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Note

Synthesis of furanose glycals from furanose 1,2-diols and their cyclic thiocarbonate esters

Rafael Robles Diaz *, Concepción Rodríguez Melgarejo, Isidoro Izquierdo Cubero, María T. Plaza López-Espinosa

Department of Organic Chemistry, University of Granada, E-18071, Granada, Spain

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Abstract

Two new methods for the synthesis of furanoid glycals are described. Both procedures were shown to be faster and cheaper that those previously reported. Protected 1,2-dihydroxy-pento- and hexo-furanose derivatives with the D-*xylo*, D-*gluco* and D-*ribo*, D-*allo* configurations were used as starting material to afford the corresponding C-3,4 D-*threo* and D-*erythro* glycals derivatives. © 1997 Elsevier Science Ltd.

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The synthesis of 1,4-anhydro-2-deoxy-pent- and -hex-1-enitol (furanose glycals) has received great attention in recent years, due to the fact that they have been used as key intermediates in the preparation of structurally diverse compounds with various biological activities such as polyether antibiotics [1], 6-*epi*-leukotrienes *C* and *D* [2], antiviral and antitumor *C*-nucleosides [3], *α-arabino* nucleosides [4], 2′,3′-dideoxynucleosides [5], and more recently 2′-deoxynucleosides [6].

To the best of our knowledge, the first glycal derivative with a furanose structure, namely 1,4-anhydro-3,5-di-*O*-benzoyl-2-deoxy-D-*erythro*-pent-1-enitol, was reported by Ness and Fletcher [7], but several protection and deprotection steps were necessary for the synthesis of the appropriate precursor and even the final product was shown to be extremely unstable, undergoing an allylic rearrangement process as well as an elimination of benzoic acid to afford furfuryl benzoate. A modification of this method has been described by Holzapfel et al. [8]. Lately, Ireland et al. [1] described a general protocol for the synthesis, in five steps, of furanose glycals with a free hydroxyl group at C-3, using 1,4-D-ribonolactone as starting material, which involved the reductive cleavage of 2,3-*O*-isopropylidene protected furanosyl chloride as the crucial step. The same protocol, but starting from the cheaper D-ribose, was subsequently used by Abramski and Chmielewski [9] for the preparation of 3,5-di-*O*-substituted 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol.

The attempt by Patroni et al. [10] of transforming 3,5-di-*O*-benzyl-1,2-*O*-thiocarbonyl-α-D-xylofuranose into the corresponding furanose glycal (1,4-anhydro-3,5-di-*O*-benzyl-2-deoxy-D-*threo*-pent-1-enitol) by a dideoxygenation-elimination process of the thiocarbonate group using tri-*n*-butyltin hydride, was almost unsuccessful since the pure glycal could not be isolated and only ^{1}H NMR evidence of its presence resulted. Recently, Larsen et al. [11] have reported the synthesis of 3,5-di-*O*-silylated 1,4-anhydro-2-de-

* Corresponding author.

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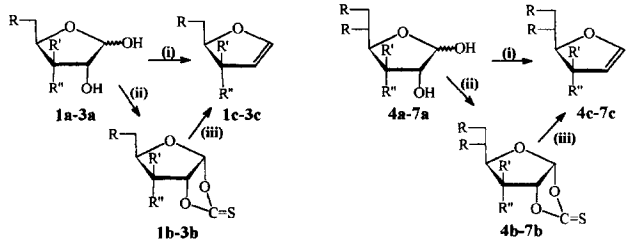
oxy-D-*erythro*-pent-1-enitol from the commercially, although expensive, available 2′-deoxythymidine by refluxing in 1,1,1,3,3,3-hexamethyldisilazane in the presence of ammonium sulfate. Finally, Kassou and Castillón [12] have reported that oxidation of phenyl 2-deoxy-1-selenofuranosides to the corresponding selenoxides gave furanoid glycals via selenoxide-elimination.

