Seven-membered ring azasugars as glycosidase inhibitors and anticancer agents†

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Synthesis of various C2 symmetrical tetrahydroxyazepanes has been reported by the reaction of bisepoxides with various primary amines. The tetrahydroxyazepanes inhibit β-glucosidases in micromolar range and also exhibit anticancer activity in various cancer cell lines with GI50 values in the range of 2 to 9×10⁻² M. The azepanes are poor inhibitors of HIV protease and their IC₅₀ values are in the range 2×10⁻⁴ M.

Glycosidases and glycosyltransferases are the important class of enzymes which play critical role in several vital processes. The seminal involvement of these enzymes on the life processes have made them desirable targets for inhibition. Inhibition of some of these enzymes has been implicated in the treatment of diabetes and other metabolic disorders and stopping microbial infections and metastasis. The active interest in the development of glycosidase inhibitors was stimulated by the isolation and identification of several naturally occurring azasugars which have been found to be very potent inhibitors. During the past decade azasugars have attracted attention of several organic and medicinal chemists because of their potential values as therapeutic agents for the treatment of cancer, diabetes and AIDS.

A number of stereoisomers of five- and six-membered ring azasugars have been synthesized and evaluated for their biological activities. Most of these azasugars are believed to inhibit glycosidase enzymes by binding to the active site of the enzyme. We assumed that seven-membered ring azasugars which are conformationally more flexible than their five- and six-membered counterparts, may have better fit in the active site of the enzyme and thereby mimic the transition state geometry of the glycosidic bond cleavage transition state more closely. With this view, we have synthesized several polyhydroxyazepanes a few years ago. We believe that the presence of acetone group at 4,5-positions of azepane may hold the ring in chair-form in order to mimic the structural cleft of deoxynojirimycin or other glycosidase inhibitors. Since, several glycosidase inhibitors are substituted at ring nitrogen position (eg. Miglitol), we also synthesized several substituted azepanes to evaluate their biological activities. While we were studying the effect of several of these azasugars on various glycosidases, Wong et al. reported similar studies on some of these polyhydroxyazepanes.

In the present article, we wish to report a general synthetic approach to a number of polyhydroxyazepanes, which is still the most chemoselective synthesis of azepanes, and the biological activities of these polyhydroxyazepanes against various glycosidase enzymes. We have also examined these azasugars for their activities against various cancer cell lines and their potential to inhibit HIV-proteases.

Chemistry

Several substituted polyhydroxyazepanes were synthesized as shown in Scheme I. Various bisepoxides were prepared by our own one-pot procedure from different hexoses in high chemical and stereocchemical purity. The bisepoxides 1 and 2 were reacted with different amines to give substituted azepanes 3 and 4 only in high yields and no other products were detected. Apart from our synthetic process no other process gave exclusively the azepanes. The reaction of various amines with epoxides always gave a mixture of polyhydroxylated piperidines and azepanes in different ratios. Various azepanes prepared by our method are given in Table I. The bisepoxide 1,2:5,6-dianhydro-3,4-
Scheme 1 — Reagents: (i) primary amine, dioxane, 100°C, 10-36 hr; (ii) 80% CF$_2$CO$_2$H. 0-30°C, 2-6 hr.

Table I — Glycosidase activities of substituted polyhydroxy azepanes

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<tr>
<th>Azepane</th>
<th>R</th>
<th>β-Glucosidase (Almonds)$^a$</th>
<th>α-Galactosidase (coffee beans)$^b$</th>
<th>α-Mannosidase (Jack beans)$^c$</th>
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<td>H</td>
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<tr>
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<td>5</td>
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</table>

$^a$% inhibition at 100 μM concentration of inhibitor.
$^b$β-Glucosidase isolated from almonds.
$^c$α-galactosidase isolated from coffee beans.
$^d$α-mannosidase obtained from jack beans.
NI = No inhibition at 100 μM of substrate.
isopropylidene-D-sorbitol \(^{14}\) and 1,2,5,6-dianhydro-3,4-O-isopropylidene-D-iditol \(^{25}\) were treated with benzylamine in refluxing dioxane for 24-48 hr to furnish 63% and 62% isolated yields of \(N\)-benzyl-3,4,5,6-tetrahydroxy-4,5-O-isopropylidenezepanes 3a and 4a, respectively. Deprotection of trans-acetonide group of the azepanes 3a and 4a were carried out in 80% aqueous trifluoroacetic acid at ambient temperature to afford \(N\)-benzyltetrahydroxyazepanes 5a and 6a in 90% and 73% yields, respectively.

