Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 2399–2403
Tetrahedron Letters

Synthesis of N-protected azaoligosaccharides and their cyclic derivatives

Daisuke Sawada,[a] Hideyo Takahashi,[a] Moto Shiro[b] and Shiro Ikegami[a,*]

[a]*Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko Kanagawa 199-0195, Japan*
[b]*Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196-0003, Japan*

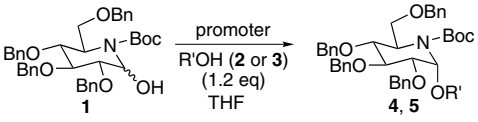
Received 17 January 2005; revised 31 January 2005; accepted 10 February 2005

Abstract—Azaoligosaccharides are prepared through the glycosylation of nojirimycin derivatives with catalytic amounts of TMSOTf. Also, the 1-6′, 1′-6-cyclic azadisaccharides are successfully synthesized, and their one-pot syntheses are demonstrated.

It is well-known that sugars play an important role in human life, and recently, functional oligosaccharides are much of interest. Azasugars, on the other hand, are rare natural products such as nojirimycin,[1] and a large number of their derivatives has been reported.[2] In those cases, researchers focused on mono-azasugars, and directed their interest mainly to glycosidase-inhibitory activities.[3] As a result, few research efforts have been made on azaoligosaccharide chemistry and limited examples of oligosaccharides containing azasugars have been reported.[4–7] Azasugars, however, have interesting properties, which are not possessed by sugars. First, azasugars are able to make a covalent bond from the ring-nitrogen to the outside of the sugar ring. By this unique bond, azaoligosaccharides are expected to have various structures and new functions. Secondly, a hydroxyl group at an anomeric carbon of an azasugar is so reactive that elongation of the azasugar chains will be easier than that of sugar chains. Here we report the synthesis of azaoligosaccharides and their cyclic compounds using their unique properties.

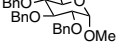
In the first place, we optimized the conditions of glycosylation with the known azasugar **1**[8] as a donor and cyclohexanol (**2**) as an acceptor (Table 1). According to Vasella's report,[8] the reaction of **1** and **2** in THF was examined using $TsOH{\cdot}H_2O$ as a promoter, and afforded the desired product **4** only in 10% yield, and by-products were derived from both **1** and **4**. After careful investigation of the promoters, $La(OTf)_3$[9] and TMSOTf[10] were found to be more effective in this reaction. Besides, the azasugars are so reactive that it is not necessary to convert the hydroxyl group at the anomeric carbons to more active leaving groups. Next, we investigated the synthesis of a disaccharide using the sugar derivative(**3**) as an acceptor with $La(OTf)_3$ and TMSOTf. The reaction of the azasugar **1** and **3** with $La(OTf)_3$ was less reactive, resulting in 29% yield of the product **5** even using excess amounts of the promoter. By using TMSOTf, the starting material **1** rapidly disappeared, and the reaction afforded 40% of **5** at 0 °C accompanied by many by-products. Therefore, the reaction was carried at −40 °C with 0.5 equiv of TMSOTf to give **5** in 86% yield. The products **4** and **5**

Table 1. Glycosylation of **1** and **2** or **3**



1 **4, 5**

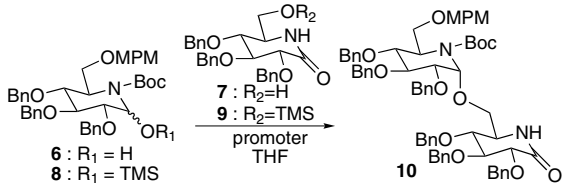
Run	Acceptor	Promoter (equiv)	Temp. (°C)	% Yield (**4** or **5**)
1	**2**	$TsOH{\cdot}H_2O$ (1)	rt	10
2	**2**	$La(OTf)_3$ (1)	0	72
3	**2**	TMSOTf (0.5)	−78	89
4	**3**	$La(OTf)_3$ (5)	rt	29
5	**3**	TMSOTf (1)	0	40
6	**3**	TMSOTf (0.5)	−40	86