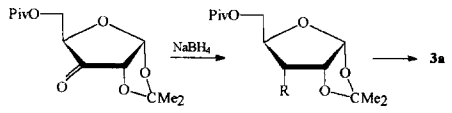
We describe herein the results of two well-known reactions in the carbohydrate field. The first refers to previous results of Garegg and Samuelsson [13] who showed that the action of the iodine-triphenylphosphine-imidazole reagent on *vic*-diol caused the substitution of both hydroxyl groups to give the unstable *vic*-diiodide that suffers an iodine-elimination reaction to the corresponding unsaturated sugar. The second reaction is related to the modified Corey's dideoxygenation procedure [14], where the action of 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMPD) on a *vic*-diol thiocarbonate was shown to result in elimination giving the unsaturated compound which has been used in the synthesis of enofuranosides [15]. It occurred to us that the application of such methods to suitably protected carbohydrate 1,2-diols in their furanose form could similarly lead to furanoid glycals (Scheme 1).

The appropriately protected 1,2-diols are by no means readily available, but a general approach should be via 1,2:3,5- or 1,2:5,6-di-*O*-isopropylidene derivatives of D-xylose and D-glucose, respectively, followed by selective hydrolysis of the less stable 3,5- or 5,6-*O*-isopropylidene group, protection of the free hydroxyl groups and finally acid hydrolysis [1] of the remaining 1,2-*O*-isopropylidene group to the required 1,2-diols. Thus, compounds with a D-*xylo* (**1,2**) or D-*gluco* (**4–6**) configuration have been synthesized by this procedure. Compounds with a D-*ribo* (**3**) or D-*allo* (**7**) [2] configuration, where an inversion in the configuration at C-3 was necessary, were synthesized



1 and 4 R = R′ = OBn; R″ = H
2 and 5 R = R′ = OBz; R″ = H
3 R = OPiv; R′ = H; R″ = OBz
6 R = OBz; R′ = OAll; R″ = H
7 R = R″ = OBz; R′ = H

Scheme 1.



8

9 R = OH
10 R = OBz

Scheme 2.

through a well-established methodology, consisting in the preparation of the adequately protected aldos-3-ulose derivative and subsequent high stereoselective reduction with sodium borohydride. Thus, the synthesis of 3-*O*-benzoyl-5-*O*-2,2-dimethylpropanoyl-D-ribofuranose (**3a**) was straightforward following this methodology. 1,2-*O*-Isopropylidene-5-*O*-2,2-dimethylpropanoyl-α-D-*erythro*-pent-3-ulofuranose (**8**) [16] was reduced with $NaBH_4$ in methanol to yield only 1,2-*O*-isopropylidene-5-*O*-2,2-dimethylpropanoyl-α-D-ribofuranose (**9**) which was transformed into its 3-*O*-benzoyl derivative (**10**) and finally hydrolyzed to **3a** (see Scheme 2).

Treatment of **1a–7a** with iodine-triphenylphosphine-imidazole at room temperature caused the instantaneous formation (TLC evidence) of the corresponding glycals **1c–7c**, in contrast with results reported by Garegg and Samuelsson [13], where refluxing in toluene for several hours was necessary to get the unsaturated sugars. This successful result must be attributed in our case to the higher reactivity of the hydroxyl group at the anomeric position [19]. On the other hand, reaction of 1,2-diols (**1a–7a**) with thiophosgene in alcaline medium yielded the related 1,2-thiocarbonate derivatives (**1b–7b**) in high yield in all cases (see Table 1). This method has the advantage with respect to that previously reported [10,20] of using the cheaper thiophosgene instead of 1,1′-thiocarbonyldiimidazole. Subsequent treatment of **1b–7b** with DMPD in toluene at 70 °C proceeded with elimination to afford the above glycals **1c–7c**.

Yields of **1c–7c** (see Table 1) vary, depending on their stability, **2c** being the most labile according to other authors [8]. We concluded that all glycals, even

[1] The 1,2-diols were prepared from the corresponding parent compounds by treatment with aq 60% trifluoroacetic acid at room temperature for 24 h, followed by column chromatography, and were shown to be mixtures of both anomers (^{1}H NMR evidence). Loss of other protecting groups was not observed.

[2] Precursors of **6a** and **7a** have been reported in ref. [17] and [18], respectively.

