A Divergent Route to 3-Amino-2,3,6-trideoxysugars Including Branched Sugar: Synthesis of Vancosamine, Daunosamine, Saccharosamine, and Ristosamine

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Four 3-amino-2,3,6-trideoxysugars were synthesized by a divergent route from a single enone **9a**. The Migita–Stille coupling introduced a methyl group at the 3-position. Stereoselective reduction of enone and the Mitsunobu reaction provided both β- and α-hydroxy groups at the 4-position. Stereospecific radical cyclization of the C4 carbamoyl moiety furnished the desired **5a**, **5b** and **6a**, **6b**, respectively.

3-Amino-2,3,6-trideoxysugars were found in nature as structural components of glycosidic and oligosaccharide antibiotics.[1] These have various configurational isomers and substituents such as a methyl group (Figure 1). L-Vancosamine (**1**) is known as a C3-branched sugar found in vancomycin antibiotics. It has been known that the sugar moieties play an important role in biological activity of these antibiotics. For instance, in doxorubicin, an anthracycline antibiotic, displacement of L-daunosamine (**2**) to its 4-epimer, L-acosamine, or its 3,4-epimer, L-ristosamine (**4**), suppresses the undesired toxic side effects while maintaining similar antitumor activity.[2,3] Recently, it has been reported that displacement of L-vancosamine in a vancomycin derivative to its demethyl sugar, L-daunosamine, exhibits significant activity against methicillin-resistant *staphylococcal strains*.[4] Therefore, 3-amino-2,3,6-trideoxysugars and its branched-sugars are in high demand although these are rare and not commercially available.

Several syntheses of 3-amino-2,3,6-trideoxysugars have been reported from both sugars and non-sugar precursors.[5] However, most of them were prepared one by one. Recently, Riera et al. reported a stereodivergent approach to four 3-amino-2,3,6-trideoxysugars using reagent-controlled stereoselective epoxidation and organometallic addition as key steps.[6] Zhang et al. also reported a divergent approach to 3-azido-2,3,6-trideoxysugars from rhamnal using stereoselective epoxidation followed by azidation.[7]

We have demonstrated a semi-synthesis of vancomycin and its glucose-modified derivatives by solid-phase glycosidation of glucose with vancomycin aglycon, followed by glycosylation with vancosamine, and then nucleophilic cleavage at the 6-position of glucose from the solid-support.[8] To synthesize vancosamine-modified vancomycin derivatives, we need an efficient synthetic method for a variety of 3-amino-2,3,6-trideoxysugars. Herein, we report a divergent synthesis of four 3-amino-2,3,6-trideoxysugars **1**–**4** including C3 methyl branch from a single starting compound.

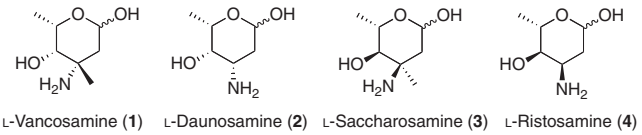
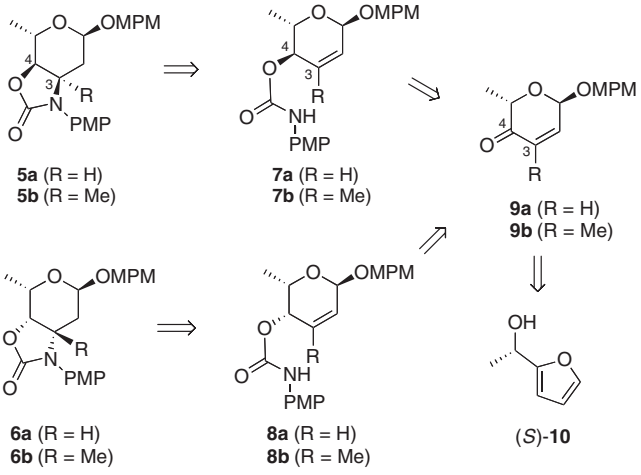


Figure 1. Structures of naturally occurring 3-amino-2,3,6-trideoxysugars.

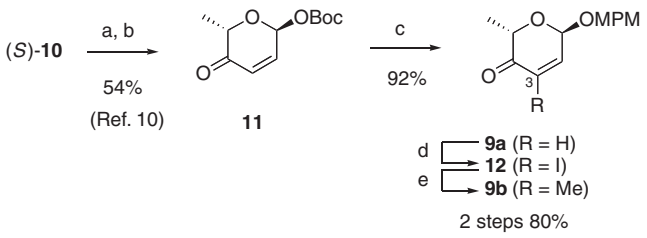
Our strategy is illustrated in Scheme 1. We envisaged four 3-amino-2,3,6-trideoxysugars **5a**, **5b**, **6a**, and **6b** to be available from stereospecific radical cyclization of carbamates **7a**, **7b**, **8a**, and **8b**, recently reported by Nicolaou et al.[9] The carbamates would be synthesized from a single synthetic intermediate **9a** (R = H) by introducing the C3 methyl group in case R = Me, followed by stereoselective reduction of the enones **9a** and **9b** and inversion of the resulting hydroxy group by the Mitsunobu reaction. The enone **9a** is readily available from furfuryl alcohol (*S*)-**10**. This synthetic method can be available to the synthesis of their enantiomers from (*R*)-**10**.

