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RESEARCH ARTICLE

Seven-step Synthesis of All-nitrogenated Sugar Derivatives Using Sequential Overman Rearrangements

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Abstract: All-nitrogenated sugars (ANSs), in which all hydroxy groups in a carbohydrate are replaced with amino groups, are anticipated to be privileged structures with useful biological activities. However, ANS synthesis has been challenging due to the difficulty in the installation of multi-amino groups. We report herein the development of a concise synthetic route to peracetylated ANSs in seven steps from commercially available monosaccharides. The key to success is the use of the sequential Overman rearrangement, which enables formal simultaneous substitution of four or five hydroxy groups in monosaccharides with amino groups. A variety of ANSs are available through the same reaction sequence starting from different initial monosaccharides by chirality transfer of secondary alcohols. Transformations of the resulting peracetylated ANSs such as glycosylation and deacetylation are also demonstrated. Biological studies reveal that ANS-modified cholesterol show cytotoxicity against human cancer cell lines, whereas each ANS and cholesterol have no cytotoxicity.

Introduction

Carbohydrates containing nitrogen atoms have been recognized as important structural motifs in pharmaceuticals. Some representative examples are aminoglycosides[1] and iminosugars (azasugars)[2] (Figure 1). Aminoglycosides such as kanamycin A (**1**)[3] and paromomycin (**2**)[4] contain amino sugar moieties bearing exocyclic amino groups in the place of one or two hydroxyl groups (Figure 1A). Aminoglycosides show strong antimicrobial activities against most Gram-negative bacteria, and are listed by the World Health Organization as critically important antimicrobials for the treatment of serious infections.[5] However, the ever-increasing social threat of multi-drug resistant pathogens requires a constant search for drugs with novel structures. Iminosugars possess a nitrogen atom instead of the endocyclic oxygen atom, represented by nojirimycin[6] (Figure 1B). They have been utilized as small-molecule therapeutics for diverse diseases such as diabetes (*N*-hydroxyethyl-1-deoxynojirimycin, miglitol: **5**)[7] and as a pharmacological chaperone for lysosomal storage disorders (1-deoxygalactonojirimycin, migalastat: **6**).[8] Iminosugars are also known to show a variety of biological activities including antiviral (6-*O*-butanoyl castanospermine, Celgosivir: **7**)[9] and anti-tumor activities (swainsonine: **8**).[10] Although the early developed iminosugars were used as glycosidase inhibitors, recent studies revealed that these pharmacological activities did not necessarily require glycosidase inhibition, which often resulted in off-target effects.[2c] In both aminoglycosides and iminosugars, current efforts are directed to find novel privileged carbohydrate-like structures. In this communication, we report the first synthesis of all-nitrogenated sugars (ANSs), artificial carbohydrate mimics, in which all hydroxy groups were replaced with amino groups (Figure 1C).[11] The peracetylated ANS was used as a glycosyl donor, and the synthetic ANS derivatives were subjected to biological tests against human cancer cell lines.

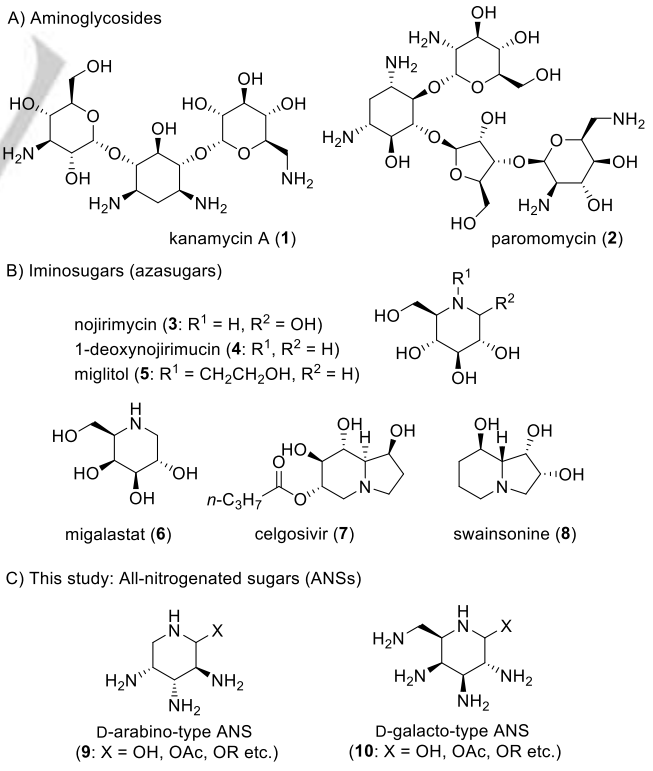

Figure 1. Carbohydrates containing amino groups. A) Aminoglycosides with carbohydrates including exocyclic amino groups. B) Iminosugars with endocyclic amino groups. C) All-nitrogenated sugars.

