

SYNTHESIS OF PYRAZOLE C-GLYCOSIDES BY 1,3-DIPOLAR CYCLOADDITION OF NITRILIMINES FORMED BY LEAD TETRAACETATE OXIDATION OF *p*-NITROPHENYLHYDRAZONES OF ALDEHYDO SUGARS

Jean M. J. Tronchet,* Jeannine F. Tronchet, and Françoise Barbalat-Rey

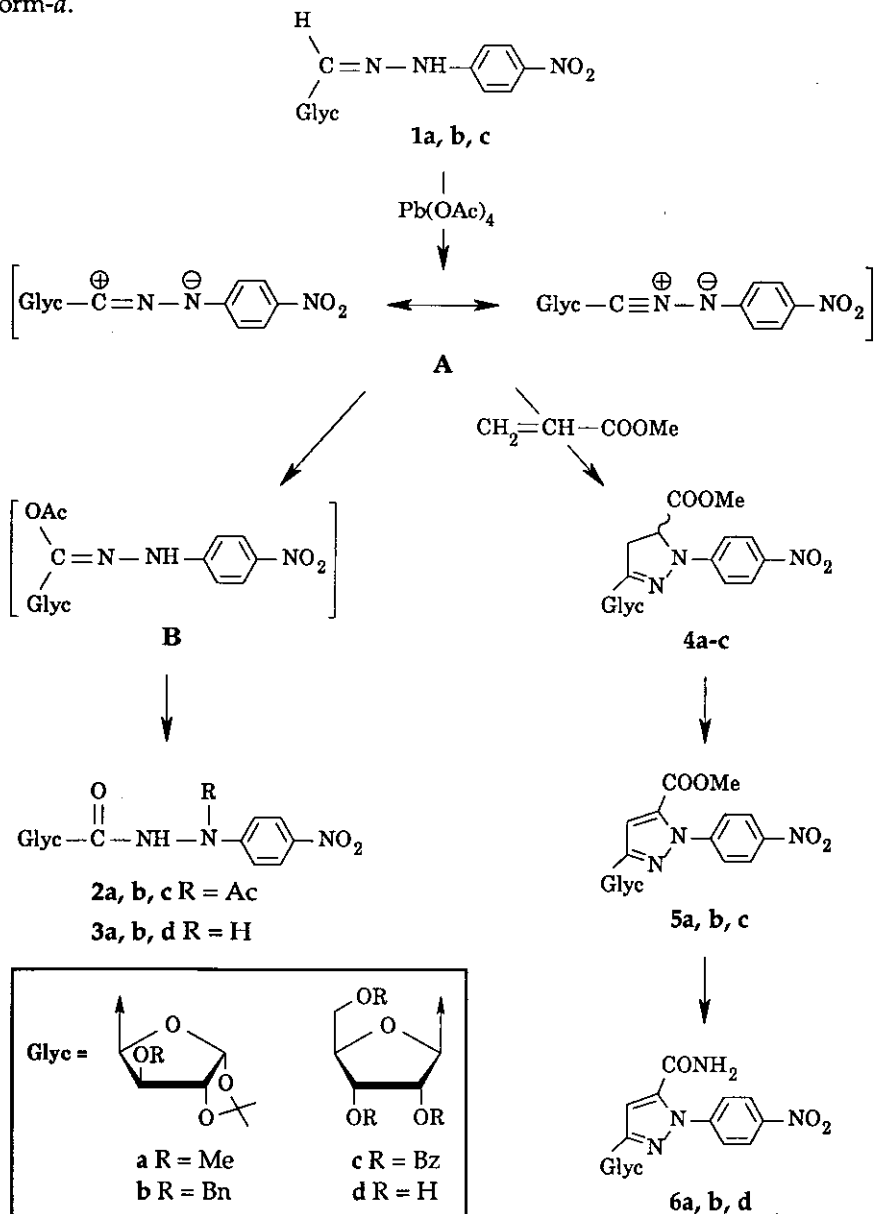
Institute of Pharmaceutical Chemistry, University of Geneva,
30, Quai E.-Ansermet, CH-1211 Geneva 4, Switzerland

Abstract - Aldehydo sugars *p*-nitrophenylhydrazones upon treatment with lead tetraacetate in the presence of an excess of methyl acrylate afforded, besides *N'*-acetylhydrazide derivatives, methyl 3-glycosyl-1-*p*-nitrophenylpyrazoline-5-carboxylates which were readily oxidized to the corresponding pyrazoles. The methyl pyrazole-5-carboxylates were converted to 5-carboxamides.

C-Glycosides and particularly C-glycosyl nucleosides constitute an interesting class of compounds which often possess useful biological properties.¹ We have previously studied the preparation of pyrazole glycosides by 1,3-dipolar cycloaddition reactions of sugar nitrilimines generated by dehydrohalogenation of hydrazoneyl bromides prepared from sugar phenylhydrazones.² In continuation of our studies on the reactivity of phenylhydrazones of sugars with lead tetraacetate,³ we investigated the behavior of *p*-nitrophenylhydrazones of aldehydo sugars towards lead tetraacetate oxidation. Some of our results have already been presented in a preliminary form.⁴

Hydrazones (1a) and (1b) were known⁵ whereas 1c was obtained in 89% yield as a mixture of *E* and *Z* isomers which were separated and crystallized. Properties of (*Z*)-1c and (*E*)-1c are collected in Table 1.

