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Direct and Stereoselective Synthesis of α-Linked 2-Deoxyglycosides

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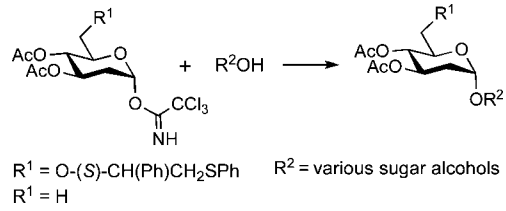
ABSTRACT



α-Linked 2-deoxyglycosides were conveniently obtained by employing a glycosyl donor having a participating (*S*)-(phenylthiomethyl)benzyl moiety at C-6, whereas 2,6-dideoxy-α-glycosides could be prepared by BF_3·Et_2O-promoted activation of allyl glycosyl donors.

Many medically important natural products are modified by oligosaccharides composed of 2-deoxysugars, and examples of such compounds include antibiotics such as erythromycin, antiparasite agents such as amphotericin, insecticides such as the avermectins, and anticancer drugs such as doxorubicin.[1−4] The sugar moiety of these compounds can wield a remarkable influence on pharmacological and pharmacokinetic properties and can dictate the molecular recognition at the drug target site. Not surprisingly, considerable efforts are directed at the development of tools that make it possible to diversify natural product glycosylation.[5−7] This approach, which has been coined glycodiversification or glycorandomization, can be achieved by metabolic, enzymatic, and chemical means.[8−14]

The stereochemical introduction of 2-deoxyglycosides is a key step in chemical glycodiversification and has mainly been achieved by indirect methods that employ a participating functionality as C-2 of a glycosyl donor such as halides and aryl selenyl and sulfenyl derivatives.[15−18] The drawback of this approach is that the introduction and removal of the participating functionality requires additional steps that need to be performed in a stereoselective manner, often leading

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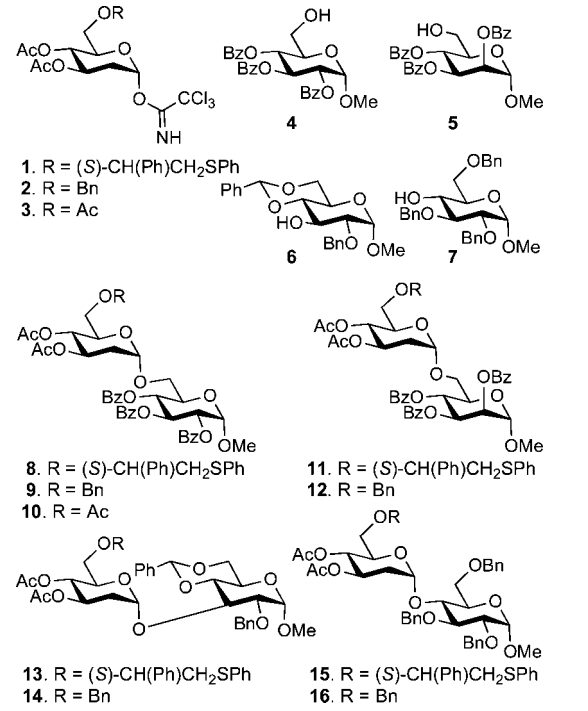
to time-consuming synthetic procedures. On the other hand, several methods are available for direct β-selective glycosylation in which α-glycosyl halides, glycosyl phosphites, and trichloroacetimidates are employed as glycosyl donors in combination with a mild promoter.[19−24] α-Glycosides of 2-deoxysaccharides have been obtained in moderate yield by acid-catalyzed activation of glycals, anomeric esters, and silyl ethers.[25−28] Furthermore, diastereoselective Pd-promoted glycosylations followed by reduction of a 2,3-double bond of the resulting compound has been employed to prepare unnatural 2,3-dideoxyglycosides.[29,30] Reasonable anomeric selectivities have also been achieved by remote assistance of a *p*-methoxybenzoyl ester at C-3 of a glycosyl donor. Remote particpiation has also been implicated in the stereoselective introduction of α-galactosides, α-glucosides, and β-mannosides.[31−37]

