A Convenient Synthesis of *C*-Glycofuranosylmalonates and Related Derivatives

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The synthesis of *C*-glycofuranosyl derivatives has received considerably attention because of the presence of such compounds in natural products. They have been synthesized as precursors of *C*-nucleosides[1], or as chiral intermediates in natural products syntheses[2]. The formation of carbon-carbon bonds at the anomeric center of a sugar often proceeds by reaction of a glycosyl halide with carbanions[1], or by Wittig reaction of the free aldehyde group and subsequent cyclization of the formed hydroxyolefin[3]. The reaction of sodiomalonates with glycosyl halides has been reported[4] and we have described a related method based on the activation of the anomeric hydroxy group by an oxyphosphonium salt[5]. In contrast, the reaction of sodiomalonates with the potential aldehyde group of sugars is poorly documented. A few reports on such a Knoevenagel-Doebner type reaction in carbohydrate field have appeared in the last years[6].

In this communication, we describe a direct method for the preparation of several *C*-glycofuranosylmalonates and related malonic derivatives in good yield, from three readily available

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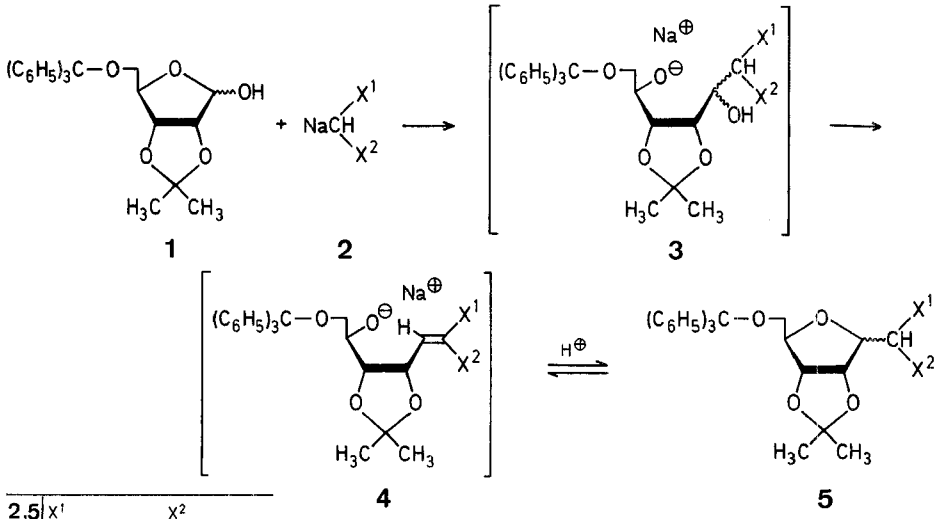
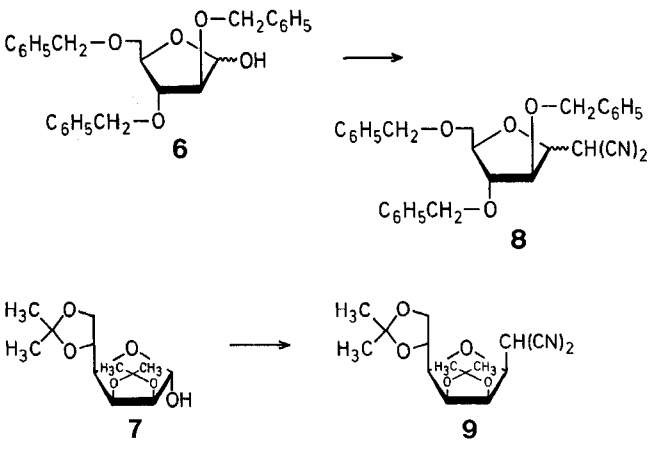
sugars bearing a free anomeric hydroxy group. Thus, the D-ribose derivative **1** reacted readily with sodiomalonitrile **(2a)** at room temperature in dry tetrahydrofuran or dimethoxyethane, to give **5a** as the sole product (Method A). After silica gel chromatography, the pure α-anomer[7] was isolated in 84% yield. Similarly, *C*-glycosides **5b** and **5c** were obtained, whose ^{1}H-N.M.R. spectra showed them to be mixtures of α- and β-anomers. Each anomer was in fact a mixture of two epimers at C-2 (heptose numbering) due to the prochirality of carbanions **2b** and **2c**. Under these conditions, diethyl sodiomalonate **(2d)** did not react with **1**, but upon refluxing the mixture for two days in tetrahydrofuran, **5d** was isolated in 30% yield as a mixture of anomers. Another procedure was used to achieve the transformation into **5** under milder conditions using phase transfer catalysis. This technique has been successfully used in the alkylation of malonic derivatives[8] and specially in carbohydrate chemistry[9]. Under these conditions (Method B) **5a–c** have been prepared in good yields but no condensation occurred with diethyl malonate. In this case the formation of an intermolecular methylene acetal was observed as previously reported[10].