Removal of \(N\)-benzyl group was achieved by transfer hydrogenation of \(N\)-benzylazepanes 3a and 4a using 10% \(Pd\)-C and ammonium formate in methanol to furnish 4,5-O-isopropylidenedezepanes 3b and 4b in 63% and 65% yields, respectively. Hydrolysis of acetonide group proceeded smoothly with 80% trifluoroacetic acid (TFAA) to furnish 72% and 73% yields of tetrahydroxyazepanes 5b and 6b, respectively. The bis-epoxide 1 was also reacted with other primary amines (Table 1) such as 2-hydroxyethylamine, 4-hydroxybutylamine, and 2-amino-1-butanol to afford azepanes 3c-3e which upon hydrolysis with 80% TFAA afforded the tetrahydroxyazepanes 5c-5e in 40-80% yields. Alternatively, the bisepoxides 1 and 2 were treated with 2-amino-1,3-dihydroxypropene (serinel) to yield azepanes 3f (64%) and 4f (36%) which upon hydrolysis with 80% TFAA afforded the tetrahydroxyazepanes 5f and 6f in 61% and 84% yields, respectively.

**Determination of enzyme activities.** In 100 mM sodium acetate (pH 5.0) buffer, an appropriate enzyme was preincubated with test compound (100 \(\mu M\)) for 15 min. at 37°C. The reaction was initiated by addition of a suitable substrate (1 mM) and was incubated further for 15 min. at 37°C. The reaction was terminated using suitable quencher and the enzyme activity determined. For \(\beta\)-glucosidase, salicin (2-hydroxymethylphenyl-\(\beta\)-D-glucopyranoside) was used as substrate and glucose released estimated to determine the enzyme activity. For \(\alpha\)-galactosidase, \(\beta\)-galactosidase and \(\alpha\)-mannosidase, suitable \(p\) or \(\alpha\)-nitrophenol esters of the corresponding hexoses were used as substrates and release of nitrophenol was measured at 410 nm which gave the measure of enzyme activity.