Table 1
Furanoid glycals from **1a–7a**

Compds	Substrates (**1a–7a**)	Ref.	1,2-Thiocarbonates [a] (**1b–7b**)		Mp (°C)	Ref.	Glycals [a] (**1c–7c**)			Mp (°C)	Ref.
			$[\alpha]_D$	(yield %)			$[\alpha]_D$	(yield %) [b]			
1	R = R′ = OBn; R″ = H	[10,20]	+20°	75	syrup	[10,20]	−132.5°	– [c]	77	syrup	[8]
2	R = R′ = OBz; R″ = H	[8]	+3°	100	155–156	–	–	– [c]	– [c]	–	–
3	R = OPiv; R′ = H; R″ = OBz	–	+157.5°	83	46–47	–	+0.5°	25	75	76–77	–
4	R = R′ = OBn; R″ = H	[8]	+35°	70	78–79	–	+72.5°	50	74	syrup	[8]
5	R = R′ = OBz; R″ = H	[8]	−14°	76	185–186	–	+33°	87	– [d]	65–66	–
6	R = OBz; R′ = OAll; R″ = H	[17]	+55.5°	77	syrup	–	−113°	55	60	syrup	–
7	R = R″ = OBz; R′ = H	[18]	+170°	100	171–172	–	+206°	70	– [d]	60–61	–

[a] All compounds gave satisfactory analytical and spectroscopic data, unless otherwise states.
[b] Yields refer to method (*i*) and (*ii*), respectively.
[c] Glycals could not be isolated in a practical yield due to their high instability but were characterized by NMR.
[d] Glycals could not be isolated in pure state due to the same mobility to that of the resulting thiophosphonamide.

Table 2
^{1}H NMR data for compounds **2b–7b** and **1c–7c** [a]

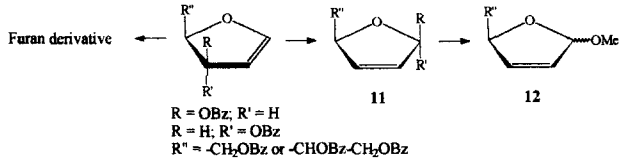
Compound	^{1}H-Chemical shifts (δ), with multiplicities [b] (only for sugar protons)									
	H-1	H-2	H-3		H-4		H-5		H-5′	H-6	H-6′
2b	6.54d	5.32d	5.82d		4.74dt		←	4.67d →	–	–	
3b	6.40d	5.55t	5.15dd		←	4.52–4.45m	→		4.62dd	–	–
4b	6.35d	5.04d	←	4.33–4.30	→		4.08m		–	3.89dd	3.64dd
5b	6.54d	5.32d	5.79d		4.80dd		5.83ddd		–	4.99dd	4.55dd
6b	6.48d	5.18d	4.25d		4.75dd		5.76ddd		–	4.95dd	4.41dd
7b	6.41d	5.62t	5.42dd		4.64dd		5.84dt		–	4.78dd	4.62dd
1c	6.65d	5.28t	4.66dd		4.50m		3.99dd		3.88dd	–	–
2c	6.76d	5.38t	6.18dd			←	4.88–4.70m	→		–	–
3c	6.70d	5.29t	5.90t		4.78dt		4.36dd		4.32dd	–	–
4c	6.59d	5.33t	4.65dd		4.35dd		4.19ddd		–	3.90dd	3.74dd
5c	6.74d	5.45t	6.18dd		4.90t		5.97ddd		–	4.99dd	4.74dd
6c	6.48d	5.18d	4.25d		4.57dd		5.76ddd		–	4.95dd	4.51dd
7c	6.72d	5.39t	6.20t		4.99dd		5.67m		–	4.78dd	4.70dd

Compound	Coupling constants (Hz)								
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
2b	4.6	0	3.0	5.7					
3b	4.7	5.5	8.7	–	5.4	13.0			
4b	4.6	0	–	–			2.0	5.0	10.7
5b	4.5	0	3.1	9.1			2.4	5.2	12.5
6b	4.6	0	3.3	8.5			2.4	5.3	12.5
7b	4.7	5.7	9.0	5.8			3.7	4.6	12.2
1c	2.8	2.6	7.0	4.6	7.6	10.6			
2c	2.7	2.7	7.0	–	–	–			
3c	2.7	2.7	2.8	4.6	5.7	11.9			
4c	2.7	2.5	6.7	8.8			1.9	5.2	10.8
5c	2.7	2.7	7.2	7.7			2.4	5.1	12.4
6c	4.6	0	3.3	8.4			2.3	5.3	12.5
7c	2.5	2.6	2.7	5.9			3.7	5.8	12.2

[a] From solutions in $CDCl_3$ containing TMS as the internal standard.
[b] From 300 and 400 MHz spectra.

