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Synthesis of polyhydroxy 7- and *N*-alkyl-azepanes as potent glycosidase inhibitors

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ABSTRACT

An effective synthetic method for polyhydroxylated azepanes that contain an alkyl group (Me or Bu) at either the 7- or N-positions is developed. The synthetic routes are accomplished in eight to ten steps from D-(−)-quinic acid. Among the compounds synthesized, the polyhydroxy 7-butyl azepane (compound **3**), which possessed the *R*-configuration at C-7 position, is shown to give potent inhibition against β-galactosidase (IC_{50} = 3 μM). Preliminary biological data indicate that the length of alkyl groups along with the proper stereochemistry at the C-7 position is essential for acquiring extra binding affinity. Using similar synthetic routes, the polyhydroxy *N*-methyl and *N*-butyl azepanes are synthesized for the comparison of their biological activities.

1. Introduction

Polyhydroxypiperidines have attracted immense attention from the synthetic community owing to their biological importance in the development of glycosidase inhibitors.[1–10] Miglitol™ (*N*-hydroxyethyl-deoxynojirimycin) was developed to target the intestinal disaccharidase and prescribed for the treatments of type II diabetes[1,11] (Fig. 1). *N*-Butyl-deoxynojimicycin (NB-DNJ, Zavescal) was used in the treatment of Gaucher disease and also as an anti-HIV drug.[1,12] Introducing an alkyl group to the ring of azasugars can make drug molecules more hydrophobic for better absorption, delivery, and enhancement of the uptake by cells.[1,13–16] The seven-member-ring azasugars (iminosugars), so-called azepanes, have attracted attention due to the activities of glycosidase inhibitors that may be related to their structural flexibility.[3,17] A recent report revealed that the alkyl groups located in the ring or at the nitrogen site of azepanes can offer potent inhibition against various enzymes.[18] We have studied extensively the discovery of polyhydroxylated azepanes as potential drugs and reported the synthesis of a series of trihydroxyazepanes.[19] We have found several azepanes as possible candidates for potent glycosidase inhibitors and their activities were shown to be compatible to the related piperidines.[20] To continue our efforts in the synthesis of polyhydroxyazepanes, several important issues are addressed: (1) how to introduce hydroxyl groups to various positions of the iminosugar ring for achieving the desired stereochemistry, and (2) how to enhance and understand the inhibition potency at the molecular level. In this article, we describe the expeditious synthesis of polyhydroxylated azepanes that contain an extra methyl or butyl group at either the C7- or N-positions in order to compare with the biological activities of Miglitol or NB-DNJ. The structures of these azepanes are unique and have not been reported previously. It is intriguing to study if the additional alkyl group can contribute to the binding affinity.

2. Results and discussion

Our synthetic strategy to the target molecules **1**–**4**, depicted in Scheme 1, is straightforward. In order to increase the synthetic flexibility, alkyl groups (Me or Bu) at the C-7 position were introduced by the corresponding lithiated reagents at an early stage. Enone **15**,[21] prepared in four steps from D-(−)-quinic acid, was treated with $CeCl_3$[22] and then a solution of methyllithium was added dropwise at −78 °C, to give the separable epimeric mixtures of **16** (the major isomer, 82% yield) and **17** (the minor isomer, ~8% yield) mixed with a trace amount of other impurities. The stereochemistry of **16** was elucidated according to the 2D-NOESY spectra due to the observation of the cross peaks between the methyl group and the hydrogen at C-1 position. As expected, the nucleophile (Me^-) can approach from the less hindered side of **15** to give **16** as the major product.

Consecutive rearrangement and allylic oxidation reactions were carried out to produce enone **20** when tertiary alcohol **16** or **17** was

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† Biological data shall be addressed to Professor C.H. Lin.

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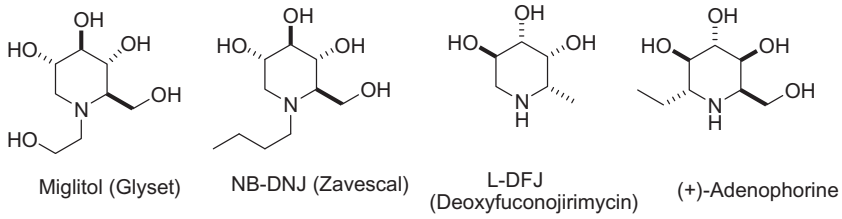


Figure 1. The representative polyhydroxylated C- and *N*-alkyl piperidines.

mixed with pyridinium chlorochromate (PCC) and silica gel[23] in CH_2Cl_2 under reflux conditions. Interestingly, the reaction rate was closely related to the stereochemical configuration at C-5 position. When compound **16** was treated with PCC (3 equiv) and refluxed in CH_2Cl_2 for 10 h, compound **20** was obtained in 41% yield (61% yield based on recovery of **16**). In contrast, compound **17** was completely converted into **20** within 1.5 h in 67% yield under the same conditions. Steric hindrance was realized to play a determining role in the reactivity because **17** was much more reactive owing to the less hindered hydroxyl group.

Luche reduction ($NaBH_4$ and $CeCl_3{\cdot}7H_2O$) of compound **20** generated the sole product **22** with exclusive stereoselectivity. The allylic alcohol of **22** was protected by using methoxymethyl chloride (MOMCl) and diisopropylethylamine to give **24**. Following our previous report,[19] the double bond of **24** was subjected to dihydroxylation (with $KMnO_4$, $MgSO_4$, EtOH, H_2O), oxidative cleavage (with $NaIO_4$), and reductive aminocyclization (with benzylamine and $NaCNBH_3$), leading to the separable epimeric products **26** and **27** in 47% and 7% isolated yields (three steps in total), respectively. The assignment of the C7-stereochemistry in **26** and **27** was established on the basis of the C7-methyl group and H5 of **26** that possessed the special correlation but not for **27** by 2D-NOESY spectra. The final deprotection of **26** and **27** was carried out individually by hydrogenation over 10% Pd–C in 2 N HCl to obtain the desired 7(*R*)-methyl-azepanes-3,4,5-triol **1** (86%) and its 7(*S*)-epimer **2** (92%), respectively.

A similar approach was used to introduce a butyl group at the C7-position of the azepanes (Scheme 1). Compound **18**, with the same stereochemical configuration as **16**, was obtained in a moderate yield (70%), but other epimer **19** was isolated only in a trace amount. The PCC oxidation of **18** gave **21** in a moderate yield (47%, 69% based on the recovery of **18**). The subsequent steps employed the same conditions described above to efficiently lead to the target molecules **3** and **4**.

On the other hand, the formation of inseparable diastereomeric mixtures **31**/**32** and **33**/**34** (both pairs in ratio of ~1:1 by NMR analysis) was observed when compound **30**[24] was either methylated or butylated, (Scheme 2). As discussed above, steric effects serve as a major factor for the successive rearrangement and oxidation of compounds **16**–**18**, whereas the mixtures **31**/**32** and **33**/**34** reacted relatively faster and were converted to compounds **35** and **36** within 4 h in 85% and 88% yield without recovering the starting materials. The subsequent reduction provided **37** and **38**, and protection with the MOM group afforded **39** and **40**, respectively. Further dihydroxylation, oxidative cleavage, and reductive aminocyclization, and purification by column chromatography produced pairs of inseparable diastereomers **41**/**42** and **43**/**44** in which both pairs were in ratio of ~10:1 in 43% and 36% total yields. Efforts were made to separate each diastereomer after final deprotection by column chromatography, which still led to the isolation of product mixtures **5**/**6** and **7**/**8** in high yields with almost the same ratios as those before deprotection. The 2D-NOESY spectra indicated that compounds **5** and **7** are the major diastereomeric products due to the close relationship between C-7 alkyl groups and H5.