**Results and Discussion**

**Glycosidase activities.** The various azepanes synthesised are collected in Table 1. The *in vitro* activities were evaluated against several glycosidases such as \(\alpha\)-glucosidase, \(\beta\)-glucosidase, \(\alpha\)-galactosidase, \(\beta\)-galactosidase and \(\alpha\)-mannosidase. Initially we examined azepanes 3a and 4a in which azepane nitrogen is substituted by benzyl group and 3,4-hydroxy groups are protected as acetonide group. In both the cases at 100 \(\mu M\) concentration, there was no inhibition of \(\alpha\)-mannosidase or \(\alpha\)-glucosidase. However, both the compounds showed moderate inhibition of \(\alpha\)-galactosidase. Removal of acetonide protecting groups resulted in azepanes 5a and 6a, respectively. Azepane 5a showed moderate improvement in \(\beta\)-glucosidase and \(\alpha\)-galactosidase activities, but did not show any activity with \(\alpha\)-mannosidase. In contrast, azepane 6a showed no inhibitory activity with any of these enzymes. On the other hand, when \(N\)-benzyl protecting group was removed from azepanes 3a and 4a, 4,5-isopropylidenedezepanes 3b and 4b, respectively, were obtained which did not show inhibitory activities against any of the enzymes at 100 \(\mu M\) concentration. Removal of acetonide protecting group resulted in tetrahydroxyazepanes 5b and 6b which showed remarkable improvement in the inhibition of \(\beta\)-glucosidase. In contrast, the azepane derivatives 5b and 6b did not inhibit \(\alpha\)-glucosidase or \(\alpha\)-galactosidase at all. On the other hand, both the compounds showed moderate inhibition of \(\alpha\)-mannosidase at 100 \(\mu M\) concentration. It is pertinent to point out that Wong et al. and Le Merrer et al. have also reported the inhibition of several enzymes using 5b in a similar range. We reasoned if nitrogen of azepane is converted into N-(CH\(_2\))\(_3\)-CH\(_2\)-OH (as in the case of miglitol\(^{15}\)), which is obtained by functionalisation of nitrogen of deoxojirimycin with N-CH\(_2\)-CH\(_2\)-OH or N-CH\(_2\)-CH\(_2\)-OH\(_2\) [as in the case of voglibose\(^{16}\) obtained by functionalisation of nitrogen of valienamine with N-CH\(_2\)-CH\(_2\)-OH\(_2\)], it might result in a good \(\alpha\)-glucosidase inhibitor. Thus, we prepared several azepanes using bisepoxides 1 and 2 with suitable aminooalcohols. For example, azepane 3c resulting from the reaction of bisepoxide 1 with 2-aminoethanol showed no inhibition of any of the glycosidases, however, when 4,5-acetonide protecting group is removed, the resultant \(N\)-hydroxyethyltetrahydro azepane 5e showed a good \(\beta\)-glucosidase inhibition at 100 \(\mu M\) concentration. Similar increase in % inhibition of \(\beta\)-glucosidase was observed with \(N\)-hydroxybutyl-3,4,5,6-tetrahydroxy-4,5-O-isopropylidenedezepane 3d and \(N\)-hydroxybutyl-3,4,5,6-tetrahydroxyazepane 5d and also with \(N\)-(1-hydroxymethyl)propyl-3,4,5,6-tetrahydroxy-4,5-O-isopropylidenedezepane 3e and \(N\)-(1-hydroxymethyl)propyl-
Further, we examined the azepanes arising from the reaction of bisepoxides 1 and 2 and serinol (Table I). Both the 4,5-isopropylidene protected azepanes 3f and 4f showed poor β-glucosidase inhibition at 100 μM concentration (ca 10% inhibition of β-glucosidase). Tetrahydroxyazepanes 5f and 6f were on the other hand, also found to inhibit β-glucosidase. Thus, in a similar range azepanes derived from serinol and bisepoxides 1 and 2, there is virtually no change in their β-glucosidase inhibition activities. All the four azepane derivatives 3f, 4f, 5f and 6f showed almost similar inhibition and are not influenced by the stereochemistry at 3 and 6 positions. However, contrary to our expectation, none of the azepane derivatives 3,4,5 and 6 (Table I) arising from the bisepoxide 1 or 2 showed α-glucosidase inhibition. It is important to point out that six-membered analog (deoxynojirimycin) derived from the bisepoxide 1 is an excellent inhibitor of α-glucosidase.

In conclusion, all the azepanes derived from various aminoalcohols and bis-epoxides 1 and 2 lead to preferential inhibition of β-glucosidase, with an exception of azepane 5b and 6b which also showed moderate α-mannosidase inhibition. We wanted to find the rationale behind the inhibitory activity of all these azepanes against β-glucosidase and not against other enzymes. Thus, we carried out structural comparison by computer assisted overlay of selected azepane derivatives with known azasugars. These studies were carried out to rationalize the fact that all the azepanes examined here showed β-glucosidase inhibition and hence should show some kind of pharmacophore similarity with known β-glucosidase inhibitors and also they should show some sort of structural dissimilarity with known α-glucosidase inhibitors. In Chart 1, some of the well known α- and β-glucosidase inhibitors are listed.

With this view in mind, models for the tetrahydroxyazepanes were built based on molecular dynamic simulation using insight-II (version 2.3.5) software at silicon work station. The energies were minimised and the low energy trajectories were compared with the known azasugars. Initially, the tetrahydroxyazepane 5b was compared with the highly potent α-glucosidase inhibitor, deoxynojirimycin with a $K_i$ value of 8.7 μM whereas, the $K_i$ value for β-glucosidase inhibition is 47.5 μM.