Recently, we demonstrated that glycosylations with glycosyl donors modified at C-2 with a (*S*)-(phenylthiomethyl)benzyl moiety give exclusively α-anomeric selectivity due to neighboring group participation resulting in an intermediate *trans*-fused 1,2-sulfonium ion.[38−40] We were curious to explore whether remote participation by a (*S*)-(phenylthiomethyl)benzyl moiety can be exploited in the stereochemical synthesis of 2-deoxyglycosides. Thus, trichloroacetimidates **1**−**3** were prepared that have either a (*S*)-(phenylthiomethyl)benzyl, a benzyl ether, or an acetyl ester at C-6 (Table 1). Interestingly, a TMSOTf-mediated glycosylation of donor **1** with glycosyl acceptor **4** gave the expected disaccharide **8** in good yield as almost exclusively the α-anomer. Similar glycosylations employing glycosyl donors **2** and **3**, having a benzyl ether or acetyl ester at C-6, provided the disaccharides **9** and **10**, respectively, as mixtures of anomers. The use of (*R*)-(phenylthiomethyl)benzyl ether at C-6 of the glycosyl donor also led to excellent anomeric selectivity indicating that the chirality of the auxiliary did not influence the anomeric outcome of the glycosylation. We were unable to identify the intermediate sulfonium ion by NMR experiments in which **1** was activated with TMSOTf probably due to the high reactivity of the intermediate. However, glycosylations of **1** with **5**−**7** led to the isolation of the corresponding disaccharides **11**, **13**, and **15** in excellent yields with almost exclusively α-anomeric selectivity. The alternative use of benzylated derivative **2** gave the disaccharides **12**, **14**,and **16** as mixtures of anomers. Glycosylations of **2** and **3** promoted by $BF_3{\cdot}Et_2O$ did not lead to an improvement of anomeric selectivity. Thus, it appears that a (phenylthiomethyl)benzyl ether at C-6 promotes high α-selectivity.

Next, attention was focused on anomeric control by employing a glycosyl donor that has a (*S*)-(phenylthiometh-

Table 1. Glycosylations with Trichloroacetimidate Donors **1**−**3**[a]



donor	acceptor	product	yield (%)	α/β
1	**4**	**8**	94	15:1
1	**5**	**11**	93	12:1
1	**6**	**13**	95	10:1
1	**7**	**15**	92	8:1
2	**4**	**9**	96	1:1
2	**5**	**12**	95	1:1
2	**6**	**14**	92	5:1
2	**7**	**16**	93	4:1
3	**4**	**10**	90	4:1

[a] All reactions were performed at −78 °C in DCM.

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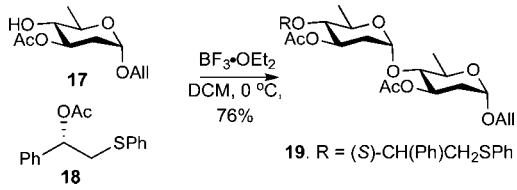
yl)benzyl ether at C-4. Surprisingly, an attempt to introduce the auxiliary at C-4 by treatment of sugar alcohol **17** with (*S*)-(phenylthiomethyl)benzyl acetate **18** in the presence of BF_3•Et_2O led to the formation of disaccharide **19** (Scheme 1). Thus, unexpected activation of the allyl glycoside of **17**

Scheme 1. Direct Activation of a 2,6-Dideoxy Allyl Glycoside

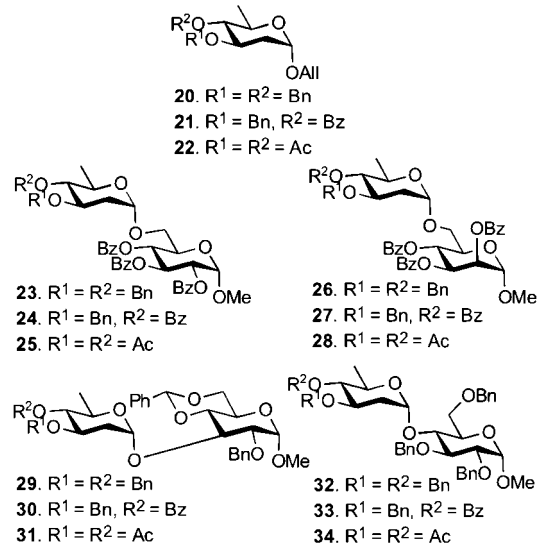


led to self-condensation. However, the allyl glycoside of disaccharide **19** did not undergo further activation indicating that **17** (or its auxiliary modified counterpart) is more reactive than **19**.

Allyl glycosides are attractive building blocks in glycoside chemistry because the allyl moiety provides convenient protection of the anomeric center but can easily be removed by isomerization to a vinyl glycoside, which can be hydrolyzed under mild conditions to give a lactol. The latter compound can be converted into various glycosyl donors such as trichloroacetimidates, phosphites, and halides. The intermediate vinyl glycoside can also directly be employed as a glycosyl donor in TMSOTf-promoted glycosylations.[41,42]