The introduction of an alkyl group to the ring nitrogen of azasugars was thought to enhance the uptake by cells.[1] Our intention was to compare the biological activities of *N*-alkyl azepanes with the corresponding piperidines (such as Miglitol or NB-DNJ). Therefore, six *N*-alkylazepanes **9**–**14** were also synthesized from compounds **45**,[19] **46**[19], and **51**[19] in a similar manner as shown in Scheme 3. The major differences included the oxidant used in the dihydroxylation, which was replaced with $RuCl_3$–$NaIO_4$[19] as well as the amine used in the reductive amination that was substituted with either methylamine or butylamine. The yields were fairly comparable to those shown in Schemes 1 and 2.

3. Conclusion

A new family of trihydroxyazepanes **1**–**14** has been synthesized that contains a methyl or butyl group at either C7- or N-positions. These unique molecules were prepared in a facile manner from D-(−)-quinic acid. The reductive aminocyclization in Schemes 1 and 2 led to moderate selectivity at C7 positions in formation of compounds **26**–**29** and **41**–**44**. However, their deprotection to yield the target molecules **1**–**8** provided us a diverse range to evaluate their biological activity. Therefore, the preliminary result in the inhibition activity indicates that the azepane **3** with the butyl substituent in 7*R*-configuration has a better inhibition potency against β-galactosidase (IC_{50} = 3 μM), as compared to the epimer **4** (no activity) and the methyl homologs compounds **1** (IC_{50} = 100 μM) and **2** (no activity). Also, the stereochemistry at C-7 is essential and the enhancement of inhibition is most likely due to an extra binding interaction with the hydrophobic residue in the vicinity of the enzyme activity site. Detailed biological data of compounds **1**–**14** are under investigation and will be disclosed in due course.

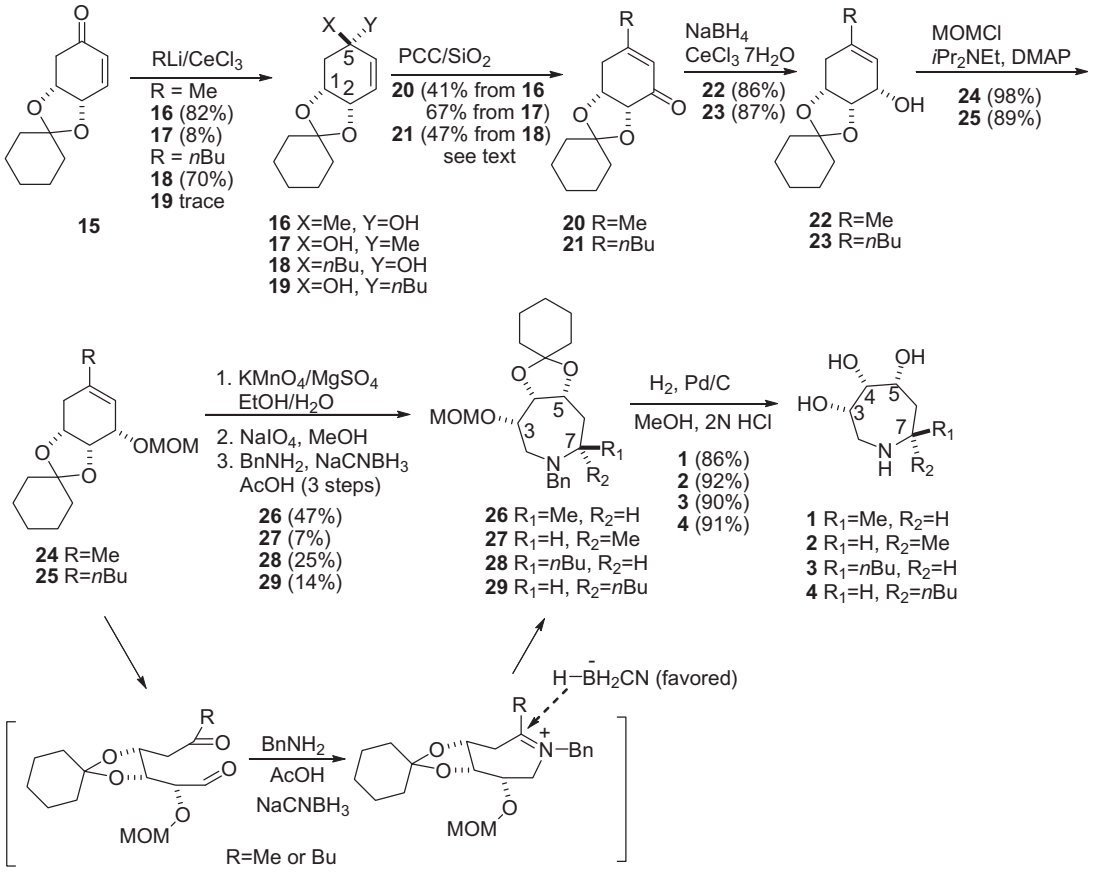
4. Experimental

4.1. General methods

Reactions were conducted under anhydrous solvents and an inert atmosphere of nitrogen unless otherwise noted. Melting points were uncorrected. ^1H (300 or 600 MHz) and ^{13}C (75 or 150 MHz) NMR spectra were recorded on either Bruker 300 or 600 MHz spectrometers. Chemical shifts are reported relative to the residual of deuterium solvents: $CDCl_3$ δ 7.26; CD_3OD δ 4.89; D_2O δ 4.6 ppm for ^1H and $CDCl_3$ δ 77.0; CD_3OD δ 49.15 ppm for ^{13}C. Optical rotations were measured with Horbia Sepa-300 polarimeter.

4.1.1. General procedure of alkylation

$CeCl_3{\cdot}7H_2O$ was heated at 110 °C under vacuum (~0.2 mmHg) for 4 h to remove water. To the dried $CeCl_3$ was added THF (~0.2 M) and the mixture was stirred for 20 min. This mixture was sonicated for 1 h before being cooled to −78 °C. Three equivalents of the corresponding lithiated reagent (MeLi or BuLi) were added to this mixture. The enone dissolved in THF was added to the above mixture via cannulation. After the media was stirred for 30 min at −78 °C, the reaction was quenched by addition of NH_4Cl (saturated)



Scheme 1. Synthesis of 7-methyl- and 7-butyl-azepanes-3,4,5-triols **1**–**4**.

and allowed to warm to ambient temperature. The mixture was extracted with ether and dried over $MgSO_4$. The resulting crude mixture was purified by flash column chromatography.

4.1.2. General procedure of PCC oxidation

To a stirred solution of compound **16** in CH_2Cl_2, for example, was treated with PCC (3 equiv) and SiO_2 (three times the weight of the amount of PCC). The mixture was heated in CH_2Cl_2 at reflux and the reaction was monitored by TLC. At the end of reaction time, the resulting mixture was filtered through a pad of silica gel, washed with CH_2Cl_2 and purified by flash column chromatography.