From Figure 1 it is clear that for both the molecules, deoxynojirimycin and azepane 5b there appears to be some overlap. For example the ring nitrogen and C2 atom of both the molecules (carbon in green), C5, C6 atoms of deoxynojirimycin and C6, C7 atoms of azepane 5b are overlapped. The oxygen atoms are indicated in red and the hydrogen atoms in white.
Figure 2 — Overlay of isofagomine and azepane Sb: 4 Pairs of atoms are chosen for overlay. The ring nitrogen (blue), C2 atom of both the molecules (carbon in green), C5, C6 atoms of isofagomine and C6, C7 atoms of azepane Sb are overlapped. The oxygen atoms are indicated in red and the hydrogen atoms in white.

Figure 3 — Overlay of isofagomine and azepane 6b: 4 Pairs of atoms are chosen for overlay. The ring nitrogen (blue), C2 atom of both the molecules (carbon in green), C5, C6 atoms of isofagomine and C6, C7 atoms of azepane 6b are overlapped. The oxygen atoms are indicated in red and the hydrogen atoms in white.

Figure 4 — Overlay of isofagomine and azepane Sc: 4 Pairs of atoms are chosen for overlay. The ring nitrogen (blue), C2 atom of both the molecules (carbon in green), C5, C6 atoms of isofagomine and C6, C7 atoms of azepane Sc are overlapped. The oxygen atoms are indicated in red and the hydrogen atoms in white.

Figure 5 — Overlay of isofagomine and azepane 5f: 4 Pairs of atoms are chosen for overlay. The ring nitrogen (blue), C2 atom of both the molecules (carbon in green), C5, C6 atoms of isofagomine and C6, C7 atoms of azepane 5f are overlapped. The oxygen atoms were indicated in red and the hydrogen atoms in white.
azepane 5b, there is no OH functionality at C2 of azepane to match with hydroxymethyl at C2 of piperidine. In addition, there is an extra hydroxy function on C4 of azepane which may be disturbing the tight binding of azepane in the enzyme cavity. These factors may account for the lack of β-glucosidase inhibition of azepane 5b. Since tetrahydroxyazepane 5b is a good inhibitor of β-glucosidase, we also compared it with isofagomine (Figure 2) which is a potent β-glucosidase inhibitor with a \( K_s \) value of 0.11 μM.

In Figure 2, azepane 5b has been overlapped with isofagomine. From this figure there appears to be good overlap between the ring nitrogen atoms of both the molecules and C2, C4, C5 and C6 atoms of isofagomine with C2, C5, C6 and C7 atoms of azepane backbone. There is also a good overlap of 4.5 OHs of isofagomine with 5.6 OHs of azepane 5b. However, hydroxymethyl group at C3 position of isofagomine seems to be away from either C3-OH or C4-OH of azepane. From this overlap study it is clear as to why azepane 5b, although shows good β-glucosidase activities, it is not as good as isofagomine.

The other isomer of tetrahydroxyazepane 6b derived from bisepoxide 2 has also shown good β-glucosidase inhibition although it was slightly inferior when compared to azepane 5b. In order to understand the decrease in β-glucosidase activity of 6b compared to 5b, we carried out a similar computer assisted overlay studies of 6b with isofagomine (Figure 3).

From Figure 3, it is clear that the carbon backbones of 6b and isofagomine overlap as good as in the case of azepane 5b, but the C5 hydroxy of isofagomine and C6 hydroxy of azepane do not superimpose quite well. We reasoned that this may be the cause of decrease in binding of 6b to the enzyme and hence further loss of activity against β-glucosidase. The N-substituted tetrahydroxyazepane 5c which shows moderate β-glucosidase inhibition was also overlapped with isofagomine (Figure 4).

In this docking experiment also there is a reasonably good superimposition of 5c with isofagomine. The ring nitrogen, C2, C3 atoms of both the molecules and C5, C6 atoms of isofagomine and C6, C7 atoms of azepane 5c superimpose reasonably well, whereas C4, C5 atoms of azepane 5c do not overlap with isofagomine. As can be seen from Figure 4, the 6-OH of azepane overlaps well with 5-OH of isofagomine, whereas other OHs are out of plane. In addition, substituent at nitrogen also contributes to the loss of activity which is evident from the model shown in Figure 4.

