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THE USE OF 2,6-ANHYDRO-2-THIO SUGAR FOR A HIGHLY STEREOCONTROLLED GLYCOSYLATION: A NOVEL STRATEGY FOR SYNTHESIS OF 2,6-DIDEOXY-α-GLYCOSIDES

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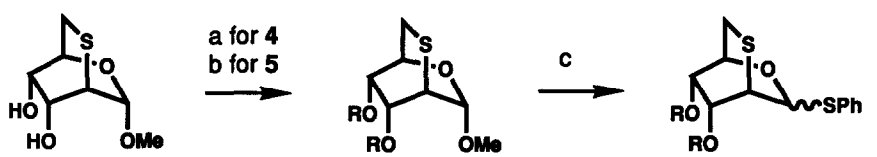
Summary: A novel and efficient synthesis of 2,6-dideoxy-α-glycosides was developed by use of phenyl 2,6-anhydro-1,2-dithio-D-altropyranosides as glycosyl donors in a highly stereocontrolled glycosylation.

Highly stereocontrolled synthesis of 2,6-dideoxy glycosides is of considerable interest from points of view of carbohydrate chemistry and natural products synthesis. Many biologically important organic compounds contain 2,6-dideoxy sugars[1] as significant functions in appearance of biological activity and, recently, a novel 2,6-dideoxy sugar was found in new attractive antitumor antibiotics, esperamicin[2] and calichemicin[3]. In this article, we would like to report the novel synthesis of 2,6-dideoxy-α-glycosides having 1,3-diaxial groups by use of phenyl 2,6-anhydro-1,2-dithio-glycosides (**1** and **2**) as glycosyl donors to illustrate a highly stereocontrolled glycosylation[4].

We designed the activated glycosyl donors **1** and **2** which had a very rigid structure of the 2,6-anhydro-2-thio bridge and could be good precursors of 2,6-dideoxy glycosides. Phenyl thioglycosides **1**[5, 6] and **2**[5, 6] were synthesized from **3**[7, 8], which was readily prepared from methyl α-D-glucopyranoside, in good overall yields as shown in Scheme I. The anomeric mixture of **1** and the β-anomer of **2**[9] were used for the following glycosylations according to Nicolaou's glycosylation method[5, 10].



3

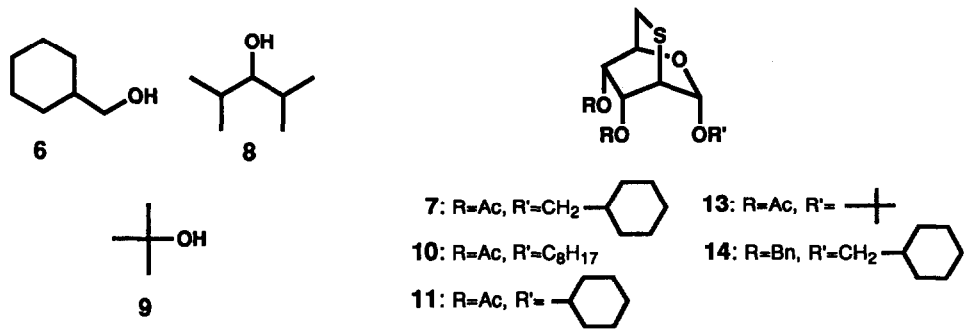
4: R=Ac (91%)
5: R=Bn (94%)

1: R=Ac (90%)
2: R=Bn (81%)

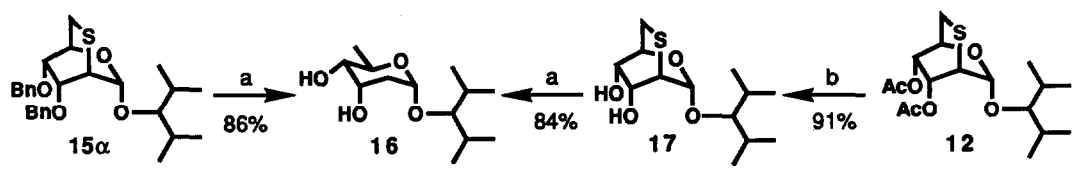
Scheme I. Preparation of phenyl 2,6-anhydro-1,2-dithio-glycosides **1** and **2**.
(a) Ac_2O, cat. 4-DMAP, Py, 26°C, 15min; (b) 2.2 equiv BnBr, 2.6 equiv NaH, DMF, 26°C, 75min; (c) 5 equiv Me_3SiSPh, 1.2 equiv TMSOTf, CH_2Cl_2, 0°C, 30min. [5]