E and *Z* configurations were assigned on the basis of the chemical shifts of H-1 (more deshielded for the *E*-isomer⁶) and H-2 (more deshielded for the *Z*-isomer⁶). Lead tetraacetate oxidation of hydrazones (1a-c) afforded the corresponding *N*-acetylhydrazides (2a-c) which were easily deacetylated to the hydrazides (3a,b,d) respectively (Scheme 1). The ¹H-nmr data of compounds (2) and (3), collected in Table 2, confirmed their structures. In particular, a small ³J_{NH,NH} coupling (*ca* 2 Hz) was noted for spectra of 3 in chloroform-*d*.



Scheme 1

Table 1. Some Properties of Hydrazones (*E*)-1c and (*Z*)-1c.

Properties		(<i>E</i>)-1c	(<i>Z</i>)-1c
mp (°C)		72.6-73.8	151.6-152.4
R_F^a		0.2	0.75
ir (cm ⁻¹)		3300 (NH), 1725 (CO), 1600-1330 (NO ₂)	3260 (NH), 1715 (CO), 1590-1330 (NO ₂)
¹ H-nmr chemical shifts (δ, ppm)	H-1	7.19 <i>d</i>	6.67 <i>d</i>
	H-2	4.95 <i>t</i>	5.17 <i>dd</i>
	H-3	5.90 <i>q</i>	5.64 <i>dd</i>
	H-4	5.87 <i>td</i>	5.56 <i>dd</i>
	H-5	4.69 <i>q</i>	4.82 <i>q</i>
	H-6a	4.54 <i>dd</i>	4.61 <i>dd</i>
	H-6b	4.82 <i>dd</i>	4.91 <i>dd</i>
	<i>p</i> NO ₂ Ph	7.00 <i>m</i> , 8.14 <i>m</i>	7.23 <i>m</i> , 8.18 <i>m</i>
	Bz	7.31-7.65 <i>m</i> , 7.90-8.15 <i>m</i>	7.36-7.69 <i>m</i> , 7.98-8.12 <i>m</i>
NH		10.5	10.12
Coupling constants (Hz)	$J_{1,2}$	6.0	4.5
	$J_{2,3}$	6.0	1.2
	$J_{3,4}$	6.0	5.0
	$J_{4,5}$	4.0	7.0
	$J_{6a,6b}$	8.5	12.0
	$J_{5,6a}$	4.0	3.2
	$J_{5,6b}$	4.0	3.2

a. 4:3 Et₂O/hexane.

The fact that lead tetraacetate oxidation of hydrazones takes place *via* nitrilimine intermediates **A** (then hydrazinoyl acetates **B**)⁷ was confirmed by the formation of cycloadducts (**4a-c**) when the oxidation of **1a-c** was performed in the presence of the 1,3-dipole scavenger methyl acrylate. Depending on the reaction conditions, the pyrazolines (**4**) were either isolable from the reaction medium (**4a,c**) or directly oxidized to the corresponding pyrazole (**4b** → **5b**). A certain amount of the *N*-acetylhydrazide was also formed. For example, *N'*-acetyl-2-*O*-benzyl-*N'*-*p*-nitrophenyl- α -D-xylofuranuronohydrazide (**2b**) was isolated and characterized after the cycloaddition reaction. Upon reacting sugar nitrilimines - obtained by dehydrobromation of the corresponding hydrazoneoyl bromides - with methyl propiolate, the formation of a nitrilimine dimer, a tetrazine, had been previously observed.⁸ This was not the case here. Pyrazoline (**4a**) was obtained as a 1:1 resolvable mixture of the (*5S*) and (*5R*) epimers [¹H-nmr

Table 2. ^1H -nmr Data (δ /ppm, J /Hz) for Compounds 2-3.

