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One-Pot Sequential Glycosylation: A New Method for the Synthesis of Branched Oligosaccharides

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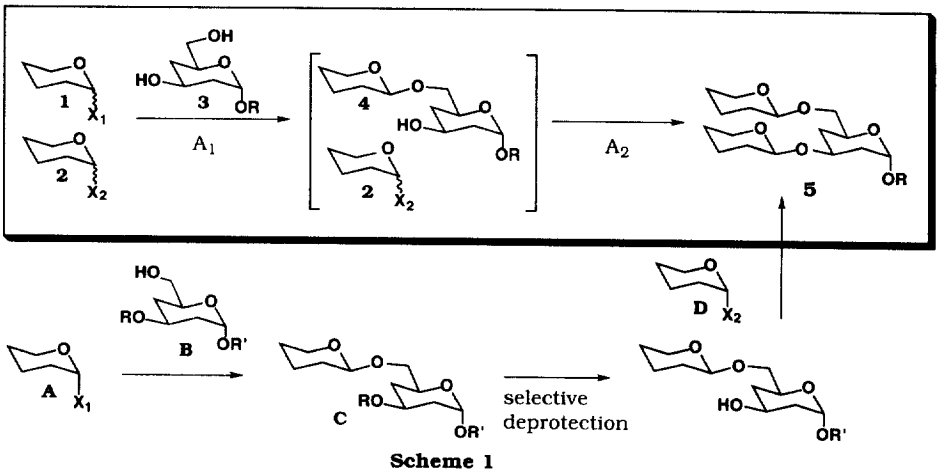
Abstract: One-pot glycosylations of glycosyl bromides and phenylthio glycosides with various dihydroxyl glycosyl acceptors have been examined to provide the corresponding branched trisaccharides.

Keywords: Onepot glycosylation, Branched trisaccharides.

The molecular diversity of oligosaccharides has been recognized in their involvement in various important biological functions.[1] These discoveries have led to the development of efficient methods for the synthesis of various oligosaccharides, such as one-pot glycosylation,[2,3] solid-phase synthesis,[4] remote glycosylation,[5] enzyme-assisted synthesis,[6] two-stage activation procedure,[7] armed/disarmed glycosylation,[8] and silicon-connected glycosylation.[9] However, only a few methods directed toward the synthesis of branched oligosaccharides have been developed.[10] Previous syntheses of the branched sugars have required multiple protection/deprotection steps. Namely, at the beginning of the synthesis a suitably protected glycosyl acceptor **B** is prepared. Following glycosylation of the glycosyl acceptor **B** with the glycosyl donor **A** to form disaccharide **C**, selective deprotection of the disaccharide **C** and a second glycosylation with another glycosyl donor **D** lead to the branched sugar **5**. Herein, we describe an approach to obtaining branched sugars by a one-pot glycosylation methodology.

Concept of Branched Type One-Pot Glycosylation



Scheme 1

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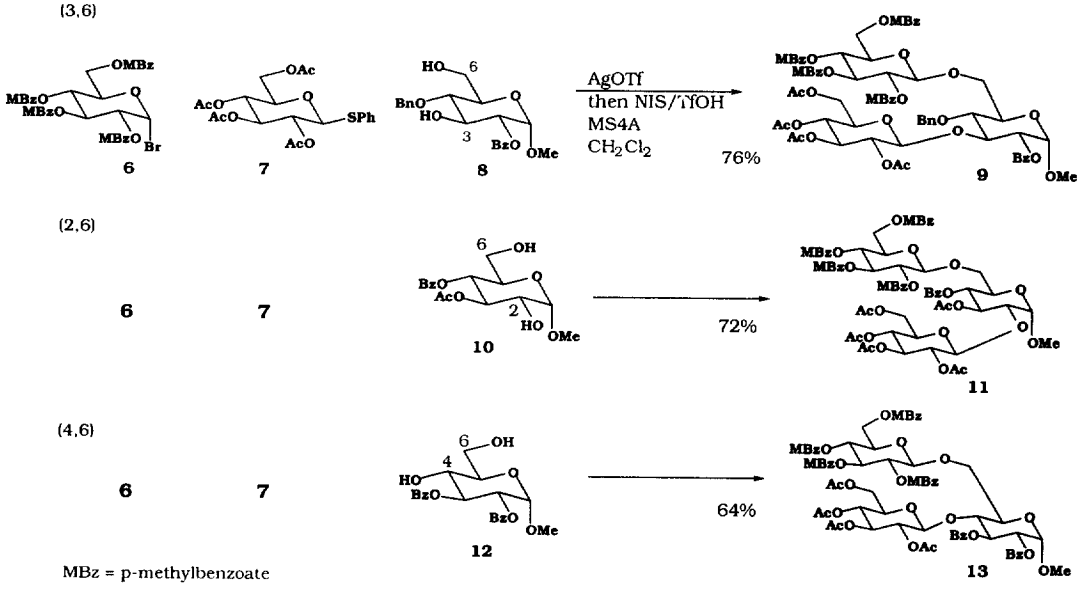
The concept of the branched-type one-pot glycosylation is summarized in Scheme 1. In the branched type one-pot glycosylation, the differences in the reactivity of the leaving groups in glycosyl donors (X_1, X_2) and hydroxyl groups in glycosyl acceptors are used to control the one-pot glycosylation. It is expected that the initial coupling of glycosyl bromide **1** (X_1=Br) with glycosyl acceptor **3** in the presence of activator $\mathbf{A_1}$ (AgOTf)[11] would take place at most reactive hydroxyl group in the acceptor **3** to give disaccharide **4**. While the glycosyl donor (X_2=SPh) in **2** is stable to the AgOTf activation, addition of a second activator $\mathbf{A_2}$ (NIS/TfOH)[12] should promote the selective activation of the phenylthio group (X_2) in **2** and the glycosylation should occur at the less reactive hydroxyl group to give the trisaccharide **5** in a one-pot procedure.