Boc: *t*-butoxycarbonyl; **2**, **4**: R′ = cyclohexyl; **3**, **5**: = 

Keywords: Amino sugars; Dimeric cycloazasugar; Azaoligosaccharide.
* Corresponding author. Tel.: +81 426853728; fax: +81 426851870; e-mail: shi-ike@pharm.teikyo-u.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.02.057

Table 2. Synthesis of an azadisaccharide



Run	Donor	Acceptor (equiv)	Promoter (equiv)	Temp. (°C)	% Yield (**10**)
1	**6**	**7** (2)	$La(OTf)_3$ (1)	0 to rt	0
2	**6**	**7** (1.2)	TMSOTf (0.5)	0	60
3	**6**	**7** (2)	TMSOTf (0.5)	0	71
4	**8**	**7** (2)	TMSOTf (0.5)	−40	47
5	**8**	**9** (2)	TMSOTf (0.5)	0	52
6	**8**	**9** (2)	TMSOTf (0.5)	−40	75
7	**8**	**9** (2)	TMSOTf (0.2)	−78 to −40	90[a]
8	**8**	**9** (3)	TMSOTf (0.5)	−40	53

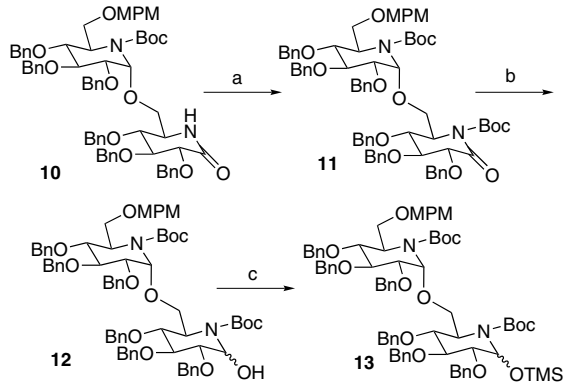
[a] A stereoisomer was obtained in 2% yield.

were obtained as a single stereoisomer irrespective of the stereochemistry at the anomeric carbon of the starting materials.

To synthesize an azadisaccharide, we investigated the reaction using the azasugar **7**[11] as an acceptor (Table 2). With $La(OTf)_3$, the reaction of **6**[11] and **7** did not proceed due to the strong coordination with $La(OTf)_3$ by the amide moiety of **7**. Using TMSOTf, we could obtain the corresponding azadisaccharide **10** in 60% yield by using 1.2 equiv of **7**, and in 71% yield by using 2 equiv of **7** at 0 °C. Next, compounds **8** and **9** with the hydroxyl groups protected as TMS ethers, were prepared for further examination of this glycosylation.[12] Fortunately, the reaction of **8** and **9** smoothly proceeded and **10** was obtained in 52% yield though some decomposition of the compounds still occurred. Then, the reaction at lower temperature gave a better result (75% yield at −40 °C, run 6). Finally, after the addition of 0.2 equiv of TMSOTf at −78 °C, the mixture was reacted at −40 °C, and this reaction afforded the azadisaccharide **10** in 90% yield (run 7).[13]

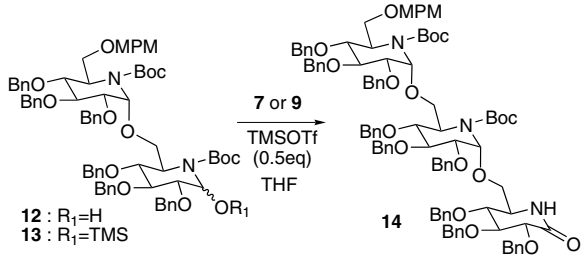
Further elongation of the azadisaccharide **10** was examined. As shown in Scheme 1, the amide nitrogen of **10** was protected by a Boc group, and the subsequent reduction by $NaBH_4$ afforded **12**, which was converted to TMS ether **13**. Using **12** or **13** as a donor, we tried to synthesize an azatrisaccharide under the above glycosylation conditions (Table 3). With 0.5 equiv of TMSOTf, **12** and **7** were reacted at 0 °C in THF to give the unexpected azadisaccharide **10**[14] instead of the desired azatrisaccharide **14**. The reaction of **13** and **9** at −78 °C to −40 °C, however, afforded **14** in 41% yield as a single stereoisomer, although the azadisaccharide **10** was still obtained in 43% yield. The same reaction at −78 °C to −60 °C gave **14** in 41% yield, **10** in 18% yield, and recovery of starting material (30%).

