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Unusual Regioselective Glycosylation of Sugar Secondary Trityloxy Function in the Presence of Primary One

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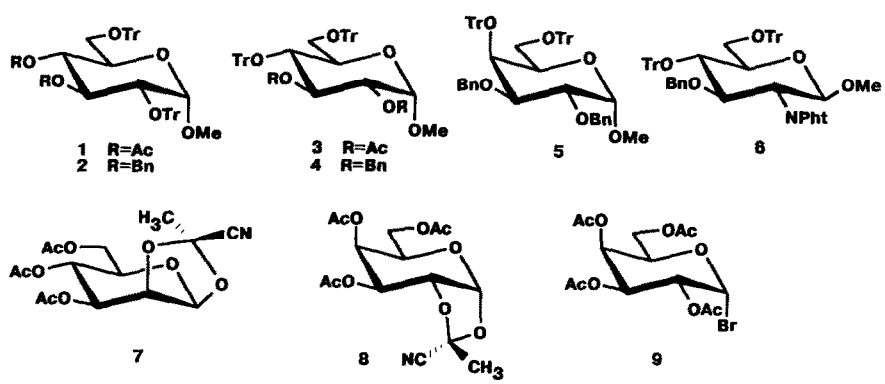
Abstract: Primary-secondary sugar ditrityl ethers are selectively glycosylated at the secondary position

The primary hydroxyl group of sugars is known to exhibit higher reactivity in glycosylation reaction than the secondary one.[1] This enables to prepare oligosaccharides containing 1-6-glycosidic bond by regioselective glycosylation of the corresponding primary-secondary diols

The reactivity of trityl ethers, which serve as glycosyl acceptors in trityl-cyanoethylidene condensation[2] and Bredereck glycosylation,[3] has not been studied until now. Recently, in the framework of investigations of the mechanism of trityl-cyanoethylidene condensation we have studied the relative reactivity of a series of primary and secondary sugar trityl ethers Unexpectedly, it was found that, unlike the corresponding alcohols, secondary trityl ethers were essentially more reactive glycosyl acceptors than the primary ones [4] Here we describe an application of this finding for unusual regioselective glycosylation of a secondary trityloxy function in the presence of the primary one exemplified by glycosylation of primary-secondary ditrityl ethers of glucose **1-4**, galactose **5**, and glucosamine **6** with cyanoethylidene derivatives of mannose **7** and galactose **8** under conditions of the trityl-cyanoethylidene reaction, and with acetobromogalactose **9** under the conditions of Bredereck reaction

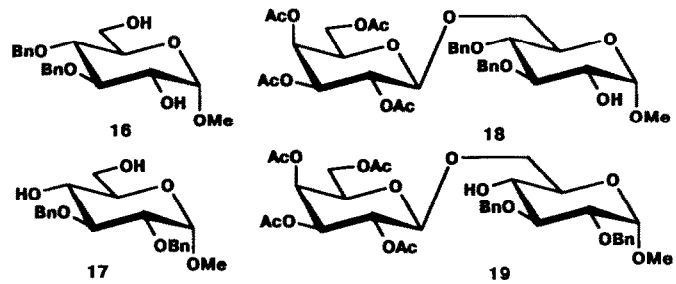


Compounds **1-3** were obtained by acetylation or benzylation of the known 2,6- and 4,6-ditrityl ethers [5]

Derivatives **4-6** were obtained by bistritylation of the respective 4,6-diols with triphenylmethylium perchlorate in the presence of 2,4,6-collidine[6] in nearly quantitative yields. Glycosylation of ditrityl ethers **1-6** was carried out with equimolar amount of glycosyl donors **7-9** in dichloromethane in the presence of 10 mol % of $TrClO_4$ (for **7** and **8**) or equimolar amount of AgOTf (for **9**)

As the result of all glycosylations we obtained 6-O-trityl derivatives of 1-2- and 1-4-linked disaccharides **10-15** in good yields (see Table). The position of glycosidic linkage in **10-15** was proved by ^{1}H-NMR data after detritylation and acetylation This resulted in a shift of H-6 signals from δ 3 1-3 8 ($C\underline{H}_2OTr$) to δ 4.1-4 6 ($C\underline{H}_2OAc$) [7]