In a similar way, the tetrahydroxyazepane 5f was also overlapped with isofagomine (Figure 5). In this overlay studies there is a good docking between the carbon backbones of both the molecules as in the case of azepane 5c. However, the bulky N-substitution may distort the binding, hence there is a further decrease in the activity compared to azepane 5c.

In many α-glucosidase inhibitors, the N-substitution of azasugars increased the inhibitory activity, e.g. deoxynojirimycin (\( K_s=8.7\times10^{-6} \) M), miglitol (\( K_s=1.44\times10^{-5} \) M) and voglibose (\( K_s=2.0\times10^{-9} \) M). This clearly indicates that α-glucosidase may have a hydrophilic pocket close to the active site, whereas β-glucosidase may not have. In summary, the three dimensional arrangements of the pharmacophores in tetrahydroxyazepanes are in agreement with β-glucosidase inhibitor isofagomine and hence they exhibit β-glucosidase inhibition.

Anticancer activities—These polyhydroxylated azepanes were also screened for their in vitro anticancer activity. The results were obtained from National Cancer Institute and the activities are reported as GI50 in molar concentration (cf. Table II).

The N-benzylazepanes 3a, 4a, 5a and 6a exhibited a moderate activity against CNS cancer, renal cancer, breast cancer and ovarian cancer in the range 3 to 10×10^{-3} M in various cell lines (Table II), whereas only azepane 3a exhibited activity against small cell lung cancer in the range 4 to 10×10^{-3} M. Interestingly, the azepane 5b was found to be a moderate inhibitor of CNS cancer and ovarian cancer, whereas its isomeric azepane 6b and also the azepane 3d were found to be inhibitors of renal cancer and breast cancer (3 to 9×10^{-5} M). The azepane 4f exhibited a moderate activity against leukemia (6.16×10^{-3} M).

Based on these results, we concluded that the seven-membered ring azasugars are moderate inhibitors of various cancer cells.

Anticancer HIV-proteases activity. Symmetrical seven-membered ring cyclic oxamides and cyclic ureas are reported as potent HIV protease inhibitors. Due to the structural similarities of these C7 symmetrical azepanes with cyclic oxamides and cyclic ureas, these seven-membered ring azasugars were also
evaluated for their in vitro inhibitory activity of HIV proteases. All the azepanes listed in Table I were found to have IC₅₀ values more than 2x10⁻⁵ M. It is important to point out that although these azepanes do inhibit HIV proteases at mM concentration, it is not of therapeutic significance.

**Experimental Section**

**General.** All chemicals were distilled or recrystallised before use and anhydrous solvents were freshly prepared by standard procedures. TLC was performed on silica gel plates (60F 254, Merck) using methanol-ethyl acetate mixture as eluent. The developing agents were Mandalines reagent or iodine vapours. Chromatography was performed on silica gel SRL 200-400 mesh. Melting points were recorded on a Veego melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT IR-1600 spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and chemical shifts are reported in δ units (ppm) relative to TMS as internal standard (coupling constants are reported in Hz). Mass spectra were obtained on an HP 5989A mass spectrometer. Data are reported in m/z (relative intensity). HPLC were run on an IB silica C₈ column using H₂O-MeOH mixtures as eluents, flow rate 0.7 mL/min, with RI detector on a 1022 LC plus instrument. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Stereochemical assignments are based on the stereochemistry of the starting sugar derivative. All moisture sensitive reactions were conducted under an argon atmosphere in oven-dried glassware.