To investigate the new function of the azaoligosaccharides, we tried the possibility of a cyclic disaccharide. By



Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, DMAP, CH_3CN; 92%; (b) $NaBH_4$, MeOH; 100%; (c) TMSCl, imidazole, DMF; 100%.

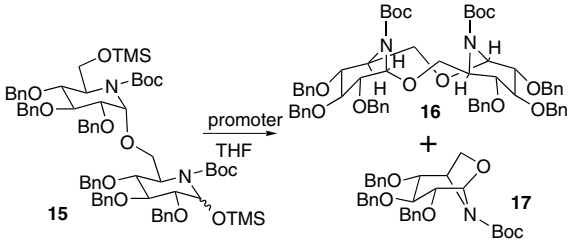
Table 3. Synthesis of an azatrisaccharide



Run	Acceptor	Donor (equiv)	Temp. (°C)	% Yield of **14**
1	**12**	**7** (2)	0	0 (**10**: 52)
2	**13**	**9** (2)	−78 to −40	41 (**10**: 43)
3	**13**	**9** (2)	−78 to −60	41 (**10**: 18)

a similar route in Scheme 1, we prepared the starting substrate for the cyclization reaction. Removal of the MPM group of **11** by DDQ oxidation (86%) and reduction by $NaBH_4$ afforded the dihydroxyl compound (95%), which was converted to di-TMS ether **15** (100%). Using this compound, the cyclization was examined (Table 4). Compound **15** was reacted with TMSOTf at −40 °C, and the cyclic compound **16**, which shows a complex asymmetric ^1H NMR due to the steric repul-

Table 4. Synthesis of cyclic azaoligosaccharides



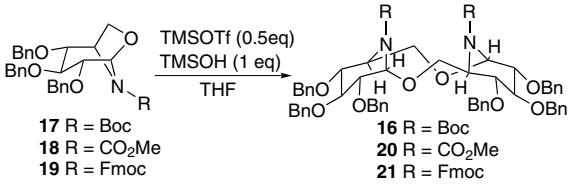
Run	Promoter (equiv)	Temp. (°C)	% Yield of **16**
1	TMSOTf (0.5)	−40	10
2	TMSOTf (0.5)	−78 to −50	60 (**17**: 42[a])
3	TBSOTf (0.5)	−78 to −50	37 (**17**: 57[a])
4	TIPSOTf (0.5)	−78	24 (**17**: 35[a])

[a] Two mol equivalents of **17** might be synthesized from **15**.

sion of the two carbamate groups, was obtained as a single stereoisomer in 10% yield. The measurement of its ^{1}H NMR at high temperature (100 °C, DMSO-d_6 solvent) resulted in broad peaks like a single sugar. Also in this reaction, TMSOTf would activate the glycosyl bond of **15** and the 1,6-anhydro azasugar **17** was also obtained. To prevent the formation of **17**, we tried the reaction at lower temperature (−78 °C to −50 °C), affording **16** in 60% yield (run 2). Using TBSOTf and TIPSOTf as a bulky promoter decreased the yield in **16** (runs 3 and 4).