4.1.3. General procedure of dihydroxylation, oxidative cleavage, and reductive aminocyclization

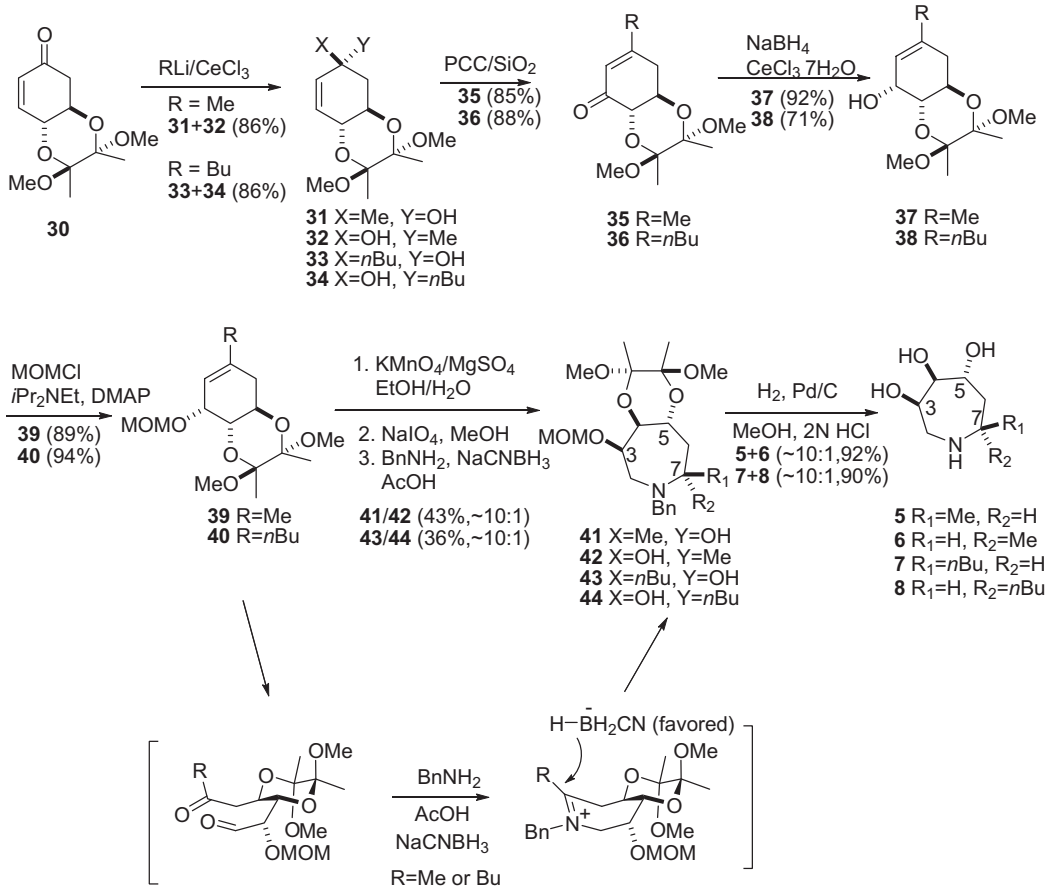
This reaction was conducted in a three-step sequence. The olefin in EtOH and H_2O (v/v = 9:1, ~0.1–0.2 M) was treated with $KMnO_4$ (2 equiv) and $MgSO_4$ (2 equiv) at 0 °C. The stirring mixture was allowed to warm up to ambient temperature and stirred for another 10 h. At the end of which time, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude mixture was extracted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The mixture was used in the next step without further purification. The mixture was dissolved in MeOH and $NaIO_4$ (3 equiv) was added. The reaction was heated at 50 °C for 10 h. The solvent was removed, extracted with EtOAc, and washed with $NaHCO_3$ (saturated). The organic layer was dried over $MgSO_4$ and concentrated. The resulting syrup was dissolved in MeOH and the dried 3 Å molecular sieve (same amount of starting material) was added. This mixture was cooled to −78 °C and a mixture solution of $BnNH_2$–AcOH–MeOH (pH 5–6) was added via cannulation. This solution was stirred for 10 min, and $NaCNBH_3$ (1 equiv) was added and stirred for 1 h. The reaction was allowed to warm to ambient temperature and stirred for another 2 h. At the end of reaction time, the mixture was extracted with EtOAc and washed with $NaHCO_3$ (saturated). The organic layer was dried over $MgSO_4$ and purified by flash column chromatography.

4.2. (1*R*,2*R*)-1,2-*O*-Cyclohexylidene-5-methyl-3-oxo-4-cyclohexene (20)

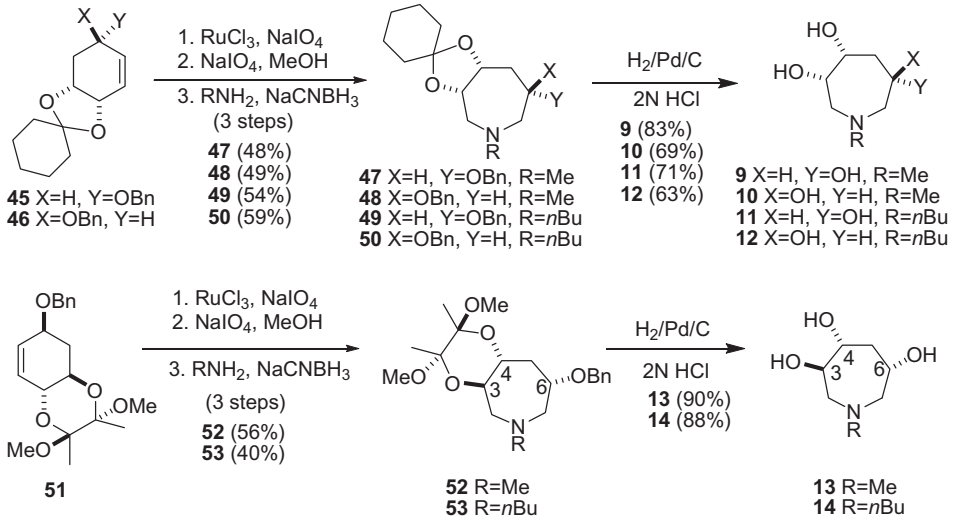
Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:15→1:4) afforded a white solid in 41% yield. Mp = 115.0–115.5 °C. $[\alpha]_D^{23}$ −51.2 (*c* 1.3, MeOH). ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.59–4.54 (m, 1H), 4.19 (d, *J* = 5.1 Hz, 1H), 2.71 (d, *J* = 4.1 Hz, 2H), 1.97 (s, 3H), 1.63–1.30 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 158.4, 135.4, 125.1, 109.8, 74.2, 72.4, 37.0, 35.4, 32.6, 24.9, 24.4, 23.7. HRMS (ESI) calcd for $C_{13}H_{18}NaO_3$ $[M+Na]^+$: 245.1154. Found: 245.1144.

4.3. (1*R*,2*R*)-5-Butyl-1,2-*O*-cyclohexylidene-3-oxo-4-cyclohexene-1,2-diol (21)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:20→1:6) afforded a colorless syrup in 47% yield. $[\alpha]_D^{26}$ −32.1 (*c* 1.0, MeOH). ^1H NMR (300 MHz, C_6D_6) δ 5.91 (s, 1H), 4.13 (td, *J* = 5.1, 1.6 Hz, 1H), 3.97 (d, *J* = 5.1 Hz, 1H), 2.30 (d, *J* = 19.1 Hz, 1H), 1.91 (dd, *J* = 19.1, 0.8 Hz, 1H), 1.74–1.45 (m, 10H), 1.22–0.95 (m, 6H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 195.1, 160.7, 125.1, 110.0, 75.4, 73.4, 38.1, 37.7, 36.5, 31.6, 29.2, 25.7, 24.6, 24.5, 22.8, 14.3. HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ ($[M+Na]^+$): 287.1618. Found: 287.1559.



Scheme 2. Synthesis of 7-methyl- and 7-butylazepanes-3,4,5-triols from TMB protected enone **30**.



Scheme 3. Synthesis of polyhydroxylated *N*-methyl and -butylazepane-3,4,6-triols **9**–**14**.

