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Synthesis of A Branched Oligosaccharide by Remote Glycosidation

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Abstract: We describe a remote glycosidation that allows us to form a branched trisaccharide in intramolecular fashion. The molecular design of the spacer molecule for the remote glycosidation was examined based on molecular mechanics calculations.

Cell surface oligosaccharides are known to be involved in a wide variety of biological recognition processes including adhesion, signal transduction, and metastasis.[1] These discoveries have led to the development of efficient methods for the synthesis of various oligosaccharides, such as one-pot glycosidation,[2] solid-phase synthesis,[3] one-step synthesis,[4] enzyme-assisted synthesis,[5] two-stage activation procedure,[6] armed/disarmed glycosidation,[7] and silicon-connected glycosidation.[8] However, only a few methods directed to the synthesis of the branched oligosaccharides have been developed.[9] Previous syntheses of the branched sugars require multiple protection/deprotection steps. Namely, at the beginning of the synthesis a suitably protected glycosyl acceptor **5** is prepared. Following glycosidation of the glycosyl acceptor **5** with the glycosyl donor to form disaccharide **6**, selective deprotection of the disaccharide **6** and second glycosidation with another glycosyl donor lead to the branched sugar **4**. Herein, we describe an approach to obtaining the branched sugar by the remote glycosidation methodology.[10]

The concept of the remote glycosidation is summarized in Figure-1. Introduction of the spacer unit to the glycosyl acceptor **1** and the glycosyl donor **2** would give the trisaccharide **3**. This trisaccharide **3** is subjected to the remote (intramolecular) glycosidation, followed by removal of the spacer molecule, leading to the branched sugar **4**. If the spacer unit attached to both glycosyl donor and acceptor prefers to adopt the appropriate conformation for the ring formation,[11] the remote glycosidation would proceed regio- and stereoselectively without protection of the hydroxyl groups of the glycosyl acceptor. To test our strategy for reaching the branched trisaccharide, the remote glycosidations of the triglucoside derivatives **7** and **8** (Figure-2) were examined.

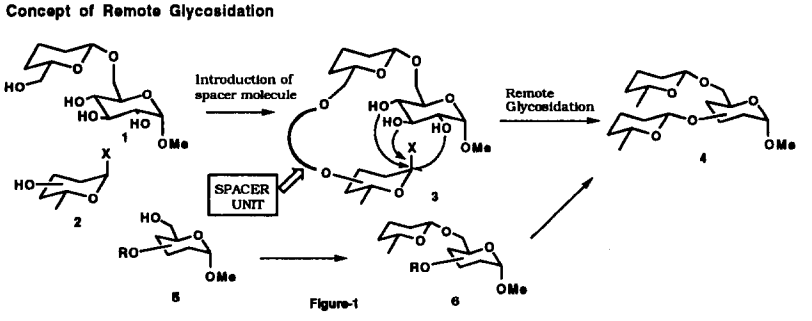

Figure-1

The spacer molecules that we have examined were the phthalic acid derivatives (as a rigid spacer) **7a** and **8a**, and the succinic acid derivatives (as a flexible spacer) **7b** and **8b**, in which both spacer molecules are attached at O-2 and O-3 in the glycosyl donor **C**, respectively, and at O-6 in the glycosyl acceptor **B**. At first, conformational studies of the triglucosides **7** and **8** were conducted as the molecular shapes of the triglucosides are essential for regio- and stereoselective formation of anomeric center. All possible conformations of **7a**, **7b**, **8a**, and **8b** were generated by Monte-Carlo (MC) conformational search method[12] and the resultant initial structures were energy-minimized by using AMBER (all atom) force field[13] implemented in MacroModel[14] to give 9, 7, 14, and 7 conformers, respectively, within 3 kcal/mol of the global minimum. Boltzmann distribution of these conformers at 25 °C revealed that more than 90% of total population would have the structures in which the anomeric carbon in the glycosyl donor **C** is close to O-4 in the glycosyl acceptor **A**. The distance between the anomeric carbon in **C** and O-4 in **A** is 3.59 Å for the global minimum structure of **7a**, while the corresponding distances are 6.06 Å, 6.59 Å, and 5.85 Å for **8a**, **7b**, and **8b**, respectively. These calculations suggested that **7a** has suitable conformation for the remote glycosidation on ground state level. Furthermore, conformational analysis of the cyclized trisaccharides obtained by the cyclization of **7a** was carried out to gain the information regarding to the stability of the cyclized product. MC conformational search and subsequent energy minimization with AMBER force field revealed that the relative steric energies of the cyclized products are calculated to be 0.00 kcal/mol, 1.64 kcal/mol, and 3.39 kcal/mol for **10a** (cyclized at O-4 position in the glycosyl acceptor **A**), **10b** (cyclized at O-3), and **10c** (cyclized at O-2), respectively. These calculations suggested that introduction of the phthalate derivative between O-2 position in **C** and O-6 position in **B** serves as optimal spacer in remote glycosidation to form the 4,6-trisaccharide.

