare dihydroxy azocine **5**, the protecting groups were removed by treating the azocine **21** with 6 N methanolic HCl to form the desired unsaturated sugar **9** in 95% yield.[27] The azocine **21** under hydrogenation conditions (H_2, Pd/C in 6 N methanolic HCl) at room temperature for three hours yielded the dihydroxy azocane **10** with 90% yield.[28]



Scheme 4 Synthesis of *cis*-dihydroxy azocine **9** and azocane **10**. *Reagents and conditions*: (a) i. Zn, AcOH, MeOH, 65 °C; ii. $NaBH_4$, EtOH, 0 °C, 89% for two steps; (b) Ph_3P, DIAD, phthalimide, dry THF, –20 °C to r.t., 3 h, 79%; (c) i. $MeNH_2$, 50 °C, 1.5 h; ii. K_2CO_3, 4-bromo-1-butene, DMF, 0 °C to r.t., 12 h; iii. $(Boc)_2O$, 1,4-dioxane, r.t., 3 h, 69% for three steps; (d) Grubbs I catalyst (10 mol%), dry CH_2Cl_2 (0.1 M), reflux, 6 h, 90%; (e) 6 N methanolic HCl, r.t., 2 h, 95%; (f) H_2, Pd/C, 6 N methanolic HCl, r.t., 3 h, 90%.

The synthesized dihydroxylated compounds were screened against carbohydrate processing enzymes, and their inhibition results are summarized in Table 1. *cis*-3,4-Dihydroxylated pyrrolidine **5** (Figure 1) is reported to be a jack bean α-mannosidase inhibitor. On the contrary, its higher analogues did not show any inhibition against jack bean α-mannosidase or any of the glycosidases tested at 1000 μM inhibitor concentration. However, at inhibitor concentrations as high as 3000 μM the *cis*-3,4-dihydroxylated piperidine exhibited a moderate but selective α-glucosidase inhibition. An interesting inhibition pattern was observed in case of seven-membered azacycles **7** and **8**, both of which showed selective α-glucosidase inhibition with a switching of inhibition due to the presence or absence of double bond. Also in contrast to *cis*-3,4-dihydroxylated pyrrolidine **5**, the higher analogues are though moderately active but are selective for a particular glycosidase. This moderate or poor activity could be attributed to the higher conformational flexibility due to absence of substituents thus indicating that the presence of hydroxymethyl substituent/polyhydroxylated scaffolds are the features better suited for glycosidase inhibition.

Table 1 Concentration of Dihydroxylated Piperidine and Its Higher Homologues Giving 50% Inhibition[a] (IC_{50}) of Various Glycosidases (IC_{50} in μM)

Enzyme	6	7	8	9	10
α-glucosidase					
yeast	NI[b]	NI	NI	NI	NI
rice	NI	NI	2208	NI	NI
Aspergillus niger	2108	2275	NI	NI	NI
β-glucosidase					
almond	NI	NI	NI	NI	NI
α-galactosidase					
green coffee beans	NI	NI	NI	NI	NI
β-galactosidase					
bovine liver	NI	NI	NI	NI	NI
α-mannosidase					
jack bean	NI	NI	NI	NI	NI
α-L-fucosidase					
bovine kidney	NI	NI	NI	NI	NI

[a] Inhibition was competitive in all cases.
[b] NI: no inhibition (less than 50% inhibition) at 3000 μM.

A diversity-oriented short and efficient synthesis of six-, seven-, and eight-membered dihydroxylated heterocyclic scaffolds/azacycles starting from iodinated D-ribose as a common intermediate has been accomplished. Vasella reductive amination, hydroboration–oxidation, Mitsunobu amination, and ring-closing metathesis reactions were employed in a simplified way to generate different ring sizes. These homologous dihydroxylated azacycles were subjected to the glycosidase inhibition assays. However, only a moderate inhibitory activity for three out of five compounds was observed against α-glucosidases. Weak enzyme inhibition due to high flexibility and the absence of hydroxymethyl group adjacent to nitrogen atom in the ring suggest important role of these structural features in glycosidase inhibition. Synthesis of more diverse iminosugar scaffolds exploiting different synthetic strategies is currently under way.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588310.