We envisaged that allyl 2-deoxyglycosides would be interesting building blocks for oligosaccharide assembly because the results presented here indicate that these compounds can be employed in direct glycosylations using BF_3•Et_2O as the promoter or converted into various conventional glycosyl donors using standard procedures. To explore the direct glycosylation of allyl 2-deoxyglycosides in more detail, compounds **20**, **21**, and **22**, which have either benzyl ether or ester at C-3 and C-4, were employed in BF_3•Et_2O-mediated glycosylations with glycosyl acceptors **4**−**7** to give the corresponding disaccharides **23**−**34** (Table 2). Interestingly, the highly activated glycosyl donor **20** having benzyl ethers at C-3 and C-4 could be activated at −78 °C to provide the expected disaccharides **23**, **26**, **29**, and **32** in excellent yields (Table 2). The somewhat less reactive glycosyl donor **21**, having a benzoyl ester C-4, required a temperature of −30 °C for activation, whereas the least reactive derivative **22** was only reactive at 0 °C. Importantly, each glycosylation resulted in the formation of the expected disaccharide (**23**−**34**) as mainly the α-anomer. Thus, these results indicated that the high α-anomeric selectivity observed in the formation of disaccharide **19** is not due to participation by the C-4 (*S*)-(phenylthiomethyl)benzyl ether but probably a result of the BF_3•Et_2O-promoted activation of the allyl glycoside. Furthermore, it was observed that the corresponding methyl glycosides of **20**−**22** were less reactive than allyl glycosides because higher reaction temperatures and a larger excess of BF_3•Et_2O (4 equiv) was required for activation. The use of catalytic TMSOTf as the promotor to activate **20**−**22** led to good anomeric selectivities; however, the yields were significantly lower compared to BF_3•Et_2O-promoted glycosylations.

Table 2. Glycosylations with Allyl Glycosyl Donors **20**−**22**[a]



donor	acceptor	T (°C)	product	yield (%)	α/β
20	**4**	−78	**23**	85	8:1
20	**5**	−78	**26**	80	5:1
20	**6**	−78	**29**	68	7:1
20	**7**	−78	**32**	62	5:1
21	**4**	−30−0	**24**	83	10:1
21	**5**	−30−0	**27**	82	8:1
21	**6**	−30−0	**30**	68	11:1
21	**7**	−30−0	**33**	65	10:1
22	**4**	0 to rt	**25**	85	14:1
22	**5**	0 to rt	**28**	82	13:1
22	**6**	0 to rt	**31**	73	15:1
22	**7**	0 to rt	**34**	72	10:1

[a] All reactions were performed in DCM.

Attempts were also made to introduce β-glycosides by treatment of compounds **20**−**22** with TMSI or TMSBr to form the intermediate halides, which can then be displaced by a sugar alcohol to form β-glycosides.[24] However, these attempts led to formation of disaccharides in good yields but with poor anomeric selectivities (see the Supporting Information).

Finally, the direct activation of allyl 2-deoxyglycosides was employed in an armed−disarmed strategy to synthesize more complex compounds.[43−45] Thus, it was envisaged that benzylated 2,6-dideoxyglycoside **20** would be more reactive

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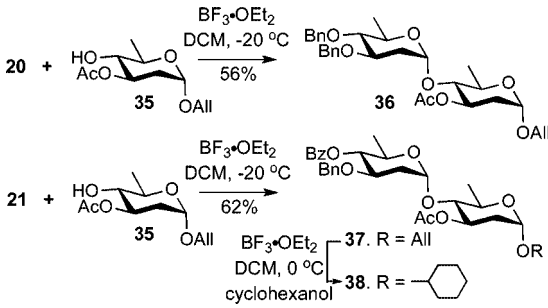
than compound **35**, which has a deactivating acetyl ester at C-3. Indeed, a BF_3•Et_2O-mediated glycosylation of **20** with **35** in DCM at −20 °C gave clean formation of disaccharide **36**, which was isolated in a yield of 56% (α/β = 6/1) and led to the recovery of a small amount of starting materials (Scheme 2). However, further activation of allyl glycoside

Scheme 2. Armed−Disarmed Glycosylation Strategy



36 at a higher reaction temperature led to decomposition of the disaccharide. It is possible to convert the allyl glycoside of the latter compound into another leaving group for conventional glycosylation. We aimed, however, to minimize manipulations during oligosaccharide assembly, and therefore, the less reactive glycosyl donor **21** was employed in a coupling with glycosyl acceptor **35** and in this case disaccharide **37** was obtained in a yield of 62% (α/β = 8/1). The successful formation of this compound indicates that the benzoyl ester at C-4 of **21** is less deactivating than the acetyl ester at C-3 of **35**. Fortunately, the allyl glycoside of **37** could be activated with BF_3•Et_2O at 0 °C, and coupling with cyclohexanol, which was used as a mimic of the aglycon of compounds such as avermectin B_{1a}, gave disaccharide **38** as mainly the α-anomer.

In conclusion, it has been demonstrated that 2-deoxyglycosyl donors having a (*S*)-(phenylthiomethyl)benzyl moiety at C-6 can be employed for the chemical synthesis of α-linked glycosides. In addition, it was found that allyl 2,6-dideoxyglycosides could easily be activated with BF_3•Et_2O and couplings with a variety of sugar alcohol provided mainly α-glycosides. It is to be expected that the methodology will be attractive for glycorandomization of medically important natural products.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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