Oligosaccharides

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Direct and Stereoselective Synthesis of β-Linked 2,6-Deoxyoligosaccharides**

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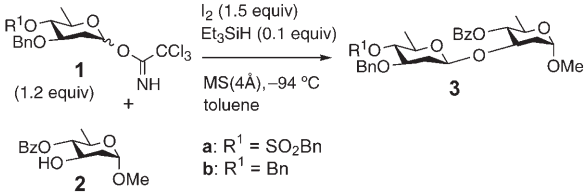
2,6-Di- and 2,3,6-trideoxysaccharides are key components of many biologically active natural products[1] and are difficult and challenging synthetic targets.[2] The absence of electron-withdrawing substituents on the saccharide units readily promotes the anomerization of β-glycosides to more than two anomeric isomers under acidic glycosylation conditions. Furthermore, the non-availability of neighboring-group participation from substituents at C2 and the enhanced conformational flexibility derived from the reduced number of substituents make it difficult to achieve glycosidation in a stereoselective manner.

Indirect methods involving the use of glycosyl donors and acceptors to which stereodirecting and electron-withdrawing substituents, such as halides and sulfides, are attached at the C2 position, have been developed to overcome these problems.[3] The substituents at C2 promote stereoselective glycosidation through an anchimetric effect and prevent the generated glycosidic linkages from anomerization under the acidic glycosidation conditions. On the other hand, several methods are available for direct β-selective glycosylations, in which α-glycosyl halides[4] and glycosyl phosphites[5] are used as glycosyl donors. However, the synthesis of β-linked 2,6-di- or 2,3,6-trideoxyoligosaccharides by direct and stereoselective glycosidation continues to be difficult to accomplish.[6] Herein, we describe a direct β-selective glycosidation based on the oxidative activation of glycosyl imidates and report its application to the synthesis of β-linked 2-deoxyoligosaccharides.

Our approach to the direct β-selective glycosidation of 2-deoxylglycosides was based on the oxidative activation of glycosyl imidates with I_2.[7] As illustrated in Table 1, the treatment of 1.2 equivalents of the 4-*O*-benzylsulfonylolivosyl imidates[8–10] **1a** with acceptor **2** in the presence of I_2 (1.5 equiv) and triethylsilane (0.1 equiv)[11] at −94 °C for 1.5 h provided the β-linked 2-deoxyglycoside **3a** in 94% yield and with excellent β selectivity (β/α > 95:5, Table 1, entry 1). The triethylsilane was oxidized in situ with I_2 to triethylsilyl iodide, which served to accelerate the oxidation of the imidates with I_2. A catalytic amount of TMSI (TMS = trimethylsilyl) and HI generated from Et_3SiH (0.1 equiv) and I_2 (0.1 equiv) did not lead to the glycosidation of imidate **1a** (Table 1, entry 3). These results indicate that the oxidative activation conditions would be effective for the β-selective glycosidation of 2-deoxyglycosyl imidates without causing any anomerization of the generated β-glycosides. Protection of the hydroxy group at C4 with an electron-withdrawing benzylsulfonate group was effective for improving the β selectivity.[12]

Table 1: β-Selective glycosidation of the 2,6-dideoxyglycosyl imidates **1** by oxidative activation with I_2.



Entry	Donor	Product	Additive	Yield [%]	β/α[a]
1	**1a**	**3a**	Et_3SiH	94	>95:5
2[b]	**1a**	**3a**	–	91	91:9
3[c]	**1a**	**3a**	Et_3SiH	8	>95:5
4	**1b**	**3b**	Et_3SiH	85	81:19

[a] Ratio estimated from ^1H NMR spectral data. [b] The reaction was conducted at −60 °C for 12 h. [c] Glycosidation initiated with 0.1 equiv of I_2 and 0.1 equiv of Et_3SiH. Bn = benzyl, Bz = benzoyl, MS = molecular sieves.

To demonstrate the feasibility of the method, β-linked deoxyglycosides composed of various 2,6-dideoxy- and 2,3,6-trideoxyglycosides were synthesized (Table 2). The glycosylation of the C6 primary alcohol of glucoside **7** as well as the C4 hydroxyl group of olivoside **8** and amicetoside **9** with **1a** under the established conditions provided the corresponding β-glycosides **11, 12**, and **13** in excellent yields and with excellent β selectivity (Table 2, entries 1–3). It should be noted that the α-linked 2,3,6-trideoxyglycoside did not decompose under the reaction conditions employed. The glycosylation of **7** and **8** with the dibenzyl-protected donor **1b** resulted in reduced β selectivity (Table 2, entries 2 and 4). We next examined the glycosidation of digitoxoside **4** and olioside **5** (Table 2, entries 6–8). The glycosylation of **2** with the 3,4-di-*O*-benzoyl-protected digitoxosyl imidate **4** provided β-glycoside **16** in 90% yield and with excellent selectivity (β/α > 95:5). Neighboring group participation by the axially oriented benzoyl group at C3 assisted in the β-selective glycosidation.[13] However, the axially oriented C4 hydroxy group on the glycosyl donor makes β-selective glycosidation

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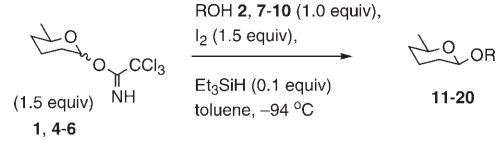
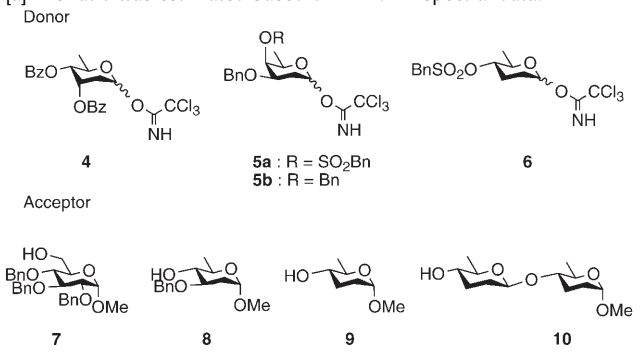
Table 2: β-Selective glycosidation of various 2,6-di- and 2,3,6-trideoxyglycosyl imidates **1** and **4**–**6** by oxidative activation with I_2.