Table 3
^{13}C NMR data for compounds **2b–7b** and **1c–7c**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C=S
2b	107.20	86.69	74.19	78.78	60.83	–	188.92
3b	106.63	80.83	71.46	77.25	61.29	–	189.73
4b	107.66	85.46	79.56	80.07	74.59	69.64	189.82
5b	107.03	86.49	73.57	78.29	67.68	66.46	188.86
6b	107.67	85.51	78.70	79.50	68.16	63.47	189.53
7b	106.27	81.00	72.84	77.10	70.01	62.69	189.49
1c	150.68	101.46	79.51	83.39	67.86	–	–
2c	152.11	101.09	76.17	80.69	62.07	–	–
3c	152.11	99.56	79.32	83.80	63.46	–	–
4c	150.40	102.44	78.96	83.09	75.46	70.63	–
5c	151.77	102.01	75.51	80.28	69.14	63.88	–
6c	150.29	102.28	79.15	82.02	69.66	64.07	–
7c	151.98	100.43	78.77	84.15	70.82	62.82	–



Scheme 3.

those in crystalline state, decomposed on standing to give the corresponding furan derivatives [8,21]. In addition, those with an acyl protecting group at C-3 underwent rearrangement to the corresponding 1-*O*-acyl-2-enofuranoses (**11**), in an aprotic solvent ($CHCl_3$), whereas the methyl α,β-2-enofuranosides (**12**) were obtained in methanol (see Scheme 3). This behavior has been also observed by various authors for furanose [21] and pyranose glycals [22]. (See Tables 2 and 3.)

1. Experimental

General methods.—Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concn under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solns in $CDCl_3$ (internal Me_4Si). IR Spectra were recorded with a Perkin–Elmer 782 instrument. Optical rotations were measured for solns in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated Silica Gel 60 F_{254} aluminium sheets (E. Merck) and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (E. Merck, 7734). The non crystalline compounds, for which elemental analyses were not obtained, were shown to be homogeneous by chromatography and characterized by NMR.

1,2-O-Isopropylidene-5-O-2,2-dimethylpropanoyl-α-D-ribofuranose (**9**).—To a cooled (ice-water) and stirred solution of 1,2-*O*-isopropylidene-5-*O*-2,2-dimethylpropanoyl-α-D-*erythro*-pent-3-ulofuranose [16] (**8**, 2 g, 7.35 mmol) in MeOH (25 mL), $NaBH_4$ (0.42 g, 11 mmol) was added portionwise, and the mixture left for 4 h. TLC (ether) then revealed the presence of a slower running product. The mixture was neutralized with AcOH, concd and the residue extracted with EtOAc. Concentration of the extracts gave pure **9** (1.78 g, 89%): mp 74–75 °C (from petroleum ether), $[\alpha]_D$ +44° (*c*, 1.2). IR (KBr): *ν* 3464 (OH), 1729 (C=O, 2,2-dimethylpropanoate), 1398 and 1380 cm^{-1} (CMe_2). NMR data: ^1H, *δ* 5.80 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.66 (bdd, 1 H, H-2), 4.43 (dd, 1 H, $J_{4,5}$ 2.6, $J_{5,5'}$ 12.3 Hz, H-5), 4.17 (dd, 1 H, $J_{4,5'}$ 4.8 Hz, H-5'), 3.94 (ddd, 1 H, $J_{3,4}$ 8.7 Hz, H-4), 3.84 (dd, 1 H, $J_{2,3}$ 5.1 Hz, H-3), 2.30 (bs, OH), 1.56 and 1.36 (2 s, 6 H, CMe_2), and 1.19 (s, 9 H, CMe_3); ^{13}C, *δ* 178.5 (CO), 112.8 (CMe_2), 104.1 (C-1), 78.6, 78.3, and 72.0 (C-2,3,4), 62.7 (C-5), 38.9 (Me_3C), 27.2 (Me_3C), 26.6 and 26.5 (Me_2C). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.90; H, 8.32.

