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Radical Cyclization in Heterocycle Synthesis. Part 9:[1] A Novel Synthesis of Aminocyclitols and Related Compounds via Stannyl Radical Cyclization of Oxime Ethers Derived from Sugars[2]

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Abstract—Stannyl radical addition–cyclization of oxime ethers derived from D-glucose, D-galactose, and D-xylose proceeded smoothly to afford alkoxyamino alcohols which were effectively converted into two types of glycosidase inhibitors or its candidates such as aminocyclitols, 1-deoxynojirimycin, and 1-deoxygalactostatin via reductive ring-expansion of *trans* alkoxyamino alcohols.

Introduction

Glycosidase inhibitors are known to be used for treating diabetes, viral diseases (HIV and influenza), bacterial infections, cancer and as insecticides. The majority of these inhibitors belong to monosaccharide analogs involving a basic nitrogen-containing functional group at a position close to the anomeric center as exemplified in 1-deoxynojirimycin and amidine derivatives.[3] On the other hand, five-membered hydroxypyrrolidines and aminocyclopentitols such as mannostatin and trehazoline are also powerful inhibitors of glycosidases.[4] Historically, the development of glycosidase inhibitors has been changed from 6-membered compounds such as 1-deoxunojirimycin to 5-membered aminocyclopentitols via amidine derivatives and hydroxypyrrolidines[4] (Fig. 1). Although there have been known many studies on glycosidase inhibitors as exemplified in the very recent Reymond report,[5] the relationship between the structure and inhibition activity remains poorly understood.

We report herein full detail of the synthesis of two types of glycosidase inhibitors such as 5-membered aminocyclopentitols and 6-membered 1-deoxynojirimycin via a route involving the radical cyclization of oxime ethers.[6] The radical cyclization has been developed recently for constructing functionalized cyclic compounds, one of which is adjacently substituted with two neighboring quaternary carbons. Additionally, we have found a very interesting reductive ring-expansion reaction of sterically fixed *anti* alkoxyamino alcohols, which has provided a novel synthesis of 1-deoxynojirimycin and 1-deoxygalactostatin.

Results and Discussion

Preparation and stannyl radical addition–cyclization of oxime ethers derived from sugars

Our synthetic strategy is shown in Scheme 1 where commercially available monosaccharides would be converted readily into oxime ethers having a carbonyl group in the same molecule, which would be subjected to

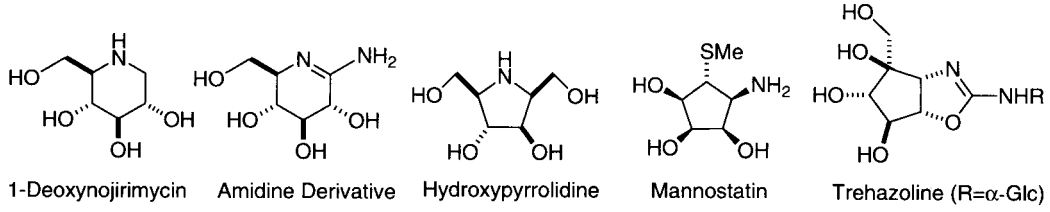

Figure 1.

Keywords: amino alcohols; piperidines; radicals and radical reactions; ring transformations.
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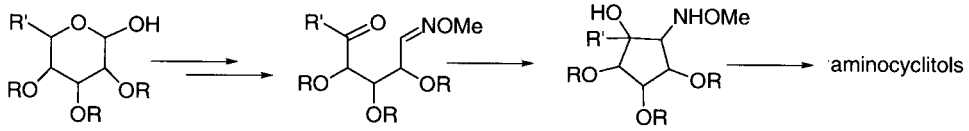


Scheme 1.

stannyl radical addition–cyclization to afford the desired aminocyclopentitols. There are known a few examples[7] of the same type of radical cyclization, but using different radical precursors, which, however, are not suitable for construction of the quaternary carbon atoms in the products.

In order to investigate not only the generality of stannyl radical addition–cyclization of oxime ethers but also the structure–activity relationship of the aminocyclitols which would be derived readily from the cyclized products, we picked up three typical monosaccharides, D-glucose, D-galactose and D-xylose, as the starting material for preparing the respective oxime ethers (Scheme 2).

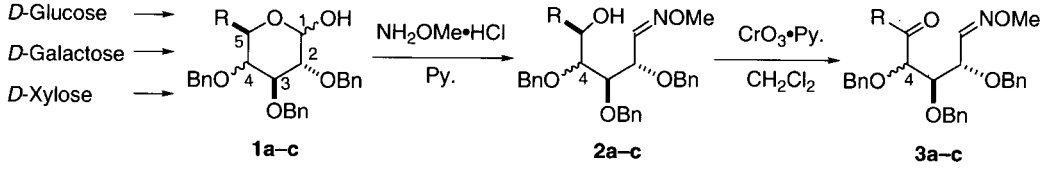
Tetra *O*-benzyl D-glucose **1a** is available commercially. The corresponding tetra *O*-benzyl D-galactose **1b** was prepared from commercially available methyl-α galactopyranoside via alkylation with benzyl chloride in the presence of KOH and subsequent hydrolysis of the acetal group.[8] The tetra *O*-benzyl D-xylose **1c** was also prepared from a tribenzyl compound via benzylation and hydrolysis of the acetal group.[9]

Three tetra *O*-benzyl compounds **1a–c** were readily converted into the oxime ethers **3a–c**, respectively, in 75–44% yield in two steps via the corresponding alcohols **2a–c** according to our procedure which involves the formation of the oxime ethers from hemiacetals and oxidation of the hydroxyl group at the 5-position.

Three oxime ethers **3a–c** were obtained as a mixture of *E*- and *Z*-isomers at the oxime ether moieties, the ratios of which were deduced from the signals due to the imino hydrogens and methoxy hydrogens in their ^{1}H NMR spectra. Thus, the *E*/*Z* ratios of **3a–c** were found to be 5/1, 3/1, and 3/1, respectively.

According to the Bartlett report[7a] that the geometry of the oxime ether group does not influence the *trans*/*cis* selectivity of the product in the radical cyclization, we investigated the radical addition–cyclization of a geometrical mixture of oxime ethers **3a–c** without their isolation. Oxime ether **3c** is less stable, probably due to the formyl group that is subjected to the radical cyclization just after characterization of the formyl group in the ^{1}H NMR spectrum.

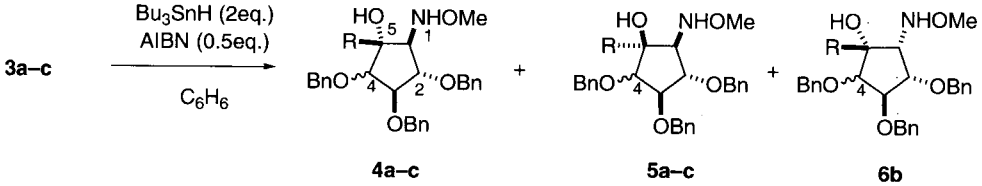
A solution containing tributyltin hydride (2 equiv.) and AIBN (0.5 equiv.) in benzene was added dropwise (10 ml h^{-1}) to a solution of the oxime ether **3a** in boiling benzene while stirring under nitrogen. The solution was then refluxed for a further 5 h to give a mixture of the cyclized products **4a**[10] and **5a**[10] which was separated by medium-pressure column chromatography (MCC). Under the same conditions, two oxime ethers **3b**,**c** gave a mixture of three **4b**, **5b**, and **6b** or two cyclized products **4c** and **5c** in the yields and ratios as shown in Table 1. The stereostructures of five-membered products **4–6** were established firmly by the chemical reactions and their spectral data in



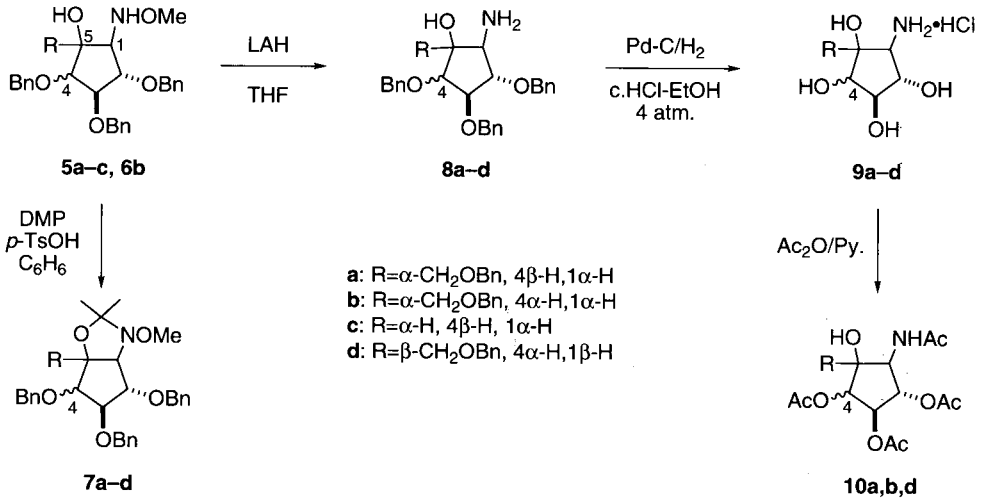
a: R=CH_2OBn, 4β-H; **b**: R=CH_2OBn, 4α-H; **c**: R=H, 4β-H

Scheme 2.

Table 1. Radical cyclization of oxime ethers **3a–c**



Entry		Substrate R	4-H	(*E*/*Z*)	Yield (%) **4**	**5**	**6**
1	**3a**	CH_2OBn	β	(5:1)	28	40	–
2	**3b**	CH_2OBn	α	(3:1)	44	8	23
3	**3c**	H	β	(3:1)	27	23	–



5a–c, 6b **8a–d** **9a–d**

7a–d **10a,b,d**

Scheme 3.

addition to the X-ray analysis[11] of **10a**. Relative configurations between the 1-, 2- and 5-positions were determined by the reaction with DMP in the presence of *p*-TsOH (Schemes 3 and 4). 1,5-*cis* Products **5a**–**c** and **6b** gave the corresponding acetonides **7a**–**d** while 1,5-*trans* isomers **4a**–**c** were recovered completely under the same reaction conditions. Thus, radical cyclization of oxime ether **3a** prepared from D-glucose gave 1,5-*cis* compound **5a** predominantly while **3b** prepared from D-galactose gave 1,5-*trans* isomer **4b** as a major in three products. In the case of **3c** prepared from D-xylose, a mixture of two compounds **4c** and **5c** was obtained in a ratio of 1.2:1. On the remaining stereostructures of the cyclized products, particularly the relative configuration between the 1- and 2-positions was deduced from comparisons of their spectra with those of the corresponding aminocyclitol derivatives as follows.

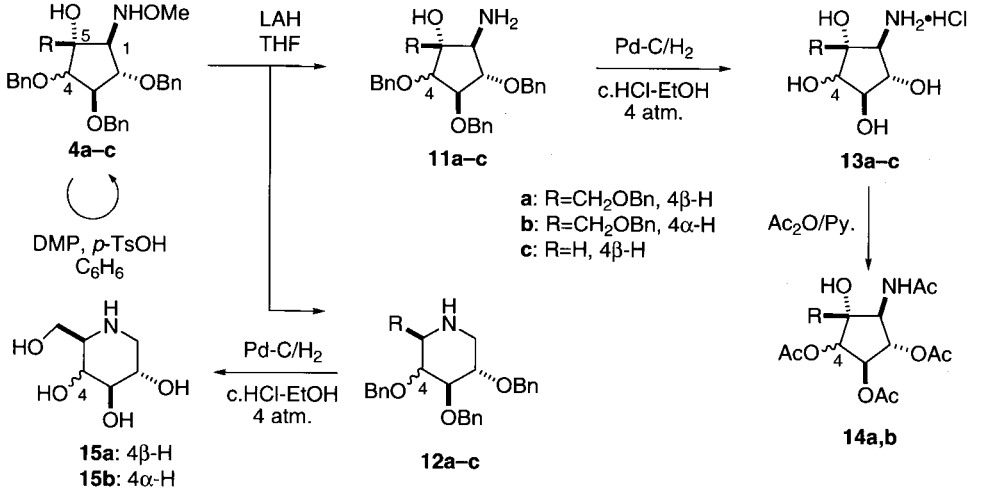
Structures of 1,5-*cis* compounds 5a–c and 6b

Concomitant catalytic hydrogenolysis of both *N*-methoxy and tetrabenzyloxy groups in 1,5-*cis* **5a** in the presence of 20% $Pd(OH)_2$–C proceeded slowly to give amino alcohol **9a**, which was acetylated successively to give the acetate **10a** in 27% yield. Stepwise deprotection of **5a** involving LAH reduction of the *N*-methoxy group, catalytic debenzylation of the multi-benzyloxy group and, finally, acetylation gave the identical acetate **10a** in a better yield. The stereostructure of the acetate **10a** was established firmly as 1,5-*cis*, 1,2-*trans* configurations by its X-ray analysis (Fig. 2). Similarly, **5b**,**c** and **6b** were converted into the corresponding aminocyclitols **9b**–**d**, of which **9b**,**d** were acetylated to give **10b**,**d** (Scheme 3).[10,12]

Structures of 1,5-*trans* compounds 4a–c

In order to prepare aminocyclitol pentaacetates, we carried out sequential reactions via a route involving reduction with LAH, catalytic hydrogenation, and acetylation (Scheme 4). Interestingly, treatment of 1,5-*trans* **4a** with LAH gave a mixture of two products **11a** and **12a** in 53 and 21% yields, respectively. Formation of ring-expanded piperidine **12a** is discussed later. The major product was found to be a demethylated amino alcohol, which was finally characterized as pentaacetate **14a**.