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(19) **Synthesis of (3*S*,4*R*)-Piperidine-3,4-diol (6)**
To a solution of compound **15** (112 mg, 0.45 mmol) in 6 N methanolic HCl (3 mL) was added a catalytic amount of 10% Pd/C (10 mg). The reaction mixture was stirred under the H_2 (balloon) atmosphere at room temperature for 6 h. After completion of the reaction, Pd/C was removed by filtering through a short pad of Celite, and the filtrate was evaporated under vacuum to give a residue. It was washed again with Et_2O to get the pure compound **6** (48 mg, 91 %) as a white solid. R_f = 0.61 (MeOH–CH_2Cl_2, 1:9); mp 129–131 °C; $[\alpha]_D^{27}$ +10.0 (*c* 0.11, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.13 (brm, 1 H), 4.00–4.02 (m, 1 H), 3.34–3.39 (m, 2 H), 3.21–3.24 (m, 1 H), 3.10–3.16 (m, 1 H), 1.94–2.12 (m, 2 H). ^{13}C NMR (100 MHz, D_2O): δ = 66.3, 65.2, 46.5, 41.4, 25.1. IR (KBr): 3400, 3020, 2926, 1403, 1216 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_5H_{12}NO_2^+$: 118.0863; found: 118.0875.
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(22) **Synthesis of (3*S*,4*R*)-2,3,4,7-Tetrahydro-1*H*-azepine-3,4-diol (7)**
Compound **17** (89 mg, 0.33 mmol) was dissolved in 6 N methanolic HCl (3 mL) and stirred at room temperature for 2 h. After completion of the reaction, the solvent was removed under reduced pressure to obtain a solid residue, which was washed with Et_2O to get the pure compound **7** (43 mg, 96%) as a white solid. R_f = 0.59 (MeOH–CH_2Cl_2, 1:9); mp 135–139 °C; $[\alpha]_D^{25}$ –37.0 (*c* 0.21, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 5.98–6.01 (m, 1 H), 5.77–5.84 (m, 1 H), 4.58–4.59 (m, 1 H), 4.10–4.12 (m, 1 H), 3.71–3.84 (m, 2 H), 3.50–3.55 (m, 1 H), 3.41–3.44 (m, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 140.2, 121.7, 73.2, 69.1, 51.7, 46.1. IR (KBr): 3683, 3399, 2927, 1476, 1216 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_6H_{12}NO_2^+$: 130.0863; found: 130.0861.
(23) **Synthesis of (3*S*,4*R*)-Azepane-3,4-diol (8)**
Catalytic amount of Pd (10% on carbon, 15 mg) was added to a solution of **17** (121 mg, 0.45 mmol) in 6 N methanolic HCl (4 mL). The reaction mixture was degassed and left for stirring under a positive pressure of H_2 (balloon) for 3 h at room temperature. After completion of the reaction (TLC control), the reaction mixture was filtered and washed with MeOH. The filtrate was evaporated to dryness to give a solid compound which was washed with Et_2O to provide compound **8** as a white solid (54 mg, 92%). R_f = 0.62 (MeOH–CH_2Cl_2, 1:9); mp 142–144 °C; $[\alpha]_D^{25}$ +1.4 (*c* 0.21, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.11–4.12 (m, 1 H), 3.80–3.84 (m, 1 H), 3.18–3.36 (m, 4 H), 1.98–2.02 (m, 1 H), 1.78–1.94 (m, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 74.3, 69.7, 46.9, 46.0, 30.0, 20.5. IR (KBr): 3393, 1386, 1219, 1061, 771 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_6H_{14}NO_2^+$: 132.1019; found: 132.1014.
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(27) **Synthesis of (3*S*,4*R*,*Z*)-1,2,3,4,7,8-Hexahydroazocine-3,4-diol (9)**
Compound **21** (105 mg, 0.37 mmol) was dissolved in 6 N methanolic HCl (3 mL), and the reaction mixture was allowed to stir at room temperature for 2 h. After completion of the reaction, the organic solvent was evaporated under reduced pressure, and the resulting residue was washed with Et_2O to afford the azocine **9** (48 mg, 95%) as a white solid. R_f = 0.61 (MeOH–CH_2Cl_2, 1:9); mp 143–145 °C; $[\alpha]_D^{26}$ –8.6 (*c* 0.32, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 5.84–5.88 (m, 1 H), 5.66–5.72 (m, 1 H), 4.57 (d, 1 H, *J* = 4.09 Hz), 4.16 (d, 1 H, *J* = 4.33 Hz), 3.27–3.41 (m, 3 H), 3.16 (td, 1 H, J_1 = 13.16 Hz, J_2 = 2.75 Hz), 2.59–2.70 (m, 1 H), 2.37–2.40 (m, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 138.4, 124.8, 71.9, 71.8, 48.2, 47.9, 23.6. IR (KBr): 3392, 3020, 1650, 1385, 1216, 1068, 771 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_7H_{14}NO_2^+$: 144.1019; found: 144.1018.
(28) **Synthesis of (3*S*,4*R*)-Azocane-3,4-diol (10)**
To a solution of compound **21** (130 mg, 0.46 mmol) in 6 N methanolic HCl was added a catalytic amount of 10% Pd/C (20 mg), and the resulting reaction mixture was stirred under hydrogen atmosphere at room temperature for 3 h. After completion of the reaction, the catalyst was filtered, and the filtrate was concentrated under vacuum to obtain a residue, which was washed with Et_2O to attain pure azocane **10** (60 mg, 90%) as a white solid. R_f = 0.64 (MeOH–CH_2Cl_2, 1:9); mp 160–163 °C; $[\alpha]_D^{26}$ +5.4 (*c* 0.81, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.09–4.11 (m, 1 H), 3.91–3.94 (m, 1 H), 3.38–3.48 (m, 1 H), 3.22–3.30 (m, 2 H), 3.09–3.13 (m, 1 H), 2.00–2.08 (m, 1 H), 1.80–1.90 (m, 3 H), 1.69–1.72 (m, 2 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 74.2, 69.2, 48.2, 47.7, 31.0, 24.5, 21.8. IR (KBr): 3392, 2924, 1650, 1385, 1216, 1068, 770 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_7H_{16}NO_2^+$: 146.1176, found: 146.1175.