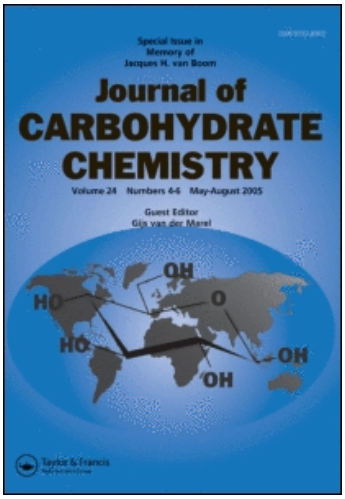

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First Stereqselective Synthesis of Nitrophenyl 2-Deoxy- β-D-glycosides

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FIRST STEREOSELECTIVE SYNTHESIS OF NITROPHENYL 2-DEOXY-β-D-GLYCOSIDES

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ABSTRACT

α-Dithiophosphates of peracetylated 2-deoxyhexopyranoses, 1a, 1b and 2, which are easily prepared by addition of organic phosphorodithioic acids to glycals react smoothly with resin-bound 2- and 4-nitrophenoxides to give stereoselectively the respective nitrophenyl 2-deoxy-β-D-hexopyranosides (3,4,5 and 6) in high yields. Glycosylation of the 2,4-dinitrophenoxide, however, leads with comparable stereoselectivity to 2,4-dinitrophenyl 2-deoxy-α-D-hexopyranosides (7 and 8).

Glycosides 3 - 6 are quantitatively deacetylated by Amberlyst A-26 (OH^-), whereas glycosides 7 and 8, under the same reaction conditions undergo splitting of the O-glycosidic bond.

INTRODUCTION

Aryl saccharides, and in particular nitrophenyl glycosides, are frequently employed as synthetic substrates for certain glycosidases and glycosyl

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transferases.[1] Furthermore, nitrophenyl glycosides allow the introduction of an active function in the aglycon thus making it possible to couple the product to macromolecules for affinity chromatography or for the synthesis of artificial antigens.[2] p-Nitrophenyl glycosides are used as parent compounds for the subsequent derivatisation and exposure of a desired hydroxyl group.[3] Alkali-labile 2,4-dinitrophenyl glycosides represent suitable models for solvolysis studies involving generation of the glycopyranosyl cations.[4] Thus, there is increasing demand for stereoselective synthesis of this class of compounds which, due to the presence of an aglycon whose light-absorption characteristics change on hydrolysis, represent versatile models for biological and chemical studies.

Although synthetic methods leading to aryl β-D-glycosides of fully hydroxylated sugars are well established, it has not been possible until now to synthesize nitrophenyl 2-deoxy-β-D-glycosides because standard methods lead unavoidably to the thermodynamically more stable α-anomers.[5]

Attempts to find a general synthetic route to aryl 2-deoxy-β-D-glycosides failed.[6] The only example described by Kiss[7] consisted of the introduction of the β-glycosidic phenolic function prior to the 2-deoxy function which, in turn, was generated by hydrogenolysis of the 2-O-p-tolylsulphonyl group using $LiAlH_4$.

We have recently reported a novel approach to the synthesis of alkyl 2-deoxy-β-D-glycosides based on the reaction of α-dithiophosphates of 2-deoxysugars with alkoxides.[8] This work suggested that similar stereoselection might be achieved for aryl 2-deoxy-β-D-glycosides via reaction of the same glycosyl donor with phenoxides.

The glycosylating reagents introduced by us[9] are readily accessible in a highly stereoselective process. In contrast to other glycosylating reagents in the 2-deoxysugar series, e.g., acyl 2-deoxyglycosyl halides, α-dithiophosphates of 2-deoxysugars are stable, crystalline compounds which can be stored for months without decomposition and configurational changes. The dithiophosphate group represents a novel type of an activating factor for the anomeric centre in glycosylation reactions which, according to our results,[8] proceed with full inversion of configuration at C-1.