For comparison, the diols **16** and **17**, which correspond to the ditrityl ethers **2** and **4**, were glycosylated with the bromide **9** under Helferich conditions (MeCN, $Hg(CN)_2$, $HgBr_2$) As expected, in these cases 1-6-linked disaccharides **18** and **19** were formed, both in 68% yield

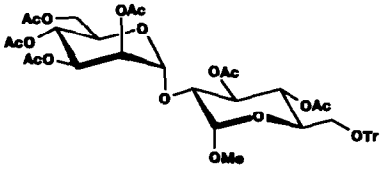
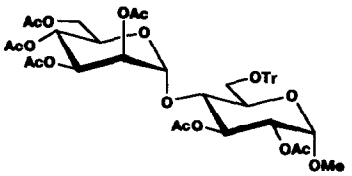
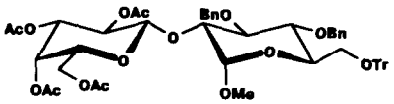
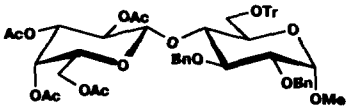
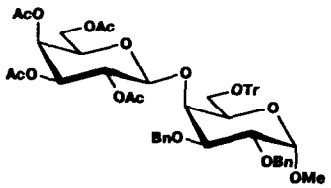
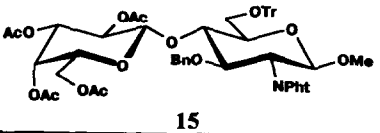


The isomeric 1-6-linked disaccharides were not detected upon the glycosylation of ditrityl ethers **1-6** Even if formed, they are likely not accumulated in the reaction mixture due to subsequent rapid glycosylation of the secondary trityloxy group to give trisaccharides Actually, when the reaction mixture of entry 1 was investigated in detail a product of bis-glycosylation, methyl 2,6-di-O-(α-D-mannopyranosyl)-α-D-glucopyranoside decaacetate was isolated in 12% yield. It should be noted that trisaccharide derivatives possess much lower chromatographic mobilities than the tritylated disaccharides **10-15** so their possible presence in the reaction mixture did not hamper the isolation of the latter

The selectivity of glycosylation of a secondary trityloxy group depends on the nature of the glycosylating monosaccharide and on the type of protective groups adjacent to the trityloxy group in a glycosyl acceptor Indeed, glycosylation of acetylated ditrityl ethers **1** and **3** with mannose cyanoethylidene derivative **7** (entries 1 and 2) gave disaccharides **10** and **11** with high regioselectivity, whereas in the case of the galactose cyanoethylidene derivative **8** regio- and stereoselectivity was achieved only with benzylated compounds **2, 4-6** Glycosylation of the acetylated glycosyl acceptor **1** with **8**, on the contrary, resulted in a complex mixture of 1-2- and 1-6-disaccharides and trisaccharides, 1-2-glycosylation proceeding with formation of both β- and α-anomers Thus, the replacement of acyl protective groups by benzyl groups increased essentially the reactivity of the neighbouring secondary trityloxy group (cf Ref 8) and weakly affected the remote primary one. The use of benzylated glycosyl acceptors allowed us to glycosylate selectively such a low-reactive position as O-4 in *gluco*-series (entries 4 and 7) and even O-4 of galactose (entry 6) Not only cyanoethylidene derivatives can be used as glycosylating agents but also glycosyl bromides under Bredereck conditions (entry 5) that expands considerably the scope of the method

An opposite reactivity of primary and secondary trityl ethers in comparison with the corresponding

Table. Glycosylation of Sugar Ditrityl Ethers

Entry	Donor	Acceptor	Product	Isolated yield(%)
1	7	1	 10	72
2	7	3	 11	53
3	8	2	 12	69
4	8	4	 13	66
5	9	4	13	58
6	8	5	 14	54
7	8	6	 15	84

alcohols could be explained by formation of an earlier transition state (TS) upon glycosylation of trityl ethers than that of alcohols. Then, a distance between C(1) of a glycosyl donor and trityl ether oxygen ought to be essentially longer in this TS than the corresponding distance C(1)–O in TS arising upon glycosylation of alcohols In this case steric factors, which control the selectivity of glycosylation of alcohols, will not dominate and an electronic factor, *i.e.* electron density at oxygen, will become determinant The latter, by analogy with proton affinity of dialkyl ethers,[9] ought to be higher for the secondary trityl ethers and therefore to stabilize "secondary" TS in comparison with the "primary" one.