4.4. (1*R*,2*S*)-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-5-methyl-3-oxo-4-cyclohexe (35)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:15→1:6) afforded a white solid in 86% yield. Mp = 153.3–153.6 °C. $[\alpha]_D^{23}$ +39.9 (*c* 1.2, MeOH). ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.18 (d, *J* = 11.3 Hz, 1H), 4.03 (ddd, *J* = 11.3, 9.9, 6.1 Hz, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 2.60–2.43 (m, 2H), 1.97 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 158.1, 126.3, 100.3, 99.3, 74.3, 67.1, 48.5, 48.1, 36.5, 24.5, 17.8 (×2). HRMS (ESI) calcd for $C_{13}H_{20}NaO_5$ $[M+Na]^+$: 279.1208. Found: 279.1200.

4.5. (5*R*,6*S*)-5,6-[(2*S*,3*S*)-2,3-Dimethoxybutan-2,3-dioxy]-3-butyl-cyclohex-2-enone (36)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:15→1:5) afforded a colorless syrup in 88% yield. $[\alpha]_D^{25}$

+40.2 (*c* 2.4, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.19 (dt, *J* = 11.3, 1.1 Hz, 1H), 4.07–3.95 (m, 1H), 3.27 (d, *J* = 1.2 Hz, 3H), 3.21 (d, *J* = 1.2 Hz, 3H), 2.62–2.42 (m, 2H), 2.21 (t, *J* = 7.7 Hz, 2H), 1.50–1.20 (m, 10H), 0.87 (td, *J* = 7.3, 0.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 162.5, 125.7, 100.8, 99.8, 75.0, 67.8, 49.0, 48.6, 38.2, 35.7, 29.6, 22.8, 18.3, 18.2, 14.4. HRMS (ESI) calcd for $C_{16}H_{26}NaO_5$ $[M+Na]^+$: 321.1678. Found: 321.1670.

4.6. (1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-Dimethoxybutan-2,3-dioxy]-5-methyl-3-*O*-methoxymethyl-4-cyclohexene-1,2,3-triol (39)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:35→1:15) afforded a colorless syrup in 89% yield. $[\alpha]_D^{24}$ +147.1 (*c* 3.0, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.31 (br s, 1H), 4.90 (d, *J* = 6.6 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.36 (dd, *J* = 7.1, 1.8 Hz, 1H), 3.94–3.79 (m, 2H), 3.30 (s, 3H), 3.20 (s, 3H), 3.06 (s, 3H), 2.13 (dd, *J* = 16.0, 9.7 Hz, 1H), 1.99 (dd, *J* = 16.0, 5.5 Hz, 1H), 1.42 (s, 3H), 1.33 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 133.8, 123.7, 123.5, 99.7, 99.6, 96.9, 75.7, 74.8, 66.6, 55.3, 47.9, 35.6, 23.2, 18.4. HRMS (ESI) calcd for $C_{15}H_{26}NaO_6$ $[M+Na]^+$: 325.1627. Found: 325.1636.

4.7. (1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-Dimethoxybutan-2,3-dioxy]-5-butyl-3-*O*-methoxymethyl-4-cyclohexene-1,2,3-triol (40)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:25→1:15) afforded a colorless syrup in 94% yield. $[\alpha]_D^{24}$ +88.2 (*c* 1.9, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.41 (br s, 1H), 4.97 (d, *J* = 6.5 Hz, 1H), 4.76 (d, *J* = 6.5 Hz, 1H), 4.49–4.46 (br m, 1H), 4.01 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.93 (td, *J* = 10.5, 5.8 Hz, 1H), 3.33 (s, 3H), 3.22 (s, 3H), 3.11 (s, 3H), 2.30–2.20 (m, 1H), 2.08 (dd, *J* = 16.3, 5.7 Hz, 1H), 1.78 (dd, *J* = 7.6, 6.6 Hz, 2H), 1.38 (s, 3H), 1.37 (s, 3H), 1.27–1.09 (m, 4H), 0.79 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 138.0, 122.7, 99.8, 99.7, 97.0, 75.9, 75.0, 66.8, 55.4, 48.0, 47.9, 37.3, 34.2, 30.2, 23.0, 18.5, 14.5. HRMS (ESI) calcd for $C_{18}H_{32}NaO_6$ $[M+Na]^+$: 367.2097. Found: 367.2082.

4.8. (1*S*,2*S*,3*S*)-1,2-*O*-Cyclohexylidene-5-methyl-4-cyclohexene-1,2,3-triol (22)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:16→1:8) afforded a white solid in 86% yield. Mp = 95.0–96.0 °C. $[\alpha]_D^{25}$ +14.2 (*c* 1.4, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.55 (t, *J* = 1.1 Hz, 1H), 4.20 (ddd, *J* = 7.5, 4.3, 1.3 Hz, 1H), 4.10 (ddd, *J* = 7.5, 4.4, 2.5 Hz, 1H), 3.99 (ddd, *J* = 9.3, 4.3, 2.2 Hz, 1H), 2.88 (d, *J* = 9.6 Hz, –OH), 2.08 (dd, *J* = 16.2, 2.6 Hz, 1H), 1.62–1.51 (m, 12H), 1.24–1.23 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 134.1, 126.0, 109.5, 76.6, 73.2, 67.7, 36.7, 34.9, 33.4, 26.0, 24.7, 24.4, 23.9. HRMS (ESI) for $C_{13}H_{20}NaO_3$ $[M+Na]^+$: 247.1310. Found: 247.1305.

4.9. (1*S*,2*R*,3*R*)-5-Butyl-1,2-*O*-cyclohexylidene-4-cyclohexene-1,2,3-triol (23)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:25→1:10) afforded a colorless syrup in 87% yield. $[\alpha]_D^{25}$ +14.1 (*c* 1.4, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.56 (t, *J* = 1.1 Hz, 1H), 4.21 (ddd, *J* = 7.6, 4.4, 1.1 Hz, 1H), 4.11 (dt, *J* = 7.6, 1.7 Hz, 1H), 3.95–3.80 (m, 1H), 2.75 (d, *J* = 15.8, 2.6 Hz, 1H), 2.14 (dd, *J* = 15.8, 2.6 Hz, 1H), 1.91 (t, *J* = 7.0 Hz, 2H), 1.65–1.50 (m, 9H), 1.34–1.20 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 138.2, 125.5, 109.5, 75.8, 73.2, 67.8, 37.5, 36.6, 34.8, 31.9, 30.1, 26.0, 24.7, 24.5, 23.0, 14.5. HRMS (ESI) calcd for $C_{16}H_{27}O_3$ $[M+H]^+$: 267.1960. Found: 267.1955.

4.10. (1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-Dimethoxybutan-2,3-dioxy]-5-methyl-4-cyclohexene-1,2,3-triol (37)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:12→1:6) afforded a white solid in 81% yield. Mp = 67.0–68.0 °C. $[\alpha]_D^{25}$ +160.2 (*c* 1.4, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.30 (s, 1H), 4.35 (t, *J* = 1.8 Hz, 1H), 3.86 (ddd, *J* = 16.8, 10.5, 6.0 Hz, 1H), 3.76 (dd, *J* = 10.5, 7.7 Hz, 1H), 3.18 (s, 3H), 3.09 (s, 3H), 2.25–2.10 (m, 2H), 2.00 (dd, *J* = 16.8, 6.0 Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 133.4, 125.0, 99.8, 99.7, 76.0, 70.9, 66.4, 47.9, 35.9, 23.1, 18.5, 18.4. HRMS (ESI) calcd for $C_{13}H_{22}NaO_5$ $[M+Na]^+$: 281.1365. Found: 281.1375.