Products **4b**,**c** radically cyclized from D-galactose and



4a–c **11a–c** **13a–c**

15a: 4β-H
15b: 4α-H

12a–c **14a,b**

Scheme 4.

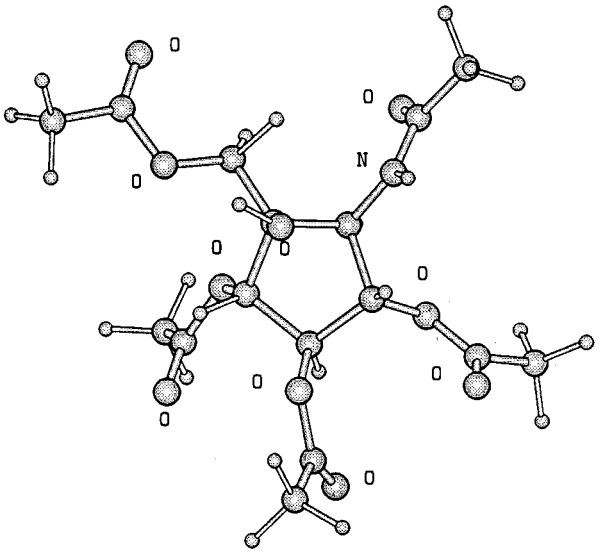


Figure 2. X-Ray structure of **10a**.

D-xylose were also converted into the corresponding aminocyclitols **13b**,**c** and acetate **14b**, which were characterized by comparison of their NOESY spectra with those of 1,5-*cis* compounds as collected in Figs. 3 and 4. During the course of our work on this radical cyclization, Chiara[14] has published a similar report on radical cyclization of oxime ether by using samarium iodide.

Since the stereostructures of products **4**, **5** and **6** have been established, we propose the possible reaction pathway in our stannyl radical cyclization of oxime ethers **3a**–**c** by comparing other related radical cyclizations using a different radical initiator developed by Bartlett,[7a] RajanBabu,[7b] Simpkins,[7c] and Reymond[5b] (Fig. 5). In the case of oxime ether **3c** derived from D-xylose, radical cyclization would proceed to give the 1,5-*trans* isomer via the more stable transition state **A** due to smaller electronic repulsion compared with the other transition state **B** in which the repulsion would exist. In the case of oxime ether **3a** derived from D-glucose, we are unable, at the moment, to offer an explanation for the major formation of the 1,5-*cis* product. Since radical cyclization of oxime ether **3b** derived from D-galactose gave three cylized products, there would be three transition states, **C**–**E**, of which **E** would be the most unstable due to the presence of hindrance between the oxime ether, stannyloxy and C_4-benzyloxy groups. Of the two other transition states, **D** would be less stable than **C** due to the presence of allylic strain in addition to hindrance between the oxime ether and stannyloxy groups. Thus, we propose that a combination of allylic strain and three electronic repulsions between the stannyloxy/oxime ether groups, oxime ether/C_4-benzyloxy groups and C_4-benzyloxy/stannyloxy groups would have subtle influence on the radical cyclization of oxime ether **3b**.

Reductive ring expansion of 1,5-*trans* methoxyamino alcohols to piperidines: new synthesis of 1-deoxynojirimycin and 1-deoxygalactostatin

As described previously, treatment of 1,5-*trans* methoxyamine **4a** with LAH gave ca 1:2 mixture of the ring-expanded product **12a** and the demethoxylated amino alcohol **11a**. Similarly, the reaction of 1,5-*trans* methoxyamine **4b** derived from D-galactose with LAH gave a 1:2

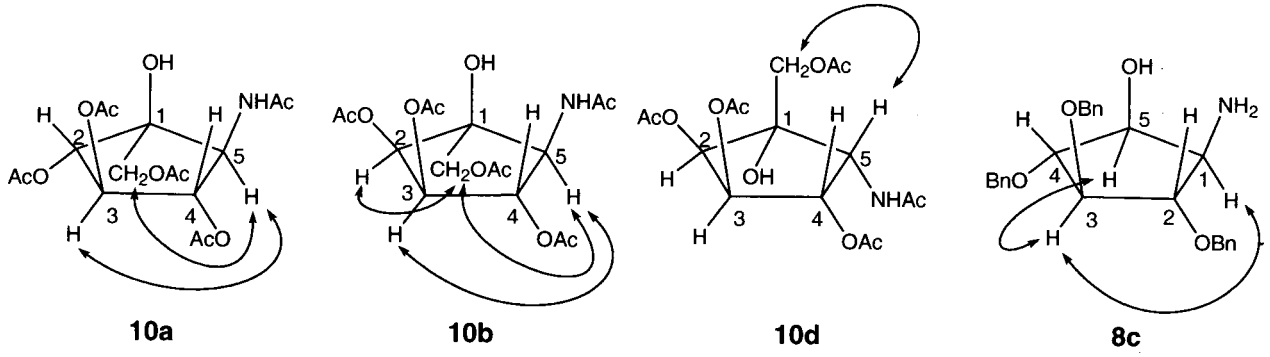


Figure 3. Key NOE correlations of 1,5-*cis* compounds.

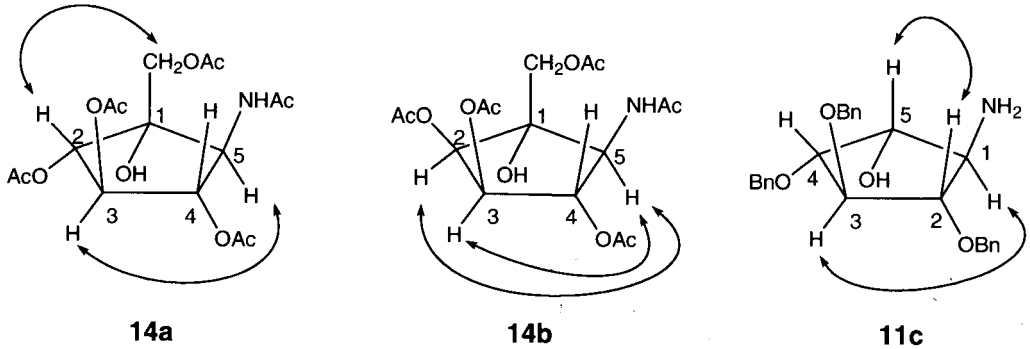


Figure 4. Key NOE correlations of 1,5-*trans* compounds.

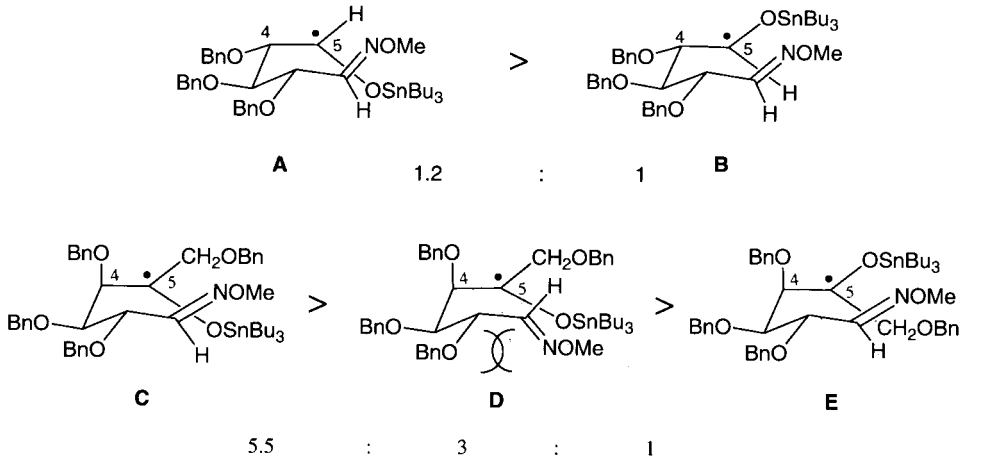
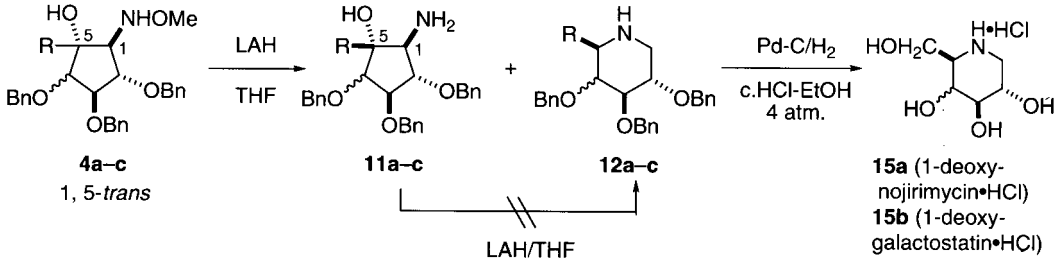


Figure 5. Transition states in radical cyclization of **3b,c.**

mixture of ring expanded and demethoxylated products **11b** and **12b**, respectively. On the other hand, under the same conditions, 1,5-*trans* methoxyamine **4c** afforded a small amount of the ring-expanded product **12c** (2% yield) together with a large amount of demethoxylated amino alcohol **11c** (80% yield) (Table 2). Interestingly, treatment of the corresponding *cis* methoxyamines **5a**–**c** and **6b** with LAH gave exclusively demethoxylated *cis* amino alcohols with no formation of the ring-expanded product. Additionally, demethoxylated 1,5-*trans* amino alcohols **11a**–**c** were recovered completely under the same reduction conditions using LAH. Two ring-expanded piperidines **12a**,**b** are found to be key intermediates for the synthesis of 1-deoxynojirimycin and 1-deoxygalactostatin and, therefore, converted into the respective authentic samples **15a**[13] and **15b**.[15] Thus, we have now succeeded in a simple synthesis of two glycosidase inhibitors.