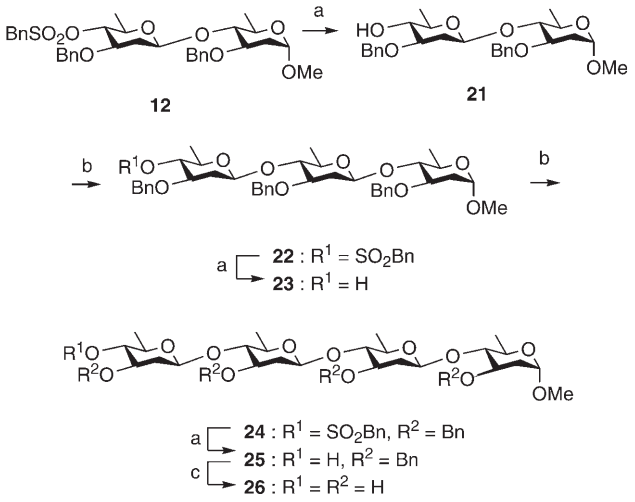
Entry	Donor	Acceptor	Product	Yield [%]	β/α[a]
1	**1a**	**7**	**11**	98	>95:5
2	**1b**	**7**	**12**	97	85:15
3	**1a**	**8**	**13**	91	>95:5
4	**1b**	**8**	**14**	92	80:20
5	**1a**	**9**	**15**	91	>95:5
6	**4**	**2**	**16**	90	>95:5
7	**5a**	**2**	**17a**	80	80:20
8	**5b**	**2**	**17b**	54	29:71
9	**6**	**2**	**18**	95	67:33
10	**6**	**9**	**19**	75	69:31
11	**6**	**10**	**20**	57	60:40

[a] The ratio was estimated based on ^{1}H NMR spectral data.



difficult, since it facilitates anomerization and could block the addition of alcohols from the β face. Treatment of the 4-*O*-benzylsulfonyl-protected imidate **5a** and acceptor **2** with I_2 and a catalytic amount of Et_3SiH provided β-glycoside **17a** in 80% yield and with good selectivity (β/α 80:20). The benzyl-protected olioside **5b** underwent α-selective glycosidation under the same reaction conditions to provide **17b**. These results indicate that protection of the C4 hydroxy group with the electron-withdrawing protecting group enabled β-selective glycosidation of the oliosides. We next examined the glycosidation of 2,3,6-trideoxyglycoside **6**, the most acid-labile saccharide unit of deoxyoligosaccharides. (Table 2, entries 9–11). Treatment of the amicetoxyl imidate **6** and the olivosyl acceptor **2** under the established conditions provided β-linked disaccharide **18** in 95% yield and with a β/α ratio of 67:33. Glycosylation of the di- and mono-amicetosides **9** and **10** with **6** afforded the β(1→4)-linked di- and triamicetosides **19** and **20**, respectively, in good yields and moderate selectivity. Although the β selectivity of the glycosidation of amicetoxide was not excellent, the preinstalled β-glycosidic linkage on **10** underwent neither anomerization nor cleavage during the glycosylation reaction. Furthermore, to the best of our knowledge, this is the first example of a direct and stereoselective synthesis of β-linked oligo-2,3,6-trideoxy-β-glycosides.

To demonstrate the applicability of the method to the synthesis of deoxyoligosaccharides we prepared the β(1→4)-



Scheme 1. Synthesis of β-(1→4)-tetraolivoside **26**. Reagents and conditions: a) $NaNH_2$, DMF, microwaves, 84% for **21**, 76% for **23**, 68% for **25**; b) **1a** (1.5 equiv), I_2, Et_3SiH, toluene, −94 °C, 93%, β/α 93:7 for **22**, 80%, β/α 93:7 for **24**; c) H_2 (1 atm), $Pd(OH)_2$, EtOAc/MeOH (1:1), 72%.

tetraolivose **26** from **12** (Scheme 1). Treatment of disaccharide **12** with sodium amide[14] under microwave irradiation provided acceptor **21** in 84% yield. The use of microwave irradiation shortened the reaction time required for the deprotection. The glycosylation of diolivoside **21** with donor **1a** provided the β-linked triolivoside **22** in 93% yield (β/α 93:7). Removal of the benzylsulfonyl group on **22** afforded the glycosyl acceptor **23** in 76% yield. The glycosylation of **23** with **1a** provided β-linked deoxytetrasaccharide **24** in acceptable yield and selectivity (80%, β/α 93:7). Removal of the benzylsulfonyl group of **24**, followed by hydrogenolysis of **25**, provided β-linked tetraolivoside **26** in 50% yield over the two steps.

In conclusion, we have described the direct and stereoselective synthesis of β-linked 2-deoxyoligosaccahrides by the oxidative activation of glycosyl imidates. The glycosidation of 2-deoxyglycosyl imidates with I_2 and a catalytic amount of triethylsilane in toluene proceeds smoothly to provide the corresponding β-linked 2-deoxyglycosides in excellent yields and selectivity. This coupling method is adaptable to the synthesis of various β-linked oligosaccharides composed of 2,6-dideoxy- and 2,3,6-trideoxyglycosides. The synthesis of deoxyoligosacharide libraries by using the glycosidation method is currently in progress.

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