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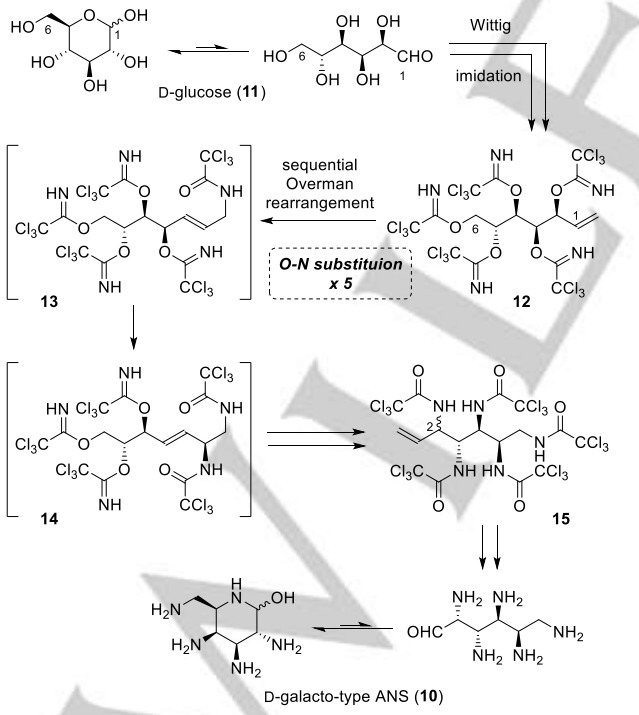
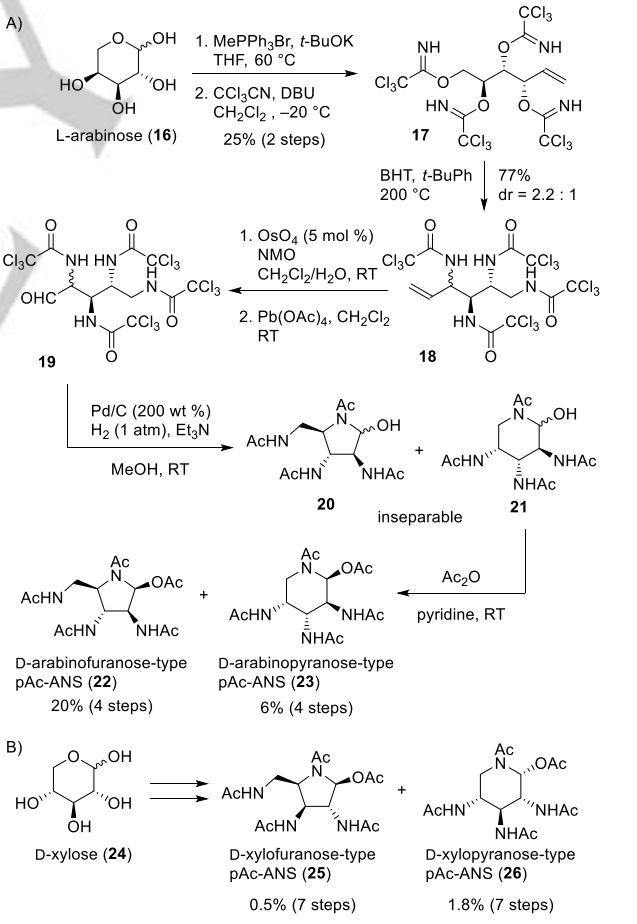
Results and Discussion

Our goal is the synthesis of ANSs from easily available monosaccharides, and elucidation of their physical and biological properties. Replacement of a hydroxy group with an amino group changes the basicity, polarity, solubility, and coordination properties of sugars, including their hydrogen bonding capabilities. Amino groups in both aminoglycosides and iminosugars play significant roles in the interaction with their target molecules such as rRNA and enzymes.[12] However, substitution of even a single hydroxy group in a carbohydrate is not a trivial transformation. Classical approaches through S_N2 reactions or reductive aminations actually require several steps including protecting group manipulation.[2b] Therefore, the synthesis of ANSs has been prohibitive due to the requisite replacement of four or five hydroxy groups in the carbohydrates. To realize this daunting synthetic challenge, we envisioned a formal simultaneous substitution of multi-hydroxy groups by taking advantage of the allylic trichloroacetimidate rearrangement (the so-called, Overman rearrangement) (Scheme 1).[13-17] For example, D-glucose (**11**), which exists in equilibrium between cyclic and acyclic forms, would be converted to pentakisimidate **12** through Wittig olefination and imidation. Under thermal conditions, pentakisimidate **12** would undergo five sequential Overman rearrangements. The first rearrangement would install the primary amino group, accompanied by transposition of the double bond. The resulting allylic imidate of **13** then would undergo the second rearrangement, resulting in the formation of **14**. The newly generated stereochemistry of **14** would be defined by chirality transfer of the secondary hydroxy groups via a chair-like transition state.[13] Eventually, the five sequential Overman rearrangements would give pentakistrichloroamide **15** in a single operation. The oxidative cleavage of the terminal olefin in **15** and removal of the trichloroacetyl groups would produce D-galacto-type ANS (**10**). A highly concise synthesis of ANSs would be possible by the formal simultaneous substitution of multi-hydroxy groups using the Overman rearrangement, and minimum protecting group manipulation. In addition, a variety of ANSs could be accessible through the same reaction sequence by simply changing the initial starting monosaccharides.