	2a	2b	3a	3b	
Chemical shifts	H-1	6.02 <i>d</i>	6.11 <i>d</i>	6.07 <i>d</i>	6.09 <i>d</i>
	H-2	4.67 <i>d</i>	4.74 <i>d</i>	4.68 <i>d</i>	4.70 <i>d</i>
	H-3	4.17 <i>d</i>	4.48 <i>d</i>	4.15 <i>d</i>	4.49 <i>d</i>
	H-4	4.90 <i>d</i>	4.96 <i>d</i>	4.87 <i>d</i>	4.89 <i>d</i>
	<i>p</i> -NO ₂ Ph	7.22 <i>m</i> , 8.12 <i>m</i>	7.40 <i>m</i> , 7.50 <i>m</i>	6.90 <i>m</i> , 8.12 <i>m</i>	6.70 <i>m</i> , 7.72 <i>m</i>
	NH	8.90 <i>s</i>	8.76 <i>s</i>	6.25 <i>d</i> , 8.20 <i>d</i>	6.38 <i>d</i> , 8.17 <i>d</i>
	COCH ₃	2.30 <i>s</i>	2.20 <i>s</i>		
	C(CH ₃) ₂	1.37 <i>s</i> , 1.52 <i>s</i>	1.39 <i>s</i> , 1.54 <i>s</i>	1.37 <i>s</i> , 1.52 <i>s</i>	1.34 <i>s</i> , 1.51 <i>s</i>
	Others	OCH ₃ 3.42 <i>s</i>	CH ₂ Ph 4.56 <i>d</i> , 4.70 <i>d</i> Ph 7.16-7.40 <i>m</i>	OCH ₃ 3.45 <i>s</i>	CH ₂ Ph 4.58 <i>d</i> , 4.71 <i>d</i> Ph 7.20-7.40 <i>m</i>
Coupling constants	$J_{1,2}$	3.8	3.8	3.9	3.5
	$J_{2,3}$	0	0	0	0
	$J_{3,4}$	3.6	3.5	3.8	3.5
	$J_{\text{NH,NH}}$	-	-	2.2	2.0
	Others		CH ₂ Ph 11.0		CH ₂ Ph 11.0
Chemical shifts		2c ^a	3d ^b		
	H-2	4.92 <i>d</i>	4.26 <i>d</i>		
	H-3	5.97 <i>td</i>	4.08 <i>m</i>		
	H-4	5.80 <i>td</i>	3.97 <i>m</i>		
	H-5	4.66-4.87 <i>m</i>	3.82 <i>dt</i>		
	<i>p</i> -NO ₂ Ph	7.49 <i>m</i> , 7.97 <i>m</i>	6.13 <i>m</i> , 8.05 <i>m</i>		
	NH	9.87 <i>s</i>	9.50 <i>bs</i> 10.02 <i>bs</i>		
	COCH ₃	2.18 <i>s</i>	-		
	H ₂ -C ₆	4.66-4.87 <i>m</i>	3.51 <i>bdd</i> , 3.70 <i>ddd</i>		
	Others	COPh 7.30-7.66 <i>m</i> 7.85-8.10 <i>m</i>	OH 5.00 <i>d</i> , 5.15 <i>bs</i> , 5.36 <i>d</i>		
Coupling constants	$J_{2,3}$	5.0	2.5		
	$J_{3,4}$	5.0	4.5		
	$J_{4,5}$	5.0	7.0		
	$J_{\text{NH,NH}}$	-	-		
	Others		$J_{3,\text{OH}} = 5$, $J_{4,\text{OH}} = 5$, $J_{6a,6b} = 12.5$, $J_{5,6a} = J_{5,6b} = 2.5$, $J_{6b,\text{OH}} \sim 5$		

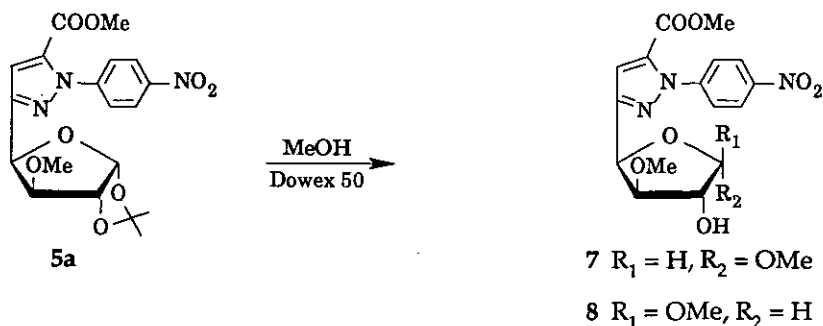
a. At 60°C. b. In DMSO-*d*₆

data: δ 3.30 (1 H, *dd*, $J_{4a,5} = 5.8$ Hz, $J_{4a,4b} = 14$ Hz, Ha-4), 3.51 (1 H, *dd*, $J_{4b,5} = 12.5$ Hz, Hb-4), 4.80 (1 H, *dd*, H-5) for one isomer and δ 3.25 (1 H, *dd*, $J_{4a,5} = 6$ Hz, $J_{4a,4b} = 18$ Hz, Ha-4), 3.51 (1 H, *dd*, $J_{4b,5} = 13$ Hz, Hb-4), 4.78 (1 H, *dd*, H-5) for the other] whereas in the case of **4c** the *ca* 1:1 mixture could not be resolved. In neither case, could the configuration at C5 be established, differences in the nmr data of epimers being too small to allow reliable assignments. When isolated, **4** readily oxidized to **5**, structures of which were established mainly from the nmr data (Table 3). As 5-carbamoylpyrazol-3-yl glycosides like pyrazomycin⁹

Table 3. ¹H-nmr Data (δ /ppm, J /Hz) for Compounds 5-6.