For the synthesis of the cyclic compounds, the 1,6-anhydro azasugar **17** should be a good precursor (Table 5). At first, TMSOTf was added to **17** in THF at −40 °C, and then temperature of the mixture was raised to 0 °C; however, this reaction gave only trace amounts of the cyclic compound. Fortunately, the addition of TMSOH promoted the reaction, and the cyclic compound **16** was obtained in 25% yield in 0.2 M and 31% yield in 0.3 M. In this reaction, there is no other cyclic compound composed of more than two azasugars. At the reduced reaction temperature (−40 °C), we could get the product in 77% yield, although the reaction proceeded a little slower, and 10% of **17** was recovered (run 4). To complete the reaction, TMSOTf was slowly added for 15 min, but this trial was not satisfactory because of the decomposition of the product (run 5). Next, for the synthesis of the azaoligosaccharide derivatives, we modified the carbamate moiety. From the same intermediate, which was converted to **6** and **17**, the methyl carbamate **18** and the Fmoc derivative **19** were synthesized in three steps: (1) the amide protection of the azasugar lactam by the methyl carbamate or Fmoc, (2) reduction by $NaBH_4$, (3) the removal of MPM by DDQ and the spontaneous intramolecular cyclization.

Table 5. One-pot synthesis of cyclic azadisaccharides

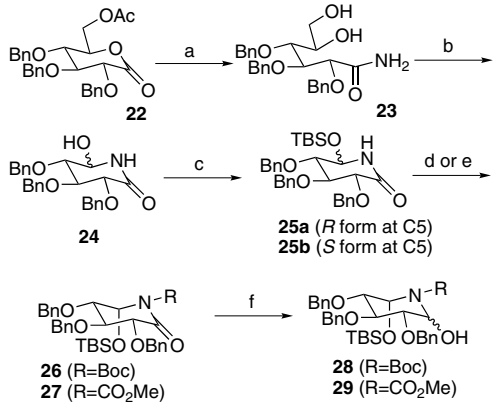


Run	Substrate	Concentration of substrate (M)	Temp. (°C)	% Yield of **16/20/21**[a] (recovery of S.M.)
1	**17**	0.2	−40 to 0	trace[b]
2	**17**	0.2	0	25 (20)
3	**17**	0.3	0	31 (17)
4	**17**	0.3	−40	77 (10)
5	**17**	0.3	0	27 (20)[c]
6	**18**	0.2	0	57 (17)
7	**18**	0.3	−78 to −40	88 (4)
8	**19**	0.2	0	43 (15)
9	**19**	0.3	−20	65 (7)

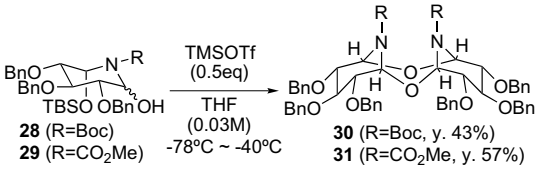
Fmoc: 9-fluorenylmethoxycarbonyl.
[a] % of weight per weight.
[b] TMSOH was not added.
[c] TMSOTf was slowly added (15 min).

Using **18** and **19**, the one-pot cyclization was also examined. The cyclic azadisaccharide **20** was obtained in 57% (0.2 M, run 6), and in 88% yield (0.3 M, run 7) from **18**, and similarly, **21** was obtained in 43% (0.2 M, run 8), and in 65% yield (0.3 M, run 9) from **19**, which are given as a single stereoisomer.

Then, we tried to synthesize another type of cyclic oligosaccharides. The known compound **22** was reacted with NH_3 in MeOH to afford the amide **23**, whose diol moiety was oxidatively cleaved by $NaIO_4$. After stirring the given mixture with 1 N HCl in THF, we could obtain the azasugar derivative **24**. The hydroxyl group of **24** was converted to TBS ether and the diastereomers were separated. The amide nitrogen of **25** was protected by Boc or methyl carbamate, and finally the reduction with $NaBH_4$ gave the precursors **28** and **29** for one-pot cyclization reactions (Scheme 2). Using these compounds, the cyclization under similar conditions used in Table 5 was carried out, and afforded the cyclic compounds **30** and **31** successfully. After several attempts, it gave the best results when the compounds, whose C5 stereochemistry was *S* (from **25b**), were reacted in the reduced substrate concentration (0.03 M) at low temperature (−78 to −40 °C) (Scheme 3). The unfavoured isomer **25a** with *R* stereochemistry at C5 was easily recycled: cleavage of the TBS group by TBAF, and then stirring with 1 N HCl in THF gave **24** with both C5 stereoisomers. The cyclic compounds **30** and **31** indicated the symmetric ^{1}H NMR.