Next, we investigated optimization of the conditions for the reductive ring-expansion reaction of 1,5-*trans* methoxyamine **4b**. As shown in Table 3, among reducing agents investigated, LAH and Red-Al are found to be better reagents though the yield of ring-expanded product was not satisfactory and did not exceed 50%. In order to disclose the relationship between the structure and reactivity and also to propose the reaction pathway, we investigated the reaction of model compounds **19** and **20** with Red-Al as shown in Table 4. The requisite substrates **19**–**20** were

Table 2. Ring expansion of *trans* methoxyamino alcohol **4** by LAH

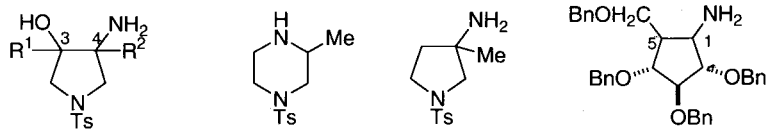


Entry		Substrate R	4-H	Yield (%) 11	12
1	**4a**	CH_2OBn	β	53	21
2	**4b**	CH_2OBn	α	45	19
3	**4c**	H	β	80	2

Table 3. Ring expansion of **4b**

Entry	Regent(s) (equiv.)	Solvent	Temp. (time)	Yield (%) **11b**	**12b**	**4b** (recovery)
1	LAH (6)	THF	Reflux (4 h)	45	18	–
2	LAH (6)	Dioxane	Reflux (2 h)	43	–	–
3	LAH (6), $A1C1_3$ (2)	Et_2O	Reflux (2 h)	53	–	–
4	DIBAL (20)	CH_2C1_2	0°C (8 h)→r.t. (2 h)	23	–	–
5	$NaBH_4$ (5), $ZrC1_4$ (1.2)	THF	rt (9 h)→reflux (5 h)	–	–	50
6	BF_3–THF (3)	THF	rt (10 h)→reflux (10 h)	–	–	98
7	Red-A1® (2.2)	C_6H_6	Reflux (6 h)	4	35	–

Table 4. Reaction of **19**–**23** and **4** with Red-A1®



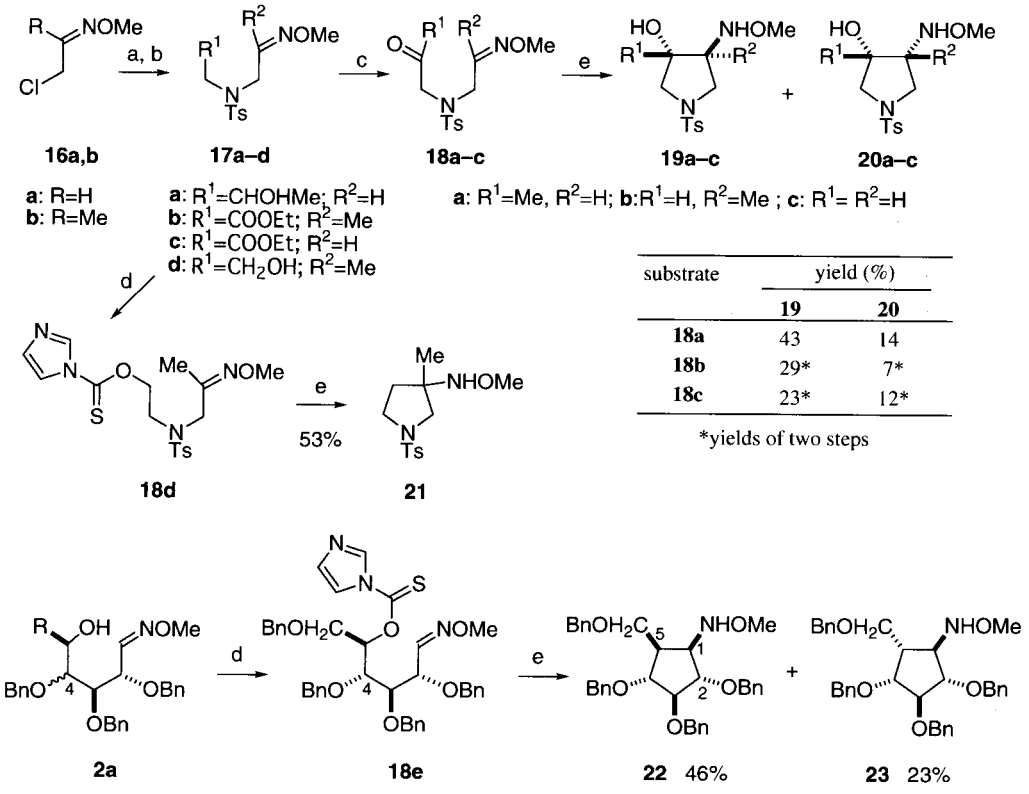
24a: R^1=β-Me, R^2=α-H
24b: R^1=β-H, R^2=α-H
24c: R^1=β-Me, R^2=β-H
24d: R^1=β-H, R^2=β-H

25 **26** **27a**:1α-H, 5α-H **27b**:1α-H, 5β-H

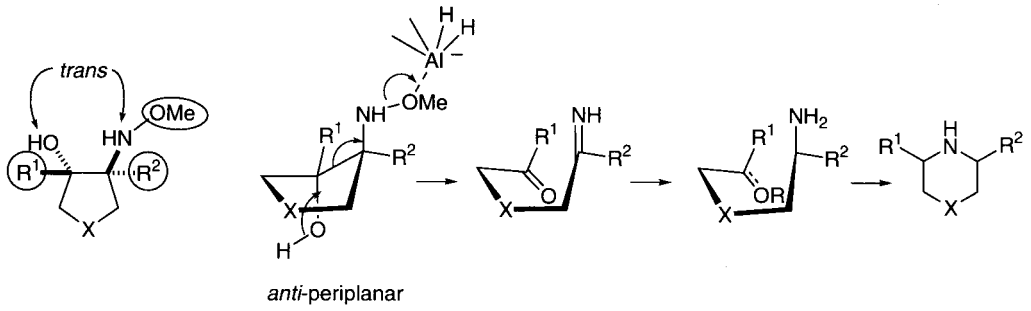
Entry	Substrate	Products (yield) Primary amine	Ring expansion product
1	**19a**	**24a** (44%)	**25** (21%)
2	**19b**	–	**25** (70%)
3	**19c**	**24b** (56%)	–
4	**20a**	**24c** (64%)	–
5	**20b**	–	–
6	**20c**	**24d** (53%)	–
7	**21**	**26** (10%)	–
8	**22**	**27a** (69%)	–
9	**23**	**27b** (77%)	–
10	**4a**	**11a** (39%)	**12a** (9%)
11	**4c**	**11c** (66%)	**12c** (7%)

prepared by our radical cyclization of oxime ethers **18a**–**c** connected by nitrogen with the carbonyl group. Other substrates **21**–**23** were prepared by radical cyclization of the thioesters **18d**,**e** (Scheme 5).

As shown in entries 1 and 2 in Table 4, *trans* compound **19a**,**b** with or without one methyl group at either the 3- or 4-position underwent reductive ring expansion to give 6-membered piperidine **25**[16] which, interestingly, was exclusively obtained from 4-methyl compound **19b** in 70% yield. Unfortunately, the *trans* compound **19c** with no methyl group at either 3- or 4-position gave only demethoxylated amino alcohol **24b**. In the case of *cis* compound **20a**, no ring-expansion reaction was observed and demethoxylated amine **24c** was obtained. Unexpectedly, both 3,4-*cis* compound **20b** having a quaternary



Scheme 5.



Scheme 6.

carbon at the root of the methoxyamino group and methoxyamine **21** with no neighboring hydroxyl group gave a complex mixture of which a small amount of demethoxylated amine **26** was isolated from the latter substrate **21**. Two methoxyamines **22** and **23** with no free hydroxy group gave only demethoxylated amine **27a**,**b** in excellent yield. Compared to the reaction with LAH as a reducing agent, treatment of **4a**,**c** with Red-Al gave unexpectedly a small amount of ring-expanded products **12a**,**c** (7–9%) in addition to demethoxylated products **11a**,**c** as major products.

Considering our results described above and the related work reported by other groups,[17] we propose the pathway in the reaction of methoxyamino alcohols with Red-Al or LAH as shown in Scheme 6. Ring expansion requires two functional groups, hydroxyl and alkoxyamino groups, which must be *trans* configuration. Additionally, smooth ring expansion (70%) of 1,5-*trans* methoxyamine **19b** in which the methoxyamino group attaches to the quaternary carbon would explain that the initial ring-opening step in the reductive ring expansion would proceed via the more stable carbocation formed from the quaternary carbon.

Conclusion

We have succeeded in the synthesis of aminocyclitols and known glycosidase inhibitors such as 1-deoxynojirimycin and 1-deoxygalactostatin via a route involving radical cyclization of oxime ethers and reductive ring-expansion reaction of the *trans* methoxyamino alcohols.

Experimental

General

^{1}H NMR spectra were measured using Varian Gemini-200 (200 MHz), Gemini-300 (300 MHz), and VXR-500 (500 MHz) instruments for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane was used as the internal reference). IR spectra were measured with a Perkin–Elmer 1600 FTIR for solutions in chloroform unless otherwise stated. Mass spectra were taken with Hitachi M-4100 instruments. Optical rotations were measured on a Jasco DIP-370 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Mps were determined with Kofler-type hot-stage apparatus and are uncorrected. TLC was performed on precoated silica gel 60F-254 (0.2 mm thick, Merck) and preparative TLC on precoated silica gel 60F-254 (0.25 mm thick, Merck), with UV detection at 254 and 300 nm. Medium-pressure column chromatography was undertaken on a 530–4-10V apparatus (Yamazen) with Lobar größe B (310–25, LiChroprep Si60, Merck) as column adsorbent. Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh) as column adsorbent. Short column chromatography was undertaken on a short glass filter using Merck Kieselgel 60 (230–400 mesh) at reduced pressure.

2,3,4,6-Tetrakis-*O*-(phenylmethyl)-D-*xylo*-hexos-5-ulose 1-(*O*-Methyloxime) (3a). A solution of tetra-*O*-benzyl-D-glucose (**1a**) (6 g, 11.1 mmol) and $NH_2OMe{\cdot}HCl$ (1.39 g, 16.6 mmol) in pyridine (30 ml) was stirred under a nitrogen atmosphere at 80°C for 3 h and then concentrated at reduced pressure. The resulting residue was diluted with C_6H_6 and washed with saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to afford the crude oxime ether **2a**. To a solution of pyridine (11.58 g, 0.15 mol) in CH_2Cl_2 (190 ml) was added CrO_3 portionwise (7.32 g, 73 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at room temperature for 15 min, a solution of the crude oxime ether **2a** in CH_2Cl_2 (70 ml) was added to the reaction mixture. The solution was stirred at the same temperature for 2 h and then concentrated at reduced pressure. The resulting residue was diluted with Et_2O and filtered through a pad of Celite, and the filtrate was concentrated at reduced pressure. Purification of the residue by flash column chromatography (AcOEt–hexane 1:3) afforded **3a** (5.18 g, 75%) as a colorless oil; IR 1731 (CO) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.42 (5/6H, d, J=7 Hz, 1-H (*E*)), 7.35–7.14 (20H, m, ArH), 6.82 (1/6H, d, J=7 Hz, 1-H (*Z*)), 5.73–3.96 (12H, m, CH_2Ph×4, 2, 4-H, 6-H_2), 4.41 (1H, dd, J=6, 4 Hz, 3-H), 3.85 (3H, s, OMe); HRMS (EI, *m*/*z*) calcd for $C_{35}H_{37}NO_6$ (M^+) 567.2622, found 567.2614.

2,3,4,6-Tetrakis-*O*-(phenylmethyl)-D-*lyxo*-hexos-5-ulose 1-(*O*-Methyloxime) (3b). The ketone **3b** was obtained in 66% yield from tetra-*O*-benzyl-D-galactose (**2b**)[8] by the procedure described for synthesis of **3a** from **1a**: a colorless oil; IR 1730 (CO) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.45 (3/4H, d, J=7 Hz, 1-H (*E*)), 7.35–7.15 (20H, m, ArH), 6.87 (1/4H, d, J=7 Hz, 1-H (*Z*)), 4.67–4.03 (13H, m, CH_2Ph×4, 2–4-H, 6-H_2), 3.85 (3H, s, OMe); HRMS (EI, *m*/*z*) calcd for $C_{35}H_{37}NO_6$ (M^+) 567.2622, found 567.2614.

2,3,4-Tris-*O*-(phenylmethyl)-D-*xylo*-pentos-5-ulose 1-(*O*-Methyloxime) (3c). The oxime ether **2c** was obtained in 98% yield from *O*-benzyl-D-xylose (**1c**)[9] by the procedure described for synthesis of **2a** from **1a**: a colorless oil; IR 3579 (OH) cm^{-1}; ^1H NMR (300 MHz) δ 7.40 (4/5H, d, J=7 Hz, 1-H (*E*)), 7.38–7.23 (15H, m, ArH), 6.88 (1/5H, d, J=7 Hz, 1-H (*Z*)), 4.85 (1/5H, dd, J=7, 4 Hz, 2-H), 4.69–4.40 (6H, m, CH_2Ph×3), 4.25 (4/5H, dd, J=7, 4 Hz, 2-H), 3.88 (3/5H, s, OMe (*Z*)), 3.85 (12/5H, s, OMe (*E*)), 3.79–3.64 (3H, m, 4-H, 5-H_2), 3.51 (1H, m, 3-H); HRMS (EI, *m*/*z*) calcd for $C_{27}H_{31}NO_5$ (M^+) 449.2200, found 449.2209. The aldehyde **3c** was obtained in 45% yield as a colorless oil after purification by flash column chromatography (AcOEt–hexane 1:2) from **2c** by the procedure described for synthesis of **3a** from **2a**. After being characterized by ^1H NMR spectra, unstable **3c** was immediately subjected to the following radical cyclization; ^1H NMR (300 MHz) δ 9.68 (1H, d, J=10 Hz, 5-H), 7.42 (3/4H, d, J=7 Hz, 1-H (*E*)), 7.37–7.18 (15H, m, ArH), 6.83 (1/4H, d, J=7 Hz, 1-H (*Z*)), 4.95–3.80 (9H, m, CH_2Ph×3, 2–4-H), 3.85 (3/4H, s, OMe (*Z*)), 3.81 (9/4H, s, OMe (*E*)).

