Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 12 (2004) 3259–3267
Bioorganic & Medicinal Chemistry

Versatile approach for the synthesis of novel seven-membered iminocyclitols via ring-closing metathesis dihydroxylation reaction

Chang-Ching Lin,[a] Yi-shin Pan,[b] Laxmikant N. Patkar,[b] Hsiu-Mei Lin,[b] Der-Lii M. Tzou,[b] Thangaiah Subramanian[b] and Chun-Cheng Lin[b,*]

[a]*Department of Chemistry, Tsing Hua University, Hsinchu 300, Taiwan*
[b]*Institute of Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan*

Received 17 December 2003; revised 29 March 2004; accepted 30 March 2004
Available online 10 May 2004

Abstract—Seven-membered iminocyclitols with diverse diastereomers were prepared starting with D- and L-serines and employing ring-closing olefin metathesis and dihydroxylation reaction sequence. The iminocyclitols were assayed for glycosidase inhibition and compound **20** was found to be a competitive inhibitor for β-glucosidase with K_i 26.3 μM.

1. Introduction

Glycosidases and glycosyltransferases are involved in the processing and synthesis of complex carbohydrates,[1] which are essential in various biological recognition processes.[2,3] Consequently, the design and synthesis of inhibitors targeting these enzymes recently has attracted considerable interest.[3,4] Iminocyclitols (azasugars), formed by the replacement of sugar ring oxygen with nitrogen, are well known for their ability to selectively inhibit glycosidases, and, hence, are considered as potentially therapeutic agents for viral, proliferative and metabolic diseases.[3–5] Over the last 30 years, most of works on the design and synthesis of glycosidase inhibitors have focused on five- and six-membered iminocyclitols, which are considered to mimic the substrate transition states with oxacarbenium ion character and a distorted six-membered ring.[3,4a,5a,e,6]

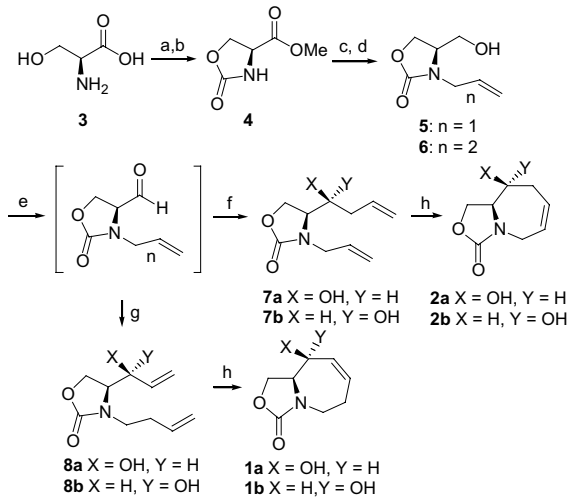
Meanwhile, polyhydroxyazepanes, seven-membered iminocyclitols,[7] received little attention before Wong and co-workers revealed that polyhydroxyazepanes exhibited promising glycosidase inhibitory profiles against a broad range of glycosidases.[8] The enhanced potency of inhibition has been hypothesized to result from the greater flexibility of seven-membered ring compared to five- or six-membered ring. Additionally, azepanes may adopt a quasi-flattened conformation, improving binding to the active site of the enzyme. This has stimulated interest in developing strategies for synthesizing new types of polyhydroxyazepanes employing hemical[9–11] and enzymatic methods.[12] Most of these methods use sugar derivatives as starting compounds[10,12] for synthesizing polyhydroxyazepanes, during which process the stereochemistry of hydroxyl groups at the carbon backbone was fixed and preserved during synthetic transformation. These approaches result in limited number of stereoisomers that can be synthesized simultaneously for SAR (structure–activity relationship) study. Thus, a synthetic method that provides access to diverse stereoisomers is extremely desirable. Here, we describe a new approach for accessing to structurally versatile stereoisomers of polyhydroxyazepanes and their glycosidase inhibitory properties.

2. Results and discussion

Recently, we delineated a convenient access to functionalized oxazolidinyl azacycles **1** and **2** (Scheme 1) using ring-closing olefin metathesis (RCM) as a key step.[13] As outlined in Scheme 1, starting from L-serine **3**, compound **4** was obtained in two steps and subjected to *N*-alkenylation using suitable alkenyl bromide in the presence of base.[13,14] The ester groups of *N*-alkenyl intermediates were reduced to give the corresponding

Keywords: Iminocyclitols; Ring-closing metathesis; Dihydroxylation; Glycosidase inhibitor.
* Corresponding author. Tel.: +886-2-27898648; fax: +886-2-278350-07; e-mail: cclin@chem.sinica.edu.tw

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.03.064

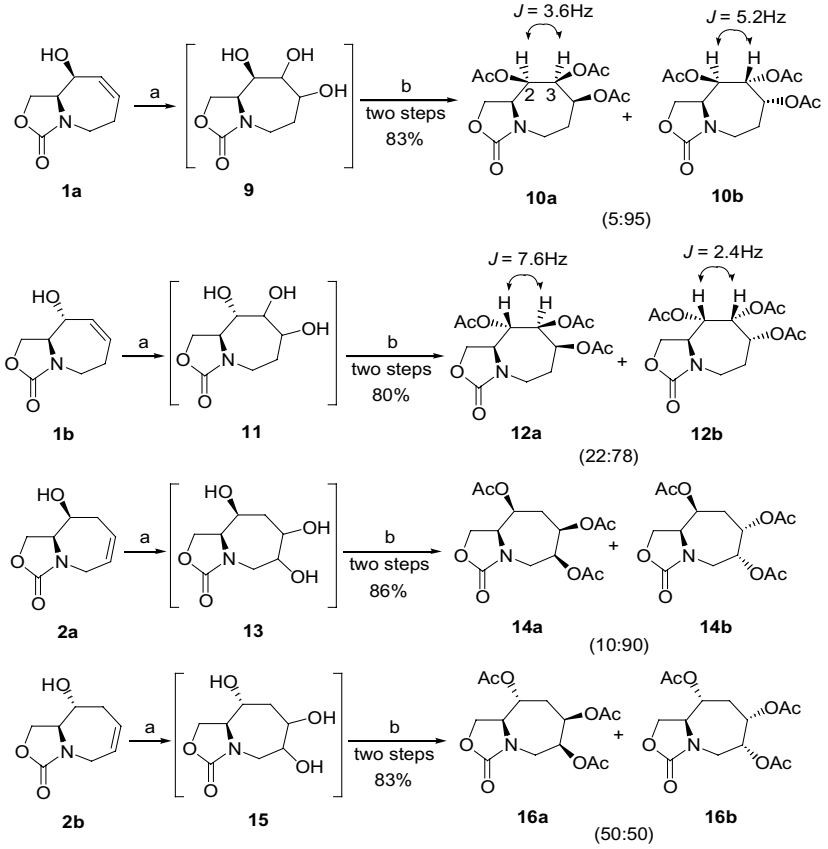


Scheme 1. Synthesis of oxazolidinyl azacycles. Reagents and conditions: (a) $SOCl_2$, MeOH reflux, overnight; (b) K_2CO_3, triphosgene, H_2O/toluene, 87%; (c) 60% NaH, allyl bromide or homoallyl bromide, DMF; (d) $NaBH_4$, MeOH; (e) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N; (f) allylmagnesium bromide; (g) vinylmagnesium bromide; (h) Grubb's catalyst (10 mol%), CH_2Cl_2, reflux, 12 h.

alcohols **5** and **6**.[13,15] Oxidation of alcohols to yield aldehydes was followed by the addition of alkenyl Grignard reagents led to the formations of the corresponding alcohols **7** and **8**, respectively. Notably, attempts to purify aldehyde intermediates resulted in isolation of the decomposed products. Finally, RCM[16] of **7** and **8** with Grubb's catalyst, $Cl_2(PCy_3)_2Ru{=}CHPh$,[17] furnished the required intermediates **1** and **2**, respectively.