Scheme 1. Synthetic plan for all-nitrogenated sugars (ANSs) from simple carbohydrates through the sequential Overman rearrangement.

Our studies commenced with the synthesis of pentose-type ANSs from L-arabinose (**16**) (Scheme 2A). Wittig olefination gave an acyclic tetraol compound, which was transformed to tetrakistrichloroimidate **17** with CCl_3CN and DBU at –20 °C. The four sequential Overman rearrangements were achieved by heating a solution of tetrakisimidate **17**, BHT (200 mol %)[18] and *t*-BuPh (10 mM) at 200 °C in a sealed tube, giving tetrakistrichloroacetamides **18** in 77% combined yield with 2.2:1 diastereoselectivity.[19] The reaction produced three stereocenters, two of which were stereospecific through chirality transfer of the secondary alcohols. The poor diastereoselectivity was derived from the fourth rearrangement of the primary imidate, but it was not a crucial issue because both resulting diastereomers gave the same ANS through epimerization at a later stage. Thus, the formal substitution of four hydroxy groups with amino groups was



Scheme 2. Syntheses of pentose-type peracetylated ANSs through four sequential Overman rearrangements. (A) Synthesis of D-arabinose-type pAc-ANSs. (B) Synthesis of D-xylofuranose-type and D-xylopyranose-type pAc-ANSs. DBU = 1,8-diazabicyclo[5,4,0]undec-7ene, NMO = 4-methylmorpholine *N*-Oxide.

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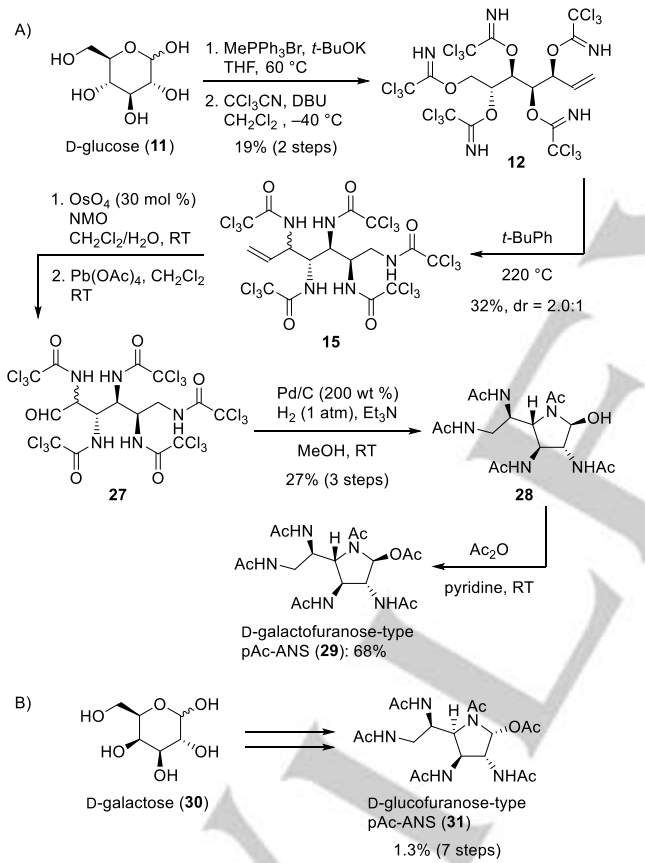
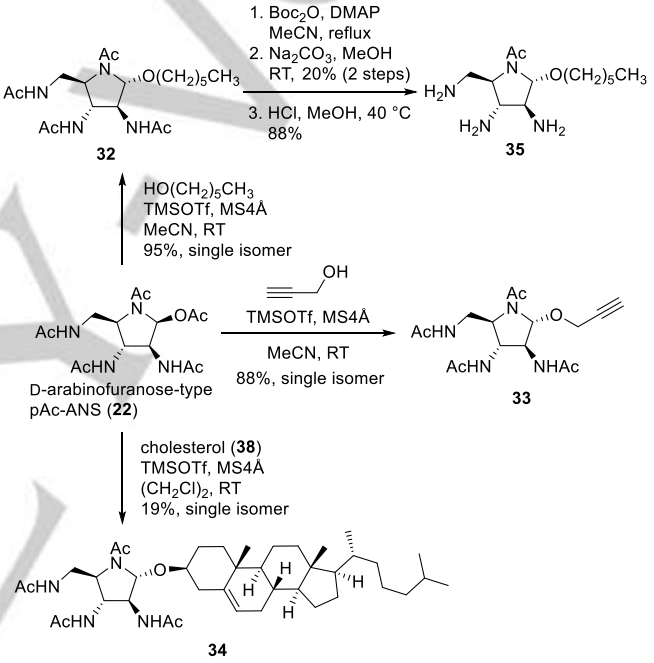
achieved by the sequential Overman rearrangement. The terminal olefin was converted to the aldehyde by a two-step procedure including dihydroxylation with OsO_4 and oxidative cleavage of the diol with $Pb(OAc)_4$. The resulting aldehydes **19** did not undergo cyclization due to the presence of the trichloromethyl groups. Thus, palladium-catalyzed hydrogenation in the presence of Et_3N caused dechlorination and subsequent cyclization to provide an inseparable mixture of hemiaminal derivatives **20** and **21** via epimerization at the α-position of the aldehyde in the acyclic form. These hemiaminals were acetylated upon treatment with Ac_2O and pyridine, giving D-arabinofuranose-type peracetylated-ANS (**22**) and D-arabinopyranose-type peracetylated-ANS (**23**) in 20% and 6% yields over four steps, respectively.[20] One of the salient features of our sequence is that different diastereomers of ANSs are available by simply changing the initial starting monosaccharides. For example, application of the same sequence to D-xylose (**24**) provided D-xylofuranose-type peracetylated ANS (**25**) and D-xylopyranose-type peracetylated ANS (**26**) (Scheme 2B).[20]