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<th>Azepane</th>
<th>Small cell lung cancer</th>
<th>CNS cancer</th>
<th>Renal cancer</th>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
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¹ IC₅₀ value in molar concentration. Different cell lines are given in parenthesis. NI: No inhibition.
4,5-O-isopropylideneazepane 4a. Compound 4a was prepared analogously to compound 3a using 1,2,5,6-dianhydro-3,4-O-isopropylidene-1-iditol\(^{11}\) (bis-epoxide 2) (186 mg, 1.0 mmoles), benzylamine (109 mg, 1.0 ml) in dioxane (2 ml). Compound 4a was isolated as a colourless syrupy liquid, yield 62%; 
\[^{1}H\text{NMR}(CDCl\text{3})\]: \(\delta\) 1.50 (s, 6H), 2.00 (brs, 2H), 2.70 (dd, \(J=3.4\) and 12.8 Hz, 2H), 3.00 (dd, \(J=3.2\) and 11.8 Hz, 2H), 3.62 (d, \(J=3.2\) Hz, 2H), 3.70-3.81 (m, 1H), 3.96 (dd, \(J=2.8\) and 8.6 Hz, 1H), 4.01-4.23 (m, 2H), 7.30 (brs, 5H); \(^{13}C\text{NMR}(CD\text{OD})\): \(\delta\) 26.65, 27.29, 60.71, 61.87, 63.88, 65.39, 72.36, 78.06, 78.53, 109.38, 127.23, 128.35, 128.51, 136.09, MS (relative intensity): m/z 294 (M+1, 10%), 276 (10%), 236 (30%), 120 (40%), 91 (100%).

(3S,4R,5S)-1-N-Benzyl-3,4,5,6-tetrahydroxyazepane 3a. Trifluoroacetic acid (80%, 2 ml) was added dropwise to azepane 3a (1.0 mmole, 293 mg) at 0°C and the reaction mixture stirred for 2 hr at 30°C. Excess of acid was removed under reduced pressure and the residue chromatographed on silica gel using a mixture (2:1) of ethyl acetate-methanol as eluent to afford the azepane 5a (230 mg, 90%) as a white gummy liquid; \[^{1}H\text{NMR}(CH\text{Cl}\text{3})\]: \(\delta\) 3.06, 3.4, 3.72, 7.52 (brs, 5H); \(^{13}C\text{NMR}(CD\text{OD})\): \(\delta\) 56.09, 62.99, 69.02, 78.53, 130.35, 130.67, 131.21, 132.30, MS (relative intensity): m/z 254 (M+1, 20%), 236 (30%), 162 (15%), 91 (100%).

(3S,4R,5S,6S)-1-N-Benzyl-3,4,5,6-tetrahydroxyazepane 6a. Compound 6a was prepared analogously to compound 5a using azepane 4a (1.5 mmoles, 439 mg) and trifluoroacetic acid (80%, 3 ml). Compound 6a was isolated as a brown syrupy liquid, yield 86%; 
\[^{1}H\text{NMR}(CD\text{Cl}\text{3})\]: \(\delta\) 2.90-3.35 (m, 4H), 3.70-3.91 (m, 3H), 4.21 (m, 1H), 4.41 (s, 2H), 7.50 (brs, 5H); \(^{13}C\text{NMR}(CD\text{OD})\): \(\delta\) 54.44, 55.19, 62.16, 67.36, 69.71, 75.73, 77.36, 130.19, 130.44, 131.08, 132.11, MS (relative intensity): m/z 254 (M+1, 20%), 236 (20%), 208 (10%), 120 (40%), 91 (100%).

(3S,4R,5S,6S)-3,4,5,6-Tetrahydroxy-4,5-O-isopropylidene azepane 3b. A mixture of azepane 3a (293 mg, 1.0 mmole), ammonium formate (252 mg, 4.0 mmoles) and 10% Pd-C (75 mg) in methanol (5 ml) was refluxed at 80°C under argon atmosphere for 3 hr. The reaction mixture was filtered through Celite and solvent removed under reduced pressure. The residue was chromatographed over silica gel using a 1:1 mixture of methanol and ethyl acetate as eluent to afford the azepane 3b (128 mg, 63%) as a brown solid, mp 74-75°C; \[^{1}H\text{NMR}(CD\text{OD})\]: \(\delta\) 1.34 (s, 6H), 2.64 (dd, \(J=6.2\) and 14.6 Hz, 2H), 3.00 (dd, \(J=5.8\) and 13.6 Hz, 2H), 3.60-3.80 (m, 4H); \(^{13}C\text{NMR}(CD\text{OD})\): \(\delta\) 27.38, 56.47, 72.20, 82.04, 110.37, MS (relative intensity): m/z 204 (20%), 188 (20%), 156 (20%), 146 (100%).