4.11. (1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-5-butyl-4-cyclohexene-1,2,3-triol (38)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:16→1:6) afforded a colorless syrup in 71% yield. $[\alpha]_D^{25}$ +153.0 (*c* 1.7, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.39 (br s, 1H), 4.43 (br s, 1H), 3.91 (ddd, *J* = 16.5, 10.5, 6.0 Hz, 1H), 3.82 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.21 (s, 3H), 3.10 (s, 3H), 2.68 (d, *J* = 3.6 Hz, –OH), 2.33–2.20 (m, 1H), 2.10 (dd, *J* = 15.9, 5.8 Hz, 1H), 1.74 (t, *J* = 7.7 Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 1.29–1.05 (m, 4H), 0.79 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 137.4, 124.2, 99.8, 99.7, 76.2, 70.9, 66.6, 48.0, 47.9, 37.1, 34.4, 30.1, 23.0, 18.5, 18.4, 14.5. HRMS (ESI) calcd for $C_{16}H_{28}NaO_5$ $[M+Na]^+$: 323.1834. Found: 323.1843.

4.12. (3*S*,4*R*,5*R*)-4,5-*O*-Cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethyl-1-methyl-1-cyclohexene (24)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:20→1:8) afforded a colorless syrup in 98% yield. $[\alpha]_D^{25}$ +20.8 (*c* 1.6, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.62 (d, *J* = 1.2 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.39 (ddd, *J* = 7.5, 3.7, 2.5 Hz, 1H), 4.14 (ddd, *J* = 7.4, 5.3, 2.5 Hz, 1H), 3.86 (dt, *J* = 5.8, 2.1 Hz, 1H), 3.27 (s, 3H), 2.12 (dd, *J* = 15.6, 2.0 Hz, 1H), 1.79–1.51 (br m, 12H), 1.27–1.22 (br m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 134.3, 123.7, 109.5, 96.1, 75.8, 73.9, 73.6, 55.5, 36.9, 35.0, 34.1, 26.1, 24.8, 24.6, 23.8. HRMS (ESI) $C_{15}H_{24}NaO_4$ $[M+Na]^+$: 291.1572. Found: 291.1567.

4.13. (1*R*,2*R*,3S)-5-Butyl-1,2-*O*-cyclohexylidene-3-*O*-methoxymethyl-4-cyclohexene-1,2,3-triol (25)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:30→1:15) afforded a colorless syrup in 89% yield. $[\alpha]_D^{24}$ +30.8 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.64 (d, *J* = 1.0 Hz, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.42 (ddd, *J* = 7.4, 3.6, 2.0 Hz, 1H), 4.16 (dd, *J* = 5.3, 2.6 Hz, 1H), 3.89 (t, *J* = 1.8 Hz, 1H), 3.30 (s, 3H), 2.19 (dd, *J* = 15.7, 2.2 Hz, 1H), 1.96 (t, *J* = 7.4 Hz, 2H), 1.76–1.53 (m, 9H), 1.37–1.20 (m, 6H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 138.5, 123.2, 109.5, 96.1, 76.0, 74.1, 73.5, 55.6, 37.6, 36.7, 34.8, 33.0, 30.2, 26.1, 24.8, 24.6, 23.1, 14.5. HRMS (ESI) calcd for $C_{18}H_{30}NaO_4$ $[M+Na]^+$: 333.2042. Found: 333.2037.

4.14. (3*S*,4*R*,5*R*,7*R*)-*N*-Benzyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethyl-7-methylazepane (26)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:60→1:20) afforded a pale yellow syrup in 47% yield. $[\alpha]_D^{25}$ −16.5 (*c* 0.9, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.51 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 2H), 4.57 (d, *J* = 6.8 Hz, 2H), 4.53 (d, *J* = 7.9 Hz, 1H), 4.00 (dt, *J* = 8.4, 2.3 Hz, 1H), 3.64 (d, *J* = 14.1 Hz, 2H), 3.58 (d,

J = 14.1 Hz, 2H), 3.38–3.30 (m, 2H), 3.22 (s, 3H), 2.89 (dd, J = 14.5, 1.1 Hz, 1H), 2.10–2.06 (br m, 1H), 1.95 (t, J = 6.0 Hz, 2H), 1.96–1.64 (m, 7H), 1.38 (dt, J = 11.7, 5.9 Hz, 2H), 1.10 (d, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 141.5, 129.5–127.4 (-Ar+C_6D_6), 108.6, 95.8, 79.6, 74.1, 72.6, 55.5, 53.4, 53.0, 51.6, 36.8, 36.3, 34.3, 26.1, 24.8, 24.5, 20.6. HRMS (ESI) calcd for $C_{22}H_{34}NO_4$ $[M+H]^+$: 376.2482. Found: 376.2526.

4.15. (3*S*,4*R*,5*R*,7*S*)-*N*-Benzyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethyl-7-methylazepane (27)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:60→1:20) afforded a colorless syrup in 7% yield. $[\alpha]_D^{24}$ −54.8 (c 0.9, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.32–7.10 (m, 5H), 4.92 (d, J = 6.6 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H), 4.64–4.61 (m, 2H), 4.13 (dt, J = 8.2, 2.7 Hz, 1H), 3.51 (d, J = 13.2 Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H), 3.30 (s, 3H), 2.96–2.90 (m, 2H), 2.77–2.72 (m, 2H), 2.15 (ddd, J = 10.1, 6.4, 2.9 Hz, 1H), 2.00–1.89 (m, 2H), 1.85–1.70 (m, 6H), 1.46–1.40 (m, 2H), 0.95 (d, J = 6.3 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 140.4, 128.5–127.0 (-Ar+C_6D_6), 107.6, 97.4, 78.3, 76.0, 75.7, 59.3, 54.8, 52.9, 49.3, 37.3, 36.8, 33.9, 25.7, 24.3, 24.0, 11.1. HRMS (ESI) calcd for $C_{22}H_{34}NO_4$ $[M+H]^+$: 376.2482. Found: 376.2325.

4.16. (3*S*,4*R*,5*R*,7*R*)-*N*-Benzyl-7-butyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethylazepane (28)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:50→1:30) afforded a colorless syrup in 25% yield. $[\alpha]_D^{25}$ −32.0 (c 0.4, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.59 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 4.60 (d, J = 8.0 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 4.54 (d, J = 6.8 Hz, 1H), 4.32 (ddd, J = 8.0, 5.2, 2.9 Hz, 1H), 4.04 (dt, J = 9.4, 1.6 Hz, 1H), 3.76 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 14.1 Hz, 1H), 3.56 (dd, J = 14.3, 9.4 Hz, 1H), 3.26 (dd, J = 15.1, 7.4 Hz, 1H), 3.21 (s, 3H), 2.00–1.85 (br m, 3H), 1.80–1.30 (br m, 15H), 1.00 (t, J = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 141.4, 129.3, 128.9, 127.5, 108.6, 95.8, 79.8, 74.5, 71.4, 57.0, 55.5, 51.4, 50.8, 36.8, 34.8, 34.2, 33.9, 29.8, 26.1, 24.7, 24.4, 23.3, 14.6. HRMS (ESI) calcd for $C_{25}H_{40}NO_4$ $[M+H]^+$: 418.2957. Found: 418.2924.