RESULTS AND DISCUSSION

The reaction of α-dithiophosphates 1a, 1b and 2 with 2- and 4-nitrophenoxides was performed under such conditions as to avoid the formation of the thermodynamically more stable α-glycosides (20°C, neutral solvents). The reaction was monitored by ^{31}P NMR spectroscopy and tlc and was usually completed within 2-3 weeks. We observed that the reaction of phenoxides with the cyclic dithiophosphates 1a and 2 proceeded faster and was completed within 2 weeks whereas with the O,O-dimethyldithiophosphates 1b was accomplished within 3 weeks. Under the conditions applied deacetylation of the sugar residue did not occur. The crude peracetylated nitrophenyl glycosides 3 - 8 were obtained in nearly quantitative total yield. The proportions of the anomers formed were evaluated by ^{1}H and ^{13}C NMR spectroscopy of the crude reaction mixtures. We found that in the case of 2- and 4-nitrophenyl 2-deoxygluco- and galactopyranosides the β-isomer predominates ($>90\%$); with 2,4-dinitro-

phenyl 2-deoxyglycosides, however, the α/β ratio favoured the α-anomer (Table 1). This fact can be explained by the strong anomeric effect of the highly electronegative substituent as well as by the steric factor.

Raising the reaction temperature to 45°C resulted in a shorter reaction time (11 days) but pronounced loss of stereoselectivity. The reaction of 1b with p-nitrophenoxide at 45°C lead to 1:1 mixture of α and β glycosides. The same α/β ratio was observed on equilibration of the anomerically pure 4-nitrophenyl 2-deoxy-β-D-glucoside by heating in methylene chloride solution at 40°C for 10 hours.

The structures of the anomerically pure glycosides, which were readily separable by crystallisation, were confirmed by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy and specific rotation values (Tables 1-4).

For precise assignment of the ^{1}H and ^{13}C chemical shift values for representative β- and α-nitrophenyl 2-deoxyglycosides the 2D $^{1}H - ^{1}H$ and 2D $^{1}H - ^{13}C$ spectra were recorded (Figure 1 and Figure 2).

Free glycosides 3a, 4a, 5a and 6a were obtained by deacetylation with Amberlyst A-26 (OH^-) resin[10] in dry methyl alcohol at 20°C. Usually 2-2.5 hours were sufficient to perform the de-blocking in quantitative yield, except for 2,4-dinitrophenyl glycosides which underwent cleavage of the glycosidic linkage under these reaction conditions.

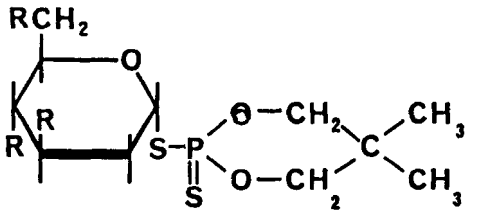
In conclusion, the introduction of this novel type of glycosylating reagent (1a, 1b and 2) gives easy access to nitrophenyl β-D-glycosides of 2-deoxysugars now available for the first time for biological studies.

TABLE 1. Analytical Data of 2- and 4-Nitrophenyl 2-deoxy-β-D-glycosides (3-6a) and 2,4-Dinitrophenyl-2-deoxy-α-D-glycosides (7,8)

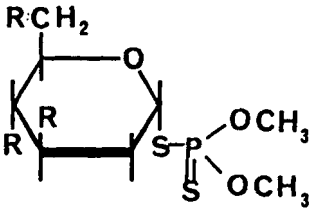
Compound	Configu-ration	Yield[x] (%)	M.p. (°C)	$[\alpha]_{578}^{20}$	^{1}H-1	^{13}C-1[f]	α/β [xx]
3	β	78	99,5-100,5[a]	+41[d]	5,29[f]	98,3	6/94
3a	β	95	155,5-157[b]	+1[e]	5,36[g]	-	-
4	β	85	117 - 119[a]	+70[d]	5,28[f]	99,2	5/95
4a	β	96	169 - 171[b]	+41[e]	5,35[g]	-	-
5	β	68	89 - 91[a]	-72[d]	5,33[f]	96,5	11/89
5a	β	90	155,5-157[b]	-84[e]	5,46[g]	-	-
6	β	80	104,5-106[a]	-53[d]	5,31[f]	97,2	5/95
6a	β	95	169,5-171[b]	-111[e]	5,48[g]	-	-
7	α	70	169 - 170,5[c]	+231[d]	5,96[f]	97,0	80/20
8	α	78	179 - 180[c]	+237[d]	6,00[f]	98,4	90/10

