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Efficient synthesis of 1-deoxy-azasugars as useful synthetic tools

Daisuke Sawada, Hideyo Takahashi and Shiro Ikegami*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko Kanagawa 199-0195, Japan

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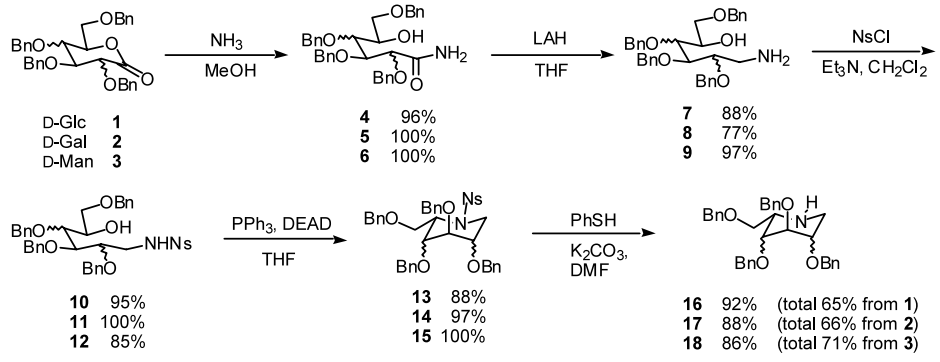
Abstract—1-Deoxy-azasugars are efficiently prepared from sugar-lactones using a stereoinversion process and they are applied to the synthesis of a natural product.

Azasugars, monosaccharide analogues having a nitrogen atom instead of the ring oxygen atom, have interesting activities for glycoside-related enzymes, and they have been intensively studied as glycosidase inhibitors[1] with potential therapeutic utility. Some strong inhibitors such as (+)-nojirimycin and (+)-deoxynojirimycin are representative.[2] 1-Deoxy-azasugars are chemically more stable than normal azasugars due to a lack of a hydroxyl group at the C1 position, and thus they must be suitable compounds for practical use.[3] As a result, it becomes necessary to supply a large amount of various 1-deoxy-azasugars by chemical synthesis. Although numerous synthetic methods have been developed,[4] they sometimes needed lengthy steps, and resulted in mixtures of the stereoisomers in low yields. Here we report a more efficient synthetic method for 1-deoxy-azasugars, and its applications to natural product synthesis as useful tools.

We have already developed the selective synthesis of L-sugars from D-sugar-lactones using the Mitsunobu reaction[5] as a key step.[6] The present synthetic plan is also based on the S_N2 type cyclization procedures. At first, we describe the synthesis of six-membered 1-deoxy-azasugars. We started with three kinds of D-glycono-1,5-lactones **1**, **2**, **3**, which are easily derived from glucose, galactose and mannose, respectively[7] (Scheme 1). The lactones **1**, **2**, **3** were converted to the amides **4**, **5**, **6**[8] by treatment with NH_3 in nearly quantitative yields. Reduction of the amides by refluxing in THF with $LiAlH_4$ gave the amines **7**, **8**, **9**, and then, the cyclization reactions were tried under the Mitsunobu conditions after converting to sulfonamide derivatives. According to the methods developed by Fukuyama et al.,[9] the amines **7**, **8**, **9** were reacted with 2-nitrobenzenesulfonyl chloride (NsCl) and triethylamine in CH_2Cl_2 to afford the corresponding 2-nitrobenzenesulfonamides **10**, **11**, **12**. Successively, they underwent the Mitsunobu conditions (triphenylphosphine and diethyl azodicarboxylate in THF), and the cyclization reactions easily proceeded through complete inversion to afford the L-1-deoxy-azasugar derivatives **13**, **14**, **15** in good



Scheme 1.

Keywords: amino sugars; carbohydrate mimics; indolizidine; Mitsunobu reaction.

* Corresponding author. Tel.: +81-42-658-3728; fax: +81-42-685-1872; e-mail: shi-ike@pharm.teikyo-u.ac.jp