Enone **11** was prepared from commercially available furfuryl alcohol (*S*)-**10** by the Achmatowicz reaction followed by protection of the resulting hemiacetal with $(Boc)_2O$ according to the reported procedure.[10] The enone **11** was obtained as a 2:1 mixture of diastereomers with its anomeric epimer and was easily separated by silica-gel column chromatography. The Boc group was converted to a 4-methoxyphenylmethyl (MPM) group by Pd-catalyzed glycosidation reaction.[10] The reaction smoothly proceeded with excellent stereoselectivity via a double inversion process leading to **9a** (R = H) in 92% yield. Next, we examined introduction of a methyl group at the 3-position. Iodination of enone **9a** with I_2–DMAP gave an α-iodo enone **12** in quantitative yield. The labile **12** was immediately subjected to the Migita–Stille coupling with Me_4Sn to avoid decomposition. After optimization of the reaction conditions, it was found that a POPd,[11] CuI, and DMF system is very effective for the coupling reaction to provide enone **9b** without addition of arsenic ligands (Scheme 2).

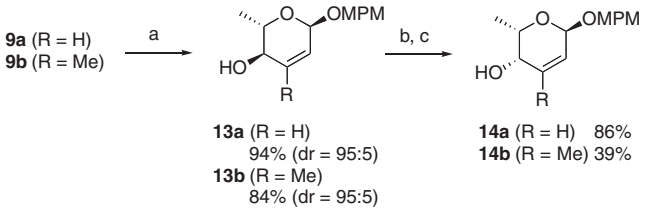
Enones **9a** and **9b** in our hand were steroselectively reduced



Scheme 1. Retrosynthesis of 3-amino-2,3,6-trideoxysugars.



Scheme 2. Synthtesis of enones **9a** and **9b**. Reagents and conditions: (a) NBS, $NaHCO_3$, NaOAc, THF–H_2O, 0 °C; (b) $(Boc)_2O$, DMAP, CH_2Cl_2, −78 °C; (c) 4-methoxybenzyl alcohol, $Pd_2(dba)_3 \cdot CHCl_3$, PPh_3, CH_2Cl_2, 0 °C; (d) I_2, DMAP, CH_2Cl_2; (e) Me_4Sn, POPd, CuI, DMF, 80 °C. MPM = 4-methoxyphenylmethyl. POPd = $PdCl_2(Pt\text{-}Bu_2OH)_2$.



Scheme 3. Synthtesis of allylic alcohols **13a**, **13b** and **14a**, **14b**. Reagents and conditions: (a) $NaBH_4$, CH_2Cl_2, MeOH, −78 to 0 °C; (b) *p*-nitrobenzoic acid, DEAD, PPh_3, THF, rt for **13a**, 70 °C for **13b**; (c) NaOMe, THF, MeOH.

with $NaBH_4$ via axial attack of hydride to provide allylic alcohol **13a** and **13b**, respectively. The Mitsunobu reaction of alcohol **13a** smoothly proceeded under conventional conditions using *p*-nitrobenzoic acid as a nucleophile.[12] The reaction of **13b** did not proceed under the same reaction conditions owing to steric hindrance by the methyl group at the 3-position. However, under heating to 70 °C the desired alcohol **14b** was provided in 39% yield after methanolysis (Scheme 3).

The four allylic alcohols **13a**, **13b**, **14a**, and **14b** were respectively converted to carbamates **7a**, **7b**, **8a**, and **8b** by treatment with (*p*-methoxyphenyl)isocyante and DBU in CH_2Cl_2 (71–83%). IBX-mediated radical cyclization[9] of the four carbamates was investigated. **7a** was initially treated with IBX (2.1 equiv.)–$NaHCO_3$ in THF–DMSO (10:1) in a sealed tube at 90 °C for 12 h. The reaction mixture was further heated with an additional amount of IBX (2.1 equiv.) for another 12 h. After silica-gel chromatography, the desired protected L-ristosamine **5a** was obtained in 56% yield and the starting material was also recovered. Although we optimized the reaction conditions such as temperature, time, molar, and equivalent of the reagent, the reaction was not complete. The reactions of **7b**, **8a**, and **8b** also proceeded under the same reaction conditions leading to the protected L-saccharosamine **5b** (62%), L-daunosamine **6a** (68%) and L-vancosamine **6b** (63%), respectively, with exclusive stero- and regioselection. Their structures were determined by ^1H NMR spectra with coupling constants of the vicinal protons and NOE obervation.[13,14] Removal of the MPM and *p*-methoxylphenyl (PMP) groups [$Ce(NH_4)_2(NO_3)_6$/MeCN–H_2O/rt], followed by saponification [$Ba(OH)_2/H_2O$/125 °C; CO_2(s)] provided 3-amino-2,3,6-trideoxysugars **1**–**4** (80–90%).[5,9] Since the MPM group at the anomeric position in **5** and **6** was selectively removed by treatment with TFA–H_2O–CH_2Cl_2 at room temperature (85–90%), the products can also be utilized for glycosylation.[5]

In summary, we have demonstrated a novel divergent synthesis of 3-amino-2,3,6-trideoxysugars **5a**, **5b**, **6a**, and **6b** from (*S*)-**10** with control of the stereochemistry of the three contiguous stereogenic centers (C3, C4, and C5). The configuration at the 4-position is controlled by stereoselective reduction and the Mitsunobu reaction. The methyl group at the 3-position was introduced by the palladium-catalyzed Migita–Stille coupling. The amino group at the 3-position is exclusively introduced by IBX-mediated radical cyclization from the C4 carbamoyl moiety. This method can be easily applied to the synthesis of their enantiomers from (*R*)-**10**.

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13 The reaction of its epimer of **6b** was demonstrated. See Ref. 9.
14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/.

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