Disaccharides of the type **10-15** obtained by regioselective glycosylation of secondary trityloxy group are useful precursors for branched oligosaccharides. They can be subjected to subsequent glycosylation at O-6 both directly and after their conversion into the corresponding 6-OH derivatives. This methodology, in our opinion, opens new prospects in the strategy of synthesis of branched oligosaccharides.

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7 *E.g.*, compound **13** ^{1}H-NMR (250 MHz, $CDCl_3$, δ, *J*, Hz) 1 67, 1 96, 2 04, 2 10 (4s, each 3H, 4 OAc), 3.11 (dd, 1H, $J_{6a.5}$ 2.5, $J_{6a,6b}$ 10 3, H-6a), 3 39 (s, 3H, OMe), 3 58 (m, 3H, H-5, 6b, 5'), 3 64 (dd, 1H, $J_{2,1}$ 3.8, $J_{2,3}$ 9 6, H-2), 3 83 (t, 1H, $J_{4,3}$~$J_{4,5}$~9 0, H-4), 4 06 (dd, 1H, $J_{6'a,5'}$ 5.8, $J_{6'a,6'b}$ 11 0, H-6'a), 4.19 (dd, 1H, $J_{6'b,5'}$ 8 6, H-6'b), 4 28 (dd, 1H, H-3), 4 46 (d, 1H, $J_{1',2'}$ 8 1, H-1'), 4.67 (dd, 1H, $J_{3',2'}$ 10 5, $J_{3',4'}$ 3.5, H-3'), 4.75, 4 99 (2d, 2H, *J* 10 2, PhC$\underline{H}_2$), 4 75, 4 90 (2d, 2H, *J* 12 2, PhC$\underline{H}_2$), 4 77 (d, 1H, H-1), 4.97 (dd, 1H, H-2'), 5.25 (dd, 1H, $J_{4',5'}$ 1 0, H-4'), 7 22-7.60 (m, 25H, aromatics). Detritylation of **13** and acetylation gave methyl 6-O-acetyl-2,3-di-O-benzyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside ^{1}H-NMR (δ) 1 96, 1 98, 2 07, 2 09, 2 12 (5s, each 3H, 5 OAc), 3 37 (s, 3H, OMe), 3 49 (dd, 1H, $J_{2,1}$ 3 5, $J_{2,3}$ 9 5, H-2), 3 64 (ddd, 1H, $J_{5',6'a}$ 5 4, $J_{5',6'b}$ 4.6, $J_{5',4'}$ 1 2, H-5'), 3 68 (dd, 1H, $J_{4,3}$ 8.2, $J_{4,5}$ 9 9, H-4), 3 80 (ddd, 1H, $J_{5,6a}$ 5.0, $J_{5,6b}$ 2.1, H-5), 3 82 (dd, 1H, $J_{6'a,6'b}$ 11 0, H-6'a), 3 93 (dd, 1H, H-6'b), 3 95 (dd, 1H, H-3), 4 12 (dd, 1H, $J_{6a,6b}$ 11.8, H-6a), 4 38 (dd, 1H, H-6b), 4 56 (d, 1H, H-1), 4.61, 4 75 (2d, 2H, *J* 12 0, PhC$\underline{H}_2$), 4 70 (d, 1H, $J_{1',2'}$ 7.9, H-1'), 4 92, 4 98 (2d, 2H, *J* 11 2, PhC$\underline{H}_2$), 4 93 (dd, 1H, $J_{3',2'}$ 10 5, $J_{3',4'}$ 3 5, H-3'), 5 19 (dd, 1H, H-2'), 5 29 (dd, 1H, H-4'), 7 25-7 40 (m, 10H, aromatics)

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