	5a	5b	6a	6b	5c	5d ^a	
Chemical shifts (δ , ppm)	H-1'	6.07 <i>d</i>	6.11 <i>d</i>	5.98 <i>d</i>	6.11 <i>d</i>	5.46 <i>d</i>	4.68 <i>d</i>
	H-2'	4.77 <i>d</i>	4.76 <i>d</i>	4.67 <i>d</i>	4.77 <i>d</i>	5.94 <i>t</i>	4.02 <i>t</i>
	H-3'	3.92 <i>d</i>	4.14 <i>d</i>	3.85 <i>d</i>	4.15 <i>d</i>	5.90 <i>t</i>	4.91 <i>m</i>
	H-4'	5.39 <i>d</i>	5.42 <i>d</i>	5.31 <i>d</i>	5.43 <i>d</i>	4.76 <i>m</i>	3.82 <i>m</i>
	<i>p</i> -NO ₂ Ph	7.62 <i>m</i>	7.62 <i>m</i>	7.60 <i>m</i>	7.64 <i>m</i>	7.57 <i>m</i>	7.68 <i>m</i>
		8.35 <i>m</i>	8.35 <i>m</i>	8.10 <i>m</i>	8.32 <i>m</i>	8.28 <i>m</i>	8.32 <i>m</i>
	C(CH ₃) ₂	1.37 <i>s</i>	1.36 <i>s</i>	1.30 <i>s</i>	1.38 <i>s</i>	-	-
		1.56 <i>s</i>	1.52 <i>s</i>	1.50 <i>s</i>	1.58 <i>s</i>	-	-
	H-4	7.22 <i>s</i>	7.24 <i>s</i>	6.87 <i>s</i>	6.94 <i>s</i>	7.12 <i>s</i>	7.02
	COOCH ₃	3.85 <i>s</i>	3.85 <i>s</i>	-	-	3.77 <i>s</i>	-
	CONH ₂	-	-	5.98 <i>bs</i>	5.65 <i>bs</i>	-	7.55 <i>s</i>
		-	-	-	5.94 <i>bs</i>	-	8.22 <i>s</i>
	Others	OCH ₃	CH ₂ -Ph	OCH ₃	CH ₂ -Ph	COPh 7.30-7.50 <i>m</i>	4.95 <i>t</i> C ₅ -OH
3.32 <i>s</i>		4.42 <i>d</i> , 4.57 <i>d</i>	2.23 <i>s</i>	4.37 <i>d</i> 4.60 <i>d</i>	7.86-8.14 <i>m</i>	4.95 <i>d</i> C ₃ -OH	
-		Ph 7.10-7.40 <i>m</i>	-	Ph 7.12-7.28 <i>m</i>	H-5'a 4.60 <i>dd</i> H-5'b 4.87 <i>dd</i>	5.09 <i>d</i> C ₂ -OH	
Coupling constants (Hz)	$J_{1',2'}$	3.9	4.1	3.9	3.8	5.0	6.0
	$J_{3',4'}$	3.5	3.6	3.0	3.2	5.0	4.0
	Others	-	CH ₂ Ph 12.0	-	CH ₂ Ph 11.8	$J_{5'a,5'b} = 12.0$	$J_{5',OH} = 5.0$
		-	-	-	-	$J_{5'a,4'} = 4.2$	$J_{3',OH} = 6.0$
-	-	-	-	$J_{5'b,4'} = 3.5$	$J_{2',OH} = 6.0$		
-	-	-	-	-	$J_{5'a,5'b} = 11.5$	$J_{5'a,4'} = 4.8$	
-	-	-	-	-	$J_{5'b,4'} = 4.0$	$J_{5'b,4'} = 4.0$	

a. In DMSO-*d*₆



Scheme 2

exhibit interesting biological activities, pyrazoles (5a-c) were converted to the amides (6a,b,d). On the other hand, 5c was methanolized to the resolvable epimeric mixture of 7 and 8 (Scheme 2).

ACKNOWLEDGEMENTS

The authors express their appreciation for the skillful technical assistance of Miss Nadine Feldmann. They thank Prof. A. Buchs and Dr F. Gulaçar for the ms and the Swiss National Science Foundation for grants # 20-26460.89 and 20-31259.91.

EXPERIMENTAL

General methods. - Solutions were concentrated under diminished pressure at <math><40\text{ }^\circ\text{C}</math>. Melting points are uncorrected and were obtained with a Mettler FP 52 melting-point microscope. Tlc was performed on silica gel HF₂₅₄ (Merck) with detection by uv light or with phosphomolybdic-sulfuric acid.¹⁰ Dry column chromatography¹¹ was conducted with silica gel 60 F₂₅₄ (Merck) and flash chromatography¹² on silica gel Merck 60 (0.04-0.063 mm). Ir spectra were recorded with a Perkin-Elmer Model 357 spectrophotometer and uv spectra with an Unicam SP 800 spectrophotometer. Nmr spectra were recorded at 35 or 20°C for solutions in CDCl₃ (internal Me₄Si) using a Bruker WP 200 Sy spectrometer. Optical rotations were measured on solutions in chloroform with a Schmidt-Haensch polarimeter. Microanalyses have been performed by Dr H. Eder from this Laboratory. Results for compounds 1-8 are collected in Table 4.

(E)- and (Z)-2,5-Anhydro-3,4,6-tri-O-benzoyl-1-deoxy-1-p-nitrophenylhydrazono-D-allitol (1c). - To 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allose¹³ (1.42 g, 2.99 mmol) in ethanol (50 ml), *p*-nitrophenylhydrazine (460 mg, 2.99 mmol) was added. After 1 h at 78 °C, the solution was evaporated until the volume was reduced to 20 ml and the precipitate was collected by filtration to give 1c (1.62 g, 89%) as a mixture of Z and E isomers which could be separated by column chromatography (4:1 ether/hexane). For their properties, see Table 1.

Table 4. Microanalytical Data for Compounds (1-8).