3-O-Benzoyl-1,2-O-isopropylidene-5-O-2,2-dimethylpropanoyl-α-D-ribofuranose (**10**).—Conventional benzoylation of **9** (1,78 g, 6.5 mmol) with benzoyl chloride (1.8 mL, 13 mmol) in dry pyridine (10 mL) catalyzed with 4-dimethylaminopyridine (DMAP, 50 mg) gave, after usual work-up and recrystallization from ether–hexane, pure **10** (2.45 g, quantitative) as fine white needles: mp 88–89 °C (from petroleum ether); $[\alpha]_D$ +82° (*c*, 1.24); IR (KBr): *ν* 3075 (C–H, aromatic), 1723 (C=O, 2,2-dimethylpropanoate and benzoate) and 718 cm^{-1} (aromatic). NMR data: ^1H, *δ* 8.14–8.06, 7.66–7.57, and 7.50–7.43 (3 m, 5 H, Ph), 5.89 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.95 (dd, 2 H, $J_{2,3}$ 5.3 Hz, H-2), 4.93 (dd, 1 H, $J_{3,4}$ 7.7 Hz, H-3), 4.49 (ddd, 1 H, $J_{4,5}$ 3.1 Hz, H-4), 4.43 (dd, 1 H, H-5), 4.20 (dd, 1 H, $J_{4,5'}$ 4.6, $J_{5,5'}$ 12.2 Hz, H-5'), 1.55, and 1.33 (2 s, 6 H, CMe_2), and 1.19 (s, 9 H, CMe_3); ^{13}C, *δ* 178.3 ($COCMe_3$), 165.8 (COPh), 133.8, 133.6, 130.3, 130.0, 128.6 (CO*Ph*), 113.3 (CMe_2), 104.5 (C-1), 77.5, 76.0, and 73.0 (C-2,3,4), 62.6 (C-5), 38.9 ($COCMe_3$), 27.2 ($COCMe_3$), 26.8 and 26.7 (CMe_2). Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.78; H, 6.73.

Synthesis of 1,2-thiocarbonates (**1b–7b**).—To a cooled (ice-water) and stirred soln of the corresponding 1,2-diol (1 mmol), *N*-ethyldiisopropylamine (0.8 mL) and DMAP (50 mg) in dry CH_2Cl_2 (5 mL), a solution of thiophosgene (0.1 mL, 1.3 mmol) in the same solvent (5 mL) was added dropwise. Reaction was monitored by TLC (ether) indicating that in all cases it had finished after 15 min. The mixture was diluted with CH_2Cl_2 (25 mL), washed, with aq 10% HCl, water, satd aq $NaHCO_3$ and brine. The organic solvent was evaporated and the residue chromatographed (mixtures of ether–hexane) to give the corresponding 1,2-thiocarbonate (**1b–7b**).

Synthesis of glycals (**1c–7c**).—*i*) To a well-stirred soln of iodine (254 mg, 1 mmol) in dry CH_2Cl_2 (10 mL), triphenylphosphine (262 mg, 1 mmol) and imidazole (272 mg, 4 mmol) were added stepwise to

give a pale yellow suspension. The corresponding 1,2-diol (0.5 mmol) was added and the reaction mixture immediately changed to brown. TLC (2:3 ether–hexane) showed the absence of 1,2-diol derivative and the presence of the corresponding glycals as a faster-running compound. A few drops of Et_3N were added to the mixture, concd to half volume, diluted with hexane, which contained a few drops of Et_3N, and then percolated (1:5 ether–hexane, with a few drops of Et_3N) through a short column of florisil to afford the corresponding glycals (**1c–7c**).

ii) To a heated (70 °C) soln of the corresponding 1,2-thiocarbonate derivative (0.5 mmol) in toluene (1 mL), 1,3-dimethyl-2-phenyldiazaphospholidine (0.2 mL) was added and the mixture maintained at this temperature until no more starting material was present (15–30 min) as revealed by TLC (3:2 ether–hexane). Concentration of the mixture, followed by column chromatography (1:6 ether–hexane) of the residue gave the corresponding glycals (**1c–7c**) (see Table 1).

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