General procedure for radical cyclization of 3

To a boiling solution of **3** (1.5 mmol) in C_6H_6 (12 ml) was added dropwise (10 ml h^{-1}) a solution of Bu_3SnH (3 mmol) and AIBN (0.75 mmol) in C_6H_6 (7 ml) under a nitrogen atmosphere. After being heated at reflux for 5 h, the solution was concentrated at reduced pressure. The resulting residue was diluted with acetonitrile and the acetonitrile phase was washed with hexane and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography [(C_6H_6–MeCN 9:1) for radical cyclization products of **3a** and (AcOEt–hexane 1:1) for radical cyclization products of **3b**,**c**] afforded **4**–**6**. Yields were shown in Table 1.

[1*S*-(1α,2β,3α,4β,5α)]-2-(Methoxyamino)-3,4,5-tris-(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (4a). Colorless needless from hexane; mp 67–69°C; $[\alpha]_D^{27}$=+22° (c=11.12, MeOH); IR 3600–3400 (OH) cm^{-1}; ^1H NMR (200 MHz) δ 7.45–7.10 (20H, m, ArH), 6.05 (1H, br s, NH), 4.79–4.43 (8H, m, CH_2Ph×4), 4.16 (1H, br t, J=7 Hz, 3-H), 3.88 (1H, d, J=7 Hz, 4-H), 3.76 (1H, t, J=6 Hz, 2-H), 3.60 and 3.49 (2H, ABq, J=10 Hz, 6-H_2), 3.47 (1H, m, 1-H), 3.44 (3H, s, OMe); HRMS (EI, *m*/*z*) calcd for $C_{35}H_{39}NO_6$ (M^+) 569.2779, found 569.2766. Anal. Calcd for $C_{35}H_{39}NO_6$: C, 73.79; H, 6.90; N, 2.46. Found: C, 74.01; H, 6.89; N, 2.32.

[1*R*-(1α,2α,3β,4α,5β)]-2-(Methoxyamino)-3,4,5-tris-(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (5a). A colorless oil; $[\alpha]_D^{27}$=−7° (c=11.0, MeOH); IR 3650–3400 (OH, NH) cm^{-1}; ^1H NMR (300 MHz) δ 7.40–7.20 (20H, m, ArH), 6.18 (1H, br s, NH), 4.80–4.50 (8H, m, CH_2Ph×4), 3.92–3.83 (3H, m, 2–4-H), 3.77 and 3.66 (2H, ABq, J=10 Hz, 6-H_2), 3.51 (1H, m, 1-H), 3.49 (3H, s, OMe); HRMS (EI, *m*/*z*) calcd for $C_{35}H_{39}NO_6$ (M^+) 569.2779, found 569.2770.

[1*S*-(1α,2β,3α,4β,5β)]-2-(Methoxyamino)-3,4,5-tris-(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (4b). A colorless oil; $[\alpha]_D^{27}$=+38° (c=11.37, MeOH); IR 3600–3450 (OH, NH) cm^{-1}; ^1H NMR (500 MHz) δ 7.39–7.23 (20H, m, ArH), 4.78–4.53 (8H, m, CH_2Ph×4), 4.32 (1H, dd, J=6, 4 Hz, 3-H), 4.03 (1H, dd, J=6, 3 Hz, 2-H), 3.88 (1H, dd, J=4, 1.5 Hz, 4-H), 3.83 and 3.68 (2H, ABq, J=9.5 Hz, 6-H_2), 3.50 (3H, s, OMe), 3.40 (1H, dd, J=3, 1.5 Hz, 1-H), 2.98 (1H, br s, OH); HRMS (EI, *m*/*z*) calcd for $C_{35}H_{39}NO_6$ (M^+) 569.2779, found 569.2786.

[1*R*-(1α,2α,3β,4α,5α)]-2-(Methoxyamino)-3,4,5-tris-(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (5b). A colorless oil; $[\alpha]_D^{27}$=−12° (c=11.31, MeOH); IR 3600–3400 (OH, NH) cm^{-1}; ^1H NMR (500 MHz) δ 7.37–7.23 (20H, m, ArH), 4.71–4.47 (8H, m, CH_2Ph×4), 4.00 (1H, d, J=5 Hz, 4-H), 3.86 (1H, dd, J=5, 3.5 Hz, 3-H), 3.82 (1H, br dd, J=5.5, 3.5 Hz, 2-H), 3.53 and 3.49 (2H, ABq, J=11 Hz, 6-H_2), 3.52 (3H, s, OMe), 3.47 (1H, d, J=5 Hz, 1-H), 3.41 (1H, br s, OH); HRMS (EI, *m*/*z*) calcd for $C_{35}H_{39}NO_6$ (M^+) 569.2779, found 569.2779.

[1*S*-(1α,2α,3α,4β,5β)]-2-(Methoxyamino)-3,4,5-tris-(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (6b). A colorless oil; $[\alpha]_D^{27}$=+22° (c=10.85, MeOH); IR 3550–3350 (OH, NH) cm^{-1}; ^1H NMR (500 MHz) δ 7.39–7.23 (20H, m, ArH), 4.71–4.45 (8H, m, CH_2Ph×4), 4.20 (1H, dd, J=8.5, 5.5 Hz, 2-H), 4.07 (1H, dd, J=5.5, 4 Hz, 3-H), 4.00 (1H, d, J=4 Hz, 4-H), 3.80 and 3.63 (2H, ABq, J=9.5 Hz, 6-H_2), 3.53 (1H, d, J=8.5 Hz, 1-H), 3.49 (3H, s, OMe); HRMS (EI, *m*/*z*) calcd for $C_{35}H_{39}NO_6$ (M^+) 569.2779, found 569.2755.

[1*S*-(1α,2β,3α,4β,5α)]-2-(Methoxyamino)-3,4,5-tris-(phenylmethoxy]cyclopentanol (4c). Colorless needless from Et_2O–hexane; mp 90–91°C; $[\alpha]_D^{27}$=+6° (c=11.6, MeOH); IR 3580–3450 (OH) cm^{-1}; ^1H NMR (500 MHz) δ 7.34–7.25 (15H, m, ArH), 5.72 (1H, br s, NH), 4.69–4.56 (6H, m, CH_2Ph×3), 4.05–4.02 (2H, m, 3, 5-H), 3.88–3.82 (2H, m, 2, 4-H), 3.51 (3H, s, OMe), 3.32 (1H, t, J=6 Hz, 1-H), 2.55 (1H, d, J=6 Hz, OH); HRMS (EI, *m*/*z*) calcd for $C_{27}H_{31}NO_5$ (M^+) 449.2200, found 449.2193.

[1*R*-(1α,2α,3β,4α,5β)]-2-(Methoxyamino)-3,4,5-tris-(phenylmethoxy)cyclopentanol (5c). A colorless oil; $[\alpha]_D^{27}$=−2° (c=11.25, MeOH); IR 3600–3450 (OH, NH) cm^{-1}; ^1H NMR (500 MHz) δ 7.36–7.26 (15H, m, ArH), 5.89 (1H, br s, NH), 4.73–4.54 (6H, m, CH_2Ph×3), 4.14 (1H, td, J=6, 3 Hz, 5-H), 3.96 (1H, br t, J=6.5 Hz, 3-H), 3.87–3.83 (2H, m, 2, 4-H), 3.54 (3H, s, OMe), 3.48 (1H, dd, J=7.5, 6 Hz, 1-H), 2.96 (1H, br d, J=3.5 Hz, OH); HRMS (EI, *m*/*z*) calcd for $C_{27}H_{31}NO_5$ (M^+) 449.2200, found 449.2189.

General procedure for acetonide formation of 5 and 6

To a solution of *cis*-product **5** or **6** (0.1 mmol) and *p*-TsOH (0.015 mmol) in C_6H_6 (10 ml) was added DMP (0.2 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 0.5 h, the solution was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography or preparative TLC (AcOEt–hexane 2:1–1:3) afforded **7**.

[3a*S*-(4α,5β,6α,6aα)]-Hexahydro-3-methoxy-2,2-dimethyl-4,5,6-tris(phenylmethoxy)-6a-[(phenylmethoxy)methyl]-2*H*-cyclopentoxazole (7a). 93% Yield from **5a**; a pale yellow oil; ^{1}H NMR (300 MHz) δ 7.33–7.21 (20H, m, ArH), 4.80–4.50 (8H, m, C*H*$_2$Ph×4), 4.20–4.05 (3H, m, 2–4-H), 3.89 (1H, br s, 1-H), 3.69 (2H, s, 6-H$_2$), 3.58 (3H, s, OMe), 1.45 and 1.31 (each 3H, s, Me×2); HRMS (EI, *m*/*z*) calcd for $C_{38}H_{43}NO_6$ (M^+) 609.3092, found 609.3096.

[3a*S*-(4α,5β,6β,6aα)]-Hexahydro-3-methoxy-2,2-dimethyl-4,5,6-tris(phenylmethoxy)-6a-[(phenylmethoxy)methyl]-2*H*-cyclopentoxazole (7b). 95% Yield from **5b**; a pale yellow oil; ^{1}H NMR (200 MHz) δ 7.45–7.20 (20H, m, ArH), 4.94–4.24 (9H, m, C*H*$_2$Ph×4, 2-H), 3.84 (1H, d, *J*=5 Hz, 4-H), 3.70 (1H, dd, *J*=8.5, 5 Hz, 3-H), 3.59 (3H, s, OMe), 3.57 (1H, d, *J*=4.5 Hz, 1-H), 3.53 and 3.33 (2H, ABq, *J*=10 Hz, 6-H$_2$), 1.40 and 1.33 (each 3H, s, Me×2); HRMS (EI, *m*/*z*) calcd for $C_{38}H_{43}NO_6$ (M^+) 609.3092, found 609.3097.

[3a*S*-(4α,5β,6α,6aα)]-Hexahydro-3-methoxy-2,2-dimethyl-4,5,6-tris(phenylmethoxy)-2*H*-cyclopentoxazole (7c). 98% Yield from **5c**; a pale yellow oil; ^{1}H NMR (200 MHz) δ 7.36–7.20 (15H, m, ArH), 4.80–4.60 (6H, m, C*H*$_2$Ph×3), 4.37 (1H, dd, *J*=9, 6 Hz, 4-H), 4.19 (1H, dd, *J*=7, 4 Hz, 2-H), 4.45–3.85 (2H, m, 3, 5-H), 3.79 (1H, m, 1-H), 3.53 (3H, s, OMe), 1.46 and 1.26 (each 3H, s, Me×2); HRMS (EI, *m*/*z*) calcd for $C_{30}H_{35}NO_5$ (M^+) 489.2551, found 489.2532.

[3a*R*-(4α,5β,6β,6aβ)]-Hexahydro-3-methoxy-2,2-dimethyl-4,5,6-tris(phenylmethoxy)-6a-[(phenylmethoxy)methyl]-2*H*-cyclopentoxazole (7d). 66% Yield from **6b**; a pale yellow oil; ^{1}H NMR (200 MHz) δ 7.41–7.22 (20H, m, ArH), 4.86–4.43 (8H, m, C*H*$_2$Ph×4), 4.27 (1H, dd, *J*=8.5, 5.5 Hz, 3-H), 4.05 (1H, dd, *J*=8.5, 6 Hz, 2-H), 3.89 (1H, d, *J*=5.5 Hz, 4-H), 3.73 and 3.60 (2H, ABq, *J*=11 Hz, 6-H$_2$), 3.71 (1H, d, *J*=6 Hz, 1-H), 3.54 (3H, s, OMe), 1.40 and 1.33 (each 3H, s, Me×2); HRMS (EI, *m*/*z*) calcd for $C_{38}H_{43}NO_6$ (M^+) 609.3092, found 609.3101.

