



Synthesis of pseudaminic acid, a unique nonulopyranoside derived from pathogenic bacteria through 6-deoxy-AltdiNAc

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ABSTRACT

Chemical synthesis of pseudaminic acid is described. Starting from *N*-acetylglucosamine, deoxygenation and deoxyamination with stereo-inversion afforded 6-deoxy-AltdiNAc, which is the key intermediate for the biosynthesis of pseudaminic acid. Subsequently, the elongation reaction via In-mediated allylation of 6-deoxy-AltdiNAc with bromomethacrylate ester derivative followed by ozonolysis and hydrolysis gave the desired pseudaminic acid. Furthermore, we demonstrated glycosylation with dibenzyl phosphite derivative of pseudaminic acid as the glycosyl donor to afford disaccharide.

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In contrary to the long standing belief, studies in recent years have revealed the presence of O- as well as N-glycosylations of proteins in various prokaryotes.^{1,2} O-Linked glycosylation by pseudaminic acid **1** (Pse) is particularly intriguing. In flagellin glycoproteins derived from several pathogenic bacteria such as *Campylobacter jejuni* and *Helicobacter pylori*,^{2,3} Pse is directly connected to their Ser/Thr residues and is known to be important for bacteria's motility and invasion to host cells.² In addition, Pse has been identified as a component of larger glycans. For instance, trisaccharide repeating unit of O-antigen polysaccharide from *Escherichia coli* O136⁴ contains Pse and *Pseudomonas aeruginosa* 1244 trisaccharide was revealed to have modified pseudaminic acid.⁵

Although its similarity to sialic acid (Neu5Ac), which exists in various glycoconjugates of eukaryotic glycoproteins and glycolipids, is obvious, Pse has structural features clearly distinct from Neu5Ac (Fig. 1). Firstly, stereochemical configurations are opposite at C-5, -7, and -8 between them. Unlike Neu5Ac, Pse is an L-sugar and its equatorial glycoside, a naturally occurring form, is defined as β. Furthermore, Pse has a 7,9-dideoxy structure and its C-7 position is substituted by an *N*-acetyl or an *N*-acetimidoyl (Am) group. On the other hand, presence of highly deoxygenated and acetamido functionalized rare sugars, such as 2,4-diacetamido-2,4,6-trideoxy-D-glucopyranose (bacillosamine, Bac),⁶ 2,4-diacetamido-2,4,6-trideoxy-D-galactopyranose (6-deoxy-GalNAc),⁷ and 2,4-diacetamido-2,4,6-trideoxy-L-altropyranose (6-deoxy-AltdiNAc)⁸ had

been identified in various bacteria. Among them, 6-deoxy-AltdiNAc is of particular interest as a biosynthetic precursor of Pse.⁹

In spite of its growing attention, chemistry of Pse has been rather unexplored. There has been only a single reported synthesis of Pse,¹⁰ in which condensation of oxalacetic acid and L-allose derivative was employed as the key reaction. However, this reaction gave the desired isomer as a minor product and the yield was low (3%). In order to conduct systematic studies to clarify the function of bacterial O-linked glycosylation, more practical means to supply highly purified Pse will be required. With these circumstances in mind, our study has aimed to establish synthetic route to the Pse.¹¹