The advantage of this approach was that with the appropriate choice of alkenyl moiety on nitrogen atom of **4** and nucleophilic addition of alkenyl nucleophiles on aldehyde intermediates derived from **5** (or **6**), six-, seven- or eight-membered rings could easily be constructed by placing the olefin double bond at the desired position in relation to the ring nitrogen. Further functionalization of the ring double bond by epoxidation followed by stereoselective epoxide-ring opening,[11,13,18] or by dihydroxylation,[11,18e–h,19] results in hydroxylated rings leading to a number of stereoisomers, and this approach has been shown to be successful in the synthesis of pyrrolizidines.[11,13,18,19]

As shown in Scheme 2, oxazolidinyl azacycles **1a** was subjected to dihydroxylation using catalytic amount of osmium tetraoxide (1 mol%) and NMO in acetone/water (8:1)[20] to yield **9**. Notably, no reaction occurred when AD mix α or β was used.[21] To simplify the purification process, **9** was further acetylated to give the derivatives **10a** and **10b**. The configurations of these two stereoisomers were assigned by comparing the proton coupling constants between the protons on carbons 2



Scheme 2. Dihydroxylation of oxazolidinyl azacycles. Reagents and conditions: (a) OsO_4, NMO, acetone/H_2O = 8:1; (b) Ac_2O, py, DMAP, CH_2Cl_2, rt, two steps 80%.

and 3 as indicated in Scheme 2. The coupling constant of the *syn*-isomer is smaller than that of the *anti*-isomer, and the proportion of **10a** to **10b** was determined to be 5:95. Similar dihydroxylation of other oxazolidinyl azacycles **1b** and **2a/b** afforded products **12a** and **12b** (22:78), **14a** and **14b** (10:90) and **16a** and **16b** (50:50), respectively.

The structures for **12a** and **12b** were easily determined by using ^{1}H NMR. To determine the stereochemistry of **14**, **14b** was recrystallized and the X-ray crystal was shown to have a configuration corresponding to compound **14b** (Fig. 1). Moreover, the stereochemistry of compounds **16a/b** was determined by comparing their ^{1}H NMR with those of their enantiomers. X-ray crystallographic analysis was used to determine the structure of **16c**, an enantiomer of **16a**, thus, automatically fixed the configurations of **16b**. Dihydroxylation of allylic alcohols of cyclic compounds using OsO_4/NMO system generally results in dihydroxylation with *anti*-diastereofacial selectivity to the existing hydroxyl group (or hetero atom) on the adjacent carbon atom.[22] The selectivity is proposed to result from a combination of steric factors and electrostatic repulsion between the hydroxyl function and the Os-complex.[23] This study noted similar *anti*-diastereofacial selectivities in the formation of products, **10b** and **14b**.

These high anti-diastereofacial selectivities probably result from two heteroatoms, O and N, with a *syn*-relationship that reinforces the individual effects. However, poor diastereofacial selectivities were observed for dihydroxylation of **1b** and **2b**, where the two heteroatoms have an *anti*-relationship. Furthermore, as shown in Figure 2, the molecular models of **1a/b** were generated by energy minimization using the DISCOVER module from Insight II (Molecular Simulations, Waltham, MA). The hydroxyl group of compound **1a** was found to significantly influence steric and electrostatic repulsion, resulting in good regioselectivity of dihydroxylation

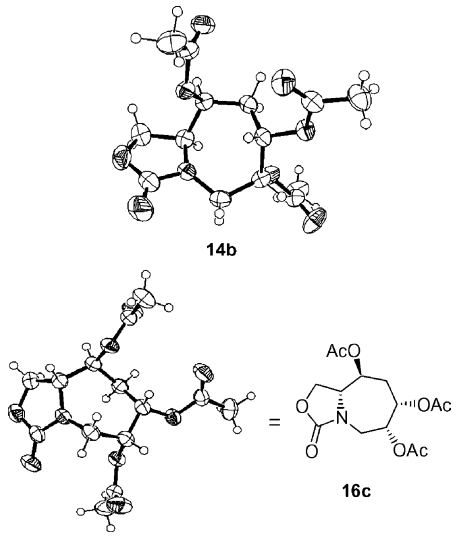


Figure 1. ORTEP represention of the X-ray crystal structures of **14b** and **16c**.

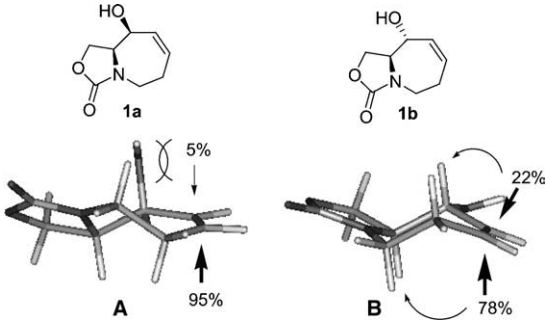
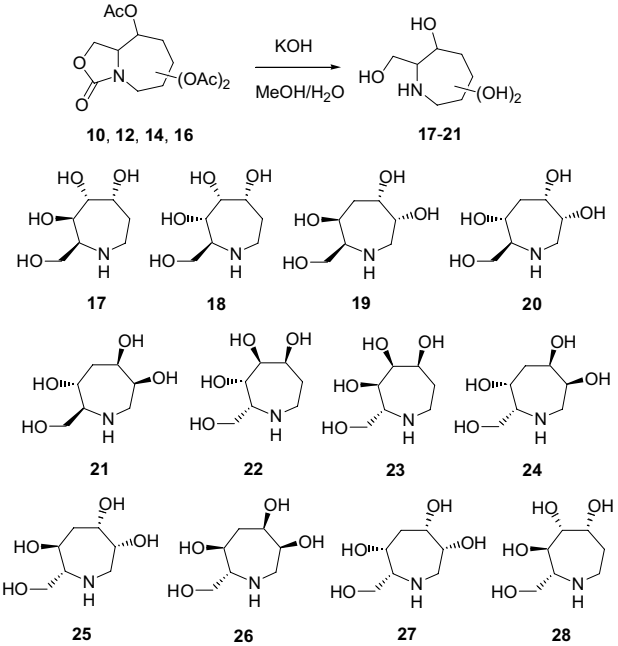


Figure 2. The molecular models of **1a/b**.

from the face opposite the hydroxyl group. As the orientation of the hydroxyl group changes from *S* to *R* form, the conformation switches from **A** to **B**. The regioselection of dihydroxylation from α face displays less steric repulsion than that of β face with the ratio between the two repulsions being 22:78.