General procedure for LAH reduction of 4–6

To a solution of **4**–**6** (1 mmol) in THF (15 ml) was added portionwise LAH (6 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 4 h, the solution was concentrated at reduced pressure, and Et_2O was added to the residue. The excess LAH was then decomposed by careful addition of H_2O. The organic phase was separated by decantation, dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt–hexane 1:1 to AcOEt–MeOH 95:5) afforded **8**, **11** and **12**.

[1*R*-(1α,2α,3β,4α,5β)]-2-Amino-3,4,5-tris(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (8a). 57% Yield from **5a**; a colorless oil; $[\alpha]_D^{27}$=+3° (*c*=11.05, MeOH); IR 3600–3400 (OH, NH_2) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.38–7.21 (20H, m, ArH), 4.80–4.51 (8H, m, C*H*$_2$Ph×4), 3.89 (1H, dd, *J*=6, 5 Hz, 3-H), 3.83 (1H, d, *J*=5 Hz, 4-H), 3.76 (1H, ddd, *J*=9, 6, 1 Hz, 2-H), 3.71 and 3.61 (2H, ABq, *J*=10 Hz, 6-H$_2$), 3.24 (1H, br d, *J*=9 Hz, 1-H); HRMS (EI, *m*/*z*) calcd for $C_{34}H_{37}NO_5$ (M^+) 539.2670, found 539.2677.

[1*R*-(1α,2α,3β,4α,5α)]-2-Amino-3,4,5-tris(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (8b). 47% Yield from **5b**; a colorless oil; $[\alpha]_D^{27}$=−16° (*c*=11.01, $CHCl_3$); IR 3600–3350 (OH, NH_2) cm^{-1}. ^{1}H NMR (200 MHz) δ 7.32–7.29 (20H, m, ArH), 4.75–4.48 (8H, m, C*H*$_2$Ph×4), 3.96 (1H, d, *J*=5.5 Hz, 4-H), 3.85 (1H, dd, *J*=9, 5.5 Hz, 3-H), 3.80 (1H, dd, *J*=9, 6 Hz, 2-H), 3.38 (2H, s, 6-H$_2$), 3.03 (1H, d, *J*=6 Hz, 1-H); HRMS (EI, *m*/*z*) calcd for $C_{34}H_{37}NO_5$ (M^+) 539.2669, found 539.2663.

[1*R*-(1α,2α,3β,4α,5β)]-2-Amino-3,4,5-tris(phenylmethoxy)cyclopentanol (8c). 54% Yield from **5c**; colorless needles from hexane–EtOH; mp 115–117°C; $[\alpha]_D^{27}$=+130° (*c*=11.61, MeOH); IR 3640–3300 (OH, NH_2) cm^{-1}; ^{1}H NMR (500 MHz) δ 7.37–7.26 (15H, m, ArH), 4.77–4.53 (6H, m, C*H*$_2$Ph×3), 3.94 (1H, dd, *J*=6.5, 4 Hz, 3-H), 3.89 (1H, dd, *J*=6, 2 Hz, 5-H), 3.81 (1H, dd, *J*=4, 2 Hz, 4-H), 3.72 (1H, br dd, *J*=8.5, 6.5 Hz, 2-H), 3.34 (1H, dd, *J*=8.5, 6 Hz, 1-H); HRMS (EI, *m*/*z*) calcd for $C_{26}H_{29}NO_4$ (M^+) 419.2095, found 419.2089. Anal. Calcd for. $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.67; H, 7.03; N, 3.32.

[1*S*-(1α,2α,3α,4β,5β)]-2-Amino-3,4,5-tris(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (8d). 41% Yield from **6b**; colorless needless from Et_2O–petroleum ether; mp 93–96°C; $[\alpha]_D^{27}$=+33° (*c*=11.21, $CHCl_3$); IR 3600–3350 (OH, NH_2) cm^{-1}; ^{1}H NMR (200 MHz) δ 7.41–7.21 (20H, m, ArH), 4.72–4.51 (8H, m, C*H*$_2$Ph×4), 4.12 (1H, dd, *J*=7, 6 Hz, 2-H), 4.05 (1H, dd, *J*=6, 4 Hz, 3-H), 3.96 (1H, d, *J*=4 Hz, 4-H), 3.70 and 3.62 (2H, ABq, *J*=10 Hz, 6-H$_2$), 3.51 (1H, d, *J*=7 Hz, 1-H); HRMS (EI, *m*/*z*) calcd for $C_{34}H_{37}NO_5$ (M^+) 539.2669, found 539.2668.

[1*S*-(1α,2β,3α,4β,5α)]-2-Amino-3,4,5-tris(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (11a). 53% Yield from **5a**; colorless needless from Et_2O–petroleum ether; mp 110–111°C; $[\alpha]_D^{27}$=+11° (*c*=12.36, $CHCl_3$); IR 3600–3450 (OH, NH_2) cm^{-1}; ^{1}H NMR (200 MHz) δ 7.50–7.20 (20H, m, ArH), 4.70–4.48 (8H, m, C*H*$_2$Ph×4), 4.01 (1H, t, *J*=6 Hz, 3-H), 3.92 (1H, d, *J*=6 Hz, 4-H), 3.56 (1H, dd, *J*=8, 6 Hz, 2-H), 3.52 and 3.47 (2H, ABq, *J*=10 Hz, 6-H$_2$), 3.26 (1H, d, *J*=8 Hz, 1-H); HRMS (EI, *m*/*z*) calcd for $C_{34}H_{37}NO_5$ (M^+) 539.2670, found 539.2666. Anal. Calcd for $C_{34}H_{37}NO_5$: C, 75.66; H, 6.91; N, 2.60. Found: C, 75.52; H, 6.89; N, 2.53.

[2*R*-(2α,3β,4α,5β)]-3,4,5-Tris(phenylmethoxy)-2-[(phenylmethoxy)methyl]piperidine (12a). 21% Yield from **5a**; a colorless oil; $[\alpha]_D^{27}$=+33° (*c*=11.13, $CHCl_3$) (lit.[12] $[\alpha]_D^{27}$=+33° (*c*=10.66, $CHCl_3$)); IR 3673 (NH) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.78–7.35 (20H, m, ArH), 5.02–4.78 (8H, m, C*H*$_2$Ph×4), 3.66 (1H, dd, *J*=9, 3 Hz, 6-H), 3.58–3.45 (3H, m, 2, 3, 6-H), 3.34 (1H, br t, *J*=9 Hz, 4-H), 3.23 (1H, dd, *J*=12, 5 Hz, 1-Heq), 2.71 (1H, ddd, *J*=9, 6, 3 Hz, 5-H), 2.50 (1H, dd, *J*=12, 10 Hz, 1-Hax); HRMS (EI, *m*/*z*) calcd for $C_{34}H_{37}NO_4$ (M^+) 523.2736, found 523.2728. The spectral data of **12a** were found to be identical with those of the authentic sample.[12]

[1*S*-(1α,2β,3α,4β,5β)]-2-Amino-3,4,5-tris(phenylmethoxy)-1-[(phenylmethoxy)methyl]cyclopentanol (11b). 45% Yield from **5b**; colorless needless from AcOEt; mp 151–153°C; $[\alpha]_D^{27}=+8°$ (c=12.35, $CHCl_3$); IR 3580–3200 (OH, NH_2) cm^{-1}; ^1H NMR (200 MHz) δ 7.41–7.20 (20H, m, ArH), 4.85–4.56 (8H, m, CH_2Ph×4), 4.23 (1H, dd, J=4, 2 Hz, 2-H), 3.92–3.84 (2H, m, 3, 4-H), 3.74 (2H, s, 6-H_2), 3.07 (1H, d, J=4 Hz, 1-H); HRMS (EI, m/z) calcd for $C_{34}H_{37}NO_5$ (M^+) 539.2670, found 539.2674. Anal. Calcd for $C_{34}H_{37}NO_5$: C, 75.66; H, 6.91; N, 2.60. Found: C, 75.48; H, 7.01; N, 2.54.

[2*R*-(2α,3α,4α,5β)]-3,4,5-Tris(phenylmethoxy)-2-[(phenylmethoxy)methyl]piperidine (12b). 19% Yield from **5b**; a colorless oil; $[\alpha]_D^{27}=-49°$ (c=1.61, $CHCl_3$); IR 3689 (NH) cm^{-1}; ^1H NMR (500 MHz) δ 7.38–7.25 (20H, m, ArH), 4.95 and 4.55 (2H, ABq, J=11.5 Hz, CH_2Ph), 4.78 (2H, br s, CH_2Ph), 4.75 and 4.66 (2H, ABq, J=11.5 Hz, CH_2Ph), 4.71 and 4.41 (2H, ABq, J=11.5 Hz, CH_2Ph), 3.96 (1H, dd, J=2.5, 1 Hz, 4-H), 3.88 (1H, td, J=10, 5.5 Hz, 2-H), 3.49–3.44 (2H, m, 3, 6-H), 3.34 (1H, dd, J=9, 7 Hz, 6-H), 3.26 (1H, dd, J=12, 5.5 Hz, 1-Heq), 2.78 (1H, td, J=7, 1 Hz, 5-H), 2.47 (1H, dd, J=12, 10 Hz, 1-Hax), 1.65 (1H, br s, NH); HRMS (EI, m/z) calcd for $C_{34}H_{37}NO_4$ (M^+) 523.2721, found 523.2723.

[1*R*-(1α,2β,3α,4β,5α)]-2-Amino-3,4,5-tris(phenylmethoxy)cyclopentanol (11c). 80% Yield from **5c**; colorless needles from hexane–EtOH; mp 103–105°C; $[\alpha]_D^{27}=-23°$ (c=11.83, MeOH); IR 3640–3450 (OH, NH_2) cm^{-1}; ^1H NMR (500 MHz) δ 7.34–7.23 (15H, m, ArH), 4.68–4.49 (6H, m, CH_2Ph×3), 3.93 (1H, dd, J=4.5, 2.5 Hz, 3-H), 3.87 (1H, dd, J=6, 2.5 Hz, 4-H), 3.71 (1H, dd, J=8, 6 Hz, 5-H), 3.54 (1H, dd, J=8, 4.5 Hz, 2-H), 3.23 (1H, t, J=8 Hz, 1-H); HRMS (EI, m/z) calcd for $C_{26}H_{29}NO_4$ (M^+) 419.2095, found 419.2098. Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.38; H, 7.01; N, 3.33.

(3α,4β,5α)-Tris(phenylmethoxy)piperidine (12c). 2% Yield from **5c**; a pale yellow oil; IR 3400 (NH) cm^{-1}; ^1H NMR (300 MHz) δ 7.40–7.25 (15H, m, ArH), 4.87–4.61 (6H, m, CH_2Ph×3), 3.53–3.38 (3H, m, 2–4-H), 3.20 (2H, dd, J=12, 5 Hz, 1, 5-Heq), 2.49 (2H, dd, J=12, 10 Hz, 1, 5-Hax); HRMS (EI, m/z) calcd for $C_{26}H_{29}NO_3$ (M^+) 403.2146, found 403.2130.

General procedure for synthesis of acetamides 10 and 14

A suspension of 10% Pd–C (430 mg) in EtOH (23 ml) was stirred under a hydrogen atmosphere at room temperature for 1 h. To this suspension was added a solution of **8** or **11** (0.18 mmol) in EtOH–conc. HCl (20 ml, 19:1). After being stirred under four atmospheric hydrogen pressure at room temperature for 1–3 days, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure to give the crude amine·HCl **9** or **13**. To a solution of the resulting crude amine·HCl **9** in pyridine (3 ml) was added Ac_2O (1.5 ml) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 3 h, EtOH was added to the reaction mixture, and the resulting solution was stirred at the same temperature for 20 min. The reaction mixture was diluted with AcOEt and washed with 10% HCl solution. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by short column chromatography (AcOEt) afforded the acetamide **10** or **14**.

[1*S*-(1α,2α,3β,4α,5β)]-*N*-[3,4,5-Tris(acetyloxy)-2-[(acetyloxy)methyl]-2-hydroxycyclopentyl]acetamide (10a). 43% Yield from **8a**; colorless needless from AcOEt); mp 91–93°C; $[\alpha]_D^{27}=-3°$ (c=12.00, MeOH); IR 3536 (NH), 1742 (OCO), 1678 (NHCO) cm^{-1}; ^1H NMR (500 MHz) δ 6.14 (1H, d, J=9 Hz, NH), 5.44 (1H, dd, J=10, 6 Hz, 2-H), 5.07 (1H, dd, J=6, 3 Hz, 3-H), 5.01 (1H, br d, J=3 Hz, 4-H), 4.53 (1H, dd, J=10, 9 Hz, 1-H), 4.21 and 4.09 (2H, ABq, J=12 Hz, 6-H_2), 2.11, 2.09, 2.08, 2.07 and 2.01 (each 3H, s, Ac×5); HRMS (EI, m/z) calcd for $C_{16}H_{23}NO_{10}$ (M^+) 390.1401, found 390.1390. Anal. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.39; H, 6.20; N, 3.31.