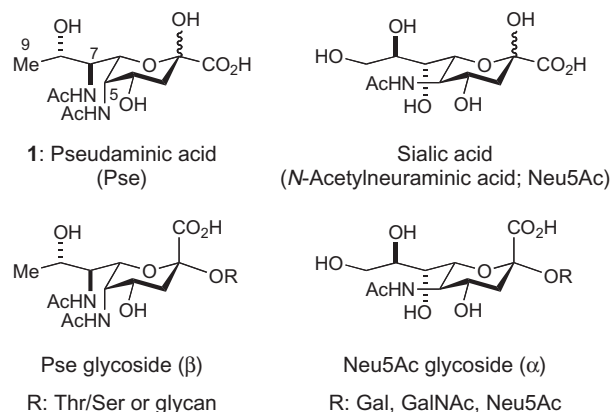
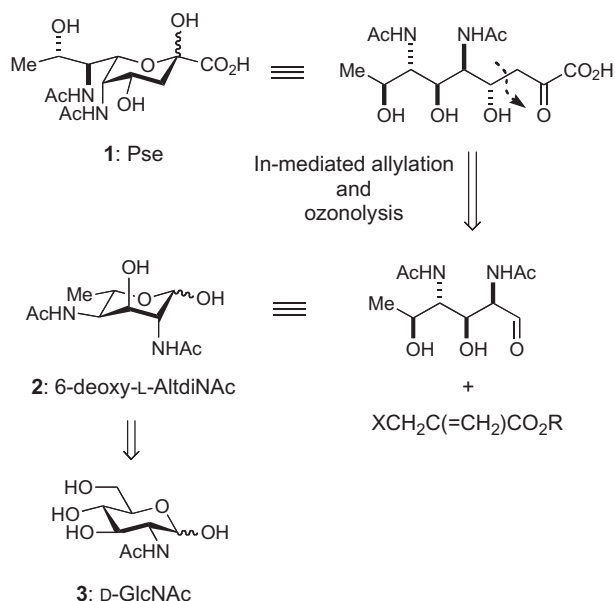


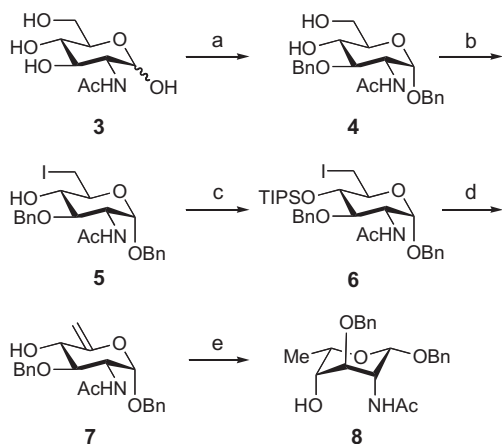
Figure 1. Pse (**1**), Neu5Ac and their glycosides.

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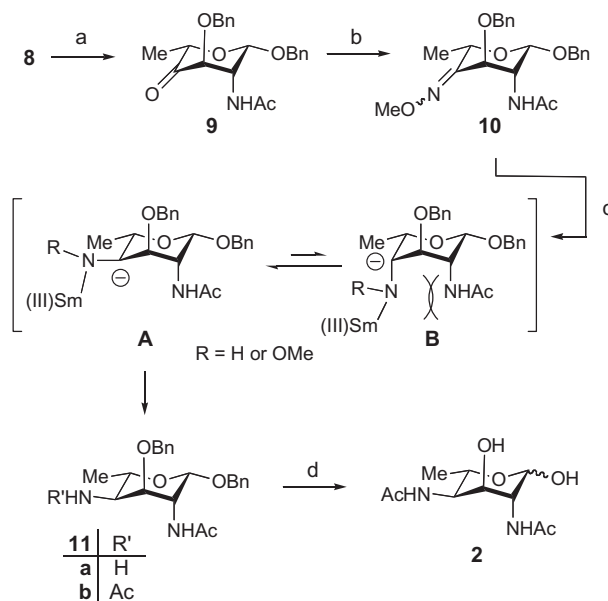
Scheme 1. Retrosynthesis of Pse (1).



Scheme 2. Reagents and conditions: (a) Ref.¹²; (b) I₂, PPh₃, imidazole, THF, 0 °C, 2 h, 88%; (c) TIPSO, 2,6-lutidine, CH₂Cl₂, 12 h, 92%; (d) *t*-BuOK, THF, 70 °C, 10 h, then TBAF, THF, 2 h, 96%; (e) H₂, RhCl(PPh₃)₃, benzene, EtOH, 3 h, 84%.

Outlined in Scheme 1 is our synthetic plan toward Pse, which intended to mimic its biosynthetic pathway, as it employed 6-deoxy-AltdiNac **2** as the key intermediate.⁹ To be brief, starting from *N*-acetylglucosamine **3**, deoxygenation, and deoxyamination with stereochemical inversion were expected to afford the 6-deoxy-AltdiNac **2**. Subsequent In-mediated allylation was going to give the framework of Pse **1** (Scheme 1).