Scheme 2. Reagents and conditions: (a) NH_3, MeOH; 95%; (b) (1) $NaIO_4$, CH_2Cl_2, H_2O, silica gel; (2) 1 N. HCl, THF; 95%; (c) TBSCl, imidazole; 100% (**25a**:**25b**/4:3); (d) $(Boc)_2O$, DMAP, CH_3CN; 100%; (e) $ClCO_2Me$, *n*-BuLi, THF, −78 °C; 87%; (f) $NaBH_4$, MeOH; 98% for **28**, 82% for **29**.



Scheme 3. One-pot synthesis of cyclic azadisaccharides.

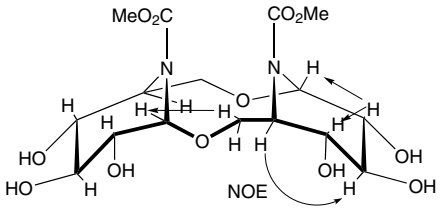


Figure 1. Proposed structure of **32**.

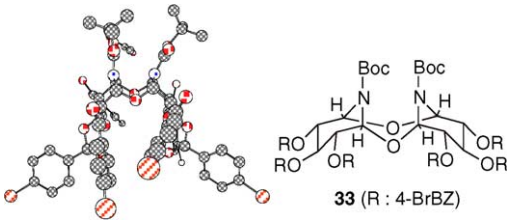


Figure 2. The X-ray single-crystal structure of **33**. Hydrogen atoms were omitted.

As mentioned above, the glycosylation of azasugars indicates high stereoselectivity. To confirm the stereochemistry of the glycosyl bonds, **20** and **30** were further transformed. The benzyl groups of **20** were removed by Pd/C and H_2 in THF to afford the hexa-hydroxyl compound **32** in quantitative yield, whose ^{1}H NMR was relatively simple.[15] Analyzing the NOE of **32**, we speculate its structure as shown in Figure 1.

Compound **30** was also debenzylated (100% yield), and converted to hexa-4-bromobenzoyl compound **33** (60% yield). The recrystallization of **33** was successful (from ethyl acetate and MeOH) and its X-ray crystallographic analysis indicates the structure of **33** as Figure 2. Thus, the stereochemistry of the glycoside bonds in the cyclic compounds was found to be all α-glycosides, and it is disclosed that the glycosylation of these azasugars affords an α-glycoside selectively.

In summary, we have developed glycosylation of azasugars to obtain azaoligosaccharides. Also, the cyclic azadisaccharides are successfully synthesized, and their one-pot syntheses are demonstrated. These azaoligosaccharides are thought to be precedents to develop various oligosaccharides, novel biologically active compounds, and new functional molecules. Study on their application as functional molecules is now in progress in our laboratory.