The acetamide **10a** was also obtained in 27% yield from **5a** by catalytic hydrogenolysis in the presence of 20% $Pd(OH)_2$–C followed by acetyltion with Ac_2O.

[1*S*-(1α,2α,3α,4α,5β)]-*N*-[3,4,5-Tris(acetyloxy)-2-[(acetyloxy)methyl-2-hydroxycyclopentyl]acetamide (10b). 40% Yield from **8b**: a pale yellow oil; $[\alpha]_D^{27}=-32°$ (c=11.35, MeOH); IR 3584 (OH), 3436 (NH), 1747 (OCO), 1683 (NHCO) cm^{-1}; ^1H NMR (500 MHz) δ 5.98 (1H, br d, J=9.5 Hz, NH), 5.39 (1H, dd, J=9, 4.5 Hz, 2-H), 5.33 (1H, d, J=8 Hz, 4-H), 5.27 (1H, dd, J=8, 4.5 Hz, 3-H), 4.44 (1H, br t, J=10 Hz, 1-H), 4.00 and 3.95 (2H, ABq, J=12 Hz, 6-H_2), 2.89 (1H, br s, OH), 2.11, 2.09, 2.09, 2.08, 2.01 (each 3H, s, Ac×5); HRMS (EI, m/z) calcd for $C_{16}H_{23}NO_{10}$ (M^+) 390.1400, found 390.1408.

[1*R*-(1α,2α,3β,4β,5α)]-*N*-[(3,4,5-Tris(acetyloxy)-2-(acetyloxy)methyl]-2-hydroxycyclopentyl]acetamide (10d). 62% Yield from **8d**; a pale yellow oil; $[\alpha]_D^{27}=-9°$ (c=11.16, MeOH); IR 3688 (OH), 3447 (NH), 1749 (OCO), 1682 (NHCO) cm^{-1}; ^1H NMR (500 MHz) δ 6.05 (1H, br d, J=9.5 Hz, NH), 5.51 (1H, t, J=5 Hz, 3-H), 5.38 (1H, dd, J=9.5, 5 Hz, 2-H), 5.29 (1H, d, J=5 Hz, 4-H), 4.78 (1H, br td, J=9.5, 1.5 Hz, 1-H), 4.29 and 4.10 (2H, ABq, J=12 Hz, 6-H_2), 3.65 (1H, d, J=1.5 Hz, OH), 2.11, 2.10, 2.09, 2.08, 2.03 (each 3H, s, Ac×5); HRMS (EI, m/z) calcd for $C_{16}H_{23}NO_{10}$ (M^+) 390.1400, found 390.1399. The spectral data of **10d** were found to be identical with those of the authentic sample.[13]

[1*S*-(1α,2β,3β,4α,5β)]-*N*-[3,4,5-Tris(acetyloxy)-2-[(acetyloxy)methyl]-2-hydroxycyclopentyl]acetamide (14a). 68% Yield from **11a**; a colorless oil; $[\alpha]_D^{27}=-18°$ (c=11.47, MeOH); IR 3439 (OH), 1743 (OCO), 1678 (MHCO) cm^{-1}; ^1H NMR (500 MHz) δ 6.60 (1H, d, J=4 Hz, NH), 5.51 (1H, dd, J=8, 5.5 Hz, 3-H), 5.18 (1H, dd, J=10, 8 Hz, 2-H), 5.14 (1H, d, J=5.5 Hz, 4-H), 4.26 (1H, dd, J=10, 4 Hz, 1-H), 4.12 and 4.10 (2H, ABq, J=12 Hz, 6-H_2), 2.16, 2.15, 2.14, 2.09 and 2.04 (each 3H, s, Ac×5); HRMS (EI, m/z) calcd for $C_{16}H_{23}NO_{10}$ (M^+) 390.1400, found 390.1397.

[1*S*-(1α,2β,3α,4α,5β)]-*N*-[(3,4,5-Tris(acetyloxy)-2-[(acetyloxy)methyl]-2-hydroxycyclopentyl]acetamide (14b).

71% Yield from **11b**: a pale yellow oil; $[\alpha]_D^{27}=+9°$ (c=11.58, MeOH); IR 3682 (OH), 3430 (NH), 1747 (OCO), 1666 (NHCO) cm^{-1}; ^1H NMR (500 MHz) δ 6.44 (1H, br d, J=5 Hz, NH), 5.52 (1H, t, J=7 Hz, 3-H), 5.35 (1H, d, J=7 Hz, 4-H), 5.30 (1H, dd, J=9, 7 Hz, 2-H), 4.91 (1H, s, OH), 4.24 and 4.10 (2H, ABq, J=12 Hz, 6-H_2), 4.19 (1H, dd, J=9, 5 Hz, 1-H), 2.13, 2.09, 2.08, 2.05, 2.04 (each 3H, s, Ac×5); HRMS (EI, m/z) calcd for $C_{16}H_{23}NO_{10}$ (M^+) 390.1400, found 390.1399.

[1*S*-(1α,2α,3β,4α,5β)]-5-Amino-1,2,3,4-cyclopentanetetrol hydrochloride (9c). The debenzylated amino alcohol·HCl **9c** was obtained in 98% yield from **8c** by the procedure described for synthesis of **9** from **8**: colorless powder from MeOH; IR 3600–3300 (OH, NH_2) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.21 (1H, dd, J=7, 6 Hz, 5-H), 4.03–3.92 (3H, m, 2–4-H), 3.47 (1H, br t, J=7 Hz, 1-H).

[1*S*-(1α,2β,3α,4β,5α)]-5-Amino-1,2,3,4-cyclopentanetetrol hydrochloride (13c). The debenzylated amino alcohol·HCl **13c** was obtained in 48% yield from **11c** by the procedure described for synthesis of **9** from **8**: as colorless powder from MeOH; IR 3600–3300 (OH, NH_2) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.15 (1H, dd, J=8, 5 Hz, 3-H), 4.04 (1H, t, J=8 Hz, 5-H), 3.85 (1H, dd, J=8, 5 Hz, 4-H), 3.74 (1H, t, J=8 Hz, 2-H), 3.57 (1H, br t, J=8 Hz, 1-H); HRMS (CI, m/z) calcd for $C_5H_{11}NO_4^+H$ (QM^+) 150.0776, found 150.0765.

[2*R*-(2α,3β,4α,5β)]-2-(Hydroxymethyl)-3,4,5-piperidinetriol (1-deoxynojirimycin) (15a). According to the procedure described for catalytic hydrogenation of **8**, **12a** (50 mg, 0.1 mmol) was reduced with 10% Pd–C (50 mg) under four atmospheric hydrogen pressure at room temperature to give 1-deoxynojrimycin·HCl (**15a**) which was purified by ion exchange column chromatography (DOWEX 1×8) to give 1-deoxynojrimycin (16 mg, 99%); IR 3500–3200 (OH) cm^{-1}; ^1H NMR (300 MHz, D_2O δ 3.83 (1H, dd, J=12, 3 Hz, 6-H), 3.62 (1H, dd, J=12, 6 Hz, 6-H), 3.49 (1H, ddd, J=10.5, 10, 5.5 Hz, 2-H), 3.32 (1H, br t, J=10 Hz, 4-H), 3.23 (1H, br t, J=10 Hz, 3-H), 3.11 (1H, dd, J=12, 5.5 Hz, 1-Heq), 2.54 (1H, ddd, J=9, 6, 3 Hz, 5-H), 2.54 (1H, br t, J=11 Hz, 1-Hax); SIMS (m/z) 164 (QM^+). The spectral data of this product were found to be identical with those of the authentic sample.[13]

[2*R*-(2α,3α,4α,5β)]-2-(Hydroxymethyl)-3,4,5-piperidinetriol hydrochloride (1-Deoxygalactostatin·HCl) (15b). 1-Deoxygalactostatin·HCl **15b** was obtained in 93% yield from **12b** by the procedure described for synthesis of **9** from **8**; $[\alpha]_D^{27}=+37°$ (c=0.54, H_2O) (lit.[15] $[\alpha]_D^{20}=+46.1°$ (c=0.9, H_2O)); IR 3550–3200 (OH, NH) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.05 (1H, br s, 4-H), 3.96 (1H, br td, J=11, 5 Hz, 2-H), 3.77 (1H, dd, J=12, 5 Hz, 6-H), 3.69 (1H, dd, J=12, 9 Hz, 6-H), 3.52 (1H, dd, J=10, 3 Hz, 3-H), 3.40 (1H, dd, J=12, 5 Hz, 1-Heq), 3.30 (1H, br dd, J=9, 5 Hz, 5-H), 2.76 (1H, t, J=12 Hz, 1-Hax). SIMS (m/z) 164 (QM^+). The spectral data of **15b** were found to be identical with those of the authentic sample.[15]

Ring expansion of 4b

Reduction of **4b** using Red-Al® is described as a typical example. To solution of **4b** (50 mg, 0.09 mmol) in benzene (1 ml) was added Red-Al® (70% in toluene) (0.055 ml, 0.2 mmol) under a nitrogen atmosphere at room temperature. After being refluxed for 6 h, 10% NaOH solution was added to the reaction mixture and the precipitate was filtered off. The filtrate was washed with H_2O, and the organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt–hexane 4:1) afforded **11b** (2 mg, 4%) and **12b** (17 mg, 35%). Other reaction conditions and yields were shown in Table 3.

General procedure for preparation of sulfonamide 17

Preparation of **17a** is described as a typical example. To a solution of 1-amino-2-propanol (7.5 g, 0.1 mol) and Et_3N (10 g, 0.1 mol) in MeOH (150 ml) was added chloroacetaldehyde *O*-methyloxime **16a**[6] (5.4 g, 0.05 mol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 4 h, the solution was concentrated at reduced pressure. The residue was diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. To a solution of the resulting residue in acetone (50 ml) was added a solution of Na_2CO_3 (5.83 g, 0.055 mol) in H_2O (28 ml) under a nitrogen atmosphere at room temperature. After a solution of toluenesulfonyl chloride (TsCl) (5.73 g, 0.03 mol) in acetone (10 ml) was added dropwise at 0°C, the reaction mixture was stirred at room temperature for 3 h. The solution was filtered through a pad of Celite, the filtrate was concentrated at reduced pressure and the residue was diluted with $CHCl_3$ and washed with H_2O. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash column chromatography (AcOEt–hexane 1:1) afforded the sulfonamide **17a** (6.75 g, 45% based on **16a**). EtOH as solvent and 0.15 mol of Et_3N were used for synthesis of **17b**,**c** in alkylation step. Chloroacetone *O*-methyloxime **16b**[6] was used for preparation s of **17b**,**d** in alkylation step.

***N*-(2-Hydroxypropyl)-*N*-(2-methoxyimino)ethyl]-4-methylbenzenesulfonamide (17a).** 45% Yield based on **16a**; a colorless oil; IR 3520 (OH), 1343, 1161 (NSOO) cm^{-1}; ^1H NMR (300 MHz) δ 7.71 (2H, br d, J=8 Hz, ArH), 7.33 (2H, br d, J=8 Hz, ArH), 7.27 (3/5H, t, J=6 Hz, HC=N (*E*)), 6.66 (2/5H, t, J=4 Hz, HC=N (*Z*)), 4.18–3.83 (3H, m, C*H*OH, CH_2CH=N), 3.86 (6/5H, s, OMe (*Z*)), 3.80 (9/5H, s, OMe (*E*)), 3.20–3.00 (2H, m, CH_2CH(OH)), 3.06 (3/5H, d, J=5 Hz, OH (*E*)), 2.44 (3H, s, ArMe), 2.37 (2/5H, d, J=5 Hz, OH (*Z*)), 1.19 (6/5H, d, J=7 Hz, Me (*Z*)), 1.16 (9/5H, d, J=7 Hz, Me (*E*)); HRMS (EI, m/z) calcd for $C_{13}H_{21}N_2O_4S$ ($M^{++}H$) 301.1220, found 301.1238.