4.17. (3*S*,4*R*,5*R*,7*S*)-*N*-Benzyl-7-butyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethylazepane (29)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:50→1:30) afforded a colorless syrup in 14% yield. $[\alpha]_D^{25}$ +30.7 (c 1.4, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.35 (d, J = 7.2 Hz, 2H), 7.35–7.26 (m, 2H), 7.21 (t, J = 7.2 Hz, 1H), 4.90 (d, J = 6.7 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 4.61 (ddd, J = 13.9, 10.4, 3.7 Hz, 1H), 4.59 (dd, J = 7.5, 3.0 Hz, 1H), 4.12 (dt, J = 7.5, 2.8 Hz, 1H), 3.63 (d, J = 13.6 Hz, 1H), 3.49 (d, J = 13.6 Hz, 1H), 3.31 (s, 3H), 3.08 (dd, J = 14.8, 1.9 Hz, 1H), 2.79–2.73 (dd+m, J = 14.7, 7.6 Hz, 2H), 2.67 (td, J = 13.2, 10.4 Hz, 1H), 2.27 (ddd, J = 13.2, 5.8, 4.0 Hz, 1H), 2.02–1.90 (m, 2H), 1.88–1.70 (m, 6H), 1.62–1.52 (m, 2H), 1.48–1.37 (m, 2H), 1.37–1.27 (m, 3H), 1.17–1.11 (m, 1H), 0.96 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 141.2, 129.2, 129.0, 128.7, 127.7, 108.2, 97.8, 79.2, 76.6, 76.3, 59.7, 55.4, 50.4, 37.5, 35.6, 34.4, 29.6, 27.9, 26.3, 24.9, 24.7, 23.7, 14.7. HRMS (ESI) calcd for $C_{25}H_{40}NO_4$ $[M+H]^+$: 418.2957. Found: 418.2924.

4.18. (3*S*,4*R*,5*R*,7*R*)-7-Methylazepane-3,4,5-triol (1)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:6:25→1:6:15) afforded a pale yellow syrup in 86% yield. $[\alpha]_D^{25}$ −27.3 (c 0.8, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 3.97 (dd, J = 4.8, 3.5 Hz, 1H), 3.95 (d, J = 2.6 Hz, 1H), 3.69 (ddd, J = 10.5, 4.7, 3.0 Hz, 1H), 2.99 (dq, J = 7.2, 6.6 Hz, 1H), 2.81 (ddd, J = 13.4, 4.7, 0.9 Hz, 1H), 2.69 (dd, J = 13.4, 10.5 Hz, 1H), 2.00 (ddd, J = 14.4, 9.4, 6.4 Hz, 1H), 1.53–1.47 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 76.8, 71.1, 68.3, 50.0, 47.8, 37.1, 22.3. HRMS (ESI) calcd for $C_7H_{16}NO_3$ $[M+H]^+$: 162.1130. Found: 162.1123.

4.19. (3*S*,4*R*,5*R*,7*S*)-7-Methylazepane-3,4,5-triol (2)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:6:25→1:6:15) afforded a colorless syrup in 92% yield. $[\alpha]_D^{24}$ +15.6 (c 0.3, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.10 (ddd, J = 8.7, 4.6, 1.7 Hz, 1H), 4.03–4.01 (br m, 1H), 3.89 (ddd, J = 11.0, 4.1, 2.4 Hz, 1H), 3.40–3.33 (m, 1H), 3.27 (dd, J = 13.6, 8.8 Hz, 1H), 3.17 (dd, J = 13.6, 4.7 Hz, 1H), 1.99 (dt, J = 15.0, 11.0 Hz, 1H), 1.84–1.78 (m, 1H), 1.27 (d, J = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 75.6, 69.5, 65.6, 50.9, 44.5, 34.9, 20.1. HRMS (ESI) calcd for $C_7H_{16}NO_3$ $[M+H]^+$: 162.1130. Found: 162.1141.

4.20. (3*S*,4*R*,5*R*,7*R*)-7-Butylazepane-3,4,5-triol (3)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:6:60→1:6:40) afforded a colorless syrup in 90% yield. $[\alpha]_D^{25}$ −10.7 (c 0.8, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 3.98 (dd, J = 8.7, 5.1 Hz, 2H), 3.70 (ddd, J = 10.6, 4.8, 2.9 Hz, 1H), 2.85 (dd, J = 13.3, 4.8 Hz, 1H), 2.81 (dd, J = 13.9, 7.1 Hz, 1H), 2.69 (dd, J = 13.3, 10.7 Hz, 1H), 1.99 (ddd, J = 14.4, 10.0, 6.5 Hz, 1H), 1.56 (ddd, J = 14.4, 7.4, 5.1 Hz, 1H), 1.36–1.31 (m, 2H), 1.26–1.21 (m, 4H), 0.81 (t, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 77.0, 71.3, 68.5, 54.5, 48.3, 36.3, 35.5, 27.5, 22.0, 12.3. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ $[M+H]^+$: 204.1600. Found: 204.1557.

4.21. (3*S*,4*R*,5*R*,7*S*)-7-Butylazepane-3,4,5-triol (4)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:6:60→1:6:40) afforded a colorless syrup in 91% yield. $[\alpha]_D^{25}$ +17.9 (c 1.0, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 3.98 (br s, 1H), 3.85 (dt, J = 11.1, 2.6 Hz, 1H), 3.77 (ddd, J = 9.2, 4.0, 2.9 Hz, 1H), 2.92 (dd, J = 14.0, 9.2 Hz, 1H), 2.76–2.71 (m, 1H), 2.63 (dd, J = 14.0, 4.0 Hz, 1H), 1.83 (dt, J = 14.3, 11.0 Hz, 1H), 1.61 (ddd, J = 14.3, 4.0, 1.1 Hz, 1H), 1.36–1.31 (m, 2H), 1.25–1.19 (m, 4H), 0.80 (t, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 75.7, 70.5, 70.3, 52.5, 44.6, 36.3, 34.8, 27.4, 22.0, 13.3. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ $[M+H]^+$: 204.1600. Found: 204.1583.

4.22. (3*R*,4*S*,5*R*,7*R*)-7-Methylazepane-3,4,5-triol (5)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:6:25→1:6:15) afforded a yellow syrup as a mixture in a ratio of 10:1 in 89% total yield (major isomer). ^{1}H NMR (600 MHz, D_2O) δ 3.71 (td, J = 9.1, 2.2 Hz, 1H), 3.48 (ddd, J = 10.4, 8.2, 3.7 Hz, 1H), 3.30 (dd, J = 17.5, 9.4 Hz, 1H), 3.09 (dt, J = 17.0, 5.5 Hz, 1H), 2.91 (dd, J = 13.9, 3.7 Hz, 1H), 2.67 (dd, J = 13.9, 10.4 Hz, 1H), 1.96 (ddd, J = 15.2, 9.1, 5.6 Hz, 1H), 1.65 (ddd, J = 15.2, 4.6, 2.3 Hz, 1H), 1.06 (d, J = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 80.2, 73.2, 68.2, 48.0, 47.6, 37.5, 21.2.

4.23. (3*R*,4*S*,5*R*,7*R*)-7-Butylazepane-3,4,5-triol (7)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:6:40→1:6:25) afforded a yellow syrup as a mixture in a ratio of 10:1 in 90% total yield (major isomer). ^{1}H NMR (600 MHz, D_2O) δ 3.68 (dd, J = 15.7, 8.8 Hz, 1H), 3.48–3.40 (m, 1H), 3.27 (t, J = 8.4 Hz, 1H), 2.91–2.85 (m, 2H), 2.63 (dd, J = 13.4, 10.8 Hz, 1H), 1.93 (ddd, J = 15.2, 9.1, 6.0 Hz, 1H), 1.69 (dd, J = 15.2, 2.2 Hz, 1H), 1.40–1.35 (m, 2H), 1.25–1.22 (m, 4H), 0.83

(t, J = 6.8 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 80.5, 73.5, 68.3, 52.5, 47.8, 36.0, 35.2, 27.7, 21.9, 23.2.