Once each of the stereoisomers was separated and their structures determined, compounds **10**, **12**, **14** and **16** were subjected to oxazolidine ring-opening hydrolysis to yield corresponding iminocyclitols, as represented in Scheme 3. Also, epimers of compounds **22**–**27** (Scheme 3) were synthesized using the established protocol and starting from D-serine.

The iminocyclitols shown in Scheme 3 were assessed as inhibitors of different glycosidases, and the results were listed in Table 1. Compound **20** showed the most potency inhibition for β-glucosidase. The Lineweaver–Burk plot (Fig. 3) for inhibiting 4-nitrophenyl β-D-glucoside hydrolysis catalyzed by β-glucosidase following the addition of **20** revealed that this compound binds



Scheme 3. Preparation of iminocyclitols **17**–**28**.

Table 1. Inhibition of glycosidase with various seven-membered iminocyclitols

Compd no	α-Glucosidase	α-Galatosidase	α-Mannosidase	β-Glucosidase	β-Galatosidase	β-Mannosidase
17	NI	21	NI	NI	NI	NI
18	10	NI	NI	NI	NI	NI
19	NI	NI	21	NI	NI	24
20	NI	10	NI	75	4	37
21	NI	16	12	47	4	24
22	NI	42	7	6	NI	NI
23	2	58	28	NI	NI	NI
24	NI	22	NI	NI	NI	34
25	NI	30	35	64	NI	32
26	NI	59	43	66	NI	33
27	NI	56	27	61	NI	30
28	1	47	22	41	19	10

- % Inhibition determined at 2 mM concentraction of inhibitor.
- NI stands for no inhibition.
- Enzyme unit: used 0.05u.
- Substrate concentration : $\sim K_m$ (mM).

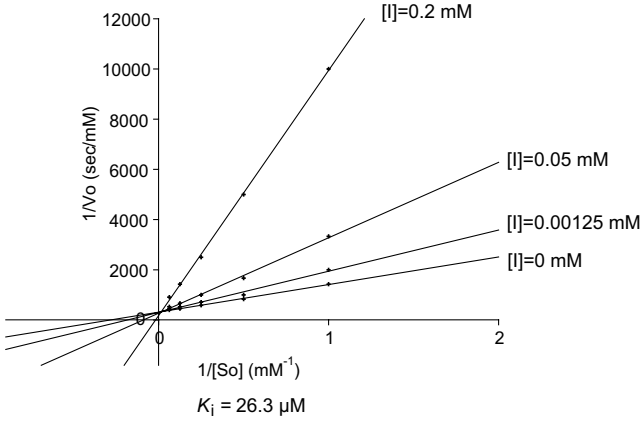


Figure 3. Lineweaver–Burk plot for inhibition of β-glucosidase by **20**.

competitively to the active site of the enzyme. The measured K_i value of **20** is 26.3 μM. Further, the four iminocyclitols, **20**, **25**, **26** and **27**, which displayed greater than 50% competitive inhibition for β-glucosidase, all bear a same *trans*-5,6 configuration (sugar numbering) found in glucose and have 4-hydroxy missing. However, one would be surprised that compound **20** with L-configuration at 6-position displayed the highest percentage inhibition. It is worth to note that the literature precedence for the seven-membered iminocyclitols with the missing hydroxymethyl side arm at the 6-position exhibit even higher activity.[8a] Our results reinforces this view.

3. Conclusion

This work has designed a versatile route for preparing diverse stereoisomers of seven-membered iminocyclitols in good yields using ring-closing olefin metathesis dihydroxylation reaction sequence. The current efforts involve the synthesis of various seven-membered iminocyclitols. The results will be reported in due course.

4. Experimental

All reactions were performed under an argon atmosphere, unless otherwise mentioned. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 or 500 MHz. Assignment of ^{1}H NMR spectra was achieved using 2D methods (COSY). Chemical shifts are expressed in ppm using residual $CDCl_3$ as reference. High-resolution mass spectra were obtained with a VG 70-250S mass spectrometer in the FAB mode. Optical rotation was measured with a Jasco DIP-370 polarimeter at ~25 °C. Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254). Silica gel 60 (E. Merck Co.) was employed for all flash chromatography. All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless indicated otherwise. All solvents were dried and distilled by standard techniques.

4.1. 4-(*S*)-Carbomethoxyl-oxazolidine-2-one (4)

To a reaction mixture containing L-serine (10 g, 95.2 mmol), thionyl chloride (7.78 mL, 106.6 mmol) in methanol (150 mL) was refluxed for overnight. The solvent was removed to give L-serine methylester hydrochloride salt in ca. quantitative yield. To a solution of L-serine methylester hydrochloride salt (14.75 g, 94.8 mmol), triphosgene (11 g, 36.97 mmol) and K_2CO_3 (20.4 g, 142.2 mmol) in toluene (85 mL) was added water (85 mL) at room temperature, and then stirred for 4 h. The solvents were removed and the resultant residues was triturated with hot ethyl acetate and then filtered. The filtrate was concentrated to give the desired compound as oily material (11.97 g, 87%). The oily material was used in next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 4.43 (dd, $J = 4.6$, 9.4 Hz, 1H), 4.54 (dd, $J = 4.6$, 9.0 Hz, 1H), 4.62 (t, $J = 9.0$ Hz, 1H), 6.25 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.1, 53.7, 66.8, 158.9, 170.4; HRMS (FAB) calcd for $C_5H_8NO_4$ ($M+H^+$) 146.0453, found 146.0436.

4.2. 4(*S*)-3-Allyl-4-hydroxymethyl-oxazolidine-2-one (5)

To a stirred solution of **4** (10 g, 68.9 mmol) in DMF (100 mL) was added NaH (3.3 g, 82.7 mmol, 60% immersion in mineral oil) at 0 °C. After the evolution of H_2 ceased, allyl bromide (7.1 mL, 82.7 mmol) was added. The reaction mixture was stirred for overnight at rt. The solvent (DMF) was evaporated and the resultant residues were dissolved in EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The resultant residues were purified by silica gel flash chromatography to obtain the desired *N*-allyl oxazolidinone (9.6 g, 75%).

