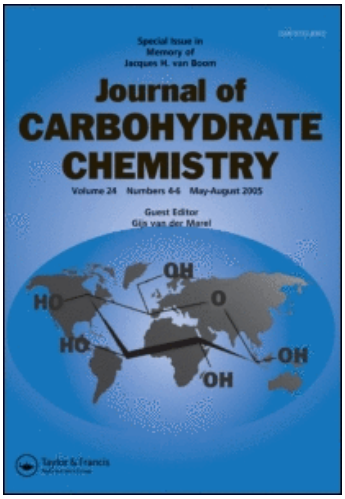

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COMMUNICATION

2-DEOXYGLYCOSYL PHOSPHORODITHIOATES. A NOVEL TYPE OF GLYCOSYL DONOR. EFFICIENT SYNTHESIS OF 2'-DEOXYDISACCHARIDES

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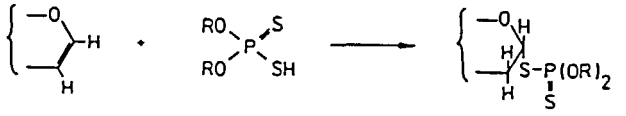
The occurrence of 2'-deoxydisaccharides as structural units of a number of biologically important natural products explains the efforts involved in their synthesis.[1] The majority of the reported procedures is based on addition reactions to glycals leading to 2-deoxyglycosyl donors which can be directly condensed with sugar aglycones yielding 2'-deoxydisaccharides or to glycosylating reagents with a "cryptodeoxy" function, which is removed under mild conditions after the formation of the glycosidic linkage. The main disadvantage of 2-deoxyglycosyl donors such as 2-deoxyglycosyl halides, is their chemical and configurational instability.

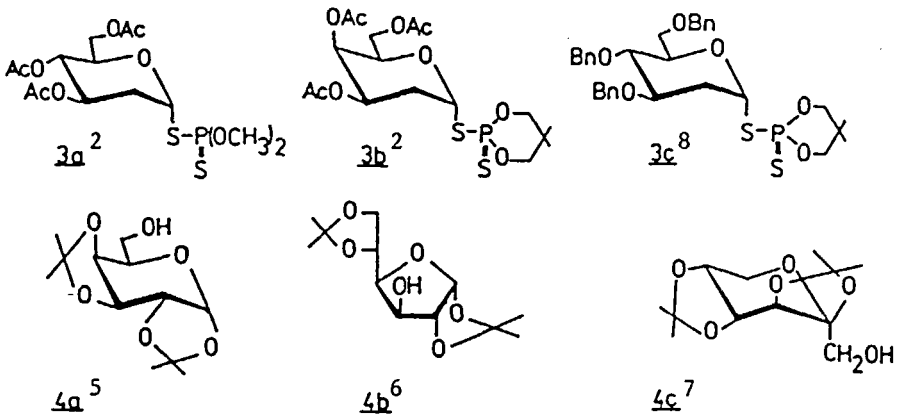
Recently we have discovered that α-2-deoxyglycosyl phosphorodithioates 3, which are readily prepared by highly stereoselective addition of O,O-dialkylphosphorodithioic acids 2 to glycals 1,[2] act as efficient glycosylating reagents. The phosphorodithioates 3 are crystalline compounds and can be stored without decomposition at ambient temperature.



1 2 3

We have employed these compounds in the stereoselective synthesis of alkyl and aryl 2-deoxy-β-D-glycosides[3,4] derived from simple alcohols and phenols, respectively.

We have found that a successful procedure for the glycosylation of more complex alcohols of biological importance requires suitable activating agents. We now describe a simple and efficient synthesis of 2'-deoxydisaccharides 5-13 using reagents 3a-c as glycosyl donors and sugars 4a-c as glycosyl acceptors in the presence of silver fluoride as activator.

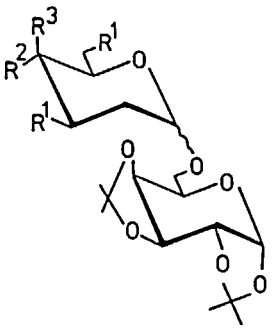


3a[2] 3b[2] 3c[8]

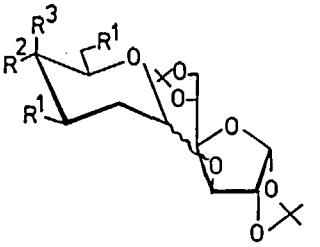
4a[5] 4b[6] 4c[7]

The following 1,1-, 1,3- and 1,6-linked 2'-deoxydisaccharides were obtained as (α,β) mixture from which pure α or β-2'-deoxydisaccharides were isolated by column chromatography on silica gel: 6-O-(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (5α), 3-O-(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-glucopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (6α), 3-O-(3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose

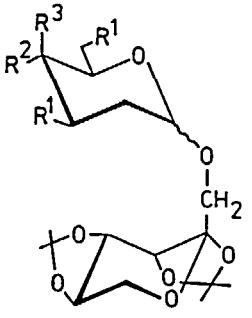
(6β), 1-O-(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-glucopyranosyl)-2,3:4,5-di-O-isopropylidene-α-D-fructopyranose (7α), 6-O-(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (8α), 3-O-(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-galactopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (9α), 1-O-(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-galactopyranosyl)-2,3:4,5-di-O-isopropylidene-α-D-fructopyranose (10α), 6-O-(3',4',6'-tri-O-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (11α), 3-O-(3',4',6'-tri-O-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (12α) and 1-O-(3',4',6'-tri-O-benzyl-2'-deoxy-α-D-glucopyranosyl)-2,3:4,5-di-O-isopropylidene-α-D-fructopyranose (13α).