Scheme 3. Syntheses of hexose-type peracetylated ANSs through five sequential Overman rearrangements. A) Synthesis of D-galactofuranose-type pAc-ANS. B) Synthesis of D-glucofuranose-type pAc-ANS.

With pentose-type ANSs in hand, we turned our attention to the synthesis of hexose-type ANSs (Scheme 3A). In general, each reaction used in the synthesis of the pentoses was also applicable to hexoses. However, the additional hydroxy group in the hexoses made the sequential Overman rearrangement more complicated probably due to byproducts including the oxazolines generated by intramolecular substitution, because trichloroimidates can act as both a nucleophile and a leaving group.[21,22] After extensive studies, we found that a lower concentration was crucial in the five sequential rearrangements. While the reaction of pentakistrichloroimidate **12** in *t*-BuPh at 10 mM under thermal conditions provided pentakistrichloroacetamides **15** in 15% yield (dr = 2.1:1), the reaction at 1 mM provided **15** in 32% combined yield (dr = 2.0:1, 80% yield per rearrangement). After oxidative cleavage of the terminal olefin[23] and dechlorination, hemiaminal **28** was isolated as a single diastereomer in 27% yield in three steps. Treatment of **28** with Ac_2O and pyridine gave D-galactofuranose-type ANS **29** in 68% yield. D-Glucofuranose-type peracetylated ANS (**31**) was also synthesized through the same sequence starting from D-galactose (**30**) (Scheme 3B).



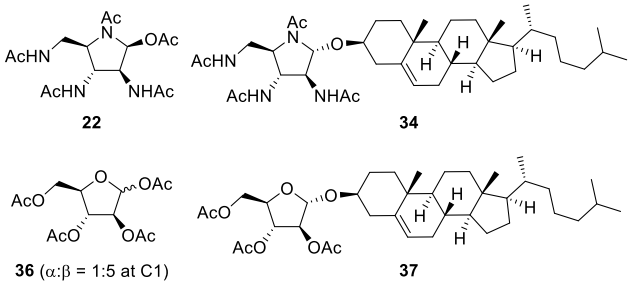
Scheme 4. Transformation of D-arabinofuranose-type pAc-ANS (**22**). Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, MS = molecular sieves, TMS = trimethylsilyl.

Further transformations of peracetylated ANSs were demonstrated to supply a variety of ANS derivatives (Scheme 4). Glycosylation of primary alcohols was possible with peracetylated ANS **22**. For example, addition of TMSOTf to a solution of **22** and hexanol in MeCN in the presence of MS4Å afforded **32** in 95% yield with complete *trans* selectivity.[24] The glycosylation also took place with propargyl alcohol, which serves as a handle for click chemistry (**33**; 88%).[25] Glycosylation of the secondary alcohol was found to be somewhat challenging, but provided glycosylated cholesterol **34** in 19% yield as a single diastereomer. Three acetyl groups on the primary amines in **32** were selectively removed to afford triamine **35** through Boc protection, hydrolysis of acetamides and cleavage of the Boc groups.

The ANS derivatives were evaluated against human cancer cell lines, including colon carcinoma (HCT 116), breast carcinoma (MDA-MB-231), fibrosarcoma (HT1080) and melanoma (WM266-

4),[26] and the data are summarized in Table 1 (see the Supporting Information for details). While neither peracetylated ANS **22** nor cholesterol showed significant cytotoxicity, glycosylated cholesterol **34** exhibited antiproliferative effects against these cancer cell lines. Interestingly, the corresponding acetylated furanose **36** and glycosylated cholesterol **37** did not exhibit cytotoxicity at 100 μM. Although the role of the ANS is yet to be elucidated, this study indicated that installation of ANSs in small molecules could change their biological properties.