Ethyl [[2-(Methoxyimino)propyl][(4-methylphenyl)sulfonyl]amino]acetate (17b).43% Yield based on **16b**; colorless crystals from Et_2O; mp 64–65°C; IR 1748 (COOEt), 1339, 1159 (NSOO) cm^{-1}; ^1H NMR (300 MHz) δ 7.72 (2H, br d, J=8 Hz, ArH), 7.30 (2H, br d, J=8 Hz, ArH), 4.07 (2H, q, J=7 Hz, OEt), 3.95 and 3.89 (each 2H, s, CH_2×2), 3.79 (3H, s, OMe), 2.43 (3H, s, ArMe), 1.87 (2H, s, Me), 1.19 (3H, t, J=7 Hz, OEt); HRMS (EI, m/z) calcd for $C_{15}H_{22}N_2O_5S$ (M^+) 342.1248, found 342.1276. Anal.

Calcd for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; N, 8.18. Found: C, 52.58; H, 6.47; N, 8.16.

Ethyl [[2-(Methoxyimino)ethyl][(4-methylphenyl)sulfonyl]amino]acetate (17c). 25% Yield based on **16a**; colorless crystals from Et_2O; mp 63–64°C; IR 1748 (COOEt), 1343, 1160 (NSOO) cm^{-1}; ^1H NMR (300 MHz) δ 7.74 (2H, br d, J=8 Hz, ArH), 7.31 (2H, br d, J=8 Hz, ArH), 7.24 (3/4H, t, J=6 Hz, HC=N (*E*)), 6.79 (1/4H. t, J=4.5 Hz, HC=N (*Z*)), 4.20–3.90 (6H, m, CH_2×3), 3.84 (3/4H, s, OMe (*Z*)), 3.80 (9/4H, s, OMe (*E*)), 2.43 (3H, s, ArMe), 1.21 (3H, t, J=7 Hz, OEt); HRMS (EI, *m/z*) calcd for $C_{14}H_{20}N_2O_5S$ (M^+) 328.1091, found 328.1077. Anal. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.04; H, 6.16; N, 8.53.

***N*-(2-Hydroxyethyl)-*N*-[(2-methoxyimino)propyl]-4-methylbenzenesulfonamide (17d).** 30% Based on **16b**; colorless crystals from Et_2O; mp 84–85°C; IR 3630–3270 (OH), 1339, 1180 (NSOO) cm^{-1}; ^1H NMR (300 MHz) δ 7.71 (2H, br d, J=8 Hz, ArH), 7.32 (2H, br d, J=8 Hz, ArH), 3.85 (2H, br s, CH_2C=N), 3.80 (3H, s, OMe), 3.66 (2H, q, J=6 Hz, CH_2CH_2OH), 3.24 (2H, t, J=6 Hz, CH_2CH_2OH), 3.03 (1H, br t, J=6 Hz, OH), 2.43 (3H, s, ArMe), 1.89 (3H, s, Me); HRMS (EI, *m/z*) Calcd $C_{13}H_{20}N_2O_4S$ (M^+) 300.1142, Found 300.1129. Anal. Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33. Found: C, 52.03; H, 6.95; N, 9.35.

***N*-[(2-Methoxyimino)ethyl]-4-methyl-*N*-(2-oxopropyl)-benzenesulfonamide (18a).** The ketone **18a** was obtained in 64% yield after purification by medium-pressure column chromatography (AcOEt–hexane 1:3) from **17a** by the procedure described for synthesis of **3** from **2**: a colorless oil: IR 1737(CO), 1352, 1161 (NSOO) cm^{-1}; ^1H NMR (300 MHz) δ 7.71 (2H, br d, J=8 Hz, ArH), 7.32 (2H, br d, J=8 Hz, ArH), 7.23 (3/5H, t, J=6 Hz, HC=N (*E*)), 6.66 (2/5H, t, J=4 Hz, HC=N (*Z*)), 4.03 (4/5H, br s, CH_2CO(*Z*)), 4.02 (4/5H, br d, J=4 Hz, CH_2CH=N (*Z*)), 4.00 (6/5H, br s, CH_2CO (*E*)), 3.87 (6/5H, br d, J=6 Hz, CH_2CH=N (*E*)), 3.83 (6/5H, s, OMe (*Z*)), 3.78 (9/5H, s, OMe (*E*)), 2.43 (3H, s, ArMe), 2.16 (3H, s, Me); HRMS (EI, *m/z*) calcd for $C_{13}H_{18}N_2O_4S$ (M^+) 298.0986, found 298.0981.

[[2-(Methoxyimino)propyl][(4-methylphenyl)sulfonyl]-amino]acetaldehyde (18b). To a solution of **17b** (2 g, 5.8 mmol) in dry Et_2O (100 ml) was added dropwise DIBALH (0.95 mol in hexane) (9.3 ml, 8.8 mmol) under a nitrogen atmosphere at −78°C. Then the solution was stirred at the same temperature for 1.5 h, and quenched with MeOH (1 ml) and H_2O (1 ml). The mixture was allowed to warm to the room temperature and stirred for 0.5 h, AcOEt and Celite were added to the mixture and the whole was stirred at the room temperature for 0.5 h. The precipitate was filtered through a pad of Celite, and the filtrate was washed with brine. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to afford the crude aldehyde **18b** as a pale yellow oil. After being characterized by ^1H NMR spectrum, unstable **18b** was immediately subjected to the following radical cyclization: ^1H NMR (200 MHz) δ 9.57 (1H, br s, CHO).

[[2-(Methoxyimino)ethyl][(4-methylphenyl)sulfonyl]amino]-acetaldehyde (18c). The aldehyde **18c** was obtained from **17c** by the procedure described for synthesis of **17b** from **18b**. After being characterized by ^1H NMR spectrum, unstable **18c** was immediately subjected to the following radical cyclization: IR 1720 (CHO), 1367, 1168 (NSOO) cm^{-1}; ^1H NMR (200 MHz) δ 9.60 (1H, br s, CHO).

***N*-[2-(1*H*-Imidazol-1-ylthioxomethyloxy)ethyl]-*N*-[(2-methoxyimino)propyl]-4-methylbenzenesulfonamide (18d).** A solution of **17d** (450 mg, 1.5 mmol) and 1,1′-thiocarbonyldiimidazole (535 mg, 3 mmol) in benzene (15 ml) was heated at reflux under a nitrogen atmosphere for 4 h and concentrated at reduced pressure. Purification of the residue by short column chromatography (AcOEt–hexane 2:1) afforded **18d** (517 mg, 84%) as a pale yellow oil. After being characterized by ^1H NMR spectrum, unstable **18d** was immediately subjected to the following radical cyclization: ^1H NMR (200 MHz) δ 8.35 (1H, br s, imidazole), 7.78–7.60 (3H, m, ArH), 7.29 (2H, br d, J=8 Hz, ArH, imidazole), 7. 03 (1H, br s, imidazole), 4.74 (2H, t, J=6 Hz, CH_2O), 3.87 (2H, s, CH_2C=N), 3.78 (3H, s, OMe), 3.59 (2H, t, J=6 Hz, CH_2CH_2O), 2.42 (3H, s, ArMe), 1.84 (3H, s, Me).

5-*O*-(1*H*-Imidazol-1-ylthioxomethyl)-2,3,4,6-tetrakis-*O*-(phenylmethyl)-D-*xylo*-hexos-5-ulose 1-(*O*-Methyloxime) (18e). According to the procedure described for synthesis of **18d** from **17d**, **2a** was treated to give **18e** in 93% yield as a colorless oil after purification by medium-pressure column chromatography (AcOEt–hexane 1:2). After being characterized by ^1H NMR spectrum, unstable **17e** was immediately subjected to the following radical cyclization: ^1H NMR (300 MHz) δ 8.15 (1H, br s, imidazole), 5.78 (1H, m, CHCS), 7.45–6.83 (23H, ArH, CHC=N, imidazole), 4.78–3.80 (16H, m, $CHOCH_2Ph$×3, CH_2OCH_2Ph, OMe); HRMS (EI, *m/z*) calcd for $C_{39}H_{41}N_3O_6S$ (M^+) 679.2713, found 679.2706.

General procedure for radical cyclization of 18

To a boiling solution of **18** (1.5 mmol) in C_6H_6 (12 ml) was added dropwise (10 ml h^{-1}) a solution of Bu_3SnH (3 mmol) and AIBN (0.3 mmol) in C_6H_6 (7 ml) under a nitrogen atmosphere. After being heated at reflux for 5 h, the solution was concentrated at reduced pressure. The resulting residue was diluted with acetonitrile, the acetonitrile phase was washed with hexane and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt–hexane 1:1–3:2) afforded the cyclized products **19**–**23**. For radical cyclization of **18a**, additional solution of AIBN (0.3 mmol) in benzene (3 ml) was used four times at 1 h intervals.

***trans*-4-(Methoxyamino)-3-methyl-1-[(4-methylphenyl)-sulfonyl]pyrrolidin-3-ol (19a).** 43% Yield in two steps from **18a**; a colorless oil; IR 3700–3350 (OH, NH), 1346, 1160 (NSOO) cm^{-1}; ^1H NMR (200 MHz) δ 7.72 (2H, br d, J=8 Hz, ArH), 7.34 (2H, br d, J=8 Hz, ArH), 5.40 (1H, br s, NH), 3.63 (1H, dd, J=11, 7 Hz, 5-H), 3.40–3.20 (3H, m, 2-H_2, 4-H), 3.31 (3H, s, OMe), 3.18 (1H, dd, J=11, 4 Hz, 5-H), 2.43 (3H, s, ArMe), 1.24 (3H, s, Me); HRMS (EI, *m/z*) calcd for $C_{13}H_{20}N_2O_4S$ (M^+) 300.1142, found 300.1121.

***cis*-4-(Methoxyamino)-3-methyl-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol (20a).** 14% Yield in two steps from **18a**; a colorless oil; IR 3700–3350 (OH, NH), 1346, 1160 (NSOO) cm^{-1};^{1}H NMR (300 MHz) δ 7.71 (2H, br d, J=8 Hz, ArH), 7.33 (2H, br d, J=8 Hz, ArH), 5.50 (1H, br s, NH), 3.59 (1H, dd, J=10, 7.5 Hz, 5-H), 3.40 (3H, s, OMe), 3.36–3.20 (3H, m, 2-H_2, 4-H), 3.04 (1H, dd, J=10, 8 Hz, 5-H), 2.43 (3H, s, ArMe), 1.31 (3H, s, Me); HRMS (EI, *m/z*) calcd for $C_{13}H_{20}N_2O_4S$ (M^+) 300.1143, found 300.1169.

***trans*-4-(Methoxyamino)-4-methyl-1-[(4-methylphenyl)-sulfonyl]pyrrolidin-3-ol (19b).** 29% Yield in two steps from **17b**; colorless crystals from AcOEt; mp 118–120°C; IR 3630–3370 (OH, NH), 1346, 1161 (NSOO) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.72 (2H, br d, J=8 Hz, ArH), 7.33 (2H, br d, J=8 Hz, ArH), 5.10 (1H, br s, NH), 4.08 (1H, br t, J=6 Hz, 3-H), 3.68 (1H, dd, J=10.5, 6 Hz, 2-H), 3.39 (3H, s, OMe), 3.12 (1H, dd, J=10.5, 5 Hz, 2-H), 3.27 and 3.09 (2H, ABq, J=10 Hz, 5-H_2), 2.44 (3H, s, ArMe), 1.98 (1H, br s, OH), 1.09 (3H, s, Me); HRMS (EI, *m/z*) calcd for $C_{13}H_{20}N_2O_4S$ (M^+) 300.1142, found 300.1158. Anal. Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33. Found: C, 51.97; H, 6.89; N, 9.29.

***cis*-4-(Methoxyamino)-4-methyl-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol (20b).** 7% Yield in two steps from **17b**; a colorless oil; IR 3600–3340 (OH, NH), 1346, 1160 (NSOO) cm^{-1}; ^{1}H NMR (200 MHz) δ 7.71 (2H, br d, J=8 Hz, ArH), 7.32 (2H, br d, J=8 Hz, ArH), 5.82 (1H, br s, NH), 3.89 (1H, m, 3-H), 3.58 (1H, m, 2-H), 3.40 (3H, s, OMe), 3.26 (1H, br dd, J=11, 3 Hz, 2-H), 3.19 and 3.07 (2H, ABq, J=10 Hz, 5-H_2), 2.43 (3H, s, ArMe), 1.11 (3H, br s, Me); HRMS (EI, *m/z*) calcd for $C_{13}H_{20}N_2O_4S$ (M^+) 300.1142, found 300.1138.