To the stirred solution of above oxazolidinone (9 g, 48.6 mmol) in methanol (50 mL) at 0 °C was added $NaBH_4$ (2.02 g, 53.5 mmol) in portions and the resultant solution was stirred for 3 h at room temperature. After the reaction was completed, the reaction was quenched with water and diluted with dichloromethane and extracted. The organic extracts were washed with brine and dried over Na_2SO_4. After removing the solvent, the residues were purified by silica gel flash chromatography to obtain the desired compound **5** (6.9 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (br, 1H), 3.62–3.66 (m, 1H), 3.72–3.81 (m, 2H), 3.85–3.90 (m, 1H), 4.09 (ddd, $J = 1.5$, 5.3, 15.7 Hz, 1H), 4.26 (dd, $J = 5.9$, 8.8 Hz, 1H), 4.37 (dd, $J = 8.8$, 8.8, Hz, 1H), 5.24–5.31 (m, 2H), 5.82 (dddd, $J = 5.3$, 7.1, 7.2, 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2, 56.1, 60.8, 64.5, 118.8, 132.4, 158.6; HRMS (FAB) calcd for $C_7H_{12}NO_3$ (M+H$^+$) 158.0817, found 158.0832.

4.3. 4(*S*)-3-But-3-enyl-4-hydroxymethyl-oxazolidine-2-one (6)

This compound was synthesized in 57% yield according to the procedure for the synthesis of **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (br, 1H), 2.31–2.43 (m, 2H), 3.19–3.26 (m, 1H), 3.53 (ddd, $J = 7.6$, 7.6, 14.3 Hz, 1H), 3.63–3.67 (m, 1H), 3.80 (dd, $J = 4.0$, 11.8 Hz, 1H), 3.86–3.92 (m, 1H), 4.24 (ddd, $J = 0.8$, 5.7, 8.9 Hz, 1H), 4.34 (dd, $J = 8.9$, 8.9 Hz, 1H), 5.08-5.17 (m, 2H), 5.79 (dddd, $J = 6.9$, 6.9, 10.2, 13.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 32.0, 41.6, 56.3, 61.0, 64.4, 117.6, 134.8, 158.8; HRMS (FAB) calcd for $C_8H_{14}NO_3$ (M+H$^+$) 172.0974, found 172.0973.

4.4. 4(*S*)-3-Allyl-4-(1-hydroxy-but-3-enyl)-oxazolidine-2-one (7)

To a stirred solution of oxlalyl chloride (670 μL, 7.6 mmol) in CH_2Cl_2 (20 mL) was added DMSO (1.13 mL, 15.9 mmol) at −78 °C. The reaction mixture was warmed to −60 °C over 20 min and the alcohol **5** (1.04g, 6.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min. The reaction mixture was allowed to gradually warm up to −35 °C over 20 min and then triethylamine (3.7 mL, 26.48 mmol) was added. The reaction mixture was then brought to −70 °C, and allylmagnesium bromide (6.6 mL, 6.6 mmol) was added to it. After stirring for 1 h, the mixture was treated with 10 mL of H_2O and 10 mL of saturated aqueous NaCl. Then it was extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was removed and the resultant residues were purified by silica gel flash chromatography (ethyl acetate/hexane, 1:1, 2.5% MeOH) to give compound **7** as mixtures (900 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04–2.28 (m, 6H), 3.82–3.88 (m, 6H), 4.14–4.37 (m, 6H), 5.15–5.30 (m, 8H), 5.78–5.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 36.3, 37.1, 44.8, 46.4, 58.2, 58.3, 62.2, 64.2, 66.8, 71.0, 118.4, 118.6, 118.8, 119.0, 132.1, 132.4, 133.6, 133.6, 158.8, 159.0; HRMS (FAB) calcd for $C_{10}H_{16}NO_3$ (M+H$^+$) 198.1130, found 198.1131.

4.5. 4(*S*)-3-But-3-enyl-4-(1-hydroxy-allyl)-oxazolidine-2-one (8)

This compound was synthesized in 53% yield according to the procedure for the synthesis of **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (br, 2H), 2.30–2.47 (m, 4H), 3.23–3.31 (m, 2H), 3.54–3.64 (m, 2H), 3.83–3.99 (m, 2H), 4.13–4.26 (m, 4H), 4.31–4.34 (m, 1H), 4.41–4.43 (m, 1H), 5.06–5.17 (m, 4H), 5.31–5.37 (m, 2H), 5.40–5.50 (m, 2H), 5.71–5.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.1, 42.0, 42.8, 58.3, 59.0, 62.5, 63.9, 69.8, 69.8, 73.5, 117.5, 117.8, 118.5, 119.4, 134.9, 135.0, 135.1, 135.3, 158.8, 159.2; HRMS (FAB) calcd for $C_{10}H_{15}NO_3$ (M+H$^+$) 198.1130, found 198.1128.

4.6. (9a*S*)-9,9a-Dihydro-9-hydroxyoxazolo[3,4-*a*]azepin-3-one (2a and 2b)

To the solution of compound **7** (0.9 g, 4.56 mmol) in dichloromethane (80 mL) was added Grubbs reagent (first generation, 375 mg, 0.456 mmol) and the resultant solution was refluxed for 12 h. After the reaction was completed, the solution was concentrated and purified by silica gel flash chromatography (ethyl acetate/hexane, 1:1, 1% MeOH) to give **2a** and **2b** (1:1, 700 mg, 90%). For **2a** $[\alpha]_D^{27}$ +38.9 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (d, $J = 10.6$ Hz, 1H), 2.47 (ddd, $J = 2.1$, 4.5, 8.6 Hz, 1H), 2.74 (m, 1H), 3.55 (m, 1H), 3.93 (br, 1H), 4.0 (dt, $J = 2.3$, 8.2 Hz, 1H), 4.34 (br, 1H), 4.36 (br, 1H), 5.72 (m, 1H), 5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.1, 42.6, 62.4, 64.0, 67.5, 126.9, 129.6, 158.5; HRMS (FAB) calcd for $C_8H_{11}NO_3$ (M+H$^+$) 170.0817, found 170.0820; For **2b** $[\alpha]_D^{34}$ −18.41 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45–2.60 (m, 2H), 2.86 (br, 1H), 3.53–3.62 (m, 2H), 3.78 (ddd, $J = 5.6$, 7.3, 8.6 Hz, 1H), 4.20 (dd, $J = 5.6$, 8.9 Hz, 1H), 4.28 (dd, $J = 6.8$, 16.7 Hz, 1H), 4.44 (dd, $J = 8.6$, 8.9 Hz, 1H), 5.75 (m, 1H), 5.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.7, 41.7, 64.0, 66.2, 71.1, 127.0, 129.8, 157.9; HRMS (FAB) calcd for $C_8H_{11}NO_3$ (M+H$^+$) 170.0817, found 170.0840.