[x] The yields refer to anomerically pure recrystallized products;

[xx] α/β ratio was established by ^{13}C NMR spectroscopy of the crude reaction mixture; a from EtOH; b from MeOH; c from EtOH-Et_2O; d in $CHCl_3$; e in MeOH; f in $CDCl_3$; g in CD_3COCD_3



1a R = OAc



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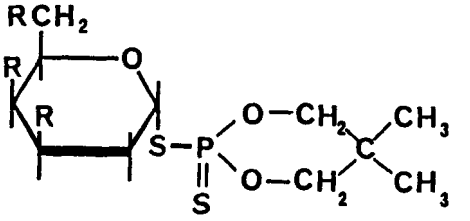
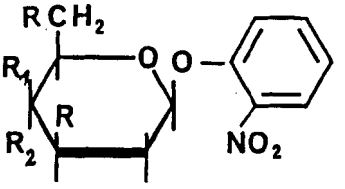
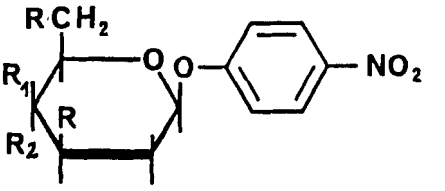
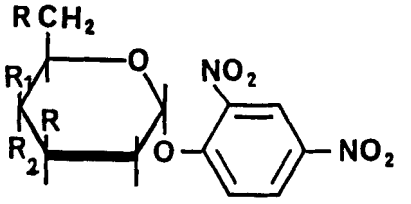


2 R = OAc





3	$R = R_2 = OAc$	$R_1 = H$	5	$R = R_2 = OAc$	$R_1 = H$
3a	$R = R_2 = OH$	$R_1 = H$	5a	$R = R_2 = OH$	$R_1 = H$
4	$R = R_1 = OAc$	$R_2 = H$	6	$R = R_1 = OAc$	$R_2 = H$
4a	$R = R_1 = OH$	$R_2 = H$	6a	$R = R_1 = OH$	$R_2 = H$



7	$R = R_2 = OAc$	$R_1 = H$
8	$R = R_1 = OAc$	$R_2 = H$

TABLE 2. Selected ^{1}H NMR chemical shift values (ppm) and J (Hz) of compounds 3,4 and 7 (400 MHz)

		3[a]		4[a]		4[b]	7[a]	
H-1	$J_{1,2}$	5,29	(2,5)	5,33	(2,3)	4,45	5,96	(1,5)
	$J_{1,2}$		(8,9)		(9,4)			(2,9)
H-2	$J_{1,2}$	2,61		2,58	(2,4)	2,17	2,64	(1,4)
	$J_{2,2}$				(12,8)			(13,6)
	$J_{2,3}$				(5,0)			(5,3)
H-2	$J_{1,2}$	2,10		2,10		1,82	2,11	(3,4)
	$J_{2,2}$							(13,7)
	$J_{2,3}$							(11,5)
H-3	$J_{2,3}$	5,10	(5,1)	5,13	(5,2)	5,03	5,46	(3,4)
	$J_{2,3}$		(10,7)		(11,0)			(13,7)
	$J_{3,4}$		(8,9)		(9,3)			(11,5)
H-4	$J_{3,4}$	5,05	(8,9)	5,08	(9,2)	5,09	5,16	(9,8)
	$J_{4,5}$		(8,9)		(9,2)			(9,8)
H-5	$J_{5,6}$	3,81	(5,1)	3,85	(5,9)	3,20	4,06	(4,4)
	$J_{5,6}$		(2,9)		(2,7)			(2,3)
	$J_{4,5}$		(8,8)		(9,2)			(10,3)
H-6	$J_{6,6}$	4,32	(12,2)	4,31	(12,1)	4,30	4,29	(12,3)
	$J_{5,6}$		(5,5)		(5,8)			(4,4)
H-6	$J_{6,6}$	4,19	(12,2)	4,16	(12,1)	4,10	4,02	(12,3)
	$J_{5,6}$		(2,9)		(2,6)			(2,3)
$COCH_3$		2,08		2,09		1,66	2,07	
		2,07		2,08		1,64	2,05	
		2,05		2,06		1,63	2,04	

a in $CDCl_3$ b in C_6D_6

TABLE 3. Selected ^{13}C chemical shift values (ppm) of glycosides 3, 4 (β) and 7 (α)