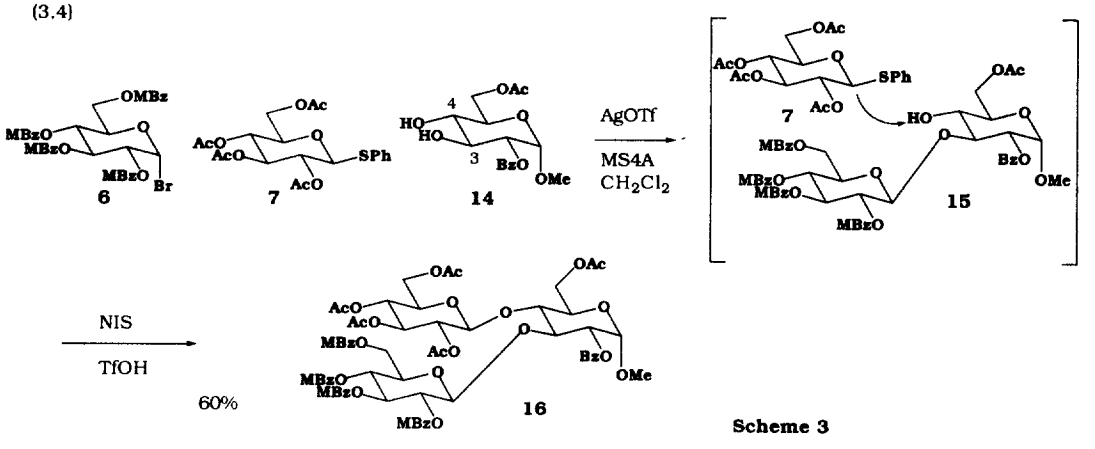
Glycosyl bromide **6** and phenylthio glycoside **7** were employed as glycosyl donors and 3,6-dihydroxy glucose **8** was used as a glycosyl acceptor. (Scheme 2) To a solution of glycosyl bromide **6** (1.05 eq.), thioglycoside **7** (2.0 eq.), glycosyl acceptor **8** (1.0 eq.), and pulverized molecular sieves **4A** in CH_2Cl_2 was added 3.0 eq. of AgOTf in toluene at -20 °C, after which the mixture was stirred for 50 min. To the solution, 5.0 eq. of NIS in CH_2Cl_2 and ca. 0.15 M solution of TfOH in CH_2Cl_2 were added at 0 °C. The reaction was quenched with powdered sodium thiosulfate and sodium hydrogencarbonate. After filtration through Celite, the mixture was purified by column chromatography on silica gel affording the corresponding trisaccharide **9**[13] in 76% yield. Under the reaction conditions the only glycosylation product obtained was trisaccharide **9**, which was isolated exclusively as the β anomer. In a similar way, glycosyl bromide **6** reacted selectively with 2,6-dihydroxy glucose **10** in the presence of AgOTf to give the intermediate disaccharide. Coupling of phenylthio glycoside **7** to this intermediate under NIS/TfOH conditions provided the 2,6-branched trisaccharide **11** in 72% yield. Treatment of 4,6-dihydroxy glucose **12** with glycosyl bromide **6** and phenylthio glycoside **7** gave the 4,6-branched trisaccharide **13** in 64% yield.