References and notes

1. (a) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *23*, 2124; (b) Ishida, N.; Kumagai, K.; Niida, T.; Tsuruoka, T.; Yumato, H. *J. Antibiot.* **1967**, *20*, 66; (c) Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219.
2. (a) Bashyal, B. P.; Chow, H.-F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205; (b) Fleet, G. W. J.; Namgoong, S. K.; Barker, C.; Baines, S.; Jacob, G. S.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 4429; (c) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043; (d) Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A., Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187; (e) Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939; (f) Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.* **1994**, *116*, 5099; (g) Heightman, T. D.; Ermert, P.; Klein, D.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 514; (h) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2527; (i) Sawada, D.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2003**, *44*, 3085; (j) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603; (k) Heck, M.-P.; Vincent, S. P.; Murray, B. W.; Bellamy, F.; Wong, C.-H.; Mioskowski, C. *J. Am. Chem. Soc.* **2004**, *126*, 1971, and references cited therein.
3. (a) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199; (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 318; (c) Papandreou, G.; Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1993**, *115*, 11682; (d) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171; (e) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; (f) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443; (g) Martin, O. R. In *Carbohydrate Mimics; Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998, p 259; (h) Depezay, J. C. In *Carbohydrate Mimics; Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998, p 307.
4. (a) Knapp, S.; Choe, Y. H.; Reilly, E. *Tetrahedron Lett.* **1993**, *34*, 4443; (b) Suzuki, K.; Hashimoto, H. *Tetrahedron Lett.* **1994**, *35*, 4119.
5. Aza-C-disaccharide, see: (a) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991; (b) Frérot, E.; Marquis, C.; Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 2023; (c) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856.
6. Oligosaccharide analogues based on azasugars, see: Ruttens, B.; Van der Eycken, J. *Tetrahedron Lett.* **2002**, *43*, 2215.
7. Disaccharides containing an azasugar at the reducing end, see: (a) Moss, S. F.; Southgate, R. *J. Chem. Soc., Perkin Trans.* **1993**, 1787; (b) Spohr, U.; Bach, M. *Can. J. Chem.* **1993**, *71*, 1943; (c) Takahashi, S.; Kuzuhara, H.; Nakajima, M. *Tetrahedron* **2001**, *57*, 6915.
8. Granier, T.; Vasella, A. *Helv. Chim. Acta* **1998**, *81*, 865.
9. Another example of a glycosidation using lanthanides, see: Hosono, S.; Kim, W.-S.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4.
10. (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717; (b) Macdonald, S. J. F.; Clarke, G. D. E.; Dowle, M. D.; Harrison, L. A.; Hodgson, S. T.; Inglis, G. G. A.; Johnson, M. R.; Shah, P.; Upton, R. J.; Walls, S. B. *J. Org. Chem.* **1999**, *64*, 5166; (c) Okitsu, O.; Suzuki, R.; Kabayashi, S. *Synlett* **2000**, 989; (d) Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605; (e) Okitsu, O.; Suzuki, R.; Kabayashi, S. *J. Org. Chem.* **2001**, *66*, 809; (f) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510.
11. These compounds were prepared through the same steps as for the synthesis of compound **1** using 6-(4-methoxybenzyl)-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone. See also Ref. 8.
12. Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165.
13. The ^{1}H NMR is so complicated that it is difficult to know the concise structure of this compound. However, it gives a reasonable HR-Mass spectrum.
14. Because the azasugar itself might be a leaving group in azaoligosaccharides, the cleavage of glycoside bond of **12** or **13** took place by TMSOTf, and same intermediate as the reaction in Table 2 was generated in situ.

15. Spectral data of **32**: $[\alpha]_D^{21}$ +9.7 (*c* 1.15, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 5.33 (br s, 1H), 5.23 (br s, 1H), 4.25 (dd, J = 2.2, 12.4 Hz, 1H), 4.17 (dd, J = 2.5, 12.1 Hz, 1H), 4.05 (dd, J = 11.0, 11.0 Hz, 1H), 4.05 (dd, J = 11.0, 11.0 Hz, 1H), 3.95 (dd, J = 0.8, 12.4 Hz, 1H), 3.91 (dd, J = 1.2, 12.1 Hz, 1H), 3.76 (d, J = 5.7 Hz, 1H), 3.73 (s, 3H), 3.73 (s, 3H), 3.76 (d, J = 5.5 Hz, 1H), 3.46 (m, 1H), 3.73 (m, 1H), 3.24 (dd, J = 5.7, 11.0 Hz, 1H), 3.24 (dd, J = 5.5, 11.0 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 158.9, 157.4, 91.6, 91.0, 79.8, 79.7, 77.9, 77.5, 70.2, 68.2, 66.7, 66.6, 61.6, 61.0, 53.8, 53.5; FAB-MS *m*/*z* 461 (M^+); FAB-HRMS calcd for $C_{16}H_{26}N_2O_{12}Na$ (M^+) 461.1384, found 461.1381.