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Direct Synthesis of 2-Deoxy-β-Glycosides via Anomeric *O*-Alkylation with Secondary Electrophiles†

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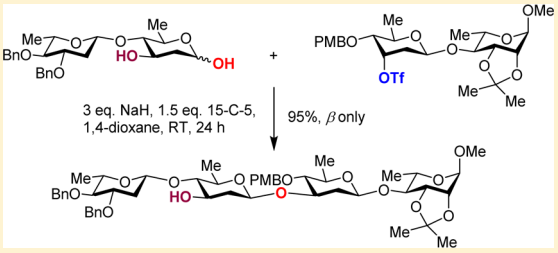
Supporting Information

ABSTRACT: An approach for direct synthesis of biologically significant 2-deoxy-β-glycosides has been developed via *O*-alkylation of a variety of 2-deoxy-sugar-derived anomeric alkoxides using challenging secondary triflates as electrophiles. It was found a free hydroxyl group at C3 of the 2-deoxy-sugar-derived lactols is required in order to achieve synthetically efficient yields. This method has also been applied to the convergent synthesis of a 2-deoxy-β-tetrasaccharide.

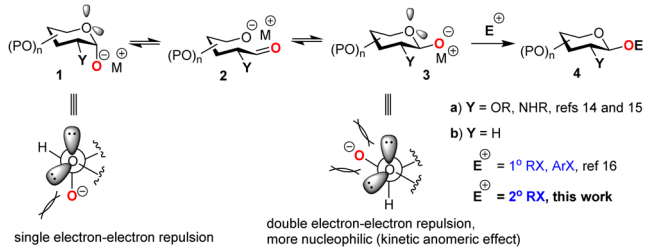


INTRODUCTION

2-Deoxy-β-glycosides, especially 2,6-dideoxy-β-glycosides, are biologically important carbohydrates existing in numerous natural products/clinical agents[1] and play critical roles in their biological activity as well as stability and solubility.[2] Despite the development of numerous glycosylation methods and technologies,[3] the efficient stereoselective synthesis of complex oligosaccharides and glycoconjugates remains a nontrivial problem. Among various types of glycosidic linkages, the stereocontrolled synthesis of 2-deoxy-β-glycosides is notoriously challenging due to the absence of a directing group at C2.[4] A most common indirect approach for stereoselective synthesis of 2-deoxy-β-glycosides involves preinstallation of a directing group at C2 followed by its removal after glycosylation.[5] Other indirect strategies, such as the use of alkoxy-substituted anomeric radicals,[6] and de novo synthesis via palladium-catalyzed stereoselective glycosylation[7] were also reported. Alternatively, in order to improve overall synthetic efficiency, direct methods for the synthesis of 2-deoxy-β-glycosides involving the use of glycosyl phosphites,[8] glycosyl halides,[9] glycosyl imidates,[10] conformationally restricted 4,6-*O*-benzylidene-2-deoxyglucosyl donors,[11,12] and glycosyl tosylates [13] have also been developed.