(3S,4R,5S,6S,7R)-3,4,5,6-Tetrahydroxy-4,5-O-isopropylidene azepane 4b. Compound 4b was prepared analogously to compound 3b using azepane 4a (1.0 g, 3.4 mmoles) ammonium formate (860 mg, 13.6 mmoles) and 10% Pd-C (280 mg) in methanol (5 ml). Compound 4b was isolated as a brown syrupy liquid, yield 65%; \[^{1}H\text{NMR}(CD\text{OD})\]: \(\delta\) 1.46 (s, 6H), 2.82-3.10 (m, 1H), 3.76-3.91 (m, 2H), 4.10 (m, 1H), 4.31 (t, \(J=11.8\) Hz, 1H); \(^{13}C\text{NMR}(CD\text{OD})\): \(\delta\) 27.03, 275.57, 55.21, 65.14, 67.27, 72.68, 79.45, 110.39, MS (relative intensity): m/z 204 (M+1, 20%), 188 (20%), 156 (30%), 146 (100%).

(3S,4R,5R,6S,7R)-3,4,5,6-Tetrahydroxyazepane 5b. The compound 5b was prepared analogously to compound 5a using azepane 3b (203 mg, 1.0 mmole) and trifluoroacetic acid (80%, 2 ml). The compound 5b was isolated as an off-white solid, yield 73%, mp 146-147°C; \[^{1}H\text{NMR}(CD\text{OD})\]: \(\delta\) 1.32 (dd, \(J=5.6\) and 14.2 Hz, 2H), 3.32 (d, \(J=7.7\) Hz, 2H), 8.72 (d, \(J=4.2\) Hz, 2H), 4.10 (t, \(J=3.8\) Hz, 2H); \(^{13}C\text{NMR}(CD\text{OD})\): \(\delta\) 48.14, 69.55, 78.28, MS (relative intensity): m/z 164 (M+1, 50%), 146 (100%).

(3S,4R,5R,6S,7R)-3,4,5,6-Tetrahydroxyazepane 6b. Compound 6b was prepared analogously to compound 5a using azepane 4b (406 mg, 2.0 mmoles) and trifluoroacetic acid (80%, 4 ml). Compound 6b was isolated as a brown solid, yield 73%, mp 190-191°C; \[^{1}H\text{NMR}(CD\text{OD})\]: \(\delta\) 3.14-3.40 (m, 4H), 3.80-3.88 (m, 2H), 4.18-4.26 (m, 2H); \(^{13}C\text{NMR}(CD\text{OD})\): \(\delta\) 48.97, 49.19, 70.01,
Compound 3c was isolated as a pale yellow solid, yield 55%; IR (Neat): 3281, 2980, 1676, 1464, 1430, 1200, 1134 cm⁻¹; ¹H NMR (CDCl₃): δ 1.06 (s, 3H), 1.51-1.54 (m, 1H), 2.66-2.78 (m, 4H), 3.36 (t, J=10.4 Hz, 1H), 3.60 (dd, J=4.6 and 12.1 Hz, 1H), 3.84 (brs, 4H); ¹³C NMR (CDOD): δ 26.0, 11.89, 17.91, 50.90, 54.11, 61.05, 64.28, 72.98, 100.65; MS (relative intensity): m/z 276 (M⁺, 20%), 258 (15%), 244 (100%), 186 (80%), 114 (40%).