	3	4	7
C-1	98,3	96,5	97,0
C-2	35,0	35,4	34,2
C-3	68,5	68,5	68,0
C-4	69,4	69,8	68,3
C-5	72,4	72,5	70,2
C-6	62,3	62,3	61,6
$\underline{C}OCH_3$	170,5	170,5	170,3
	170,1	170,1	169,7
	169,6	169,7	169,7
$CO\underline{C}H_3$	20,8	20,9	20,9
	20,7	20,7	20,7
	20,7	20,7	20,7

EXPERIMENTAL

General Procedures. Melting points were determined with Boetius PHMK05 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Centre of Molecular and Macromolecular Studies of the Polish Academy of Sciences. ^1H NMR spectra were determined in $CDCl_3$ or C_6D_6 (Varian 60 MHz, Bruker 90 MHz, Bruker 200 MHz, Jeol 400 MHz, Bruker 400 MHz). ^{13}C NMR spectra were determined in $CDCl_3$ (Bruker 22.6 MHz, Bruker 50.3 MHz, Bruker 74.9 MHz, Jeol 100.4 MHz). ^{31}P NMR spectra were

TABLE 4. Analytical Data of Nitro- and Dinitrophenyl 2-deoxy-hexopyranosides (3 - 8)

Compound	Formula	Anal. Calc. (%)			Found (%)		
		C	H	N	C	H	N
3	$C_{18}H_{21}NO_{10}$	52.55	5.10	3.40	52.64	5.27	3.41
3a	$C_{12}H_{15}NO_7$	50.50	5.25	4.90	50.45	5.55	5.15
4	$C_{18}H_{21}NO_{10}$	52.55	5.10	3.40	52.60	5.45	3.47
4a	$C_{12}H_{15}NO_7$	50.50	5.25	4.90	50.82	5.60	4.69
5	$C_{18}H_{21}NO_{10}$	52.55	5.10	3.40	52.33	5.22	3.37
5a	$C_{12}H_{15}NO_7$	50.50	5.25	4.90	50.31	5.49	5.13
6	$C_{18}H_{21}NO_{10}$	52.55	5.10	3.40	52.44	5.43	3.63
6a	$C_{12}H_{15}NO_7$	50.50	5.25	4.90	50.76	5.51	4.65
7	$C_{18}H_{20}N_2O_{12}$	47.30	4.40	6.10	47.11	4.53	5.95
8	$C_{18}H_{20}N_2O_{12}$	47.30	4.40	6.10	47.30	4.68	5.99

