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Highly Stereoselective Synthesis of 2-Deoxy-α- glycosides and α-Disaccharides

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Abstract :

Highly stereoselective synthesis of 2-deoxy-α-glycosides including disaccharides is described, using S-(2-deoxyglycosyl)phosphorodithioates as glycosyl donors, in the presence of silver perchlorate in acetonitrile.

Key words: *2-deoxy-α-glycosides and -disaccharides; S-(2-deoxyglycosyl)phosphorodithioates.*

Stereoselective synthesis of 2-deoxyglycosides and oligosaccharides is not easy due to the lack of stereodirecting assistance from the C-2 position of the 2-deoxyglycosyl donor. To overcome this, various strategies have been developed involving modification of the glycosyl donor, choice of activator and protecting groups for glycosyl donors as well as glycosyl acceptors, and generation of steric assistance by glycosyl donors[1-5]. 2-Deoxy-α-glycosides are, in general, more accessible than the β-ones because they are thermodynamically more stable. All the same, there is a demand for an efficient, highly stereoselective synthesis of these derivatives using simple methodology.

We have recently introduced S-(2-deoxyglycosyl)phosphorodithioates which are easily accessible and efficient glycosyl donors [6-8] in the synthesis of O-alkyl and O-nitroaryl 2-deoxy-β-D-glycosides[9-10], N-alkyl (2-deoxy-β-D-*arabino*-hexopyranosyl) amines [11] and 2-deoxy(α,β)disaccharides [12]. We found that they are versatile glycosylating reagents which, depending on the mode of activation, can be used in the synthesis of β as well as α-2-deoxyglycosides.

In this report we describe a highly stereoselective synthesis of 2-deoxy-α-D- and 2-deoxy-α-L-glycosides and disaccharides employing easily accessible S-(2-deoxy-α-D- and α-L-glycosyl)phosphorodithioates as glycosylating reagents. To achieve this goal we carried out meticulous studies to find a suitable thiophilic activator and appropriate solvent. Application of AgF, Ag silicate, Ag zeolite, Ag triflate / collidine, Ag silicate / $ZnCl_2$, Ag carbonate / $ZnCl_2$ and similar systems in variety of solvents led invariably to mixtures of α and β glycosides in very

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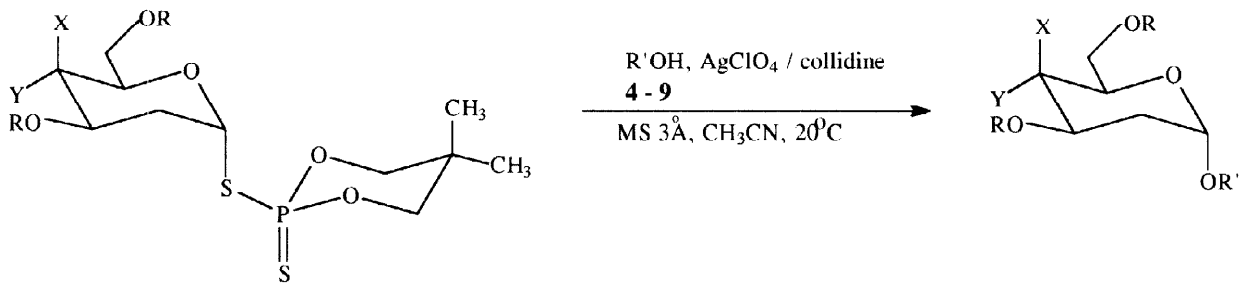
good chemical yield but with low stereoselectivity. But silver perchlorate in acetonitrile and in the presence of sym-collidine secures high yields of 2-deoxy-α-glycosides and α-disaccharides. This is the reagent of choice.

Starting from configurationally pure S-(2-deoxy-α-D-glycosyl)phosphorodithioates **1** and **2** and S-(2-deoxy-α-L-fucosyl)phosphorodithioate **3** [13] the corresponding α-glycosides and α-disaccharides **10-16** were obtained in 80-92% yield of isolated compounds [14] (Scheme 1). ^{13}C NMR analysis of crude reaction mixtures indicated the absence of β-isomers.

Scheme 1



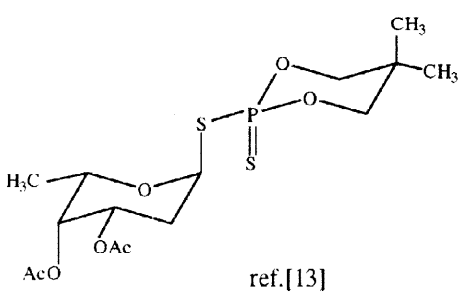
1 - 3 **10 - 16**

Donors

1 : X=H; Y=OBn; R=Bn

2 : X=OAc; Y=H; R=Ac

3 :



ref.[13]

Acceptors

4 n-Octanol

5 n-Hexadecanol

6 Cholesterol

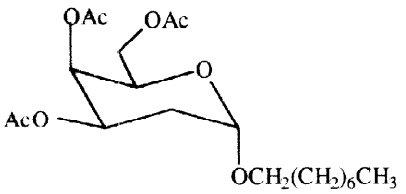
7 2,3;4,5-di-O-isopropylidene-α-D-fructo-pyranose

8 1,2;5,6-di-O-isopropylidene-α-D-gluco-furanose

9 1,2;3,4-di-O-isopropylidene-α-D-galacto-pyranose

The stereochemistry of glycosidation (α-donor→α-glycoside) is, according to Schmidt and Rücker [15] controlled by the formation of nitrilium acetonitrile conjugates as intermediates.These are generated *in situ* in the course of reactions performed with silver perchlorate in acetonitrile; these authors claim on the basis of ^{1}H NMR data and strong IR