Compound 3e was prepared analogously to compound 3a using the bisepoxide 1 (186 mg, 1.0 mmole) and D₂-amino-1-butanol in dioxane (2 mL). Compound 3e was isolated as a brown solid oil, yield 55%; mp 120-121°C; [α]⁺¹ = +26.0° (c 0.65, CH₂OH); IR (Neat): 3383, 2932, 1456, 1373, 1234, 1051 cm⁻¹; ¹H NMR (CDCl₃): δ 0.88 (t, J=7.5 Hz, 3H), 1.19-1.25 (m, 1H), 1.42 (s, 6H), 1.51-1.54 (m, 1H), 2.66-2.78 (m, 4H), 3.36 (t, J=10.4 Hz, 1H), 3.60 (dd, J=4.6 and 12.1 Hz, 1H), 3.84 (brs, 4H); ¹³C NMR (CDOD): δ 26.0, 11.89, 17.91, 50.90, 54.11, 61.05, 64.28, 72.98, 100.65; MS (relative intensity): m/z 276 (M⁺, 20%), 258 (15%), 244 (100%), 186 (80%), 114 (40%).

(3S,4R,5R,6S)-1-N-(1-Hydroxymethyl)propyl-3,4,6-tetrahydroxy-4,5-O-isopropylidene azepane 3e. Compound 3e was prepared analogously to compound 3a using azepane 3c as a solid, yield 73%; mp 120-121°C; [α]⁺¹ = +33.3° (c 0.65, CH₂OH); IR (Neat): 3383, 2932, 1456, 1373, 1234, 1051 cm⁻¹; ¹H NMR (CDCl₃): δ 1.06 (s, 3H), 1.51-1.54 (m, 1H), 2.66-2.78 (m, 4H), 3.36 (t, J=10.4 Hz, 1H), 3.60 (dd, J=4.6 and 12.1 Hz, 1H), 3.84 (brs, 4H); ¹³C NMR (CDOD): δ 26.0, 11.89, 17.91, 50.90, 54.11, 61.05, 64.28, 72.98, 100.65; MS (relative intensity): m/z 276 (M⁺, 20%), 258 (15%), 244 (100%), 186 (80%), 114 (40%).
110.26; MS (relative intensity): m/z 278 (M+1, 60%), 260 (20%), 246 (90%), 220 (40%), 188 (100%).

(3R,4R,5R,6S)-1-oxa-3,4,5-1,2,3-Dihydroxypropyl)-3,4,5,6-tetrahydroxy-4,5-O-isopropylideneazepane 4f. Compound 4f was prepared analogously to compound 3a by using the bisepoxide 2 (0.86 g, 10 mmole) and serinol (1.80 g, 2.0 mmole) in dioxane (10 mL). Compound 4f was isolated as a brown viscous liquid, yield 61%, mp 160-161°C; [α]D 13.7, 16.77, 1327, 1080, 1076 cm⁻¹; 1H NMR (D2O): 6 1.42 (s, 6H), 2.88-3.14 (m, 5H), 3.54-3.66 (m, 4H), 3.76-3.88 (m, 1H), 4.00-4.14 (m, 2H), 4.36 (d, J=12.2 Hz, 1H); 13C NMR (CD3OD): δ 28.43, 28.83, 60.85, 61.74, 62.01, 62.68, 69.44, 70.83, 74.89, 80.81, 81.24; 112.31; MS (relative intensity): m/z 278 (M+1, 20%), 246 (90%), 220 (90%), 188 (100%).

(3R,4R,5R,6S)-1-oxa-(2,3,4,5-Dihydroxypropyl)-3,4,5,6-tetrahydroxyazepane 5f. Compound 5f was prepared analogously to compound 3a using azepane 3f (277 mg, 1.0 mmole) and trifluoroacetic acid (80%, 2 mL). Compound 5f was isolated as a brown viscous liquid, yield 61%, [α]D 21.40 (c 1.0, CH3OH); IR (Neat): 3558, 2919, 2949, 1676, 1413, 1202 cm⁻¹; 1H NMR (CDCl3): δ 2.96 (dd, J=6.6 and 12.8 Hz, 2H), 3.11 (dd, J=3.4 and 10.8 Hz, 2H), 3.42 (m, 1H), 3.48-3.66 (m, 8H); 13C NMR (CDCl3): δ 57.51, 59.81, 60.31, 70.09, 73.62, 77.28; MS (relative intensity): m/z 238 (M+1, 50%), 220 (40%), 206 (100%).

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