Anomeric *O*-alkylation, an alternative to the traditional glycosylation, has been successfully developed by Schmidt[14] and others[15] for stereoselective synthesis of β-linked oligosaccharides and glycoconjugates (**a**, Scheme 1). It was postulated that a rapid equilibrium occurs between *axial* anomeric alkoxide **1** and its *equatorial* isomer **3** via an open intermediate **2**. The *equatorial* alkoxide should be more reactive than its *axial* isomer due to enhanced nucleophilicity by double electron−electron repulsion in **3** compared to a single gauche interaction in **1**, which was referred to as a kinetic anomeric effect.[14] Subsequent selective *O*-alkylation of the more reactive *equatorial* anomeric alkoxide **3** by suitable electrophiles should lead to the selective production of β-glycosides **4**. Thus, stereoselective synthesis of β-glycosides via anomeric *O*-alkylation does not demand the participation of C2 substituent, which would be an ideal approach for the synthesis of 2-deoxy-β-glycosides. Early in 2009, Shair and co-workers reported stereoselective synthesis of 2-deoxy-β-glycosides (**4**, *Y* = H) via anomeric *O*-alkylation/arylation using primary or aromatic electrophiles (**b**, E^+ = 1° RX or ArX, Scheme 1).[16] However, the use of more challenging secondary electrophiles failed in *O*-alkylation of 2-deoxy-sugar-derived anomeric alkoxides.[16] In view of the fact that a vast majority of naturally occurring 2-deoxy-β-glycosides, especially 2,6-dideoxy-β-sugars, contain 1→3 or 1→4 linkages, it would be appealing to develop stereoselective anomeric *O*-alkylation protocols tolerating secondary electrophiles. On the basis of our previous success in umpolung *S*-glycosylation for stereoselective synthesis of 2-deoxy-thioglycosides,[17] we describe herein a direct stereospecific synthesis of 2-deoxy-β-(1→3) and (1→4)-linked glycosides via anomeric *O*-alkylation using secondary electrophiles (**b**, E^+ = 2° RX, Scheme 1).

Scheme 1. Synthesis of Complex Glycosides via Anomeric *O*-Alkylation



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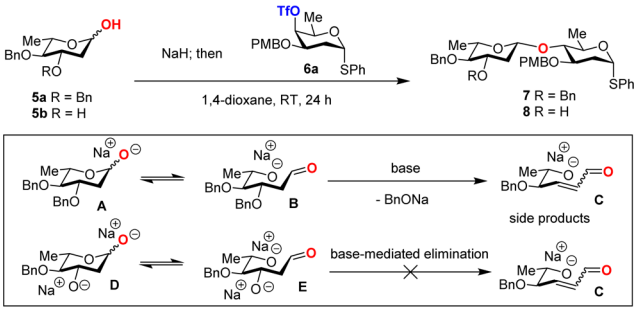
RESULTS AND DISCUSSION

Initially, L-oliose-derived lactol **5a** was chosen to react with D-olivose-derived C4-triflate **6a** for the formation of disaccharide **7** via anomeric *O*-alkylation (Table 1). Not surprisingly, applying the same condition reported previously (sodium hydride, 1,4-dioxane, RT) did not provide detectable product **7** (entry 1, Table 1).[16] Gratifyingly, addition of 15-crown-5,[14b,c] known to chelate with sodium ion and increase the reactivity of the corresponding anion,[18] afforded the desired disaccharide **7** in 51% yield in toluene (β only) (entry 2). Switching the solvent to 1,4-dioxane slightly dropped the yield to 41% (β only) (entry 3). Examination of the ^{1}H NMR spectra of the crude reaction mixture indicated that a number of side products bearing aldehyde functionality were formed, probably due to the decomposition of anomeric alkoxides **A** (e.g., base-mediated elimination of the open intermediate **B** to form a mixture of *E*- and *Z*-isomers of **C**, Table 1). Thus, we speculated that suppressing the decomposition of anomeric alkoxides would lead to the desired disaccharide in improved yield. Such a problem may be circumvented by the use of modified lactols (cf. **5b**) bearing a free hydroxyl group at C3.[19] Accordingly, upon deprotonation of both hydroxyl groups at C-1 and C-3 of **5b** with excess sodium hydride, the corresponding anomeric alkoxides, dianions **D**, may be reversibly opened to form the open intermediate, aldehyde **E**. However, due to less acidity of the α-H of the aldehyde **E** (as compared to **B**) and the poor leaving ability of the sodium oxide anion (NaO^-), subsequent enolization−elimination of the aldehyde **E** should be suppressed, which would hopefully improve the yield of the desired disaccharide **8** (Table 1). It should be noted that the C1-anomeric alkoxide of **D** was reported to be more nucleophilic than the C3-alkoxide due to the aforementioned double electron−electron repulsion.[14c,16]