Table 1. Cytotoxicity of glycosylated cholesterol **34** against various human cancer cell lines (IC_{50} values in μM)[a]



Cell Line	IC_{50} (μM)				
	34	**22**	cholesterol (**38**)	**36**	**37**
HCT116	20.3	>100	>100	>100	>100
MDA-MB-231	27.6	>100	>100	>100	>100
HT1080	13.1	>100	>100	>100	>100
WM266-4	13.6	>100	>100	>100	>100

[a] Antiproliferative effects of tested compounds against human cancer cell lines in a 72 h growth inhibitory assay using the MTT method. IC_{50} = half maximal (50%) inhibitory concentration, MTT = 3-(4,5-dimethylthial-2-yl)-2,5-diphenyltetrazolium bromide.

Conclusion

The concise synthesis of all-nitrogenated sugars (ANSs) was realized from easily available monosaccharides for the first time. The key to success was use of the Overman rearrangement, which enabled formal simultaneous substitution of four or five hydroxy groups with amino groups. The sequential rearrangement simplified the synthetic route by omitting differentiation and protecting group manipulation of hydroxy groups. A variety of ANSs were accessible through the same synthetic route starting from different monosaccharides. Thus, pentose- and hexose-type peracetylated ANSs were prepared in a total of seven steps from the corresponding monosaccharides. Peracetylated ANSs were utilized as glycosyl donors of primary alcohols and cholesterol. Our cytotoxic test against human cancer cell lines indicated that glycosylation with ANSs could add new biological functions to existing small molecules. Further application of ANSs and studies to reveal their biological roles are in progress.

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Keywords: all-nitrogenated sugar • aminoglycoside • domino reaction • iminosugar • sigmatropic rearrangement

[1] For recent selected reviews on aminoglycosides, see: a) Y. Doi, J. Wachino, Y. Arakawa, *Infect. Dis. Clin. North Am.* **2016**, *30*, 523–537; b) Y. Takahashi, M. Igarashi, *J. Antibiot.* **2018**, *71*, 4–14; c) E. C. Böttger, D. Crich, *ACS Infect. Dis.* **2020**, *6*, 168–172.

[2] For recent selected reviews on iminosugars, see: a) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochem.* **2001**, *56*, 265–295; b) M. S. M. Pearson, M. Mathé-Allainmat, V. Fargeas, J. Lebreton, *Eur. J. Org. Chem*. **2005**, 2159–2191; c) R. J. Nash, A. Kato, C.-Y. Yu, G. W. J. Fleet, *Future Med. Chem.* **2011**, *3*. 1513–1521.

[3] H. Umezawa, M. Ueda, K. Maeda, K. Yagishita, S. Kondo, Y. Okami, R. Utahara, Y. Osato, K. Nitta, T. Takeuchi, *J. Antibiot.* **1957**, *10*, 181–188.

[4] a) R. P. Frohardt, T. H. Haskell, E. John, K. M. Penner, **1959**, US2916485A; b) T. H. Haskell, S. Hanessian, *J. Org. Chem.* **1963**, *28*, 2598–2604.

[5] World Health Organization. Critically important antimicrobials for human medicine, 6th revision, **2019**.

[6] For isolation and biology of nojirimycin, see: a) N. Ishida, K. Kumagai, T. Niida, T. Tsuruoka, H. Yumoto, *J. Antibiot. Ser. A,* **1967**, 20, 66–71; b) S. Inouye, T. Tsuruoka, T. Ito, T. Niida, *Tetrahedron* **1968**, *24*, 2125–2144; c) D. D. Schmidt, W. Frommer, L. Müller, E. Truscheit, *Naturwissenschaften* **1979**, *66*, 584–585; d) T. Niwa, S. Inouye, T. Tsuruoka, Y. Koaze, T. Niida, *Agric. Biol. Chem.* **1970**, *34*, 966–968; e) E. T. Reese, F. W. Parrish, M. Ettlinger, *Carbohydr. Res.* **1971**, *18*, 381–388; f) G. Hanozet, H.-P. Pircher, P. Vanni, B. Oesch, G. Semenza, *J. Biol. Chem.* **1981**, *256*, 3703–3711.

[7] For a review on miglitol, see: L. J. Scott, C. M. Spencer, *Drugs*, **2000**, *59*, 521–549.

[8] E. R. Benjamin, J. J. Flanagan, A. Schilling, H. H. Chang, L. Agarwal, E. Katz, X. Wu, C. Pine, B. Wustman, R. J. Desnick, D. J. Lockhart, K. J. Valenzano, *J. Inherit. Metab. Dis.* **2009**, *32*, 424–440.

[9] a) L. A. Sorbera, J. Castaner, L. Garcia-Capdevila, *Drugs Future* **2005**, *30*, 545–552; b) D. L. Taylor, P. S. Sunkara, P. S. Liu, M. S. Kang, T. L. Bowlin, A. S. Tyms, *AIDS* **1991**, *5*, 693–698.