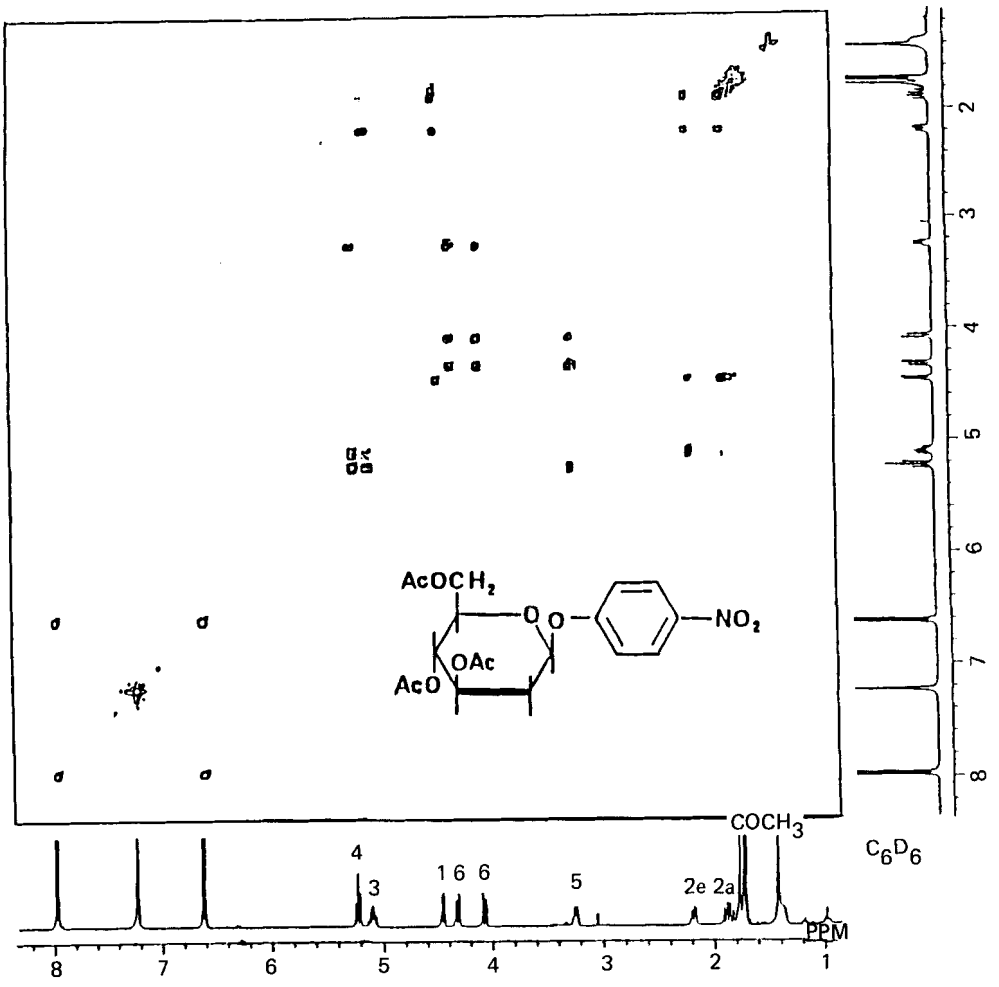


FIG 1. ^{1}H-^{1}H-Correlated 2D-NMR Spectrum of 4'-Nitrophenyl 2-Deoxy-β-D-Glucopyranoside.

determined in $CDCl_3$ with H_3PO_4 as standard (Jeol 60 MHz FT operating at 24.3 MHz). Specific rotations were determined with Polamat A polarimeter.

Tlc was carried out on silica gel plates (Sklo Union, Silufol ^{R} UV 254) with benzene-chloroform-acetone mixture 3:1:1. Detection was effected by exposure to iodine vapours. Column chromatography was carried out