To our delight, treatment of a solution of lactol **5b** in 1,4-dioxane with 3 equiv of sodium hydride followed by addition of triflate **6a** and 1.5 equiv of 15-crown-5, produced desired product **8**, isolated in 81% yield after 24 h at room temperature

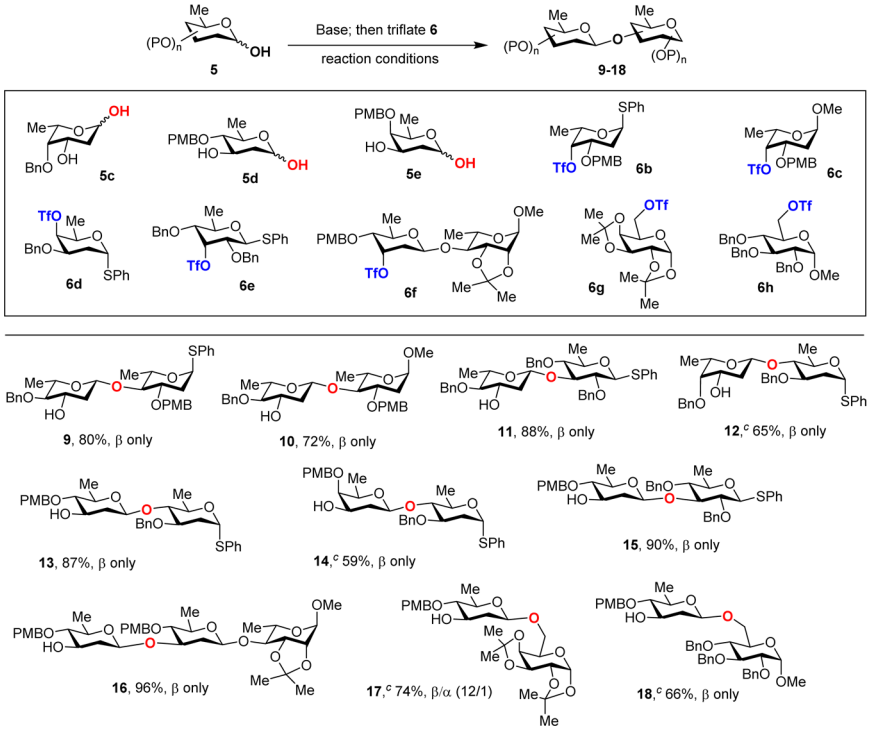
Table 1. Optimization of Synthesis of 2,6-Dideoxy-β-glycosides[a]



entry	reaction condition	yield[b], (β/α)
1	**5a**, NaH (2 equiv)	7, <1%, ND[c]
2[d]	**5a**, NaH (2 equiv), 15-C-5 (1.5 equiv)	7, 51%, β only
3	**5a**, NaH (2 equiv), 15-C-5 (1.5 equiv)	7, 41%, β only
4	**5b**, NaH (3 equiv), 15-C-5 (1.5 equiv)	8, 81%, β only
5[e]	5b, NaH (3 equiv), 15-C-5 (1.5 equiv)	8, 70%, β only
6[d,f]	**5b**, NaH (3 equiv), 15-C-5 (1.5 equiv)	8, 45%, β only
7	**5b**, NaH (3 equiv), 15-C-5 (30 mol %)	8, 22%, β only
8	**5b**, NaH (3 equiv), 15-C-5 (1.0 equiv)	8, 48%, β only
9	**5b**, KO^{t}Bu (2 equiv), 18-C-6 (1.5 equiv)	8, <1%, ND[c]

[a]General conditions: lactol **5a** or **5b** (1.0 equiv), sodium hydride, 1,4-dioxane, RT 10 min; then triflate **6a** (2.0 equiv), 15-C-5, RT, 24 h. [b]Isolated yield. [c]ND = not detected. [d]Toluene was used as solvent. [e]THF was used as solvent. [f]Lactol **5b** is not well soluble in toluene.