Compounds 13 - 16



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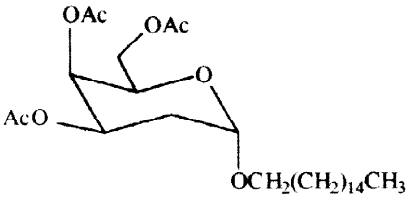

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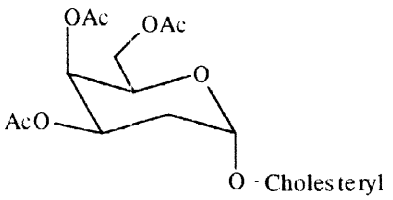

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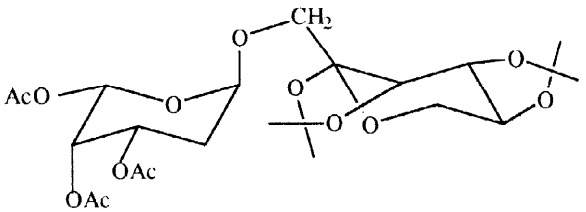

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Selected NMR and physical data of compounds **10-16** are presented in Table 1.

Table 1.**Selected NMR and Physical Data of 2-deoxy-α-glycosides and α-disaccharides**

Entry	Donor	Acceptor	Product	^{1}H NMR[a] (H-1); $J_{1,2ax}$	^{13}C NMR[b] (C-1)	m.p.°C	Yield (%)[c]	$[\alpha]_{578}$ ($CHCl_3$)
1	2	7	10[d]	5.05; 2.7Hz	97.34	syrup	84	+56.8 (1.5)$^{20°C}$
2	1	8	11[d]	5.01; 2.5Hz	97.88	syrup	80	+64.0 (2.0)$^{20°C}$
3	1	9	12[d]	5.02; 2.6Hz	97.06	syrup	82	+49.6 (1.6)$^{20°C}$
4	2	4	13[e]	4.99; 2.7Hz	97.42	syrup	89	+82.0 (1.7)$^{29°C}$
5	2	5	14[e]	4.96; 2.7Hz	97.23	syrup	85	+35.6 (1.2)$^{22°C}$
6	2	6	15[e]	5.13; 5.0Hz	97.27	125-128	92	-36.3 (1.5)$^{25°C}$
7	3 [13]	7	16[e]	5.00; 3.0Hz	97.38	syrup	54	-86.4 (0.8)$^{25°C}$

[a] $CDCl_3$, Bruker AC 200 MHz; [b] $CDCl_3$, Bruker AC 200 MHz operating at 50.32 MHz; [c] Analytically pure compounds; [d] see ref. [12]; [e] new compounds, correct data for elemental analysis.

absorption at 1640 cm^{-1} that the intermediate nitrilium acetonitrile conjugates exist in a β configuration due to a reverse anomeric effect. In consequence, S_N2 displacement by the acceptor leads to α-glycosides and α-disaccharides.

In conclusion, we have achieved a simple, efficient and highly stereoselective synthesis of 2-deoxy-α-glycosides and 2-deoxy-α-disaccharides using easily accessible and stable S-(2-deoxyglycosyl)phosphorodithioates as glycosyl donors. Under the reaction conditions described herein, formation of the β isomers was not observed. Thus, this glycosidation method provides a useful alternative to the hitherto described procedures.

Acknowledgement

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[13] S-(2-deoxy-3,4-di-O-acetyl-α-L-fucosyl)phosphorodithioate (**3**) was obtained by the method described in references [6] and [7] in a 7:1 mixture of α and β phosphorodithioates, respectively. Crystallization from diethyl ether afforded analytically pure α isomer, mp.: 128-130° C, in 55% yield. NMR data for **α isomer** ($CDCl_3$): ^{31}P δ 85.56 ppm; ^1H (H-1) δ 6.22 ppm; (dd, $J_{1,P}$ 10.58 Hz; $J_{1,2a}$ 4.93 Hz; $J_{1,2e} \leq$ 1Hz); ^{13}C (C-1) δ 86.98 ppm; **β isomer**: ^{31}P δ 83.77 ppm.

[14] **Typical procedure for the preparation of 2-deoxy-α-glycosides and α-disaccharides:**
A mixture of S-(2-deoxy-α-D-glycosyl)phosphorodithioate **1-3** (0.25 mmol), glycosyl acceptor **4-9** (0.25 mmol) and molecular sieves 3A was stirred in acetonitrile solution (5 mL). After 30 min collidine (0.25 mmol) and dry $AgClO_4$ (0.25 mmol) were added consecutively and the reaction mixture kept in dark at 20°C until TLC showed no traces of the donor (48 h)[16]. The crystalline colourless precipitate of silver phosphorodithioate and molecular sieves was filtered off (Cellite), the filtrate diluted with chloroform, the organic layer washed successively with water, 5% aq. HCl and water, then dried ($MgSO_4$) and concentrated under reduced pressure.Yield: 80 - 92%. ^{13}C NMR analysis showed that corresponding β anomers were not present at all. In the case of α-L-2-deoxy- fucopyranosyl-(1→1)-D-fructose **16**, the yield of analytically pure compound after column chromatography was 54%.

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[16] The solvent and reagents should be as dry as possible.