1 2 3 4 5

2,5	X¹	X²
a	–CN	–CN
b	–CN	–CO–NH$_2$
c	–CN	–COOCH$_3$
d	–COOC$_2$H$_5$	–COOC$_2$H$_5$

In addition, we carried out the reaction of two representative furanoses with sodiomalonitrile **(2a)**. We used 2,3,5-tri-*O*-benzyl-D-arabinose **(6)** and the D-mannose derivative **7**, which, in turn, could be transformed into the D-lyxo derivative. *C*-Glycosides **8** and **9** were obtained in good yield (Method A), respectively, as a mixture of α- and β-anomers in equal amount for **8**, while **9** was the pure β-anomer.



6 8 7 9

This reaction seems to proceed via condensation of the carbanion with the aldehyde group of the sugar giving **3**, followed by dehydration. Ring closure occurs by Michael addition on the activated olefin **4**, thus affording two anomers. The presence of an acidic proton at C-2 of the *C*-glycosylmalonates **5**, **8**, and **9** gives rise to an "anomeric" equilibration in basic medium. Thus, the thermodynamically more stable anomer will be predominant in the mixture. For compounds **5a** and **9**, only the more stable anomer is obtained, in which the malonyl and isopropylidene moieties are *cis*, according to the theory of Ohrui et al.[11]. In contrast, in the D-arabino series, none of the anomers seems to be stabilized, both anomers of **8** are isolated in equal amounts. It seems that the nature of the malonic derivative dramatically influences the course of the reaction. Strongly activating groups (e.g. nitrile) facilitate the reaction and the anomeric equilibration.

This method provides a short route to *C*-glycofuranosylmalonates, avoiding the preparation of rather unstable glycosyl halides. Sodiomalononitrile **(2a)** is the most suitable reagent for the preparation of versatile precursors of *C*-nucleosides.

Tetrahydrofuran is distilled just before use over sodium/benzophenone, sodium hydride (Fluka) is washed three times with dry tetrahydrofuran. T.L.C. analyses are performed on Merck precoated silica gel plates, solvent: ethyl acetate/hexane (1/1) or toluene/ether (8/2), visualization by spraying with sulfuric acid and heating.

C-Glycosidylmalonic Derivatives 5, 8, and 9; General Procedure:

Method A: A solution of the malonic derivative **2** (15 mmol) in dry tetrahydrofuran (15 ml) is added to a stirred suspension of sodium hydride (50%, 720 mg, 15 mmol) in dry tetrahydrofuran (20 ml) at 0 °C under argon and then the sugar derivative (5 mmol) in dry tetrahydrofuran (10 ml) is added. Stirring is continued at room temperature overnight, the mixture is poured into saturated ammonium chloride solution (20 ml), extracted with dichloromethane (3 × 100 ml). The organic layer is washed with water (2 × 30 ml) and brine (50 ml), then dried with magnesium sulfate. The solvent is evaporated under reduced pressure, the crude residue is chromatographed over silica gel using ethyl acetate/hexane (1/1) for compounds **5b** and **8** or toluene/ether (8/2) for **5a, c, d**, and **9**. In the case of derivative **5d**, the mixture is refluxed for 2 days.