Scheme 2

One-pot glycosylation of the glycosyl bromide **6**, phenylthio glucoside **7** and 3,4-dihydroxy acceptor **14** was examined. (Scheme 3) Selective activation of bromoglycoside **6** in the presence of **14** and molecular sieves **4A** by treatment with AgOTf in CH_2Cl_2 at -20 °C resulted in the formation of the disaccharide **15**. Since the C-3 and C-4 hydroxyl groups in acceptor **14** have considerably different reactivity toward the glycosyl donor **6**, the first glycosylation took place selectively at the more reactive C-3 position. Subsequently, the phenylthio group in **7** was activated by treatment with NIS and TfOH at room temperature to provide 3,4-branched trisaccharide **16**[14] in 60% yield in one-pot operation. The one-pot glycosylation also proved successful in the case of 3,4-dihydroxy acceptor **14** in which both hydroxyl groups were secondary alcohols.

(3.4)



Scheme 3

The ability to control the reactivity of both the glycosyl donors and the glycosyl acceptors provides a novel strategy for the synthesis of branched trisaccharides in practically one step. The synthetic utility of this methodology was demonstrated by the one-pot preparation of 2,6-, 3,6-, 4,6- and 3,4-branched trisaccharides. This protocol allows one to eliminate the protecting group manipulations previously required for the synthesis of branched type oligosaccharides and has resulted in a considerable savings in time and labor. Chemoselective activation of glycosyl donors is of considerable importance in one-pot glycosylations, and a variety of powerful strategies have emerged for the synthesis of oligosaccharides where the reactivity of the glycosyl donors can be controlled by the substituent in the leaving group[3a] or by applying the armed/disarmed concept.[3b] A major advance in our one-pot glycosylation[2] involves the use of halide and thioglycoside as leaving groups and appropriate activating reagents for chemoselective activation of the leaving group. The halide and thioglycoside methods for glycosylation with the reactivity tuning via the armed/disarmed concept has proved to be especially effective for the synthesis of a wide variety of structures. This methodological advance in the one-pot glycosylation should enable the synthesis of biologically significant oligosaccharides in a rapid and efficient fashion.

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13) **9**: $[\alpha]_D^{25}$ = +29.2 (c = 1.12, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ = 1.70 (s, 3H, acetyl), 1.89 (s, 3H, acetyl), 1.91 (s, 3H, acetyl), 1.98 (s, 3H, acetyl), 2.28 (s, 3H, *p*-toluyl), 2.33 (s, 3H, *p*-toluyl), 2.34 (s, 3H, *p*-toluyl), 2.39 (s, 3H, *p*-toluyl), 3.09 (s, 3H, OMe), 3.39 (dd, 1H, *J* = 8.9, 9.6 Hz), 3.62-3.82 (m, 3H), 3.97 (dd, 1H, *J* = 2.3, 12.5 Hz), 4.06-4.21 (m, 4H), 4.34 (dd, 1H, *J* = 8.9, 9.6 Hz), 4.49 (dd, 1H, *J* = 5.0, 12.2 Hz), 4.58 (dd, 1H, *J* = 3.6, 12.2 Hz), 4.78-5.03 (m, 7H), 5.54 (dd, 1H, *J* = 7.6, 9.6 Hz), 5.63 (dd, 1H, *J* = 9.6, 9.9 Hz), 5.87 (dd, 1H, *J* = 9.6, 9.9 Hz), 7.05-8.06 (m, 26H, aromatic); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 20.6, 21.6, 29.6, 54.8, 68.4, 69.6, signals for anomeric carbons at 96.4, 101.1, 101.5, signals for aromatic carbons at 165.1, 165.2, 167.7, 165.9, 166.2, 169.5, 170.1, 170.7, 177.8.

14) **16**: $[\alpha]_D^{25}$ = +35.9 (c = 0.90, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ = 1.93 (s, 3H, acetyl), 2.01 (s, 3H, acetyl), 2.03 (s, 3H, acetyl), 2.13 (s, 3H, acetyl), 2.21 (s, 3H, acetyl), 2.26 (s, 3H, *p*-toluyl), 2.31 (s, 3H, *p*-toluyl), 2.34 (s, 3H, *p*-toluyl), 2.37 (s, 3H, *p*-toluyl), 3.30 (s, 3H, OMe), 3.68-3.95 (m, 3H), 4.08-4.33 (m, 3H), 4.36-4.53 (m, 3H), 4.59-4.73 (m, 3H), 4.87-5.00 (m, 3H), 5.08-5.20 (m, 3H), 5.41-5.70 (m, 3H), 6.90-8.03 (m, 21H, aromatic); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 14.1, 29.6, 29.7, 31.3, 32.0, 38.2, 55.3, 68.6, 72.0, 72.2, 73.3, 76.3, signals for anomeric carbons at 96.1, 100.5, 100.5, signals for aromatic carbons at 126.3, 133.8, 143.5, 144.0, 165.1, 165.2, 165.4, 165.8, 166.2, 169.1, 169.3, 170.4, 170.6, 171.3.