Compd	Formula	Elementary analyses					
		Calcd			Found		
		C	H	N	C	H	N
(E)-1c	C ₃₃ H ₂₇ N ₃ O ₉	65.02	4.46	6.89	65.12	4.46	6.99
(Z)-1c	C ₃₃ H ₂₇ N ₃ O ₉	65.02	4.46	6.89	64.99	4.52	6.87
2a	C ₁₇ H ₂₁ N ₃ O ₈	51.64	5.35	10.63	51.73	5.32	10.71
2b	C ₂₃ H ₂₅ N ₃ O ₈	58.59	5.34	8.91	58.31	5.36	8.71
2c	C ₃₅ H ₂₉ N ₃ O ₁₁	62.97	4.38	6.29	63.25	4.66	6.01
3a	C ₁₅ H ₁₉ N ₃ O ₇	50.99	5.42	11.89	51.25	5.48	11.99
3b	C ₂₁ H ₂₃ N ₃ O ₇	58.74	5.40	9.79	58.62	5.32	9.80
3d	C ₁₂ H ₁₅ N ₃ O ₇	46.01	4.83	13.41	45.92	4.80	13.23
4a	C ₁₉ H ₂₃ N ₃ O ₈	54.15	5.50	9.97	54.25	5.58	10.19
4c	C ₃₇ H ₃₁ N ₃ O ₁₁	64.07	4.50	6.06	63.93	4.49	6.06
5a	C ₁₉ H ₂₁ N ₃ O ₈	54.41	5.05	10.02	54.53	5.20	10.06
5b	C ₂₅ H ₂₅ N ₃ O ₈	60.60	5.09	8.48	60.83	5.29	8.20
5c	C ₃₇ H ₂₉ N ₃ O ₁₁	64.25	4.23	6.08	63.99	4.34	5.84
6a	C ₁₈ H ₂₀ N ₄ O ₇	53.46	4.99	13.85	53.72	5.19	13.61
6b	C ₂₄ H ₂₄ N ₄ O ₇	60.00	5.03	11.66	59.71	5.00	11.50
6d	C ₁₅ H ₁₆ N ₄ O ₇	49.45	4.43	15.38	49.41	4.36	15.24
7	C ₁₇ H ₁₉ N ₃ O ₈	51.91	4.87	10.68	51.86	4.86	10.62
8	C ₁₇ H ₁₉ N ₃ O ₈	51.91	4.87	10.68	51.88	4.86	10.65

Preparation of *N'*-acetyl-*p*-nitrophenylhydrazides (2a-c) (Tables 2 and 5).

Procedure A. - Preparation of *N'*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl-*N'*-*p*-nitrophenyl- α -*D*-xylofuranuronohydrazide (2a). - To a solution of 1,2-*O*-isopropylidene-3-*O*-methyl- α -*D*-xylopentodialdo-1,4-furanose 5-(*p*-nitrophenylhydrazone)⁵ (100 mg, 0.29 mmol) in a mixture of THF (1 ml) and benzene (5 ml) at 0 °C,¹⁴ lead tetraacetate (257 mg, 0.58 mmol) was added. After 1.5 h, ethylene glycol (1 ml) and H₂O (10 ml) were added. The organic layer was decanted, dried (MgSO₄) and the solvents were removed by evaporation. 2a was purified by recrystallization (ether/hexane).

Procedure B. Preparation of *N'*-acetyl-2,5-anhydro-3,4,6-tri-*O*-benzoyl-*N'*-*p*-nitrophenyl-*D*-

allonohydrazide (2c). - A solution of 1c (230 mg, 0.37 mmol) in dichloromethane (20 ml) was slowly dropped into a solution of lead tetraacetate (164 mg, 0.37 mmol) in dichloromethane (10 ml) at 0 °C. After 1.5 h, the mixture was treated as described in procedure A and purified by column chromatography (4:1 ether/hexane).

Procedure C. - Compounds (2a-c) were obtained as by-products during preparation of compounds (4a-c, 5a-c). They were isolated by column chromatography (*vide infra*).

Preparation of 1,2-O-isopropylidene-3-O-methyl-N'-p-nitrophenyl- α -D-xylofuranuronohydrazide (3a); 3-O-benzyl-1,2-O-isopropylidene-N'-p-nitrophenyl- α -D-xylofuranuronohydrazide (3b) and 2,5-anhydro-N'-p-nitrophenyl-D-allonohydrazide (3d).

Procedure D. - To a solution of 2 (~ 1 mmol) in anhydrous methanol (30 ml) sodium methanolate (3 mg, 0.05 mmol) was added. The mixture was heated to reflux for 0.5 h. To the cooled solution Dowex 50 (H⁺, in methanol) was added until neutralization. Filtration and evaporation of methanol afforded crystalline 3 which were recrystallized (see Table 5).

Methyl 3-(1,2-O-isopropylidene-3-O-methyl- α -D-xylo-tetro-1,4-furanos-4-yl)-1-p-nitrophenylpyrazoline-5-carboxylate (4a) and methyl 3-(1,2-O-isopropylidene-3-O-methyl- α -D-xylo-tetro-1,4-furanos-4-yl)-1-p-nitrophenylpyrazole-5-carboxylate (5a) (Tables 3 and 5).

Procedure E1. - To a solution of 1a (600 mg, 1.78 mmol) and methyl acrylate (6 ml, 66 mmol) in dichloromethane (15 ml) at -30 °C, under nitrogen, a solution of lead tetraacetate (1.57 g, 3.56 mmol) in dichloromethane (45 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature. After 48 h, filtration under celite and evaporation of the solvent gave a mixture of 2a, 4a, and 5a. Separation by flash column chromatography (ether) afforded 2a (140 mg, 35.4%), 4a (330 mg, 44%), and 5a (70 mg, 9%).