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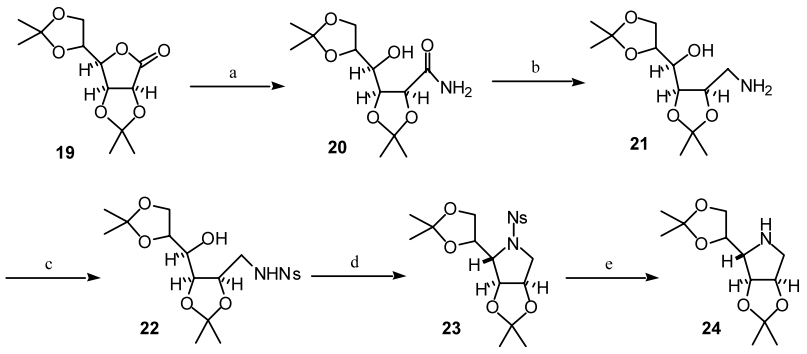
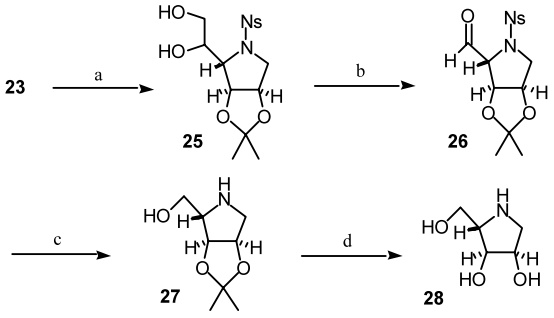


Scheme 2. *Reagents and conditions*: (a) NH_3, MeOH; 80%; (b) $LiAlH_4$, THF, reflux; 76%; (c) NsCl, Et_3N, CH_2Cl_2; 93%; (d) PPh_3, DEAD, THF; quant.; (e) PhSH, K_2CO_3, DMF; 79%.

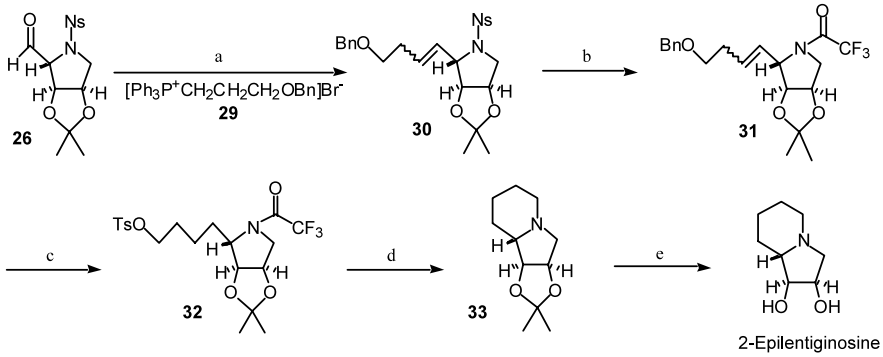
yields. After removing an Ns group using PhSH, the corresponding azasugars **16**, **17**, **18**[10] were obtained in 65, 66, 71% overall yields from **1**, **2**, **3**, respectively. Thus, we were able to develop an excellent method for the synthesis of the 1-deoxy-aza-derivaives of L-idose (**16**), L-altrose (**17**), and L-gulose (**18**) converted from D-glucose, D-galactose and D-mannose, respectively, in excellent yields.

Next, we turned our attention to the synthesis of five-membered 1-deoxy-azasugars. 2,3,5,6-Di-*O*-isopropylidene-D-mannono-1,4-lactone[11] (**19**), which is easily converted from D-mannono-1,4-lactone, was used as the starting material (Scheme 2). The γ-lactone **19** was converted to the amide **20** by reacting with NH_3 and then reduced to the amine **21**. After nosylation of the amine, the Mitsunobu reaction was conducted to give the cyclized product **23** in quantitative yield. Finally, the removal of an Ns group resulted in the formation of the five-membered L-1-deoxy-azasugar derivative **24**.



Scheme 3. *Reagents and conditions*: (a) TFA, THF, H_2O; 70% (conv. y. 82%); (b) $NaIO_4$, silica gel, CH_2Cl_2, H_2O; 96%; (c) 1, $NaBH_4$, MeOH; quant; 2, PhSH, K_2CO_3, CH_3CN; 75%; (d) 1N, HCl, reflux; quant.

This material **24** is provided as the starting material for the synthesis of biologically important compounds, in which one example is described. Intermediate **23** was selectively hydrolyzed to the diol **25** by TFA in 70% yield (conv. y. 82%), which was oxidized to the aldehyde **26** by the $NaIO_4$-cleavage (Scheme 3). Reduction of the aldehyde, then the removal of an Ns group afforded **27** in good yields. Finally, it was hydrolyzed with 1N HCl to give the 1-deoxy-aza-analogue of L-ribose **28**, that is L-iminoribitol.[4j–m,12] Also, the aldehyde **26** could be applicable as the key compound for natural product synthesis (Scheme 4). Wittig reaction to **26** using the reagent **29** afforded the adduct **30** in 69% yield as an *E*–*Z* mixture. The nosyl group was removed, and the resultant amine was protected as a trifluoroacetamide to give **31** in 91% yield (two steps). Both the hydrogenation of the olefin part and the removal of the benzyl group resulted in an alcohol, which was trans-