Table 2. Synthesis of Various 2,6-Dideoxy-β-glycosides[a,b]



[a]General conditions: lactol **5** (1.0 equiv), sodium hydride (3 equiv), 1,4-dioxane, RT 10 min; then triflate **6** (2.0 equiv), 15-C-5 (1.5 equiv), RT, 24 h. [b]Isolated yield. [c]Sodium hydride (2 equiv) was used.

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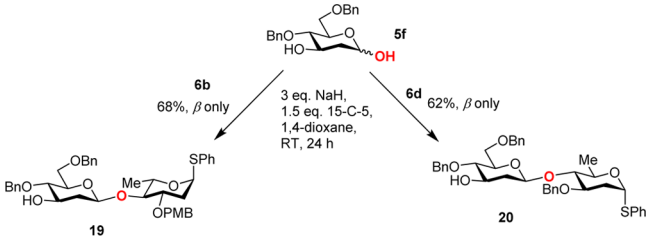
(β only, entry 4). The yields dropped when THF or toluene was used as solvent (entries 5 and 6). The use of less 15-crown-5 also led to the lower yields (entries 7 and 8). Furthermore, the use of mild base, KO^{t}Bu, and 18-C-6[15b] did not afford noticeable product (entry 9). To the best of our knowledge, this is the first time that a 2-deoxy-sugar-derived lactol bearing a C3-hydroxyl group has been successfully used in the anomeric *O*-alkylation to form (1→4)-β-linked 2-deoxy-disaccharide in good yield and excellent anomeric selectivity. In addition, the C3-free OH in the disaccharide product **8** may be directly employed in the subsequent glycosylation if needed.

Given this encouraging result, we have investigated the reaction scope for preparation of various 2,6-dideoxy-β-oligosaccharides (Table 2). Accordingly, three additional 2,6-deoxy sugar-derived lactols **5c−e** bearing a C3-hydroxyl group, four additional sugar-derived secondary triflates **6b−e**, and a disaccharide-derived C3-triflate **6f** were prepared.[20] As shown in Table 2, under optimal conditions these lactols (**5b−e**) reacted with secondary triflates (**6a−f**) via anomeric *O*-alkylation to afford a number of desired β-linked oligosaccharides (**9−16**) in good-to-excellent yields and excellent anomeric selectivity. Notably, this method has demonstrated its application in efficient preparation of synthetically challenging β-oliosides[10,21] (e.g., **12** and **14**). In addition, we carried out anomeric *O*-alkylation of lactol **5d** using primary triflates **6g−h** which afforded desired disaccharides **17** and **18** in comparable yields and anomeric selectivity as reported previously.[16]

This anomeric *O*-alkylation was next applied to the synthesis of 2-deoxy-β-glycosides (Scheme 2). Treatment of 2-deoxy-D-glucose-derived lactol **5f**[22] with sodium hydride followed by addition of secondary triflates, **6b** and **6d**, afforded desired 2-deoxy-β-glycosides **19** and **20** in 68% and 62% yield, respectively. In general, these reactions involving 2-deoxy-sugar-derived lactols (cf. **5f**) afforded the desired disaccharides in slightly lower yield than those involving 2,6-dideoxy sugar-derived lactols (cf. **5b−e**), probably due to the relatively lower reactivity of 2-deoxy-sugar-derived anomeric alkoxide as compared with 2,6-dideoxy-sugar-derived anomeric alkoxide.