Procedure F. - As described for the procedure E1, except that after 48 h, a second portion of lead tetraacetate (1.57 g, 3.56 mmol) in dichloromethane (45 ml) was added in the reaction mixture in order to oxidize 4a in 5a. The reaction was followed by thin layer chromatography (4:1 ether/hexane) and after 24 h, treated as described in procedure E1. Separation by flash column chromatography (ether) gave 2a (140 mg, 35.4%) and 5a (380 mg, 50.9%).

Procedure G. - As described in the procedure E1, a solution of 1a (1.8 g, 5.34 mmol) and methyl acrylate (18 ml, 200 mmol) in dichloromethane (25 ml) was treated with lead tetraacetate (4.7 g, 10.7 mmol) in dichloromethane (50 ml). After 12 h, filtration under celite and evaporation of the solvent gave a

Table 5. Methods of Preparation and Some Properties of Compounds (2-8).

Compd	Method	Yield (%)	mp (solvent) °C	$[\alpha]_D$ (t, c) ^a	R_F (solvent) ^b
2a	A	61	196.2-196.4 (Et ₂ O/hexane)	-40.2° (24, 0.8)	0.08 ¹⁾
	C	35.4			
2b	C	28	164.9-166.3 (Et ₂ O/hexane)	+97.7° (24.5, 0.8)	0.20 ¹⁾
2c	B	68	non crystalline solid	-8.2° (22.0, 0.8)	0.30 ²⁾
	C	18.7			
3a	D	62	136.8-138.2 (AcOEt/hexane)	-6.87° (23, 0.9)	0.48 ³⁾
3b	D	77	180.4-180.8 (AcOEt/hexane)	+34.3° (24, 1.2)	0.55 ²⁾
3d	D	72	177.3-179.4 (CHCl ₃ , EtOH)	0° (22, 1.4) ^c	0.40 ⁴⁾
4a	E1	44	167.5-168.2 (Et ₂ O/hexane) ^d	+11.7° (22, 0.1) ^d	0.72 ⁵⁾
4c	E2	27			0.48 ¹⁾
5a	E1	9	142.1-143.2 (Et ₂ O/hexane)	-81.2° (23, 1.2)	0.48 ¹⁾
	F	50.9			
	G	60			
5b	F	66	51.4-52.1 (Et ₂ O/hexane)	-73.3° (23, 0.8)	0.68 ¹⁾
5c	E2	18	non crystalline solid	-133° (26, 1.1)	0.63 ¹⁾
	H	70	non crystalline solid		
6a	see text	85	109.1-109.5 (Et ₂ O/hexane)	-61.9° (28, 1.0)	0.42 ³⁾
6b	see text	70	143.4-144.7 (Et ₂ O/hexane)	-89.9° (20, 1.0)	0.32 ⁵⁾
6d	see text	51	206.0-208.0 (methanol)	-35.4° (22, 0.4) ^e	0.36 ⁴⁾
7	see text	42 ^f	128.5-129.2 (methanol)	+46° (22, 0.6)	0.48 ⁶⁾
8	see text	21 ^f	123.7-124.1 (methanol)	-78° (22, 1.0)	0.30 ⁶⁾

a. In CHCl₃. b. Solvents: 1) 4:1 Et₂O/hexane; 2) Et₂O; 3) 4:1 AcOEt/hexane; 4) 5:1 AcOEt/MeOH; 5) 1:1 AcOEt/hexane; 6) 9:1 CHCl₃/Acetone. c. In EtOH. d. One isomer e. In pyridine. f. 98% yield for the ca 1:1 mixture of 7 and 8.

mixture of 2a and 4a which were separated by flash chromatography (ether) giving 2a (560 mg, 26%) and 4a (1.40 g, 3.32 mmol, 62%). 4a was immediately dissolved in dichloromethane (20 ml) and treated with a solution of lead tetraacetate (1.7 g, 3.8 mmol) in dichloromethane (20 ml) at 0 °C, under nitrogen. After 24 h, ethylene glycol (1 ml) then ice-cold water (20 ml) were added in the reaction mixture. The organic layer was separated, dried (MgSO₄) and evaporated. Purification by flash chromatography

(ether) gave 5a (1.36 g, 60% from 2a).

Methyl 3-(3-O-benzyl-1,2-O-isopropylidene- α -D-xylotetro-1,4-furanos-4-yl)-1-(p-nitrophenyl)pyrazole-5-carboxylate (5b). - According to procedure F, 1b (900 mg, 2.18 mmol) and methyl acrylate (6 ml, 66.6 mmol) in dichloromethane (30 ml) were treated with lead tetraacetate (2x2.4 g, 2x5.51 mmol) in dichloromethane (20 ml). Treatment of the reaction mixture as described in procedure E1 and flash chromatography (4:1 ether/hexane) gave 5b (720 mg, 66%) and 2b (287 mg, 28%).

Methyl 3-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-1-(p-nitrophenyl)pyrazoline-5-carboxylate (4c) and methyl 3-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-(1-p-nitrophenyl)pyrazole-5-carboxylate (5c).