Scheme 4. *Reagents and conditions*: (a) NaHMDS, THF, **29**, –78 to 0°C; 69%; (b) 1, PhSH, K_2CO_3, DMF; 95%; 2, $(CF_3CO)_2O$, Py, CH_2Cl_2; 96%; (c) 1, Pd·C, MeOH, H_2; 79%; 2, TsCl, DABCO, CH_2Cl_2, quant.; (d) K_2CO_3, MeOH, H_2O, 50°C; 75%; (e) 1N HCl, reflux; 90%.

formed to the tosylate (**32**). Then, treatment with K_2CO_3 in MeOH and H_2O caused both the hydrolysis of the trifluoroacetamide of **32** and the continuous cyclization. The bicyclic product **33** was successfully obtained in 75% yield. Finally, the deprotection of an acetonyl group afforded 2-epilentiginosine.[13]

In summary, we have developed a novel method to prepare 1-deoxy-azasugars more efficiently from sugar-lactones with the inversion of stereochemistry. This method could be applied to numerous lactones, and would afford biologically important compounds.

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10. **16**: $[\alpha]_D^{21}$ −11.6 (*c* 1.65, $CHCl_3$); IR (neat) 3088, 3063, 3030, 2918, 2862, 1604, 1587, 1497, 1455, 1366, 1206, 1094, 1073, 1028, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.33 (m, 20H), 4.64 (s, 2H), 4.60–4.52 (m, 6H), 3.68 (dd, $J=9.5$, 9.5 Hz, 1H), 3.60–3.64 (m, 2H), 3.55 (dd, $J=5.3$, 9.5 Hz, 1H), 3.41–3.47 (m, 1H), 3.36–3.41 (m, 1H), 3.02 (dd, $J=4.2$, 13.0 Hz, 1H), 2.86 (dd, $J=6.6$, 13.0 Hz, 1H), 2.35 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 138.2, 138.1, 128.2, 128.1, 128.1, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.3, 77.9, 77.0, 76.8, 74.0, 73.3, 72.5, 72.0, 67.1, 54.6, 44.2; EI-S *m*/*z* 523 (M^+); EI-HRMS calcd for $C_{34}H_{37}NO_4$ (M^+): 523.2722, found: 523.2717. **17**: $[\alpha]_D^{18}$ −11.9 (*c* 0.325, $CHCl_3$); IR (neat) 3063, 3030, 2924, 2862, 1732, 1651, 1585, 1496, 1454, 1364, 1208, 1100, 1028, 741, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.35 (m, 20H), 4.71 (d, $J=14.0$ Hz, 1H), 4.40–4.59 (m, 7H), 3.81–3.89 (m, 2H), 3.80 (dd, $J=2.9$, 8.6 Hz, 1H), 3.66 (dd, $J=2.0$, 9.1 Hz, 1H), 3.53–3.55 (m, 1H), 3.20 (dt, $J=2.7$, 10.3 Hz, 1H), 3.07 (dd, $J=1.8$, 14.2 Hz, 1H), 2.97 (m, 1H), 2.42 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 138.2, 128.1, 128.0, 128.1, 127.7, 127.4, 127.3, 127.3, 127.3, 127.2, 75.4, 75.0, 73.4, 73.1, 72.6, 71.4, 70.7, 70.0, 54.5, 44.0; EI-MS *m*/*z* 523 (M^+); EI-HRMS calcd for $C_{34}H_{37}NO_4$ (M^+): 523.2722, found: 523.2726. **18**: $[\alpha]c_D^{19}$ 1.92 (*c* 0.9, $CHCl_3$); IR (neat) 3088, 3063, 3030, 2924, 2858, 1604, 1587, 1495, 1454, 1365, 1207, 1101, 1028, 742, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.35 (m, 18H), 7.09–7.15 (m, 2H), 4.73 (d, $J=12.2$ Hz, 1H), 4.34–4.57 (m, 7H), 3.80–3.82 (m, 1H), 3.73–3.79 (m, 1H), 3.50–3.60 (m, 1H), 3.48 (dd, $J=0.9$, 8.5 Hz, 1H), 3.46 (dd, $J=6.9$, 8.5 Hz, 1H), 3.37–3.42 (m, 1H), 3.02 (d, $J=8.1$ Hz, 2H), 2.09 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.4, 138.0, 137.9, 128.1, 128.0, 127.9, 127.6, 127.6, 127.5, 127.4, 127.3, 127.3, 127.3, 75.4, 75.0, 73.3, 73.2, 72.8, 72.6, 70.9, 70.5, 53.6, 44.3; EI-MS *m*/*z* 523 (M^+); EI-HRMS calcd for $C_{34}H_{37}NO_4$ (M^+): 523.2722, found: 523.2729.
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