Method B: The sugar (5 mmol) is dissolved in dichloromethane or benzene (20 ml), 10% aqueous sodium hydroxide (20 ml) is added together with tetrabutylammonium hydrogen sulfate (1.86 g, 5 mmol). The malonic derivative **2** (15 mmol) is added and the mixture is vigorously stirred for ~3 h (T.L.C. monitoring using ethyl acetate/hexane or toluene/ether mixtures as eluent, see above). The mixture is then diluted with dichloromethane (100 ml) and water (50 ml). The aqueous layer is extracted with dichloromethane (50 ml) and the combined extracts are washed as described in Method A.

Table. *C*-Glycofuranosylmalonic Derivatives prepared

Product	Yield [%][a] by Method A	Method B	Anomeric Ratio[b]	Physical Data	Molecular formula[c] or Lit. Data	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
5a	84	80	α	$[\alpha]_D^{20}$: −26° (*c* 0.4, $CHCl_3$)	$C_{30}H_{28}N_2O_4$ (480.5)	2150 (CN)	1.37 (s, 3H); 1.55 (s, 3H); 3.17 (dd, 1H); 3.47 (dd, 1H); 4.06 (d, 1H); 4.30 (t, 1H); 4.8 (m, 2H); 4.95 (dd, 1H); 7.2–7.6 (m, 15H)
5b	80	62	$\alpha:\beta=3:1$	—	$C_{30}H_{30}N_2O_5$ (498.5)	3500–3400; 1700 ($CONH_2$)	1.3 (m, 3H); 1.5 (m, 3H); 3.3 (m, 2H); 3.8 (m, 1H); 4.3 (m, 1H); 4.7 (m, 1H); 4.8 (m, 1H); 4.9 (m, 1H); 6.5 (m, 2H); 7.2–7.6 (m, 15H)
5c	61	57	$\alpha:\beta=3:1$	—	$C_{31}H_{31}NO_6$ (513.6)	1755 (ester)	1.3 (m, 3H); 1.5 (m, 3H); 3.1 (m, 1H); 3.4 (m, 1H); 3.80 (s, 3H); 3.9 (m, 1H); 4.3 (m, 1H); 4.73 (d, 1H); 4.80 (dd, 1H); 4.9 (m, 1H); 7.2–7.6 (m, 15H)
5d	30	—	$\alpha:\beta=2:1$	pure α: $[\alpha]_D^{25}$: +43° (*c* 0.3, $CHCl_3$)	$[\alpha]_D^{25}$: +35.6° (*c* 1, $CHCl_3$)[4b]	1750 (ester)	1.27 (t, 3H); 1.30 (s, 3H); 1.50 (s, 3H); 3.1 (m, 1H); 3.3 (m, 1H); 3.8 (m, 1H); 4.2 (m, 3H); 4.6 (m, 1H); 4.9 (m, 1H); 5.0 (m, 1H); 7.2–7.6 (m, 15H)
8	82	—	$\alpha:\beta=1:1$	—	$C_{29}H_{28}N_2O_4$ (468.5)	2150 (CN)	3.5 (m, 2H); 3.9 (m, 1H); 4.1 (m, 2H); 4.2–4.4 (m, 8H); 7.2 (m, 15H)
9	78	—	β	$[\alpha]_D^{25}$: −57° (*c* 0.3, $CHCl_3$)	$C_{15}H_{20}N_2O_5$ (308.3)	2150 (CN)	1.37 (s, 6H); 1.40 (s, 3H); 1.50 (s, 3H); 3.73 (dd, 1H); 4.1 (m, 3H); 4.20 (s, 1H); 4.4 (m, 1H); 4.8 (m, 2H)

[a] Yield of isolated product.
[b] Determined by ^{1}H-N.M.R. spectrometry.
[c] Satisfactory microanalyses obtained: C ±0.37, H ±0.06, N ±0.33.

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