Procedure E2. - As described in procedure E1 but 1c (200 mg, 0.32 mmol) was dissolved in 1:5 THF/benzene (24 ml) at 0 °C and treated with methyl acrylate (2 ml, 22 mmol) and lead tetraacetate (285 mg, 0.64 mmol) in 1:5 THF/benzene (24 ml). After 24 h, filtration under celite and evaporation of the solvent gave a mixture of 2c, 4c, and 5c. Separation by flash chromatography (4:1 ether/hexane) gave 5c (40 mg, 18%), 4c (60 mg, 27%) and 2c (40 mg, 18.7%).

Procedure H. - To a solution of 1c (500 mg, 0.82 mmol) and methyl acrylate (3 ml, 33 mmol) in 1:5 THF/benzene (30 ml) at 0 °C, under nitrogen, a solution of lead tetraacetate (727 mg, 1.64 mmol) in 1:5 THF/benzene (30 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature. After 12 h, filtration under celite and evaporation of the solvents yielded a mixture of 2c and 4c. Separation by flash chromatography (4:1 ether/hexane) gave 2c (101 mg, 18%) and 4c (450 mg, 79%). 4c was dissolved in 1:5 THF/benzene (20 ml) and oxidized with a solution of lead tetraacetate (443 mg, 1 mmol) in 1:5 THF/benzene (20 ml). After 24 h, ethylene glycol (1 ml) and ice-cold water (20 ml) were added, and the organic layer was separated and dried (MgSO₄). Evaporation of the solvent gave 5c (400 mg, 70%).

3-(1,2-O-Isopropylidene-3-O-methyl- α -D-xylotetro-1,4-furanos-4-yl)-1-p-nitrophenylpyrazole-5-carboxamide (6a). - To a solution of 5a (300 mg, 0.72 mmol) in dioxane (15 ml) concentrated ammonia (25 ml) was added and the solution was stirred for 24 h at room temperature. After distillation of the solvents, the residue was dissolved in dichloromethane (20 ml) and the organic phase was washed with H₂O (15 ml), dried (MgSO₄), and was evaporated to give crystalline 6a (250 mg, 85%) (Table 5). Ir: 3420, 3360 (NH₂), 1692 (C=O), 1532, and 1355 (NO₂) cm⁻¹; uv: 203 nm (ϵ 15000), 218 (12300), and 302 (10700); ms *m/z* (%): 404 (1, M⁺), 389 (5, M⁺ - Me), 346 (2.2), 319 (4), 288 (2.5), 261 (53), 244 (24), 142 (4.8), 85 (100), 68 (15), and 59 (65). ¹H-nmr, see Table 3.

3-(3-O-Benzyl-1,2-O-isopropylidene- α -D-xylotetrofuranos-4-yl)-1-p-nitrophenylpyrazole-5-carboxamide (6b). - According to the procedure described for the preparation of 6a, 6b was synthesized from 5b (570 mg, 1.15 mmol). Purification by column chromatography (1:1 AcOEt/hexane) afforded 6b (390 mg, 70%) (Table 5). Ir: 3420, 3340 (NH₂), 1690 (C=O), and 1535-1350 (NO₂) cm⁻¹; uv: 205 nm (ϵ 23000) and 303 (12500); ms *m/z* (%): 480 (5, M⁺), 465 (6, M⁺ - Me), 345 (18), 316 (33), 287 (64), 261 (28), 230 (13), 162 (23), 129 (32), and 91 (100). ¹H-nmr, see Table 3.

1-p-Nitrophenyl-3-(β -D-ribofuranosyl)pyrazole-5-carboxamide (6d). - To a solution of 5c (450 mg, 0.65 mmol) in dioxane (10 ml) concentrated ammonia (20 ml) was added and the mixture was stirred for 4 days at room temperature. Removal of the solvents, then flash chromatography (5:1 ethyl acetate/methanol) afforded 6d (121.5 mg, 51%) (Table 5). Ir: 3466, 3355, 3300, 3244 (NH₂, OH), 1689 (C=O), 1511 and 1350 (NO₂) cm⁻¹; uv: 202 nm (ϵ 3834), 217 (2799), and 302 (2376); ms (*m/z* %): 364 (5, M⁺), 334 (9), 275 (78), 261 (100), 245 (18), 215 (10), 199 (4), 142 (4), 73 (14), and 57 (11). ¹H-nmr, see Table 3.

Methyl 3-(methyl 3-O-methyl- α - and β -D-xylotetro-1,4-furanosid-4-yl)-1-p-nitrophenylpyrazole-5-carboxylate (7) and (8). - To a solution of 5a (500 mg, 1.2 mmol) in anhydrous methanol (50 ml) Dowex 50 (H⁺ in anhydrous methanol ~ 1.5 ml) was added. After 20 h at 65 °C, the reaction mixture was filtered, the solvent was distilled and the residue, submitted to chromatography (9:1 chloroform/acetone), afforded pure 7 (200 mg, 42%), pure 8 (100 mg, 21%) and a fraction containing both anomers (167 mg, cumulated yield 98%) (Table 5). 7. - Ir: 3280 (OH), 1720 (C=O), 1515, and 1345 (NO₂) cm⁻¹; uv: 226 nm (ϵ 8952), and 299 (10674). ¹H-nmr: δ 2.86 (1 H, *d*, $J_{2,\text{OH}} = 6.8$ Hz, OH-2'), 3.32, 3.54, and 3.82 (3x3 H, 3 *s*, 3 OMe), 3.94 (1 H, *dd*, $J_{2,3} = 3.8$ Hz, $J_{3,4} = 6$, H-3'), 4.35 (1 H, *ddd*, $J_{1,2} = 6.8$ Hz, $J_{2,\text{OH}} = 6.8$ Hz, $J_{2,3} = 3.8$ Hz, H-2'), 5.12 (1 H, *d*, H-1'), 5.39 (1 H, *d*, H-4'), 7.14 (1 H, *s*, H-4), 7.64 and 8.31 (2x2 H, 2 *m*, Ph); ms (*m/z* %): 363 (0.5), 362 (2.5), 304 (26.8), 301 (5.3), 276 (24.6), 259 (9.2), 258 (4.2), 118 (7.6), 117 (6.2), 103 (13.2), 101 (31.5), and 87 (100).