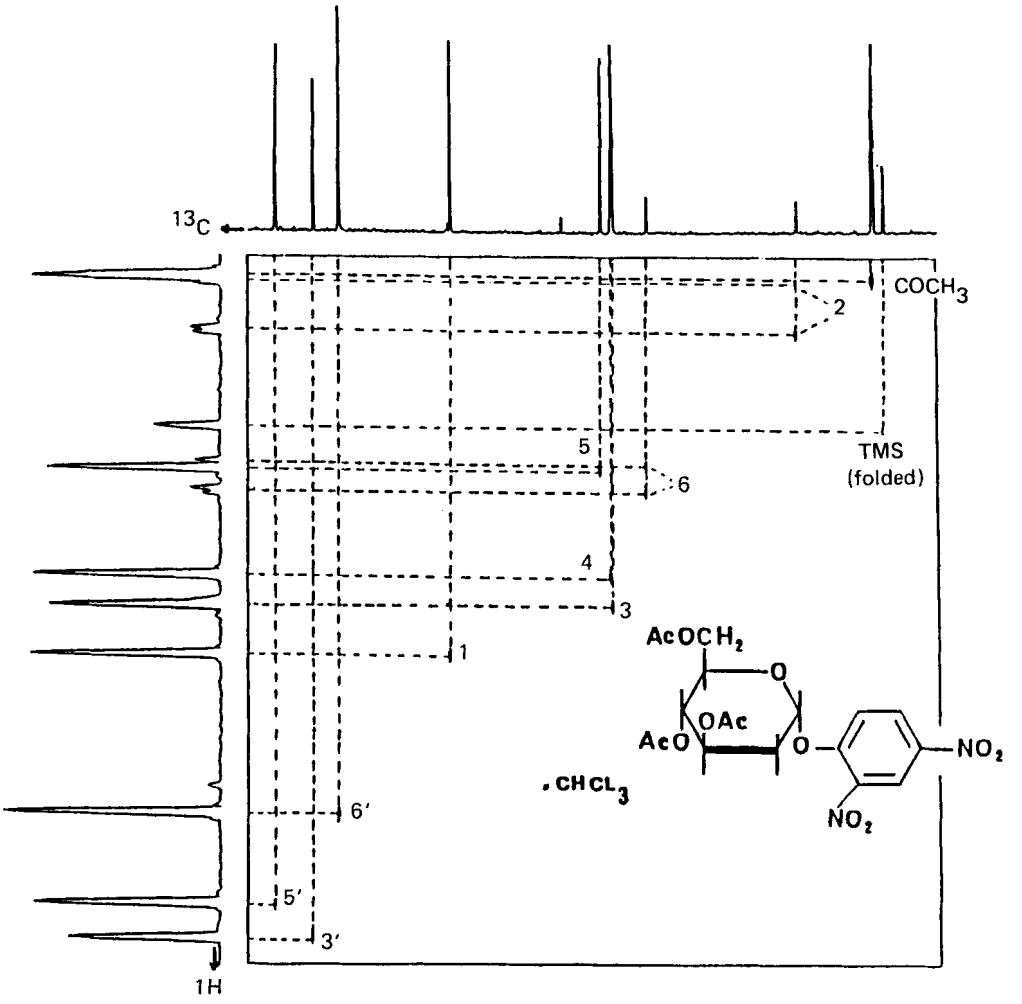


FIG. 2. ^{13}C-^{1}H-Correlated 2D-NMR Spectrum of 2', 4'-Dinitrophenyl 2-Deoxy-∝-D-Glucopyranoside.

by using silica gel (E.Merck 0.2-0.5 mm) and a mixture of hexane-chloroform as eluent.

Starting Materials. α-Dithiophosphates 1a, 1b and 2 were obtained according to J.Borowiecka and M.Michalska.[9] Amberlyst A-26 2-, 4-nitro and 2,4-dinitrophenoxides were prepared according to T.Iversen and R.Johansson.[11]

General Glycosylation Procedure. A mixture of equimolar amounts (2 mmol) of the appropriate α-dithiophosphate (1a, 1b or 2) and of Amberlyst A-26 nitrophenoxide (2 mmol) in propanol-benzene (10:1) (33 ml) was stirred at 20°C. The reaction was monitored by ^{31}P NMR spectroscopy and tlc. After one week a second batch of resin (2 mmol) was added and stirring continued. The reaction was usually accomplished within 2-3 weeks. Reaction time for 3,4,5,6,7 and 8, starting from 1a and 2 was two weeks, starting from 1b - three weeks. The resin was removed by filtration, washed with CH_2Cl_2 and MeOH, the combined filtrates evaporated in vacuo at 20°C. The residue was dissolved in $CHCl_3$, washed with 10% $NaHCO_3$ and water; the chloroform solution was dried ($MgSO_4$) and concentrated in vacuo. The residual syrup or crystalline mass was purified by crystallization or column chromatography followed by crystallization.
Yields, physical and spectroscopic data of acetylated glycosides, 3 - 8 , are collected in Tables 1-3. Table 4 contains the results of elemental analysis.

General Deacetylation Procedure. A solution of the acetylated glycoside in dry methanol was stirred at 20°C for 2 - 2.5 hr in the presence of catalytic amount of the Amberlyst A-26 (OH^-) resin. The resin was filtered off and the filtrate evaporated to give colourless, crystalline product which was purified by crystallization from methanol. Yields and physical data of the free glycosides 3a, 4a, 5a and 6a are collected in Table 1. The results of elemental analysis - in Table 4.

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