[10] J. Hamaguchi, H. Nakagawa, M. Takahashi, T. Kudo, N. Kamiyama, B. Sun, T. Oshima, Y. Sato, K. Deguchi, S. Todo, S. Nishimura, *Mol. Cancer* **2007**, *6*, 58–67.

[11] Since all hydroxy groups in acyclic forms of monosaccharides are replaced with amino groups, we propose that such monosaccharides be defined as all-nitrogenated sugars. Therefore, a substituent at the C1 position in the cyclic form can be any functional group such as a hydroxy group, acetate or alcohol.

[12] For selected examples, see: a) A. P. Carter, W. M. Clemons, D. E. Brodersen, R. J. Morgan-Warren, B. T. Wimberly, V. Ramakrishnan, *Nature* **2000**, *407*, 340–348; b) M. A. Borovinskaya, R. D. Pai, W. Zhang, B. S. Schuwirth, J. M. Holton, G. Hirokawa, H. Kaji, A. Kaji, J. H. Doudna Cate, *Nat. Struct. Mol. Biol.* **2007**, *14*, 727–732.

[13] a) L. E. Overman, *J. Am. Chem. Soc*. **1974**, *96*, 597–599. For reviews on the Overman rearrangement, see: b) L. E. Overman, N. E. Carpenter, In *Organic Reactions*; L. E. Overman, Ed.; Wiley: New York, NY, 2005; Vol. 66, pp 1–107.

[14] For selected recent reviews on cascade, tandem, and domino reactions including a sigmatropic rearrangement, see: a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed*. **2006**, *45*, 7134–7186; *Angew. Chem.* **2006**, *118*, 7292–7344; b) H. Pellissier, *Tetrahedron* **2006**, *62*, 1619–1665; c) A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341–5378; d) J. Poulin, C. M. Grisé-Bard, L. Barriault, *Chem. Soc. Rev.* **2009**,

38, 3092–3101; e) E. A. Ilardi, C. E. Stivala, A. Zakarian, *Chem. Soc. Rev.* **2009**, *38*, 3133–3148; f) H. Pellissier, Chem. Rev. 2013, 113, 442–524; g) L. F. Tietze, *Domino Reactions –Concepts for Efficient Organic Synthesis*, Wiley-VCH, Weinheim, **2014**; h) T. Chanda, J. C.-G. Zhao, *Adv. Synth. Catal.* **2018**, *360*, 2–79.

[15] For two sequential sigmatropic rearrangements including the Overman rearrangement, see: a) T. Momose, N. Hama, C. Higashino, H. Sato, N. Chida, *Tetrahedron Lett*. **2008**, *49*, 1376–1379; b) N. Hama, T. Matsuda, T. Sato, N. Chida, *Org. Lett.* **2009**, *11*, 2687–2690; c) K. Kitamoto, M. Sampei, Y. Nakayama, T. Sato, N. Chida, *Org. Lett*. **2010**, *12*, 5756–5759; d) N. Hama, T. Aoki, S. Miwa, M. Yamazaki, T. Sato, N. Chida, *Org. Lett*. **2011**, *13*, 616–619; e) K. Kitamoto, Y. Nakayama, M. Sampei, M. Ichiki, N. Furuya, T. Sato, N. Chida, *Eur. J. Org. Chem.* **2012**, 4217–4231; f) Y. Nakayama, R. Sekiya, H. Oishi, N. Hama, M. Yamazaki, T. Sato, N. Chida, *Chem. Eur. J.* **2013**, *19*, 12052–12058; g) Y. Nakayama, Y. Maeda, M. Kotatsu, R. Sekiya, M. Ichiki, T. Sato, N. Chida, *Chem. Eur. J.* **2016**, *22*, 3300–3303; h) Y. Nakayama, Y. Maeda, N. Hama, T. Sato, N. Chida, *Synthesis* **2016**, *48*, 1647–1654; i) K. Ishii, Y. Seki-Yoritate, M. Ishibashi, M. W. Liaw, T. Oishi, T. Sato, N. Chida. *Heterocycles* **2019**, *99*, 111–117; j) A. A. Tjeng, K. L. Handore, R. A. Batey, *Org. Lett.* **2020**, *22*, 3050–3055; k) Y. Okuyama, R. Okamoto, S. Mukai, K. Kinoshita, T. Sato, N. Chida, *Org. Lett.* **2020**, *22*, 8697–8701.