5 $R^1=R^2=OAc$; $R^3=H$
8 $R^1=R^3=OAc$; $R^2=H$
11 $R^1=R^2=OBn$; $R^3=H$



6 $R^1=R^2=OAc$; $R^3=H$
9 $R^1=R^3=OAc$; $R^2=H$
12 $R^1=R^2=OBn$; $R^3=H$



7 $R^1=R^2=OAc$; $R^3=H$
10 $R^1=R^3=OAc$; $R^2=H$
13 $R^1=R^2=OBn$; $R^3=H$

Bn = $CH_2C_6H_5$
Ac = $COCH_3$

TABLE 1

2'-Deoxydi-saccharide	Donor	Acceptor	Yield[a] %	$[\alpha]_{578}^{20}$ ($CHCl_3$)	mp °C	α/β
5α	3a	4a	40	+25.4 (1.8)	syrup	55/45
6α	3a	4b	65	+73.4 (0.56)	syrup	70/30
6β	3a	4b	25	- 3.7 (1.0)	188-190	70/30
7α	3a	4c	68	+38.5 (1.6)	syrup	71/29
8α	3b	4a	42	+37.6 (1.7)	syrup	55/45
9α	3b	4b	40	+66.9 (1.6)	syrup	52/48
10α	3b	4c	80	+56.8 (1.5)	syrup	92/8
11α	3c	4a	60	+49.6 (1.6)	syrup	87/13
12α	3c	4b	65	+64.0 (2.0)	syrup	90/10
13α	3c	4c	75	+54.7 (2.0)	127-129	100/0

a. Yield of the isolated pure anomer

TABLE 2. Selected NMR data for 2'-deoxydisaccharides 5-13[9]

2'-Deoxy-disaccharide (pure isolated)	$\delta^{13}C$ ($CDCl_3$)		$\delta^{1}H$ ($CDCl_3$)		
	C-1'	C-2'	H-1'[a]	H-2'ax	H-2'eq
5α	97.04	34.93	4.87	2.26	1.82
6α	96.97	34.93	4.95	2.30	1.75
6β	100.25	35.98	4.65	2.34	1.75
7α	96.90	34.86	4.95	2.25	1.76
8α	97.36	30.16	5.05	2.10	1.90
9α	97.30	30.01	5.05	2.12	1.90
10α	97.34	30.01	4.97	2.08	1.88
11α	97.23	35.38	5.02	2.30	1.74
12α	97.70	35.46	4.99	2.28	1.75
13α	97.64	35.31	5.02	2.27	1.72

a. $J_{1',2'ax}$ for α-disaccharides = 2.9-3.3 Hz; $J_{1',2'eq} < 1$ Hz; $J_{1',2'ax}$ for 6β = 10 Hz; $J_{1',2'eq}$ = 3.3 Hz

In a typical experiment equimolar amounts of 3 and 4 are allowed to react in dichloroethane or acetonitrile solution in the presence of 4A molecular sieves and 2.7 moles of silver fluoride.

$$3 + 4 \xrightarrow[\text{dichloroethane}]{\text{AgF}} \underset{(5\text{-}13)}{2'\text{-deoxy}(\alpha,\beta)\text{disaccharides}}$$

The glycosylation is performed at 20-25 °C, with continuous stirring, until the disappearence of the ^{31}P NMR signal corresponding to the starting phosphorodithioate. The required reaction time for the benzylated glycosyl donors usually is 7 days, for those containing acetyl protecting groups, 12 days. Precipitated silver phosphorodithioate and molecular sieves containing absorbed hydrogen fluoride are filtered off and the filtrate is condensed under reduced pressure. Two successive triturations of the syrupy residue with diethyl ether are necessary in order to remove further portions of silver phosphorodithioate. The mixture of anomeric 2'-deoxydisaccharides formed in quantitative total yield is separated by column chromatography on silica gel. Proportions of α- and β-linked 2'-deoxydisaccharides, evaluated by ^{13}C NMR of the crude reaction mixture, and unoptimised yields of the isolated α-isomers are given in Table 1. We were not able to isolate pure β-isomers using the above methodology with the exception of 6 which was isolated by fractional crystallization. It is of interest to note that the benzylated glycosyl donors react relatively faster than those containing acetyl protecting groups, and with higher α selectivity.

In summary, the presented method gives an easy access to α-linked 2'-deoxydisaccharides. Further extensions of this method are in progress.

ACKNOWLEDGMENT

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8. Compound 3c was obtained in an analogous manner to compounds 3a and 3b; mp 104-105 °C; $[\alpha]_{578}^{20}$ = +158.6 ($CHCl_3$).

9. All new compounds gave satisfactory analytical and spectral data which are available upon request. ^1H NMR spectra were determined in $CDCl_3$ (Bruker 360 Mz, Varian 300 MHz, Varian 60 MHz), ^{13}C NMR spectra in $CDCl_3$ (Tesla BS 567A, 252 MHz, Varian 75 MHz, Bruker 90, 55 MHz.