Effective One-pot Synthesis of H type 1 and 2 Trisaccharide Derivatives Using Glycal Epoxide

Hiroshi Tanaka, Nobuatsu Matoba, and Takashi Takahashi*
Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-2 Ookayama, Meguro, Tokyo 152-5882

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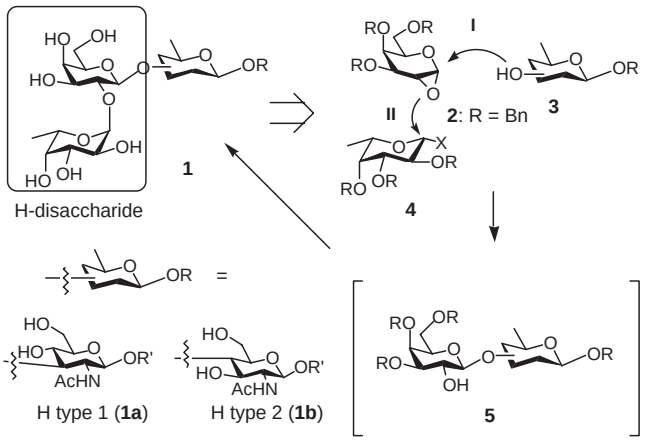
We describe an efficient synthesis of H type 1 and 2 trisaccharides by one-pot glycosylation involving glycosidation of glycal epoxide.

Oligosaccharides play important roles in biological processes on cell surface and have served as important tumor markers. β-Galactoside **1** attached with α-fucoside at the C2 position (H-disaccharide) is often found in biologically active oligosaccharides such as H type 1 and 2 epitopes (**1a**) and (**1b**), and is known to be an appropriate tumor antigen (Scheme 1).[1] In order to develop chemical probes based on the structure of the H-disaccharide, an effective methodology for the synthesis of glycoconjugates containing the H-disaccharide is required.[2]

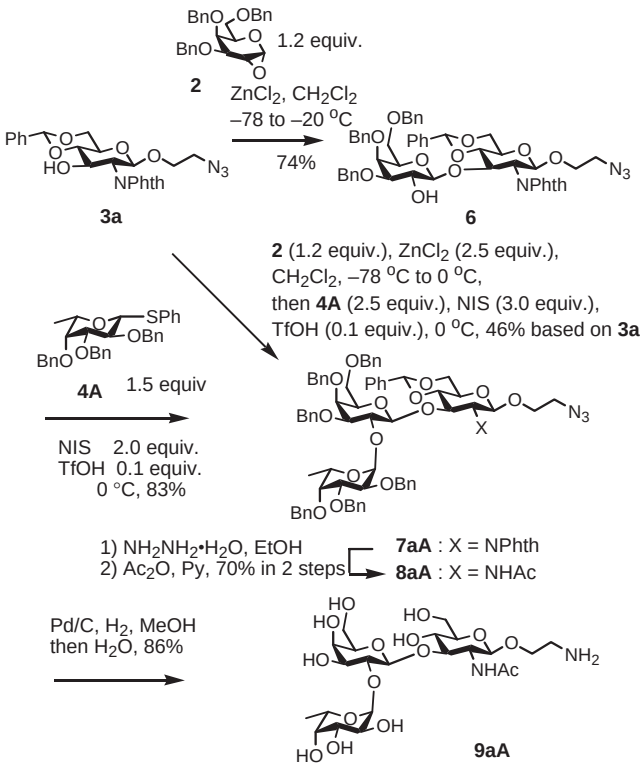


Scheme 1.

One-pot sequential glycosylation to form two and more glycosidic bonds, is an effective approach for the liquid-phase oligosaccharide synthesis.[3] This approach involves sequential chemo- and regio-selective glycosylations without any protecting group manipulations and purification of each intermediate. In the one-pot glycosylation, reagents and resulting products should not interfere any following glycosylations. We have investigated one-pot glycosylation based on the chemoselective activation of various glycosyl donors with an appropriate activator, and recently reported the synthesis of a protected linear and branched trisaccharide libraries by the one-pot glycosylation method.[4] Most of synthetic strategies are based on the in situ synthesis of oligosaccharides with a leaving group. Therefore, the synthesis of the trisaccharides **1** based on the one-pot glycosylation strategy requires the glycosidation of glycosyl donor attached with saccharide at the C2 position to from 1,2-*trans*-glycosidic bonds. However, the absence of the participating substituents of the glycosyl donors at the C2 position makes it difficult to stereoselectively form the 1,2-*trans*-glycosidic bond. Therefore, an effective one-pot glycosylation method for the synthesis of various C2 glycosylated oligosaccharides is required. Herein we report the one-pot synthesis of H Type 1 and 2 trisaccharide units using a glycal epoxide.

Our strategy for the one-pot synthesis of H Type 1 and 2 trisaccharide units **1** is based on the preparing glycosyl acceptors **5** by glycosylation of acceptor **3** with glycal epoxide **2**. The glycal epoxides are known to undergo stereoselective glycosidation to provide glycosides **5** bearing a hydroxy group at the C2 position linked through a 1,2-*trans*-glycosidic bond.[5] Subsequent glycosylation of the hydroxy group with glycosyl donor **4** would provide the protected H Type 1 and 2 trisaccharides **1**.

We first conducted the one-pot synthesis of H type 1 trisaccharide **9aA** bearing a primary amino group using the three building blocks **2**, **3a**, and **4A** (Scheme 2). Our initial investigation involves the stepwise synthesis of the protected trisaccharide **7aA** as shown in Scheme 2. Treatment of glucosamine **3a** with 1.2 equiv. of the glycal epoxide **2** in the presence of $ZnCl_2$ in CH_2Cl_2 provided the desired disaccharide **6** in 74% yield with complete β-selectivity. Use of TMSOTf as an activator resulted in a significant amount of silylated products. Fucosylation of the resulting disaccharide **6** with thiofucoside **4A** smoothly proceeded in stereoselective manner to provide α-fucoside **7aA** in good yield with complete α-selectivity.