4.7. (9a*S*)-5,6,9,9a-Tetrahydro-9-hydroxyoxazolo[3,4-*a*]-azepin-3(1H)-one (1)

This compound was synthesized in 86% yield (**1a**/**1b** = 1.13:1) according to the procedure for the synthesis

of **2.** For **1a** ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25–2.35 (m, 2H), 2.48 (1H, br), 2.92 (ddd, $J = 3.4$, 9.6, 16.8 Hz, 1H), 3.63 (ddd, $J = 5.6$, 8.5, 14.2), 3.86 (ddd, $J = 3.9$, 8.5, 16.8 Hz, 1H), 4.34 (dd, $J = 5.6$, 9.1 Hz, 1H), 4.41 (dd, $J = 9.1$, 8.5 Hz, 1H), 5.77 (ddd, $J = 2.04$, 4.2, 13.8 Hz, 1H), 5.91–5.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.7, 41.71, 64.0, 66.2, 71.1, 127.0, 129.8, 157.9; HRMS (FAB) calcd for $C_8H_{11}NO_3$ (M+H$^+$) 170.0817, found 170.0840; For **1b** ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (br, 1H), 2.38 (m, 1H), 2.46–2.55 (m, 1H), 3.30 (ddd, $J = 2.9$, 8.1, 13.1 Hz, 1H), 3.74 (ddd, $J = 3.1$, 8.5, 13.1 Hz, 1H), 4.06 (m, 2H), 4.32–4.40 (m, 2H), 5.94 (m, 1H), 6.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 42.9, 59.6, 66.1, 73.0, 129.2, 136.4, 158.2; HRMS (FAB) calcd for $C_8H_{11}NO_3$ (M+H$^+$) 170.0817, found 170.0820.

4.8. General procedure for dihydroxylation and peracetylation

To a solution of alkene (138.1 mg, 0.816 mmol) in acetone/water (2 mL, 8:1) was added *N*-methyl morpholine *N*-oxide (286 mg, 2.44 mmol) and OsO_4 (502 μL, 0.04 mmol as a 2.5% wt/wt solution in *t*-BuOH). The solution was stirred at room temperature for 4 h and then aqueous Na_2SO_3 (saturated, 1 mL) and MeOH (1 mL) were added. The mixture was filtered and filtrate was concentrated in vacuo. The triol was used without further purification for acetylation.

Acetic anhydride (2.5 mL) was added to the above residues in 5 mL of anhydrous pyridine and stirred at room temperature for 3 h then concentrated in vacuo. The isomers were separated by HPLC (ethyl acetate/hexane, 1:1, 1% MeOH, ZORBAX column, 3 mL/min).

4.9. (7*S*,8*S*,9*R*,9a*S*)-7,8-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (10a)

$[\alpha]_D^{34}$ +0.32 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (m, 1H), 2.06 (s, 3H), 2.131 (s, 3H), 2.129 (s, 3H), 2.30 (dtd, $J = 3.3$, 10.4, 13.8 Hz, 1H), 3.08 (ddd, $J = 2.3$, 10.4, 14.6 Hz, 1H), 3.86 (ddd, $J = 3.3$, 6.6, 14.6 Hz, 1H), 4.21 (dd, $J = 4.0$, 8.3 Hz, 1H), 4.30 (t, $J = 8.3$, 1H), 4.34 (t, $J = 4.0$, 8.3 Hz, 1H), 5.20 (ddd, $J = 2.6$, 4.2, 10.4 Hz), 5.28 (d, 3.6 Hz, 1H), 5.37 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 20.6, 20.9, 26.9, 38.5, 54.5, 63.5, 70.7, 71.4, 73.9, 157.6, 168.1, 169.8, 169.8; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ 330.1189 (M+H$^+$), found 330.1190.

4.10. (7*R*,8*R*,9*R*,9a*S*)-7,8-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (10b)

$[\alpha]_D^{34}$ +0.09 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (m, 1H), 2.04 (s, 3H), 2.15 (s, 3H), 2.17 (s, 3H), 2.31 (dtd, $J = 4.0$, 10.5, 14.8 Hz, 1H), 3.45 (dt, $J = 4.0$, 13.0, 1H), 3.65 (td, $J = 4.0$, 13.0 Hz, 1H), 4.10 (dd, $J = 3.5$, 8.9 Hz, 1H), 4.31 (dd, $J = 3.5$, 8.9 Hz, 1H), 4.37 (t, $J = 8.9$ Hz, 1H), 5.03 (d, $J = 5.2$ Hz, 1H), 5.11 (dt, $J = 1.9$, 10.5 Hz, 1H), 5.32 (dd, $J = 1.9$, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 20.8, 20.9, 26.0, 40.4, 52.9, 65.1, 69.5, 69.8, 71.5, 157.9, 168.9, 169.7, 169.7; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ 330.1189 (M+H$^+$), found 330.1181.

4.11. (7*S*,8*S*,9*S*,9a*S*)-7,8-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (12a)

$[\alpha]_D^{34}$ +16.42 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (ddt, $J = 3.2$, 6.3, 14.3 Hz, 1H), 2.07 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.36 (dtd, $J = 4.2$, 10.2, 14.3 Hz, 1H), 3.08 (ddd, $J = 3.2$, 9.8, 14.3 Hz, 1H), 3.83 (ddd, $J = 4.2$, 6.3, 14.3 Hz, 1H), 3.96 (dt, $J = 4.5$, 9.2 Hz, 1H), 4.04 (dd, $J = 4.5$, 9.2 Hz, 1H), 4.45 (t, $J = 9.2$ Hz, 1H), 5.15 (dd, $J = 4.5$, 7.6 Hz, 1H), 5.27 (dd, $J = 1.7$, 7.6 Hz, 1H), 5.34 (ddd, $J = 1.7$, 3.2, 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.7, 20.9, 21.1, 27.2, 39.1, 59.1, 66.5, 69.9, 72.7, 73.6, 157.5, 169.6, 169.9, 170.4; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ (M+H$^+$) 330.1189, found 330.1195.

4.12. (7*R*,8*R*,9*S*,9a*S*)-7,8-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (12b)

$[\alpha]_D^{34}$ +0.46 (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (m, 1H), 2.03 (s, 3H), 2.04 (s, 3H), 2.19 (s, 3H), 2.29 (dtd, $J = 5.2$, 10.1, 15.1 Hz, 1H), 3.46 (dt, $J = 5.2$, 13.5 Hz, 1H), 3.74 (ddd, $J = 5.2$, 10.1, 13.5 Hz, 1H), 4.02 (dd, $J = 5.4$, 9.0 Hz, 1H), 4.21 (dt, $J = 5.4$, 9.6 Hz, 1H), 4.37 (t, $J = 9.0$ Hz, 1H), 4.93 (dd, $J = 2.4$, 9.6 Hz), 5.08 (ddd, 1.8, 3.2, 10.1 Hz, 1H), 5.59 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 20.9, 20.1, 25.0, 40.9, 53.2, 65.3, 70.8, 71.3, 73.0, 157.9, 169.5, 169.7, 170.0; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ (M+H$^+$) 330.1189, found 330.1185.