[16] For selected examples of sequential reactions including sigmatropic rearrangements, see: a) A. F. Thomas, *J. Am. Chem. Soc*. **1969**, *91*, 3281–3289; b) F. E. Ziegler, J. J. Piwinski, *J. Am. Chem. Soc*. **1979**, *101*, 1611–1612; c) S. Raucher, J. E. Jr. Burks, K.-J. Hwang, D. P. Svedberg, *J. Am. Chem. Soc*. **1981**, *103*, 1853–1855; d) K. Mikami, S. Taya, T. Nakai, Y. Fujita, *J. Org. Chem.* **1981**, *46*, 5447–5449; e) V. J. Mulzer, H. Bock, W. Eck, J. Buschmann, P. Luger, *Angew. Chem. Int. Ed.* **1991**, *30*, 414–416; *Angew. Chem.* **1991**, *103*, 450–452; f) G. H. Posner, J.-C. Carry, R. D. Crouch, N. Johnson, *J. Org. Chem.* **1991**, *56*, 6987–6993; g) D. Villemin, M. Hachemi, *Synthetic Commun*. **1996**, *26*, 1329–1334; h) K. Banert, W. Fendel, J. Schlott, *Angew. Chem. Int. Ed*. **1998**, *37*, 3289–3292; *Angew. Chem.* **1998**, *110*, 3488–3491; i) S. Demay, A. Kotschy, P. Knochel, *Synthesis* **2001**, 863–866; j) L. Barriault, I. Denissova, *Org. Lett.* **2002**, *4*, 1371–1374; k) O. V. Singh, H. Han, *Org. Lett*. **2004**, *6*, 3067–3070; l) E. L. O. Sauer, L. Barriault, *J. Am. Chem. Soc*. **2004**, *126*, 8569–8575; m) M. J. Pelc, A. Zakarian, *Org. Lett.* **2005**, *7*, 1629–1631; n) Y. Ichikawa, H. Egawa, T. Ito, M. Isobe, K. Nakano, H. Kotsuki, *Org. Lett*. **2006**, *8*, 5737–5740; o) Y. Ichikawa, T. Yamaoka, K. Nakano, H. Kotsuki, *Org. Lett*. **2007**, *9*, 2989–2992; p) X. Li, T. V. Ovaska, *Org. Lett.* **2007**, *9*, 3837–3840; q) E. A. Ilardi, M. J. Isaacman, Y.-C. Qin, S. A. Shelly, A. Zakarian, *Tetrahedron* **2009**, *65*, 3261–3269; r) Q. Xiao, J. J. Jackson, A. Basak, J. M. Bowler, B. G. Miller, A. Zakarian, *Nature Chem.* **2013**, *5*, 410–416; s) Y. Zhou, L. Lin, X. Liu, X. Hu, Y. Lu, X. Zhang, X. Feng, *Angew. Chem. Int. Ed*. **2018**, *57*, 9113–9116; *Angew. Chem.* **2018**, *130*, 9251–9254.

[17] For selected reports on the synthesis of natural products and related compounds utilizing the Overman rearrangement, see: a) T. Nishikawa, M. Asai, N. Ohyabu, N. Yamamoto, Y. Fukuda, M. Isobe, *Tetrahedron* **2001**, *57*, 3875–3883. b) T. Tsujimoto, T. Nishikawa, D. Urabe, M. Isobe, *Synlett* **2005**, 433–436; c) N. Ohyabu, T. Nishikawa, M. Isobe, *J. Am. Chem. Soc.* **2003**, *125*, 8798–8805; d) T. Nishikawa, D. Urabe, K. Yoshida, T. Iwabuchi, M. Asai, M. Isobe, *Chem. Eur. J.* **2004**, *10*, 452–462; e) H. Sato, T. Maeba, R. Yanase, A. Yamaji-Hasegawa, T. Kobayashi, N. Chida, *J. Antibiot.* **2005**, *58*, 37–49; f) A. E. Håkansson, A. Palmelund, H. Holm, R. Madsen, *Chem. Eur. J.* **2006**, *12*, 3243–3253; g) M. Matveenko, O. J. Kokas, M. G. Banwell, A. C. Willis, *Org. Lett.* **2007**, *9*, 3683–3685; h) H. Sato, K. Sato, M. Iida, H. Yamanaka, T. Oishi, N. Chida, *Tetrahedron Lett.* **2008**, *49*, 1943–1947; i) D. P. Dickson, D. J. Wardrop, *Org. Lett.* **2009**, *11*, 1341–1344; j) T. Momose, Y. Kaiya, J. Hasegawa, T. Sato, N. Chida, *Synthesis* **2009**, 2983–2991; k) H. Yamanaka, K. Sato, H. Sato, M. Iida, T. Oishi, N. Chida, *Tetrahedron* **2009**, *65*, 9188–9201; l) T. Imaoka, O. Iwamoto, K. Noguchi, K. Nagasawa, *Angew. Chem. Int. Ed.* **2009**, *48*, 3799–3801; *Angew. Chem.* **2009**, *121*, 3857–3859; m) T. Imaoka, T. Akimoto, O. Iwamoto, K. Nagasawa, *Chem. Asian J.* **2010**, *5*, 1810–1816; n) Y. Kaiya, J. Hasegawa, T. Momose, T. Sato, N. Chida, *Chem. Asian J.* **2011**, *6*, 209–219; o) N. D. Collett, R. G. Carter, *Org. Lett.* **2011**, *13*, 4144–4147; p) A. M. Zaed, A. Sutherland, *Org. Biomol. Chem.* **2011**, *9*, 8030–8037; q) K. Takahashi, D. Yamaguchi, J. Ishihara, S. Hatakeyama, *Org. Lett.* **2012**, *14*, 1644–1647; r) E. D. D. Calder, A. M. Zaed, A. Sutherland, *J. Org. Chem.* **2013**, *78*, 7223–7233; s) J. S. Clark, C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 4332–4335; *Angew. Chem.* **2016**, *128*, 4404–4407; t) X. Tong, B. Shi, K. Liang, Q. Liu, C. Xia, *Angew. Chem. Int. Ed.* **2019**, *58*, 5443–5446; *Angew. Chem.* **2019**, *131*, 5497–5500; u) A. Burtea, J. DeForest, X. Li, S. D. Rychnovsky, *Angew. Chem. Int. Ed.* **2019**, *58*, 16193–16197; *Angew. Chem.* **2019**, *131*, 16339–16343; v) L. Decultot, R. L. Policarpo, B. A. Wright, D. Huang, M. D. Shair, *Org. Lett.* **2020**, *22*, 5594–5599.