4.24. (3*S*,4*R*,6*S*)-6-*O*-Benzyl-3,4-*O*-cyclohexylidene-1-methylazepane (47)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:32→1:4) afforded a pale yellow syrup in 48% yield. $[\alpha]_D^{25}$ +21.0 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.35 (d, J = 7.6 Hz, 2H), 7.29–7.25 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 4.43–4.36 (m, 2H), 4.35–4.28 (m, 2H), 3.38 (tdd, J = 11.2, 4.0, 1.3 Hz, 1H), 3.09 (dt, J = 11.6, 2.0 Hz, 1H), 2.84 (ddd, J = 13.3, 4.9, 1.5 Hz, 1H), 2.62–2.52 (m, 2H), 2.32 (t, J = 10.1 Hz, 1H), 2.21 (s, 3H), 2.11 (ddd, J = 13.4, 11.2, 2.0 Hz, 1H), 1.90–1.65 (m, 8H), 1.42–1.35 (m, 2H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.2, 129.0–126.0 (-Ar), 108.6, 76.4, 74.4, 74.2, 70.3, 65.5, 58.6, 48.0, 37.8, 36.7, 34.4, 25.5, 24.3, 24.0. HRMS (ESI) calcd for $C_{20}H_{30}NO_3$ $[M]^+$: 332.2220. Found: 332.2181.

4.25. (3*S*,4*R*,6*R*)-6-*O*-Benzyl-3,4-*O*-cyclohexylidene-1-methylazepane (48)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:32→1:4) afforded a pale yellow syrup in 49% yield. $[\alpha]_D^{26}$ −14.9 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.39 (d, J = 7.5 Hz, 2H), 7.29–7.25 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 4.77 (t, J = 9.8 Hz, 1H), 4.55 (t, J = 10.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 3.60–3.53 (br s, 1H), 2.80 (td, J = 16.0, 3.5 Hz, 2H), 2.63 (dd, J = 13.4, 9.4 Hz, 1H), 2.40–2.33 (m, 1H), 2.29 (s, 3H), 2.26 (d, J = 12.8 Hz, 1H), 2.02 (dd, J = 14.0, 9.6 Hz, 1H), 1.92 (dd, J = 10.4, 5.2 Hz, 2H), 1.82 (dt, J = 12.2, 6.1 Hz, 2H), 1.73–1.64 (m, 4H), 1.45–1.35 (m, 2H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.2, 108.2, 76.7, 73.7, 70.2, 63.1, 58.9, 47.7, 38.0, 34.6, 33.6, 25.5, 24.4, 24.0. HRMS (ESI) calcd for $C_{20}H_{30}NO_3$ $[M^+]$: 332.2220. Found: 332.2205.

4.26. (3*S*,4*R*,6*S*)-6-*O*-Benzyl-1-butyl-3,4-*O*-cyclohexylideneazepane (49)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:32→1:16) afforded a clear syrup in 54% yield. $[\alpha]_D^{25}$ −2.5 (*c* 0.8, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.36 (d, J = 7.4 Hz, 2H), 7.30–7.25 (m, 2H), 7.20 (t, J = 7.3 Hz, 2H), 4.46 (d, J = 12.1 Hz, 1H), 4.43–4.33 (m, 3H), 3.39 (tdd, J = 11.2, 4.1, 1.6 Hz, 1H), 3.19 (ddd, J = 11.7, 3.8, 1.6 Hz, 1H), 3.04 (ddd, J = 13.5, 5.0, 1.6 Hz, 1H), 2.65 (dd, J = 13.6, 10.4 Hz, 1H), 2.56 (ddt, J = 12.8, 5.6, 1.5 Hz, 1H), 2.49 (dd, J = 11.6, 9.9 Hz, 1H), 2.45–2.34 (m, 2H), 2.16 (dt, J = 13.0, 11.2 Hz, 2H), 1.90 (t, J = 5.9 Hz, 2H), 1.82–1.77 (m, 2H), 1.77–1.68 (m, 4H), 1.44–1.33 (m, 4H), 1.30–1.22 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, 129.0–126.0 (-Ar), 108.7, 76.8, 75.0, 74.8, 70.4, 63.8, 59.4, 56.5, 37.9, 37.0, 34.5, 29.7, 25.5, 24.3, 24.0, 20.4, 13.9. HRMS (ESI) calcd for $C_{23}H_{36}NO_3$ $[M+H]^+$: 374.2695. Found: 374.2651.

4.27. (3*S*,4*R*,6*R*)-6-*O*-Benzyl-1-butyl-3,4-*O*-cyclohexylideneazepane (50)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:32→1:8) afforded a pale yellow syrup in 59% yield. $[\alpha]_D^{26}$ +13.2 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.41 (d, J = 7.6 Hz, 2H), 7.30–7.25 (m, 2H), 7.19 (t, J = 7.4 Hz, 1H), 4.78 (t, J = 9.5 Hz, 1H), 4.51–4.45 (m, 2H), 4.43 (d, J = 12.0 Hz, 1H), 3.66–3.60 (br s, 1H), 2.95–2.87 (m, 2H), 2.67 (dd, J = 13.7, 9.5 Hz, 1H), 2.50–2.42 (m, 3H), 2.40–2.32 (m, 1H), 2.09 (dd, J = 14.0, 9.5 Hz, 1H), 1.94 (t, J = 6.6 Hz, 2H), 1.83 (dt, J = 12.1, 5.6 Hz, 2H), 1.76–1.67 (m, 4H), 1.48–1.30 (m, 6H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, 129.0–126.0 (-Ar), 108.2, 77.1, 73.9, 73.8, 70.2, 61.2, 58.9, 56.7, 38.0, 34.7, 33.8, 30.0, 25.5, 24.4, 24.0, 20.4, 14.0. HRMS(ESI) calcd for $C_{23}H_{36}NO_3$ $[M+H]^+$: 374.2695. Found: 374.2651.

4.28. (3*R*,4*R*,6*S*)-6-*O*-Benzyl-3,4-dihydroxy-1-*N*-methyl-3,4-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-dioxy] azepane (52)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:16→1:2) afforded a clear syrup in 56% yield. $[\alpha]_D^{26}$ +117.6 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.37 (d, J = 7.5 Hz, 2H), 7.29–7.25 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 4.77 (d, J = 12.1 Hz, 1H), 4.36 (d, J = 12.1 Hz, 1H), 4.07 (td, J = 8.9, 5.9 Hz, 1H), 3.87 (td, J = 11.1, 1.7 Hz, 1H), 3.57 (ddd, J = 15.4, 10.2, 4.9 Hz, 1H), 3.22 (s, 3H), 3.19 (s, 3H), 2.91 (dd, J = 12.8, 5.8 Hz, 1H), 2.75 (dd, J = 13.9, 4.8 Hz, 1H), 2.57 (ddd, J = 12.8, 8.9, 2.3 Hz, 1H), 2.43 (ddd, J = 13.0, 5.5, 1.4 Hz, 1H), 2.31 (s, 3H), 2.26 (ddd, J = 13.0, 10.9, 2.5 Hz, 1H), 1.49 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, 129.0–126.0 (-Ar), 99.0, 98.6, 75.4, 71.9, 70.1, 68.0, 62.9, 61.4, 47.9, 47.4, 47.3, 35.8, 17.8, 17.7. HRMS (ESI) calcd for $C_{20}H_{32}NO_3$ $[M+H]^+$: 366.2280. Found: 366.2215.