4.13. (6*S*,7*R*,9*S*,9a*S*)-6,7-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (14a)

$[\alpha]_D^{34}$ −12.58 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (d, $J = 14.2$ Hz, 1H), 2.05 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.58 (dt, $J = 9.8$, 14.2 Hz, 1H), 3.05 (dd, $J = 1.2$, 14.8 Hz, 1H), 4.13 (dd, $J = 5.6$, 14.8 Hz, 1H), 4.16 (t, $J = 8.5$ Hz, 1H), 4.28 (t, $J = 8.5$ Hz, 1H), 4.33 (td, $J = 2.4$, 8.5 Hz, 1H), 5.06 (dt, $J = 2.5$, 9.8 Hz, 1H), 5.17 (m, 1H), 5.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.0, 21.0, 29.1, 41.9, 56.2, 63.9, 69.5, 70.2, 71.4, 158.2, 169.9, 170.0, 170.4; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ (M+H$^+$) 330.1189, found 330.1183.

4.14. (6*R*,7*S*,9*S*,9a*S*)-6,7-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (14b)

$[\alpha]_D^{34}$ −14.23 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.11 (br, 2H), 2.14 (s, 3H), 2.15 (s, 3H), 3.48 (dd, $J = 4.8$, 14.6 Hz, 1H), 3.86 (dd, $J = 4.8$, 14.6 Hz, 1H), 4.08 (dd, $J = 5.0$,

8.8 Hz, 1H), 4.20 (m, 1H), 4.37 (t, $J = 8.8$ Hz, 1H), 5.20 (br, 2H), 5.48 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.2, 21.6, 31.7, 44.5, 57.5, 65.5, 68.6, 70.6, 71.5, 158.2, 169.4, 170.0, 170.5; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ ($M+H^+$) 330.1189, found 330.1191.

4.15. (6*S*,7*R*,9*R*,9a*S*)-6,7-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (16a)

$[\alpha]_D^{34}$ −14.06 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H), 2.09 (s, 3H), 2.15 (s, 3H), 2.21 (t, $J = 7.6$ Hz, 1H), 2.21 (t, $J = 6.5$ Hz, 1H), 3.38 (dd, $J = 5.4$, 14.5 Hz, 1H), 3.99 (dd, $J = 5.4$, 14.5 Hz, 1H), 4.00 (td, $J = 5.0$, 9.2 Hz, 1H), 4.11 (dd, $J = 5.0$, 9.2 Hz, 1H), 4.41 (t, $J = 9.2$ Hz, 1H), 4.86 (ddd, $J = 6.5$, 7.6, 9.2 Hz, 1H), 5.11 (td, $J = 1.5$, 7.6 Hz, 1H), 5.36 (td, $J = 1.5$, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 20.9, 20.9, 31.8, 45.1, 58.5, 66.5, 69.7, 70.2, 72.6, 157.8, 169.2, 169.6, 169.7; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ ($M+H^+$) 330.1189, found 330.1185.

4.16. (6*R*,7*S*,9*R*,9a*S*)-6,7-Bis(acetyloxy)-3-oxohexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-azepin-9-yl acetate (16b)

$[\alpha]_D^{34}$ +12.33 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (dd, $J = 6.3$, 14.6 Hz, 1H), 2.05 (s, 3H), 2.12 (s, 3H), 2.17 (s, 3H), 2.50 (t, $J = 14.6$ Hz, 1H), 3.03 (d, $J = 5.2$ Hz, 1H), 3.94 (m, 2H), 4.19 (dd, $J = 4.0$, 15.2 Hz, 1H), 4.55 (m, 1H), 4.98 (d, $J = 6.3$, 1H), 5.27 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 20.9, 20.9, 28.9, 42.9, 61.8, 65.7, 68.6, 69.7, 71.8, 157.7, 169.9, 170.0, 170.4; HRMS (FAB) calcd for $C_{14}H_{20}NO_8$ ($M+H^+$) 330.1189, found 330.1183.

4.17. General procedure for hydrolysis of oxazolidinones

To a stirred solution of **10** (30 mg, 0.09 mmol) in 50% aqueous EtOH (3 mL) at 23 °C was added solid KOH (51.06 mg, 1.64 mmol), and the mixture was heated at 90 °C for 10 h. After this period, the mixture was cooled to 23 °C and neutralized with dilute HCl. The mixture was concentrated under reduced pressure. The residues were subjected to Bio-Gel P2 (fine, 45–90 μm) column chromatography eluting with water. After removal of water via lyophilization, the azasugar was obtained (14.6 mg, ~90%).

4.18. (2*S*,3*R*,4*R*,5*R*)-2-(Hydroxymethyl)azepane-3,4,5-triol (17)

^{1}H NMR (400 MHz, CD_3OD): δ 1.58 (m, 1H), 2.22 (m, 1H), 2.81–2.93 (m, 2H), 2.96 (td, $J = 1.2$, 7.2 Hz, 1H), 3.48 (d, $J = 7.2$ Hz, 1H), 3.67 (dd, $J = 1.2$, 4.4 Hz, 1H), 3.88 (m, 1H), 4.04 (dt, $J = 2.0$, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 30.9, 44.1, 57.1, 64.4, 70.7, 71.8, 77.6; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1072.

4.19. (2*S*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)azepane-3,4,5-triol (18)

^{1}H NMR (400 MHz, CD_3OD): δ 1.81–1.86 (m, 2H), 2.81–2.94 (m, 3H), 3.41–3.46 (m, 2H), 3.80 (dd, $J = 4.0$, 11.2 Hz, 1H), 3.95–3.99 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 34.5, 43.9, 64.2, 64.5, 73.5, 74.2, 79.7; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$), 178.1079 Found 178.1082.

4.20. (3*R*,4*S*,6*S*,7*S*)-7-(Hydroxymethyl)azepane-3,4,6-triol (19)

^{1}H NMR (400 MHz, CD_3OD): δ 1.84 (m, 1H), 2.17 (ddd, $J = 3.6$, 10.0, 14.0 Hz 1H), 2.76 (dd, $J = 6.0$, 14.0 Hz 1H), 2.91 (m, 1H), 3.17 (dd, $J = 5.6$, 14.0 Hz, 1H), 3.48 (dd, $J = 7.6$, 10.8 Hz, 1H), 3.53 (dd, $J = 6.4$, 10.8 Hz, 1H), 3.95 (m, 2H), 4.14 (dt, $J = 2.4$, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 38.6, 52.0, 64.3, 64.4, 67.9, 70.0, 75.4; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, Found 178.1072.

4.21. (3*R*,4*S*,6*R*,7*S*)-7-(Hydroxymethyl)azepane-3,4,6-triol (20)

^{1}H NMR (400 MHz, CD_3OD): δ 1.90 (br, 1H), 2.30 (ddd, $J = 2.0$, 10.8, 14.0 Hz 1H), 3.05 (m, 2H), 3.23 (dd, $J = 2.0$, 14.0 Hz, 1H), 3.70 (m, 2H), 3.84 (dt, $J = 2.8$, 10.8 Hz, 1H), 3.90 (dd, $J = 3.6$, 11.6 Hz, 1H), 3.95 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 38.9, 47.0, 61.7, 66.1, 67.5, 70.0, 71.8; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1082.