[18] J. Ammenn, K.-H. Altmann, D. Belluš, *Helv. Chim. Acta* **1997**, *80*, 1589–1606.

[19] The thermal conditions were suitable for the sequential Overman rearrangements. For example, Pd(II)-catalyzed rearrangements resulted in no reaction.

[20] Although the factors controlling the stereoselectivity at C1 were not elucidated, all pAc-ANSs were obtained as a single diastereomer at C1.

[21] a) D. M. Roush, M. M. Patel, *Synthetic Commun.* **1985**, *15*, 675–679; b) S. Tsuzaki, S. Usui, H. Oishi, D. Yasushima, T. Fukuyasu, T. Oishi, T. Sato, N. Chida, *Org. Lett.* **2015**, *17*, 1704–1707; c) T. Sugai, S. Usui, S. Tsuzaki, H. Oishi, D. Yasushima, S. Hisada, T. Fukuyasu, T. Oishi, T. Sato, N. Chida, *Bull. Chem. Soc. Jpn.* **2018**, *91*, 594–607.

[22] The formation of oxazolines was indicated by ESI-MS spectra of the crude compound. However, the structures were not fully characterized because of a number of possible patters to form oxazolines.

[23] The amount of OsO_4 (30 mol %) was not optimized in the synthesis of the hexose-type ANSs.

[24] For TsOH-, TMSOTf-, and $BF_3{\cdot}Et_2O$-mediated glycosidation using an iminosugar as the acceptor, see: a) T. Granier, A. Vasella, *Helv. Chim. Acta* **1998**, *81*, 865–880; b) D. Sawada, H. Takahashi, M. Shiro, S. Ikegami, *Tetrahedron Lett.* **2005**, *46*, 2399–2403; c) E. M. Sánchez-Fernández, R. Rísquez-Cuadro, C. O. Mellet, J. M. G. Fernández, P. M. Nieto, J. Angulo, *Chem. Eur. J.* **2012**, *18*, 8527–8539; d) E. M. Sánchez-Fernández, R. Gonçalves-Pereira, R. Rísquez-Cuadro, G. B. Plata, J. M. Padrón, J. M. G. Fernández, C. O. Mellet, *Carbohydrate Research* **2016**, *429*, 113–122; e) E. M. Sánchez Fernández, C. D. Navo, N. Martínez-Sáez, R. Gonçalves-Pereira, V. J. Somovilla, A. Avenoza, J. H. Busto, G. J. L. Bernardes, G. Jiménez-Osés, F. Corzana, J. M. G. Fernández, C. O. Mellet, J. M. Peregrina, *Org. Lett.* **2016**, *18*, 3890–3893.

[25] For selected reviews, see: a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075; b) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015; c) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302–1315; d) A. Mandoli, *Molecules* **2016**, *21*, 1174.

[26] a) S. Miyazaki, Y. Sasazawa, T. Mogi, T. Suzuki, K. Yoshida, N. Dohmae, K. Takao, S. Simizu. *FEBS Lett.* **2016**, *590*, 1163–1173; b) K. Otake, K. Yamada, K. Miura, Y. Sasazawa, S. Miyazaki, Y. Niwa, A. Ogura, K. Takao, S. Simizu, *Bioorg. Med. Chem.* **2019**, 27, 3334–3338.

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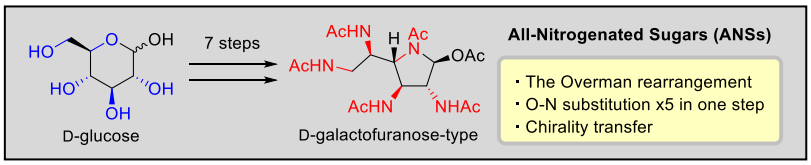

Concise synthesis of all-nitrogenated sugar derivatives was achieved in seven steps from commercially available monosaccharides. The sequential Overman rearrangement enabled formal simultaneous substitution of four or five hydroxy groups in the monosaccharides with amino groups. A variety of ANSs were available by the same synthetic route starting from different carbohydrates. Transformation and biological activities of ANS derivatives were also reported.