Scheme 2.

Next, we examined one-pot glycosylation using **2**, **3a**, and **4A**. To glucosamine **3a** was added 1.2 equiv. of the glycal epoxide **2** and 2.5 equiv. of $ZnCl_2$ at −78 °C. The reaction mixture was stirred at 0 °C for 2 h. Subsequently, 2.5 equiv. of thiofucoside **4A**, 3.0 equiv. of NIS, and a catalytic amount of TfOH at 0 °C were added to the reaction mixture. After stirring at the same temperature for 2 h, the reaction mixture was quenched. After removal of the solvent, the residue was purified by silica gel chromatography and gel permeable chromatography to provide trisaccharide **7aA** in 46% yield based on **3a**. The analytical data of trisaccharide **7aA**, synthesized by one-pot glycosylation were identical with those of trisaccharide **7aA** by the stepwise synthesis.

Deprotection of the protected trisaccharide **7aA** was investigated. Treatment of **7aA** with $NH_2NH_2 \cdot H_2O$ in EtOH at reflux for 18 h, followed by acetylation of the amine provided acetamide **8aA** in 70% yield. Hydrogenolysis of both benzyl ethers and an azido group with H_2 in the presence of Pd/C provided the H type 1 trisaccharide **9aA** bearing with an amino alkyl chain at the reducing end in quantitative yield.

In order to demonstrate the feasibility of the method, we planned the combinatorial synthesis of a small oligosaccharide library **7aA-cB** based on the structure of H type 1 and 2 trisaccharide by one-pot glycosylation. (Figure 1 and Scheme 3). Six building blocks **2**, **3a**–**3c**, and **4A**–**4B** were designed for the library synthesis.

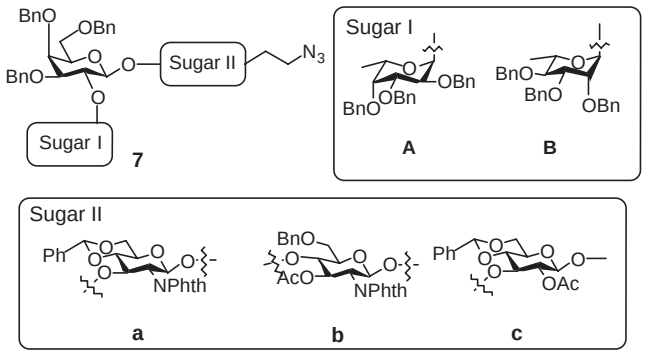
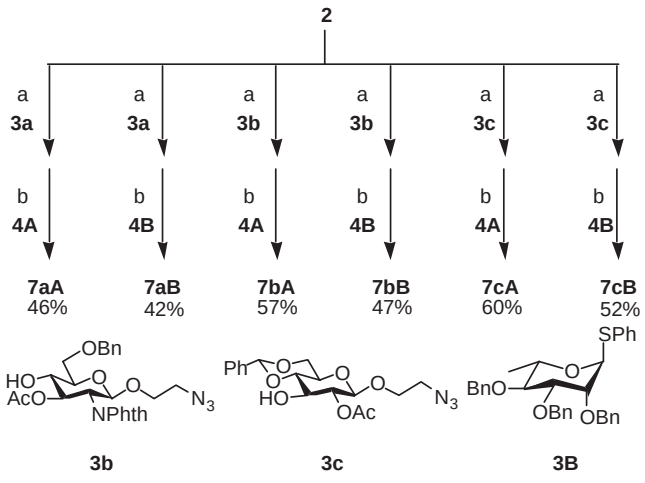


Figure 1.



Scheme 3. Reagents and conditions: a) $ZnCl_2$, CH_2Cl_2, −78 to −20 °C, 2.0 h; b) NIS, TfOH, CH_2Cl_2, 0 °C, 2.0 h.

The parallel synthesis of the 6 oligosaccharides **7** by one-pot glycosylation was performed utilizing Carusel®, which controls the reaction temperature and the stirring rate in 10 reaction vessels. The six reaction vessels were set up with activated MS-4Å. Each acceptor **3a**–**3c** was added to the two reaction vessels, respectively and the reaction vessels were cooled to −78 °C. The glycal epoxide **2** (1.2 equiv.) and $ZnCl_2$ (2.5 equiv.) were added to all the vessels at −78 °C. The reaction mixtures were warmed to −20 °C and stirred for 2 h at the same temperature. Subsequently, 2.5 equiv. of thiofucoside **4A** (2.5 equiv.) or thiorthamnoside **4B** (2.5 equiv.), NIS (3.0 equiv.), and a catalytic amount of TfOH at 0 °C were added to the reaction mixture. After stirring for 2 h at the same temperature, the reaction mixture was quenched with NEt_3. The residues were purified by silica gel chromatography, followed by gel permeable chromatography to provide trisaccharide **7aA-bC** in moderate yields (42–60% yields) based on **3**.

In conclusion, we have demonstrated one-pot synthesis of H type 1 and 2 trisaccharides **7** using the glycal epoxide **2**. The glycosydation of glycal epoxide **2** with $ZnCl_2$ provided disaccharide possessing the hydroxy-free C2. The secondary hydroxy group subsequent undergo glycosylation to provide trisaccharide in good yield in one-pot. The one-pot sequential glycosylation should be useful to prepare oligosaccharides containing the H-disaccharide moiety.

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