4.22. (3*S*,4*R*,6*R*,7*S*)-7-(Hydroxymethyl)azepane-3,4,6-triol (21)

^{1}H NMR (400 MHz, CD_3OD): δ 1.69 (m, 1H), 2.43 (ddd, $J = 3.6$, 10.4, 14.0 Hz, 1H), 2.60 (m, 1H), 2.82 (dd, $J = 2.4$, 14.0 Hz, 1H), 3.15 (dd, $J = 4.8$, 14.0 Hz, 1H), 3.44 (dd, $J = 8.0$, 11.2 Hz, 1H), 3.70 (m, 1H), 3.74 (dd, $J = 4.0$, 11.2 Hz, 1H), 3.85 (m, 1H), 4.03 (dt, $J = 2.0$, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 37.5, 52.5, 64.6, 68.7, 68.8, 69.7, 73.5; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1072.

4.23. (2*R*,3*S*,4*S*,5*S*)-2-(Hydroxymethyl)azepane-3,4,5-triol (22)

^{1}H NMR (400 MHz, CD_3OD): δ 1.58 (m, 1H), 2.22 (m, 1H), 2.81–2.93 (m, 2H), 2.96 (td, $J = 1.2$, 7.2 Hz, 1H), 3.48 (d, $J = 7.2$ Hz, 1H), 3.67 (dd, $J = 1.2$, 4.4 Hz, 1H), 3.88 (m, 1H), 4.04 (dt, $J = 2.0$, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 30.9, 44.1, 57.0, 64.4, 70.7, 71.8, 77.6; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1074.

4.24. (2*R*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)azepane-3,4,5-triol (23)

^{1}H NMR (400 MHz, CD_3OD): δ 1.81–1.86 (m, 2H), 2.81–2.94 (m, 3H), 3.41–3.46 (m, 2H), 3.80 (dd, $J = 4.0$, 11.2 Hz, 1H), 3.95–3.99 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 34.5, 43.9, 64.2, 64.5, 73.5, 74.2, 79.7; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1075.

4.25. (3*S*,4*R*,6*R*,7*R*)-7-(Hydroxymethyl)azepane-3,4,6-triol (24)

^{1}H NMR (400 MHz, CD_3OD): δ 1.84 (m, 1H), 2.17 (ddd, $J = 3.6$, 10.0, 14.0 Hz, 1H), 2.76 (dd, $J = 6.0$, 14.0 Hz 1H), 2.91 (m, 1H), 3.17 (dd, $J = 5.6$, 14.0 Hz, 1H), 3.48 (dd, $J = 7.6$, 10.8 Hz, 1H), 3.53 (dd, $J = 6.4$, 10.8 Hz, 1H), 3.95 (m, 2H), 4.14 (dt, $J = 2.4$, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 38.6, 52.0, 64.3, 64.4, 67.9, 70.0, 75.4; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1072.

4.26. (3*R*,4*S*,6*S*,7*R*)-7-(Hydroxymethyl)azepane-3,4,6-triol (25)

^{1}H NMR (400 MHz, CD_3OD): δ 1.69 (m, 1H), 2.43 (ddd, $J = 3.6$, 10.4, 14.0 Hz, 1H), 2.60 (m, 1H), 2.82 (dd, $J = 2.4$, 14.0 Hz, 1H), 3.15 (dd, $J = 4.8$, 14.0 Hz, 1H), 3.44 (dd, $J = 8.0$, 11.2 Hz, 1H), 3.70 (m, 1H), 3.74 (dd, $J = 4.0$, 11.2 Hz, 1H), 3.85 (m, 1H), 4.03 (dt, $J = 2.0$, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 37.5, 52.5, 64.6, 68.7, 68.8, 69.7, 73.5; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1071.

4.27. (3*S*,4*R*,6*S*,7*R*)-7-(Hydroxymethyl)azepane-3,4,6-triol (26)

^{1}H NMR (400 MHz, CD_3OD): δ 1.90 (br, 1H), 2.30 (ddd, $J = 2.0$, 10.8, 14.0 Hz 1H), 3.05 (m, 2H), 3.23 (dd, $J = 2.0$, 14.0 Hz, 1H), 3.70 (m, 2H), 3.84 (dt, $J = 2.8$, 10.8 Hz, 1H), 3.90 (dd, $J = 3.6$, 11.6 Hz, 1H), 3.95 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 38.6, 47.0, 61.7, 66.1, 67.5, 70.0, 71.8; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1074.

4.28. (3*R*,4*S*,6*R*,7*R*)-7-(Hydroxymethyl)azepane-3,4,6-triol (27)

^{1}H NMR (400 MHz, CD_3OD): δ 2.10 (m, 2H), 2.63 (td, $J = 2.0$, 6.8 Hz 1H), 2.78 (dd, $J = 2.4$, 14.4 Hz, 1H), 3.06 (dd, $J = 4.8$, 14.4 Hz, 1H), 3.51 (bd, 2H), 3.87 (m, 1H), 3.91 (m, 1H), 3.96 (td, $J = 2.0$, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 39.3, 52.8, 63.9, 64.3, 67.8, 73.4, 75.8; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1081.

4.29. (2*R*,3*R*,4*R*,5*R*)-2-(Hydroxymethyl)azepane-3,4,5-triol (28)

^{1}H NMR (400 MHz, CD_3OD): δ 1.73 (ddd, $J = 4.0$, 9.6, 13.6 Hz, 1H), 2.02 (m, 1H), 2.53 (dt, $J = 4.0$, 8.0 Hz, 1H), 2.59 (ddd, $J = 4.0$, 10.8, 13.6 Hz, 1H), 3.15 (ddd, $J = 4.0$, 6.0, 13.6 Hz, 1H), 3.39 (dd, $J = 8.0$, 10.8 Hz, 1H), 3.44 (dd, $J = 5.2$, 8.0 Hz, 1H), 3.72 (d, $J = 5.2$ Hz, 1H), 3.79 (dd, $J = 4.0$, 10.8 Hz, 1H), 4.05 (dd, $J = 4.0$, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 33.1, 63.0, 65.2, 68.4, 71.5, 72.9, 81.2; HRMS (FAB) calcd for $C_7H_{16}NO_4$ ($M+H^+$) 178.1079, found 178.1075.

Acknowledgements

We acknowledge financial support from the Academia Sinica, National Science council in Taiwan (NSC91-2113-M-001-013) and National Tsing-Hua University.