***trans*-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-pyrrolidin-3-ol (19c).** 23% yield in two steps from **17c**; colorless needless from AcOEt-Et_2O; mp 111–113°C; IR 3680–3300 (NH, OH), 1345, 1160 (NSOO) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.72 (2H, br d, J=8.5 Hz, ArH), 7.34 (2H, br d, J=8.5 Hz, ArH), 5.39 (1H, br s, NH), 4.18 (1H, m, 3-H), 3.66 (1H, dd, J=10.5, 5 Hz, 2-H), 3.50 (1H, dd, J=10.5, 6.5 Hz, 5-H), 3.45 (1H, m, 4-H), 3.41 (3H, s, OMe), 3.18 (1H, dd, J=10.5, 3.5 Hz, 2-H), 3.13 (1H, dd, J=10.5, 4 Hz, 5-H), 2.44 (3H, s, ArMe), 2.07 (1H, br s, OH); HRMS (EI, *m/z*) calcd for $C_{12}H_{18}N_2O_4S$ (M^+) 286.0986, found 286.098. Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.34; H, 6.34; N, 9.78. Found: C, 50.26; H, 6.30; N, 9.74.

***cis*-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol (20c).** 12% Yield in two steps from **17c**; colorless needless from Et_2O; mp 89–90°C; IR 3600–3350 (OH, NH), 1347, 1163 (NSOO) cm^{-1}; ^{1}H NMR (300 MHz) δ: 7.71 (2H, br d, J=8 Hz, ArH), 7.33 (2H, br d, J=8 Hz, ArH), 5.77 (1H, br s, NH), 4.25 (1H, br s, 3-H), 3.60–3.50 (2H, m, 4, 5-H), 3.49 (1H, dd, J=11, 4.5 Hz, 2-H), 3.45 (3H, s, OMe), 3.35 (1H, br dd, J=11, 2.5 Hz, 2-H), 2.96 (1H, m, 5-H), 2.58 (1H, br s, OH), 2.43 (3H, s, ArMe); HRMS (EI, *m/z*) calcd for $C_{12}H_{18}N_2O_4S$ (M^+) 286.0986, found 286.0995. Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.34; H, 6.34; N, 9.78. Found: C, 50.33; H, 6.30; N, 9.73.

3-Methoxyamino-3-methyl-1-[(4-methylphenyl)sulfonyl]-pyrrolidine (21). 53% yield from **18d**; pale yellow crystals from Et_2O; mp 92–93°C; IR 1343, 1160 (NSOO) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.72 (2H, br d, J=8 Hz, ArH), 7.33 (2H, br d, J=8 Hz, ArH), 5.20 (1H, br s, NH), 3.40–3.20 (2H, m, 5-H_2), 3.37 (3H, s, OMe), 3.32 and 2.94 (2H, ABq, J=10 Hz, 2-H_2), 2.44 (3H, s, ArMe), 1.86 (1H, br ddd, J=12, 8, 5 Hz, 4-H), 1.63 (1H, dt, J=13, 8 Hz, 4-H), 1.15 (3H, s, Me); HRMS (EI, *m/z*) calcd for $C_{13}H_{20}N_2O_3S$ (M^+) 284.1194, found 284.1175. Anal. Calcd for $C_{13}H_{20}N_2O_3S$: C, 54.91; H, 7.09; N, 9.85. Found: C, 54.80; H, 7.37; N, 9.83.

[1*R*-(1α,2β,3α,4β,5α)]-1-Methoxyamino-2,3,4-tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]cyclopentane (22). 46% Yield from **18e**; a colorless oil; ^{1}H NMR (500 MHz) δ 7.39–7.23 (20H, m, ArH), 5.97 (1H, br s, OH), 4.70–4.44 (8H, m, CH_2Ph×4), 4.00 (1H, br t, J=6 Hz, 3-H), 3.96 (1H, br dd, J=8, 5.5 Hz, 4-H), 3.86 (1H, br t, J=5 Hz, 2-H), 3.66–3.60 (2H, m, 6-H_2), 3.59 (1H, m, 1-H), 3.47(3H, s, OMe), 2.54 (1H, br quint., J=7 Hz, 5-H); HRMS (EI, *m/z*) calcd for $C_{35}H_{39}NO_5$ (M^+) 553.2826, found 553.2816.

[1*R*-(1α,2β,3α,4β,5β)-1-Methoxyamino-2,3,4-tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]cyclopentanamine (23). 23% Yield from **18e**; a colorless oil; ^{1}H NMR (500 MHz) δ 7.36–7.23 (20H, m, ArH), 5.78 (1H, br s, NH), 4.67–4.48 (8H, m, CH_2Ph×4), 3.99–3.92 (3H, m, 2–4-H), 3.79 (1H, dd, J=9.5, 7 Hz, 6-H), 3.68 (1H, dd, J=9.5, 7 Hz, 6-H), 3.48 (3H, s, OMe), 3.39 (1H, m, 5-H), 2.49 (1H, m, 1-H); HRMS (EI, *m/z*) calcd for $C_{35}H_{39}NO_5$ (M^+) 553.2826, found 553.2804.

General method for reaction of methoxyamines 19–23 with Red-Al®

To solution of the methoxyamine **19**–**23** (0.17 mmol) in benzene (2 ml) was added Red-Al® (70% in toluene) (112 mg, 0.5 mmol) at room temperature. After being refluxed for 1–2 h, 20% NaOH solution was added to the reaction mixture and the mixture was diluted with AcOEt. The precipitate was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure. Purification of the residue by short column chromatography ($CHCl_3$–MeOH 9:1) afforded the corresponding demethoxylated amines and/or the ring expansion product **25**. Yields were shown in Table 4. The spectral data of **25** were found to be identical with those of the authentic sample.[16]

***trans*-4-Amino-3-methyl-1-[(4-methylphenyl)sulfonyl]-pyrrolidin-3-ol (24a).** Colorless crystals from $CHCl_3$–Et_2O; mp 144–146°C; IR 3650–3400 (OH, NH), 1347, 1160 (NSOO) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.72 (2H, br d, J=8 Hz, ArH), 7.34 (2H, br d, J=8 Hz, ArH), 3.64 (1H, br dd, J=10, 7 Hz, 5-H), 3.34 and 3.22 (2H, ABq, J=10 Hz, 2-H_2), 3.12 (1H, br t, J=6 Hz, 4-H), 2.99 (1H, br dd, J=10, 7 Hz, 5-H), 2.42 (3H, s, ArMe), 1.19 (3H, s, Me); HRMS (EI, *m/z*) calcd for $C_{12}H_{18}N_2O_3S$ (M^+) 270.1037, found 270.1048. Anal. Calcd for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36. Found: C, 53.04; H, 6.55; N, 10.34.

***trans*-4-Amino-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol (24b).** Colorless crystals from $CHCl_3$; mp 115–116°C;

IR 3367–3300 (NH, OH), 1347, 1163 (NSOO) cm^{-1}; ^1H NMR (200 MHz) δ 7.72 (2H, br d, J=8 Hz, ArH), 7.32 (2H, br d, J=8 Hz, ArH), 3.91 (1H, br q, J=5 Hz, 3-H), 3.62 (1H, dd, J=11, 5 Hz, 2-H), 3.55 (1H, dd, J=11, 6 Hz, 5-H), 3.24 (1H, m, 4-H), 3.16 (1H, dd, J=11, 3.5 Hz, 2-H), 3.03 (1H, dd, J=11, 3.5 Hz, 5-H), 2.95 (1H, m, OH), 2.44 (3H, s, ArMe); HRMS (EI, *m/z*) calcd for $C_{11}H_{16}N_2O_3S$ (M^+) 256.0880, found 256.0899.

***cis*-4-Amino-3-methyl-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol (24c).** Colorless crystals from $CHCl_3$; mp 98–99°C; IR 3600–3225 (OH, NH), 1349, 1161 (NSOO) cm^{-1}; ^1H NMR (200 MHz) δ (200 MHz) 7.70 (2H, br d, J=8 Hz, ArH), 7.32 (2H, br d, J=8 Hz, ArH), 3.58 (1H, m, 5-H), 3.37 (1H, d, J=11 Hz, 2-H), 3.25 (1H, br dd J=10, 1 Hz, 2-H), 3.10–2.88 (2H, m, 4, 5-H), 2.42 (3H, s, ArMe), 1.14 (3H, s, Me); HRMS (EI, *m/z*) calcd for $C_{12}H_{18}N_2O_3S$ (M^+) 270.1037, found 270.1013. Anal. Calcd for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36. Found: C, 53.31; H, 6.79; N, 10.43.

***cis*-4-Amino-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol (24d).** Colorless powder; IR 3600–3230 (OH, NH), 1343, 1161 (NSOO) cm^{-1}; ^1H NMR (300 MHz) δ: 7.71 (2H, br d, J=8 Hz, ArH), 7.33 (2H, br d, J=8 Hz, ArH), 3.98 (1H, br td, J=4.5, 3 Hz, 3-H), 3.53 (1H, dd, J=10, 7 Hz, 5-H), 3.50 (1H, dd, J=11, 5 Hz, 2-H), 3.39 (1H, br td, J=7, 4.5 Hz, 4-H), 2.60 (1H, dd, J=11, 3 Hz, 2-H), 2.93 (1H, dd, J=10, 8 Hz, 5-H), 2.34 (3H, s, ArMe); HRMS (EI, *m/z*) calcd for $C_{11}H_{16}N_2O_3S$ (M^+) 256.0880, found 256.0868.

3-Methy1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-amine (26). pale yellow powder; IR 1344, 1159 (NSOO) cm^{-1}; ^1H NMR (300 MHz) δ: 7.72 (2H, br d, J=8.5 Hz, ArH), 7.33 (2H, br d, J=8.5 Hz, ArH), 3.50–3.22 (2H, m, 5-H_2), 3.09 and 3.07 (2H, AB q, J=10 Hz, 2-H_2), 2.43 (3H, s, ArMe), 1.80–1.62 (2H, m, 4-H_2); HRMS (EI, *m/z*) calcd for $C_{12}H_{19}N_2O_2S$ (M^++H) 255.1166, found 255.1157.

[1*R*-(1α,2β,3α,4β,5α)]-2,3,4-Tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]cyclopentanamine (27a). 69% Yield from **22**; a colorless oil; ^1H NMR (300 MHz) δ 7.45–7.20 (20H, m, ArH), 4.76–4.40 (8H, m, CH_2Ph×4), 4.00–3.86 (2H, m, 3, 4-H), 3.70–3.50 (3H, m, 2-H, 6-H_2), 3.44 (1H, br dd, J=8, 7 Hz, 1-H), 2.38 (1H, m, 5-H); HRMS (EI, *m/z*) calcd for $C_{34}H_{37}NO_4$ (M^+) 523.2720, found 523.2713.

[1*R*-(1α,2β,3α,4β,5β)]-2,3,4-Tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]cyclopentanamine (27b). 77% Yield from **23**; a colorless oil; ^1H NMR (500 MHz) δ 7.40–7.20 (20H, m, ArH), 4.72–4.48 (8H, m, CH_2Ph×4), 3.92 (1H, br dd, J=4.5 2 Hz, 4-H), 3.87 (1H, dd, J=4.5, 2 Hz, 3-H), 3.80 (1H, dd, J=9, 8 Hz, 6-H), 3.66 (1H, dd, J=9, 6.5 Hz, 6-H), 3.61 (1H, ddd, J=7.5, 4.5, 1 Hz, 2-H), 3.26 (1H, dd, J=11, 7.5 Hz, 1-H), 2.21 (1H, m, 5-H); HRMS (EI, *m/z*) calcd for $C_{34}H_{37}NO_4$ (M^+) 523.2720, found 523.2729.

Ring expansion of 4a with Red-Al®

According to the procedure described for reduction of **4b** with Red-Al®, treatment of **4a** with Red-Al® gave **11a** (39%) and **12a** (9%).

Ring expansion of 4c with Red-Al®

According to the procedure described for reduction of **4b** with Red-Al®, treatment of **4b** with Red-Al® gave **11c** (66%) and **12c** (7%).

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10. Position numberings of cyclopentane and piperidine derivatives **4**–**15**, **22**, **23** and **27** in ^1H NMR data are specified in Schemes 3–5 and Tables 2 and 4.
11. Crystal data for **10a.** $C_{16}H_{23}NO_{10}$, M=389.357, space group $p61$, a=b=19.235 (2), c=10.863 (2) Å, V=3480.8 (8) Å^3, R value 0.075 for 2886 reflections.
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