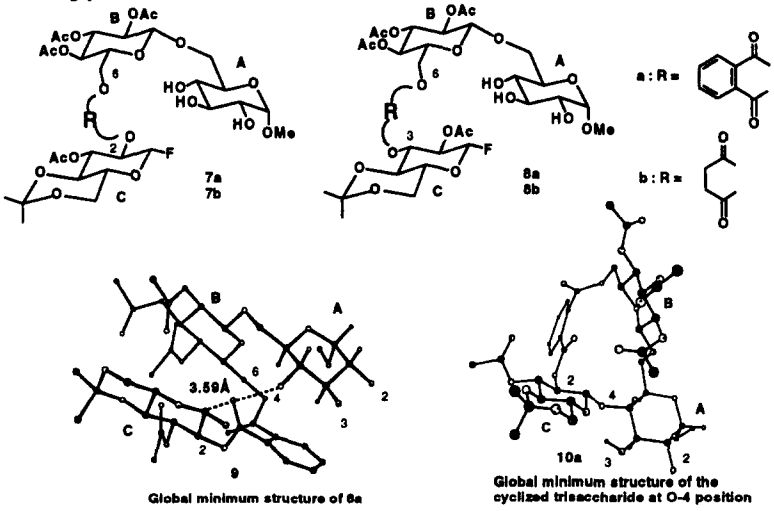

Figure-2

To apply the remote glycosidation methodology described above in the synthesis of the 4,6-trisaccharide, trisaccharide **13** was synthesized from the thioglycoside **12** and 6-hydroxy diglycoside **11**. (Figure-3) Treatment of **11** and **12** with DCC in the presence of DMAP in toluene gave the spacer-linked triglucoside in 97% yield. The anomeric phenylthio group was converted to the glycosyl fluoride[6a] with DAST and NBS in CH_2Cl_2 in 89% yield. Selective cleavage of the p-methylbenzyl ethers was accomplished by the treatment of the glycosyl fluoride in ethyl acetate with $Pd(OH)_2/C$ under hydrogen to provide the trisaccharide **13** in 93% yield.

Then, the trisaccharide **13** was subjected to the remote glycosidation. Slow addition of the trisaccharide **13** in CH_2Cl_2 to a solution of Cp_2HfCl_2[15] (3.6 eq.) and AgOTf (7.5 eq.) in CH_2Cl_2 over a 4.5 h period under reflux produced the cyclized product **14**[16] in 37% yield along with polar products after the short-column chromatography.[17] To confirm the regio- and stereochemistry of the remote glycosidation, the cyclized product **14** was converted to the peracetyl-trisaccharide **15** as follows. Base treatment of the cyclized product **14** with NaOMe, followed by acid hydrolysis of the acetal group provided the trisaccharide in 34% yield. The resultant alcohol was directly acetylated with acetic anhydride and pyridine to give the 4,6-trisaccharide **15** in 65% yield. NMR analysis of the trisaccharide **15** revealed that the remote glycosidation produced the expected O-4 glycosidated product with β stereochemistry. The high regio- and stereoselectivity of the remote glycosidation was rationalized by the conformational preference of **7a**.

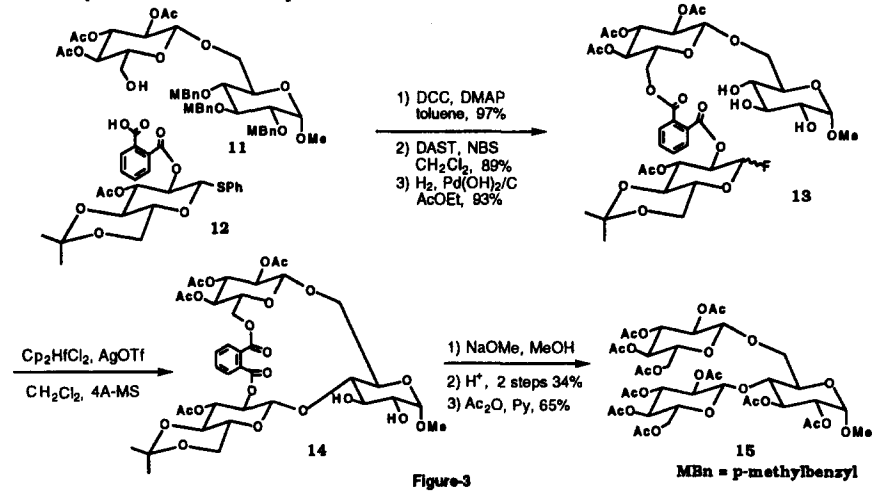

Figure-3

In order to test the effect of the spacer molecule, intermolecular glycosidation of 2,3,4-trihydroxy glucose **16** with glycosyl fluoride **17** was examined. Treatment of **16** and **17** with Cp_2HfCl_2 and AgOTf in CH_2Cl_2 led to the formation of 2,6-triglucoside **18**, 3,6-triglucoside **19**, and tetraglucoside in 21%, 11%, and 3% yield, respectively. We could not obtain any product that was glycosidated at O-4 position of the glycosyl acceptor **16**. This intermolecular glycosidation indicated that the phthalate spacer in **13** could effectively control the conformation of **13** to be glycosidated at the least reactive hydroxy group (O-4).

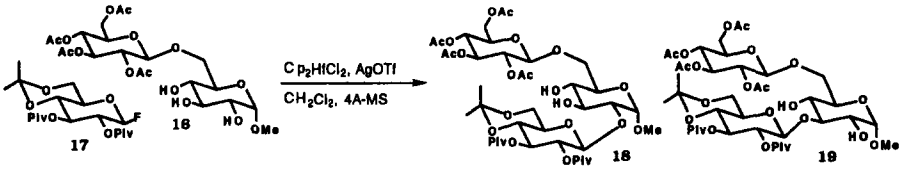

Figure-4 21% 11%

In summary, we have developed a new method for the synthesis of the branched sugar using the remote glycosidation methodology. The conformational study of the substrates having the spacer molecule would be useful for the prediction of the regio- and stereoselectivity of the remote glycosidation.

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16) **14**; 1H-NMR(300 MHz, $CDCl_3$) δ 4.97 (d, 1H, anomeric, J = 6.3Hz), 4.68 (d, 1H, anomeric, J = 3.8 Hz), 4.65 (d, 1H, anomeric, J = 7.9 Hz); MS (FD) m/z 857 (M^++1).

17) We could not detect any product that was glycosidated at O-2 or O-3 position, and was obtained by intermolecular glycosidation.

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