8. - Ir: 3280 (OH), 1720 (C=O), 1515, and 1345 (NO₂) cm⁻¹; uv: 220 nm (ϵ 12456), and 301 (11320). ¹H-nmr: δ 2.32 (1 H, *bs*, OH-2'), 3.20, 3.58, and 3.83 (3x3 H, 3 *s*, 3 OMe), 3.93 (1 H, *dd*, $J_{2,3} = 3$ Hz, $J_{3,4} = 5.5$ Hz, H-3'), 4.37 (1 H, *dd*, $J_{1,2} = 1.75$ Hz, $J_{2,3} = 3$ Hz, H-2'), 4.97 (1 H, *d*, $J_{1,2} = 1.75$ Hz, H-1'), 5.52 (1 H, *d*, $J_{3,4} = 5.5$ Hz, H-4'), 7.23 (1 H, *s*, H-4), 7.64 and 8.32 (2x2 H, 2 *m*, Ph); ms (*m/z* %): 362 (1.69), 304 (19.2), 276 (25.4), 259 (10.9), 258 (3.1), 228 (2.9), 118 (8.3), 117 (6.9), 103 (14.4), 88 (11.9), and 87 (100).

REFERENCES

1. R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley, New York, 1970; R. J. Suhadolnik, "Nucleosides as Biological Probes", Wiley, New York, 1979.
2. J. M. J. Tronchet, A. Jotterand, and N. Le Hong, *Helv. Chim. Acta*, 1969, **52**, 2569; J. M. J. Tronchet and F. Perret, *Helv. Chim. Acta*, 1970, **53**, 648; J. M. J. Tronchet, A. Jotterand, N. Le Hong, F. Perret, S. Jaccard-Thorndahl, J. F. Tronchet, J.-M. Chalet, L. Faivre, C. Hausser, and C. Sebastian, *Helv. Chim. Acta*, 1970, **53**, 1484; J. M. J. Tronchet and F. Perret, *Helv. Chim. Acta*, 1971, **54**, 683; J. M. J. Tronchet and A. Jotterand, *Helv. Chim. Acta*, 1971, **54**, 1131.
3. J. M. J. Tronchet, J. F. Tronchet, F. Rachidzadeh, and F. Barbalat-Rey, *Carbohydr. Res.*, 1988, **181**, 97.
4. J. M. J. Tronchet, J. F. Tronchet, and S. Zerelli, 13th International Symposium on Carbohydrates, Cornell Univ., 10-15 August 1986, Abstract A-92.
5. J. M. J. Tronchet, B. Baehler, N. Le Hong, and P. F. Livio, *Helv. Chim. Acta*, 1971, **54**, 921.
6. G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Am. Chem. Soc.*, 1962, **84**, 753; G. J. Karabatsos and R. A. Taller, *Tetrahedron*, 1968, **24**, 3923; J. M. J. Tronchet, B. Baehler, A. Jotterand, and F. Perret, *Helv. Chim. Acta*, 1971, **54**, 1660.
7. R. N. Butler, F. L. Scott, and T. A. F. O'Mahony, *Chem. Rev.*, 1973, **73**, 93; R. N. Butler, *Chem. Rev.*, 1984, **84**, 249.
8. F. Perret, "Utilisation de dipoles-1,3 pour la synthèse de C-nucleosides", Ph. D. Thesis No 1668, University of Geneva, 1974.
9. J. Descamps and E. De Clercq, "Broad-spectrum Antiviral Activity of Pyrazofurin (Pyrazomycin)" in *Current Chemotherapy*, W. Sigenthaler and R. Luthy Eds, American Chemical Society for Microbiology, Washington DC, 1978, pp. 354-357; F. Kawana, S. Shigeta, M. Hosoya, H. Susuki, and E. De Clercq, *Antimicrob. Agents Chemother.*, 1987, **31**, 1225; S. Shigeta, K. Kouno, Y. Yokota, K. Nakamura, and E. De Clercq, *Antimicrob. Agents Chemother.*, 1988, **32**, 906.
10. W. Meyer zu Reckendorf, *Chem. Ber.*, 1963, **96**, 2019.
11. M. Loew and M. M. Goodman, *Chem. Ind. (London)*, 1967, 2026.
12. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
13. H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, 1973, **38**, 1836.
14. T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn*, 1970, **43**, 1254.

Received, 28th September, 1992