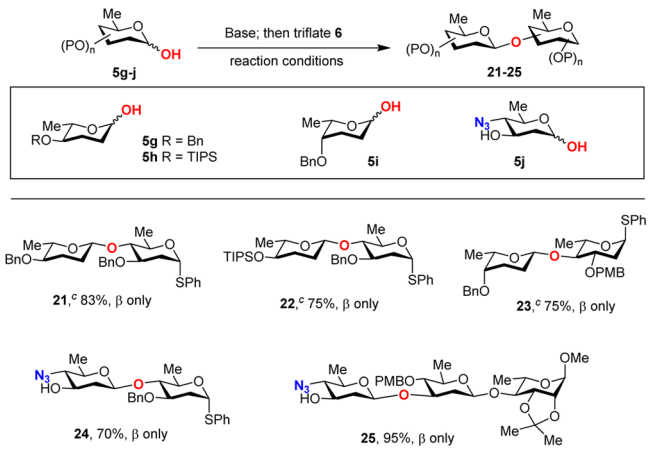
Scheme 2. Synthesis of 2-Deoxy-β-glycosides



We also sought to prepare synthetically demanding 2,3,6-trideoxy and 2,4,6-trideoxy-4-amino-β-glycosides via anomeric *O*-alkylation with secondary triflates (Table 3). Accordingly, we have prepared three 2,3,6-trideoxy-sugar-derived lactols **5g−i** and a 2,4,6-trideoxy-4-azidosugar-derived lactol **5j**. As shown in Table 3, under optimal conditions these lactols (**5g−j**) reacted with secondary triflates **6** via anomeric *O*-alkylation to afford a number of desired β-linked oligosaccharides (**21−25**) in good yields and excellent anomeric selectivity.

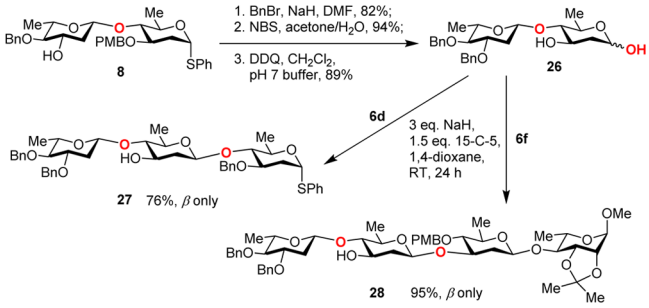
In order to further demonstrate the utilization of this method in the synthesis of complex 2-deoxy-oligosaccharides, we initiated the synthesis of 2,6-dideoxy-trisaccharide **27** and tetrasaccharide **28** containing all β-linkages (Scheme 3).

Table 3. Synthesis of 2,3,6-Trideoxy-β-glycosides and 2,4,6-Trideoxy-4-azido-β-glycosides[a,b]



[a]General conditions: lactol **5** (1.0 equiv), sodium hydride (3 equiv), 1,4-dioxane, RT 10 min; then triflate **6** (2.0 equiv), 15-C-5 (1.5 equiv), RT, 24 h. [b]Isolated yield. [c]Sodium hydride (2 equiv) was used.

Scheme 3. Synthesis of β-Linked 2,6-Dideoxy-Tri- and -Tetra- saccharides Using Iterative Anomeric *O*-Alkylation



Accordingly, disaccharide **8**, obtained via anomeric *O*-alkylation of **5b** with triflate **6a**, underwent a sequential benzyl protection (82%), NBS-mediated oxidation of the anomeric phenylsulfide (94%),[10] and DDQ-mediated PMB deprotection (89%) to afford disaccharide lactol **26** bearing a C3-free OH. As expected, this lactol **26** reacted with C-4 triflate **6d** and disaccharide-derived C3-triflate **6f** via anomeric *O*-alkylation under optimal conditions to afford 2-deoxy-trisaccharide **27** and tetrasaccharide **28** in 76% and 95% yield (β only), respectively.

CONCLUSION

In summary, an efficient approach for stereospecific synthesis of 2-deoxy-β-(1→3) and (1→4)-linked glycosides via anomeric *O*-alkylation using secondary electrophiles has been described. It is believed that this excellent anomeric stereochemical outcome is controlled by a kinetic anomeric effect. This type of glycosylation (anomeric *O*-alkylation) performed in basic reaction conditions is beneficial for the synthesis of acid-labile 2-deoxy-glycosides. Application of this methodology to the synthesis of naturally occurring bioactive molecules bearing 2-deoxy-sugar subunits is currently underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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