References and notes

1. (a) Lis, H.; Sharon, N. *Eur.J. Biochem.* **1993**, *218*, 1–27; (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720; (c) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683–4696; (d) Ernst, B.; Hart, G. W.; Sinaÿ. In *Carbohydrates in Chemistry and Biology*; Wiley–VCH: Weinheim, 2000; Vol. 3.
2. (a) Varki, A. *Glycobiology* **1993**, *3*, 97–130; (b) Sears, P.; Wong, C.-H. *Cell. Mol. Life Sci.* **1998**, *54*, 223–252.
3. Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301–2324.
4. (a) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770; (b) Winchester, B.; Fleet, G. W. J. *J. Carbohydr. Chem.* **2000**, *19*, 471–483; (c) Lillelund, V. H.; Jensen, H. H.; Laing, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553.
5. (a) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171–1202; (b) Winchester, B.; Fleet, G. W. *J. Glycobiology* **1992**, *2*, 199–210; (c) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605–611; (d) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley–VCH: Weinheim, Germany, 1999; (e) Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11–18; (f) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265–295; (g) Asano, N. *Glycobiology* **2003**, *23*, 93R–104R.
6. (a) Varrot, A.; Tarling, C. A.; Macdonald, J. M.; Stick, R. V.; Zechel, D. L.; Withers, S. G.; Davies, G. J. *J. Am. Chem. Soc.* **2003**, *125*, 7496–7497; (b) Zechel, D. L.; Boraston, A. B.; Gloster, T.; Boraston, C. M.; Macdonald, J. M.; Tilbrook, D. M. G.; Stick, R. V.; Davies, G. J. *J. Am. Chem. Soc.* **2003**, *125*, 14313–14323.
7. Previous studies on the the synthesis of azepanes see: (a) Paulsen, H.; Todt, K. *Chem. Ber.* **1976**, *100*, 512–520; (b) Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293–3296; (c) Lohray, B. B.; Jayamma, Y.; Chatterji, M. *J. Org. Chem.* **1995**, *60*, 5958–5960.
8. (a) Moris-Varas, F.; Qian, X.-H.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7647; (b) Qian, X.-H.; Moris-Varas, F.; Wong, C. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1117–1122; (c) Qian, X.-H.; Moris-Varas, F.; Fitzgerald, M. C.; Wong, C. H. *Bioorg. Med. Chem.* **1996**, *4*, 2055–2069.
9. For recent studies on the the synthesis of azepanes from bis-epoxides see: (a) Damour, D.; Barreau, M.; Blanchard,

J. C.; Burgevin, M. C.; Doble, A.; Herman, F.; Pantel, G.; Evelyne, J. S.; Vuilhorgne, M.; Mignani, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1667–1672; (b) Merrer, Y. L.; Poitout, L.; Depazy, J.; Dosbaa, I.; Geoffroy, S.; Foglietti, M. *Bioorg. Med. Chem.* **1997**, *5*, 519–533; (c) Gauzy, L.; Le Merrer, Y.; Depezay, J.-C.; Clere, F.; Mignani, S. *Tetrahedron Lett.* **1999**, *40*, 6005–6008; (d) McCort, I.; Sanièrè, M.; Merrer, Y. L. *Tetrahedron* **2003**, *59*, 2693–2700.

10. For recent studies on the the synthesis of azepanes from sugar derivatives see: (a) Fuentes, J.; Olano, D.; Pradera, M. A. *Tetrahedron Lett.* **1999**, *40*, 4063–4066; (b) Anderson, S. M.; Ekhart, C.; Lundt, I.; Stutz, A. E. *Carbohydr. Res.* **2000**, *326*, 22–33; (c) Painter, G. F.; Falshaw, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1157–1159; (d) Tezuka, K.; Com-pain, P.; Martin, O. R. *Synlett* **2000**, *12*, 1837–1839; (e) Gallos, J. K.; Demeroudi, S. C.; Stathopoulou, C. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 7497–7499; (f) Fuetes, J.; Gasch, C.; Olano, D.; Pradera, M. A.; Repetto, G.; Sayago, F. J. *Tetrahedron: Asymmetry* **2002**, *13*, 1743–1753; (g) Weinberg, K.; JanKowski, S.; Le Nouen, D.; Frankowski, A. *Tetrahedron Lett.* **2002**, *43*, 1089–1092; (h) Joseph, C. C.; Regeling, H.; Zwaneneburg, B.; Chittenden, G. J. F. *Tetrahedron* **2002**, *58*, 6907–6911; (i) Tilekar, J. N.; Patil, N. T.; Jadhav, H. S.; Dhavale, D. D. *Tetrahedron* **2003**, *59*, 1873–1876.
11. For recent studies on the the synthesis of azepanes from norbornane derivatives see: Mehta, G.; Lakshminath, S. *Tetrahedron Lett.* **2002**, *43*, 331–334.
12. Andreana, P. R.; Sanders, T.; Janczuk, A.; Warrick, J. I.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 6525–6528.
13. Subramanian, T.; Lin, C.-C.; Lin, C.-C. *Tetrahedron Lett.* **2001**, *42*, 4079–4082.
14. Falb, E.; Bechor, Y.; Hassner, A.; Albeck, A.; Gottlib, H. E. *J. Org. Chem.* **1999**, *64*, 498–506.
15. Miyata, O.; Ozawa, Y.; Ninomiya, I.; Aoe, K.; Hiramatsu, H.; Naito, T. *Heterocycles* **1997**, *46*, 321–333.
16. Other approaches to azasugars by ring-closing methatesis: (a) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraügel, H. *Eur.J. Org. Chem.* **1999**, *5*, 959–968; (b) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360; (c) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61–67.
17. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.
18. (a) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360; (b) Asano, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commum.* **1999**, 41–42; (c) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142; (d) Jakobsen, P.; Lundbeck, J. M.; Kristiansen, M.; Breinhol, J.; Demuth, H.; Pawlas, J.; Candeal, M. P. T.; Andersen, B.; Westergaard, N.; Lundgren, K.; Asano, N. *Bioorg. Med. Chem.* **2001**, *9*, 733–744; (e) Lennartz, M.; Steckhan, E. *Tetrahedron* **2001**, *57*, 675–680; (f) Banba, Y.; Abe, C.; Nemoto, H.; Kato, A.; Adachi, I.; Takahata, H. *Tetrahedron: Asymmetry* **2001**, *12*, 817–819; (g) Garcia, A. L.; Correia, C. R. D. *Tetrahedron Lett.* **2003**, *44*, 1553–1557; (h) Chapman, T. M.; Courttney, S.; Hay, P.; Davis, B. G. *Chem. Eur. J.* **2003**, *9*, 3397–3414.
19. (a) Ikota, N.; Nakagawa, H.; Ohno, S.; Noguchi, K.; Obkuyama, K. *Tetrahedron* **1998**, *54*, 8985–8998; (b) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971–3974; (c) Han, H. *Tetrahedron Lett.* **2003**, *44*, 1567–1569; (d) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387–2391.
20. Hermitage, S. A.; Murphy, A.; Nielsen, P.; Roberts, S. M. *Tetrahedron* **1998**, *54*, 13185–13202.
21. Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657–10670.
22. Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946–7956, and references cited therein.
23. (a) Cha, J. K.; Kim, N. S. *Chem. Rev.* **1995**, *95*, 1761; (b) Donohoe, T. J.; Moore, P. R.; Beddoes, R. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 43.