First, we examined the glycosylation of **1** by using cyclohexylmethanol (**6**) as the glycosyl acceptor in several solvents. The results (entries 1~6) in Table 1 showed some excellent feature of

the present glycosylation. These reactions proceeded very rapidly (within 30 min) even at low temperature (-25°C) to give the glycoside 7[6] in excellent yields (>90%) and the selectivities of the glycosylations were quite α-specific in all cases. Remarkably, the stereoselectivity of the glycosylation was completely independent on both solvent effect and the stereochemistry of anomeric center of phenyl thioglycoside **1**. Further, we examined the glycosylation of **1** with several alcohols. The results (entries 7~10) in Table 1 showed some additional efficiencies of our method. Even hindered 2,4-dimethyl-3-pentanol (**8**) and *t*-butanol (**9**) were smoothly glycosylated with high stereocontrol in excellent yields. Our next attention was turned to the effect of protecting groups of **1** in selectivity of glycosylation. Results of the glycosylation of **2** having the bulky protecting groups in CH_2Cl_2 at two different temperatures are summarized as entries 11~14. Only in the glycosylation of a hindered secondary alcohol **8** at higher temperature, surprisingly, the selectivity was dramatically changed and the β-glycoside was obtained in excellent yield (entry 13), although the reaction at lower temperature gave exclusively the α-glycoside (entry 14).



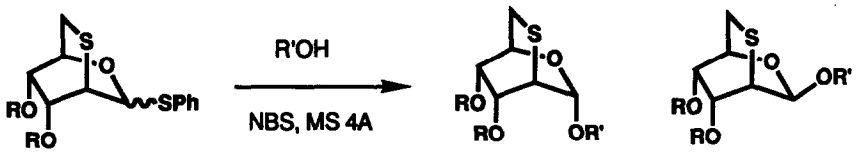
To accomplish the synthesis of 2,6-dideoxy glycosides, the 2,6-anhydro-2-thio system in glycosides was converted into the desired 2,6-dideoxy system which was often found in natural products. For example, di-O-benzyl glycoside 15α[6] was desulfurized with de-O-benzylation by hydrogenolysis in the presence of Raney-Ni (W4) at 40°C to afford the 2,6-dideoxy-α-glycoside 16[6] in 86% yield. On the other hand, di-O-acetyl glycoside 12[6] was deacetylated to 17[6], followed by desulfurization to give **16** in 76% overall yield (Sheme II).



Scheme II. Synthesis of 2,6-dideoxy-α-glycoside.
(a) H_2, Raney-Ni (W4), EtOH-dioxane (3:1), 40°C, 0.5h; (b) NaOMe, MeOH, 26°C, 0.5h.

In conclusion, we developed a novel strategy for the highly stereocontrolled synthesis of 2, 6-dideoxy-α-glycosides by use of 2,6-anhydro-2-thio sugar as an efficient glycosyl donor.

Table 1. Glycosylations of **1** or **2** with several alcohols.[a)]



1: R=Ac
2: R=Bn

Entry	Sugar	Alcohol	Solvent	Temp.	Time	Product[6)]	Yield (%)[b)]	α/β[c)]
1	**1**	**6**	CH_2Cl_2	-25°C	15min	**7**	94	α
2	**1**	**6**	$(CH_2Cl)_2$	-25°C	15min	**7**	92	α
3	**1**	**6**	Et_2O	-25°C	30min	**7**	96	α
4	**1**	**6**	THF	-25°C	15min	**7**	98	α
5	**1**	**6**	CH_3CN	-25°C	15min	**7**	97	α
6	**1**	**6**	PhMe	-25°C	30min	**7**	92	α
7	**1**	$C_8H_{17}OH$	CH_3CN	-40°C	15min	**10**	91	α
8	**1**	*c*-$C_6H_{11}OH$	CH_3CN	-40°C	10min	**11**	92	α
9	**1**	**8**	CH_3CN	-40°C	10min	**12**	96	97/3
10	**1**	**9**	CH_3CN	-40°C	10min	**13**	92	83/17
11	**2**	**6**	CH_2Cl_2	-10°C	10min	**14**	90	α
12	**2**	**6**	CH_2Cl_2	-40°C	10min	**14**	99	α
13	**2**	**8**	CH_2Cl_2	-10°C	10min	**15β**	90	β
14	**2**	**8**	CH_2Cl_2	-40°C	10min	**15α**	92	α

a) All reactions were carried out by use of 2.0 equiv. of alcohol and 1.1equiv. of NBS to the glycosyl donor.

b) Isolated yields after purification by column chromatography.

c) α:β Ratios were determined by ^{1}H-NMR spectroscopy[11)] and /or isolation of pure isomers.