As a precursor of **2**, *L*-idosamine derivative **8** was prepared as depicted in Scheme 2. To begin with, *N*-acetylglucosamine **3** was converted to benzyl glycoside **4** according to the known procedure.¹² Iodination with I₂, imidazole, and Ph₃P cleanly afforded compound **5**. Subsequent β-elimination in the presence of DBU gave **7**, however, in a modest yield (45%). More practically, the compound **5** was once converted into 4-*O*-trisopropylsilyl (TIPS) ether **6**, treatment of which with *t*-BuOK caused clean formation of the olefin, and subsequent desilylation gave 5,6-anhydroglucosamine derivative **7** in 88% overall yield. Saturation of the exocyclic olefin was conducted by catalytic hydrogenation in the presence of Wilkinson's catalyst. Pleasingly, it afforded stereoselectively the



Scheme 3. Reagents and conditions: (a) Dess–Martin periodinane, NaHCO₃, CH₂Cl₂, 17 h, 94%; (b) MeONH₂·HCl, NaHCO₃, MeOH, 65 °C, 17 h, 95%, major/minor = 2:1; (c) SmI₂, MeOH, THF, 12 h, then Ac₂O, pyridine, 6 h, 66%; (d) H₂, Pd(OH)₂, EtOH, 4 h, 94%, α/β = 2:1.

desired 2,6-dideoxy-*N*-acetyl-*L*-idosamine derivative **8** in 84% yield together with a minor amount (4%) of 6-deoxy-*D*-glucosamine type stereoisomer (Scheme 2).

Introduction of an amino-functionality to C-4 position of the compound **8** with stereochemical inversion turned out to be non-trivial. Unexpectedly, S_N2-type displacements of various sulfonate esters derived from **8** with N₃ anion were not successful. As an alternative approach, reductive amination through oxime derivative was examined. Thus, oxidation of alcohol **8** with Dess–Martin periodinane gave ketone **9**, which was treated with *O*-methylhydroxylamine hydrochloride and NaHCO₃ to afford the oxime **10** as a 2:1 mixture due to the *E/Z* isomerism. Since configuration of the C=N linkage was not consequential, rigorous assignment of the stereochemistry was not made. Subsequent reduction of **10** with SmI₂¹³ in THF containing MeOH followed by immediate acetylation of resultant **11a** afforded the desired 4-acetamidoaltrose derivative **11b** as a single isomer. We speculate that initially formed carbanion is under equilibration between two isomers **A** and **B**. Between them, equatorially oriented anion **B** would be less favored because of destabilization by 1,3-diaxial repulsion between steric hindrance of Sm(III)^{13b} and NHAc and formation of **11a** via **A** was predominant.¹⁴ Finally, hydrogenolysis of benzyl ether of **11b** afforded 6-deoxy-AltdiNac **2** (Scheme 3), which corresponds to the biosynthetic intermediate of Pse.

Thus obtained **2** was subjected to chain elongation through In-mediated allylation.¹⁵ Namely, it was reacted with bromomethacrylate ester **12** under Whitesides' conditions to give the desired erythro product **13** together with a slightly smaller amount of its *threo* isomer **14** (77%, **13**:**14** = 5:4). Although all attempts to improve the selectivity, including the use of Lewis acid, such as La(OTf)₃, Ba(OTf)₃, or Ce(OTf)₄·xH₂O in various amounts, in the presence or absence of chiral ligand,¹⁶ failed to improve the selectivity; chromatographic separation allowed us to obtain stereochemically homogeneous **13**. Subsequent ozonolysis was accompanied by spontaneous cyclization of the 2-oxo product and cleanly afforded, after purification by a column of Iatrobeads (CHCl₃/MeOH/H₂O, 65:30:5), ethyl pseudamine **15** (85%, α:β = 5:1). Finally, saponification of **15** under mildly basic condi-

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