4.29. (3*R*,4*R*,6*S*)-6-*O*-Benzyl-1-*N*-butyl-3,4-dihydroxy-3,4-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-dioxy] azepane (53)

Flash column chromatography (230–400 mesh SiO_2, EtOAc–hexane 1:30→1:8) afforded a pale yellow syrup in 40% yield. $[\alpha]_D^{26}$ +92.8 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.39 (d, J = 7.2 Hz, 2H), 7.28–7.25 (m, 2H), 7.19 (t, J = 7.4 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.39 (d, J = 12.1 Hz, 1H), 4.05 (td, J = 9.2, 5.8 Hz, 1H), 3.87 (ddd, J = 11.2, 9.5, 1.9 Hz, 1H), 3.57 (dtd, J = 15.7, 10.3, 4.7 Hz, 1H), 3.24 (s, 3H), 3.21 (s, 3H), 3.07 (ddd, J = 13.0, 5.8, 0.8 Hz, 1H), 2.89 (dd, J = 14.1, 4.0 Hz, 1H), 2.65 (td, J = 10.5, 4.7 Hz, 2H), 2.55–2.50 (m, 2H), 2.44 (ddd, J = 13.1, 5.7, 1.9 Hz, 1H), 2.29 (ddd, J = 13.1, 10.7, 8.3 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.48–1.44 (m, 2H), 1.38–1.32 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.4, 129.0–126.0 (-Ar), 99.0, 98.6, 75.7, 72.4, 70.1, 68.3, 60.4, 59.5, 58.9, 47.4, 47.3, 35.8, 30.1, 20.4, 17.8, 17.7, 14.0. HRMS (ESI) calcd for $C_{23}H_{38}NO_3$ $[M+H]^+$: 408.2750. Found: 408.2729.

4.30. (3*S*,4*R*,6*S*)-1-*N*-Methylazepane-3,4,6-triol (9)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:20:70→1:20:50) afforded a clear syrup in 83% yield. $[\alpha]_D^{26}$ +9.9 (*c* 0.9, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.00 (dd, J = 9.5, 4.8 Hz, 1H), 3.99–3.95 (m, 1H), 3.89 (ddd, J = 9.5, 4.4, 2.9 Hz, 1H), 3.00 (dd, J = 13.3, 4.1 Hz, 1H), 2.97 (dd, J = 13.8, 3.2 Hz, 1H), 2.88 (dd, J = 12.8, 6.3 Hz, 1H), 2.80 (dd, J = 12.4, 7.9 Hz, 1H), 2.52 (s, 3H), 2.07–1.96 (m, 2H). ^{13}C NMR (150 MHz, D_2O) δ 69.8, 69.1, 65.1, 63.1, 59.2, 46.9, 36.8. HRMS (ESI) calcd for $C_7H_{16}NO_3$ $[M+H]^+$: 162.1125. Found: 162.1194.

4.31. (3*S*,4*R*,6*R*)-1-*N*-Methylazepane-3,4,6-triol (10)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:20:70→1:20:50) afforded a clear syrup in 69% yield. $[\alpha]_D^{25}$ +23.6 (*c* 0.5, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.07–4.01 (m, 2H), 3.90–3.85 (m, 1H), 2.78 (dd, J = 13.7, 5.1 Hz, 1H), 2.66–2.58 (m, 2H), 2.48 (dd, J = 13.7, 6.7 Hz, 1H), 2.27 (s, 3H), 2.23 (dt, J = 9.4, 4.8 Hz, 1H), 1.65 (ddd, J = 14.6, 6.5, 1.8 Hz, 1H). ^{13}C NMR (150 MHz, D_2O) δ 71.5, 68.3, 65.4, 63.4, 60.3, 47.2, 35.9. HRMS (ESI) calcd for $C_7H_{16}NO_3$ $[M]^+$: 162.1125. Found: 162.1097.

4.32. (3*S*,4*R*,6*S*)-1-*N*-Butylazepane-3,4,6-triol (11)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:20:70) afforded a clear syrup in 71% yield. $[\alpha]_D^{26}$

−9.4 (*c* 1.3, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 3.89–3.82 (m, 3H), 2.81 (dd, *J* = 13.0, 4.5 Hz, 1H), 2.78 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.60 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.50 (dd, *J* = 13.0, 8.3 Hz, 1H), 2.46 (t, *J* = 8.0 Hz, 2H), 1.98–1.88 (m, 2H), 1.42–1.35 (m, 2H), 1.20 (sextet, *J* = 7.5 Hz, 2H), 0.82 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 70.9, 69.1, 66.9, 61.7, 58.3, 57.5, 37.3, 27.6, 20.1, 13.3. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ $[M]^+$: 204.1521. Found: 204.1609.

4.33. (3*S*,4*R*,6*R*)-1-*N*-Butylazepane-3,4,6-triol (12)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:20:70) afforded a pale yellow syrup in 67% yield. $[\alpha]_D^{26}$ +1.8 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.07–4.01 (m, 2H), 3.90 (s, 1H), 2.90 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.74 (d, *J* = 5.3 Hz, 2H), 2.58–2.50 (m, 3H), 2.34 (ddd, *J* = 14.2, 8.9, 4.6 Hz, 1H), 1.66 (dd, *J* = 14.5, 6.8 Hz, 1H), 1.47–1.37 (m, 2H), 1.21 (sextet, *J* = 7.3 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 71.4, 68.6, 65.4, 60.7, 58.5, 57.4, 36.3, 27.4, 20.0, 13.22. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ $[M]^+$: 204.1594. Found: 204.1531.

4.34. (3*R*,4*R*,6*S*)-1-*N*-Methylazepane-3,4,6-triol (13)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:20:70–1:20:50) afforded a white solid in 90% yield. Mp = 215.2–220.2 °C. $[\alpha]_D^{25}$ −5.7 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.25–4.21 (m, 1H), 4.03 (ddd, *J* = 7.3, 7.3, 2.5 Hz, 1H), 3.88 (ddd, *J* = 7.0, 7.0, 5.3 Hz, 1H), 3.50 (d, *J* = 13.6 Hz, 1H), 3.38 (dd, *J* = 13.3, 2.9 Hz, 1H), 3.30–3.21 (m, 2H), 2.28 (ddd, *J* = 14.9, 4.7, 3.7 Hz, 1H), 1.93 (ddd, *J* = 14.9, 8.5, 7.5 Hz, 1H). ^{13}C NMR (150 MHz, D_2O) δ 70.5, 70.2, 63.3, 61.9, 58.0, 46.2, 37.9. HRMS (ESI) calcd for $C_7H_{15}NO_3$ $[M+H]^+$: 162.1125. Found: 162.1167.

4.35. (3*R*,4*R*,6*S*)-1-*N*-Butylazepane-3,4,6-triol (14)

Flash column chromatography (230–400 mesh SiO_2, NH_4OH–MeOH–CH_2Cl_2 1:20:60→1:20:40) afforded a pale yellow syrup in 88% yield. $[\alpha]_D^{25}$ −17.2 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.07 (dddd, *J* = 13.7, 9.7, 7.9, 4.0 Hz, 1H), 3.77 (td, *J* = 7.1, 3.4 Hz, 1H), 3.70 (ddd, *J* = 9.7, 7.7, 3.5 Hz, 1H), 3.13 (dd, *J* = 14.0, 2.5 Hz, 1H), 3.09 (dd, *J* = 13.1, 3.8 Hz, 1H), 2.91 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.86–2.79 (m, 3H), 2.10 (dt, *J* = 14.0, 3.5 Hz, 1H), 1.84 (dt, *J* = 14.0, 9.7 Hz, 1H), 1.60–1.47 (m, 2H), 1.27 (sextet, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 72.6, 71.2, 64.9, 60.8, 58.8, 57.2, 38.8, 26.4, 19.6, 13.0. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ $[M+H]^+$: 204.1594. Found: 204.1591.

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