Mechanistic studies of this reaction and application of this method to the synthesis of other types of 2, 6-dideoxy glycosides and the relating natural products are now in progress.

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6) All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means. Significant ^{1}H-NMR(270MHz, $CDCl_3$) spectra [δ (TMS), J(Hz)] are the following. **1**: 2.09 (4/23H, s, OAc(β)), 2.11 (4/23H, s, OAc(β)), 2.17 (19/23H, s, OAc(α)), 2.20 (19/23H, s, OAc(α)), 2.80 (4/23H, dd, J=12.0 and 3.0, H-6(β)), 2.83 (19/23H, dd, J=12.0 and 2.8, H-6(α)), 3.25 (19/23H, dd, J=12.0 and 3.0, H-6'(α)), 3.25-3.3 (4/23H, m, H-2(β)), 3.34 (19/23H, d, J=3.7, H-2(α)), 3.68 (4/23H, dd, J=12.0 and 2.6, H-6'(β)), 4.33 (4/23H, dd, J=3.0 and 2.6, H-5(β)), 4.41 (19/23H, ddd, J=3.0, 2.8 and 0.4, H-5(α)), 5.09 (19/23H, dd, J=8.2 and 0.4, H-4(α)), 5.14 (4/23H, d, J=8.2, H-4(β)), 5.52 (19/23H, ddd, J=8.2, 3.7 and 1.0, H-3(α)), 5.58 (4/23H, dd, J=8.2 and 4.0, H-3(β)), 5.70 (19/23H, br s, H-1(α)), 5.82 (4/23H, d, J=3.4, H-1(β)); **2**: 2.57 (1H, dd, J=11.8 and 2.8, H-6), 3.17 (1H, dd, J=3.6 and 4.1, H-2), 3.59 (1H, dd, J=11.8 and 2.4, H-6'), 3.84 (1H, d, J=7.9, H-4), 4.21 (1H, dd, J=7.9 and 4.1, H-3), 4.36 (1H, dd, J=2.8 and 2.4, H-5), 4.57 and 4.70 (each 1H, ABq, J=12.0), 4.68 and 4.72 (each 1H, ABq, J=12.2), 6.04 (1H, d, J=3.6, H-1), 7.2-7.6 (15H, m); **7**: 0.9-1.1 (2H, m), 1.1-1.35 (3H, m), 1.5-1.9 (6H, m), 2.03 (3H, s, OAc), 2.12 (3H, s, OAc), 2.70 (1H, dd, J=12.0 and 2.0, H-6), 3.06 (1H, dd, J=2.6 and 1.2, H-2), 3.08 (1H, dd, J=12.0 and 4.0, H-6'), 3.21 (1H, dd, J=8.6 and 6.0), 3.63 (1H, dd, J=8.6 and 6.0), 4.38 (1H, ddd, J=4.0, 2.0 and 1.6, H-5), 5.02 (1H, dd, J=8.2 and 1.6, H-4), 5.21 (1H, dd, J=1.2 and 1.2, H-1), 5.30 (1H, ddd, J=8.2, 2.6 and 1.2, H-3); **16**: 1.31 (1H, d, J=6.2, H-6), 2.48 (1H, br d, J=10.4, OH), 3.62 (1H, d, J=10.2, OH), 4.92 (1H, dd, J=3.6 and 1.4, H-1).
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9) Only β-isomer was obtained.
10) In original paper, the reaction by using NBS as an activator in the presence of MS 4A was carried out in CH_2Cl_2 or CH_3CN at 25°C and selectivity of the glycosylation was dependent on solvent with low stereocontrol. See ref. 5.
11) ^{1}H-NMR spectroscopies of all α-isomers showed W-coupling between H-1 and H-3.

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