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β-ELIMINATION IN ALDONOLACTONES. STRUCTURE OF THE FURAN-2-ONE DERIVATIVE OBTAINED BY BENZOYLATION OF D-GLYCERO-D-GULO-HEPTONO-1,4-LACTONE

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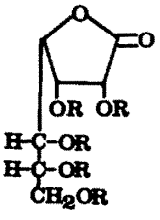
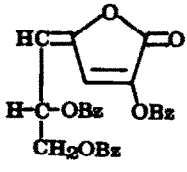
Abstract - A tri-unsaturated derivative, i. e. 3-benzoyloxy-5-(3-benzoyloxy-allylidene)-(5H)-furan-2-one (5), previously described as 3-benzoyloxy-5-(2-benzoyloxyallylidene)-(5H)-furan-2-one (3), was obtained from per-O-benzoyl-D-glycero-D-gulo-heptono-1,4-lactone via β-elimination in basic conditions. Stereoespecific catalytic hydrogenation rendered 2,7-di-O-benzoyl-3,5,6-trideoxy-(DL)-threo-heptono-1,4-lactone (6). Structures 5 and 6 were assigned on the basis of spectral studies.

In previous papers, we have reported the formation of di- and tri-unsaturated derivatives on benzoylation of aldono-1,4-lactones[1-4]. Thus, D-glycero-D-gulo-heptono-1,4-lactone (1) yielded two (5H)-furan-2-one derivatives, which were described as 3-benzoyloxy-5-(2,3-dibenzoyloxypropylidene)-(5H)-furan-2-one (2) and 3-benzoyloxy-5-(2-benzoyloxyallylidene)-(5H)-furan-2-one (3), respectively[3]. These structures were assigned considering that the working mechanism is the same for all the elimination steps[2].



1 R = H

4 R = Bz



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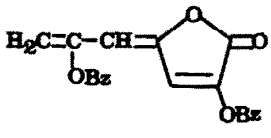

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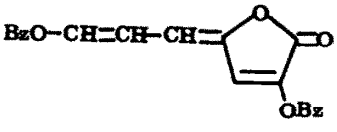

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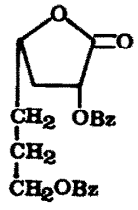

6 (DL)

With the aim to use these di- and tri-unsaturated derivatives for the synthesis of deoxylactones and deoxysugars via sequential catalytic hydrogenation and diborane reduction, attention was focussed on optimizing their synthesis. The yields on the furan-2-one derivatives obtained on benzoylation of D-glycero-D-gulo-heptono-1,4-lactone (1) in pyridine, were poor[3]. Better results were obtained when the β-elimination reaction was carried out on previously synthesized 2,3,5,6,7-penta-O-benzoyl-D-glycero-D-gulo-heptono-1,4-lactone[5] (4) by triethylamine in chloroform solution at room temperature. The maximum yield on the tri-unsaturated derivative was achieved in 6 h and the compound was undistinguishable from the product obtained with pyridine in our laboratory[3]. Its structure was reassigned now as 3-benzoyloxy-5-(3-benzoyloxyallylidene)-(5H)-furan-2-one (5) on the basis of ^{1}H- and ^{13}C-n.m.r. spectra and of the structure of the hydrogenated product (6).

The ^{1}H-n.m.r. spectrum of 5 at 200 MHz is reproduced in Fig. 1. Assignment of the vinylic protons was achieved as follows. Irradiation of the multiplet at δ 7.60 (aromatic protons and H-7) caused simplification of the signals at δ 6.23 (H-6). When H-5 (δ6.42) was irradiated, the signal at δ 6.23 appeared as a doublet and the allylic coupling ($J_{5,7}$) was not observed for H-7. On irradiation at δ 6.23, the signals at δ 6.42 (H-5) and δ 7.60 (H-7) respectively collapsed.

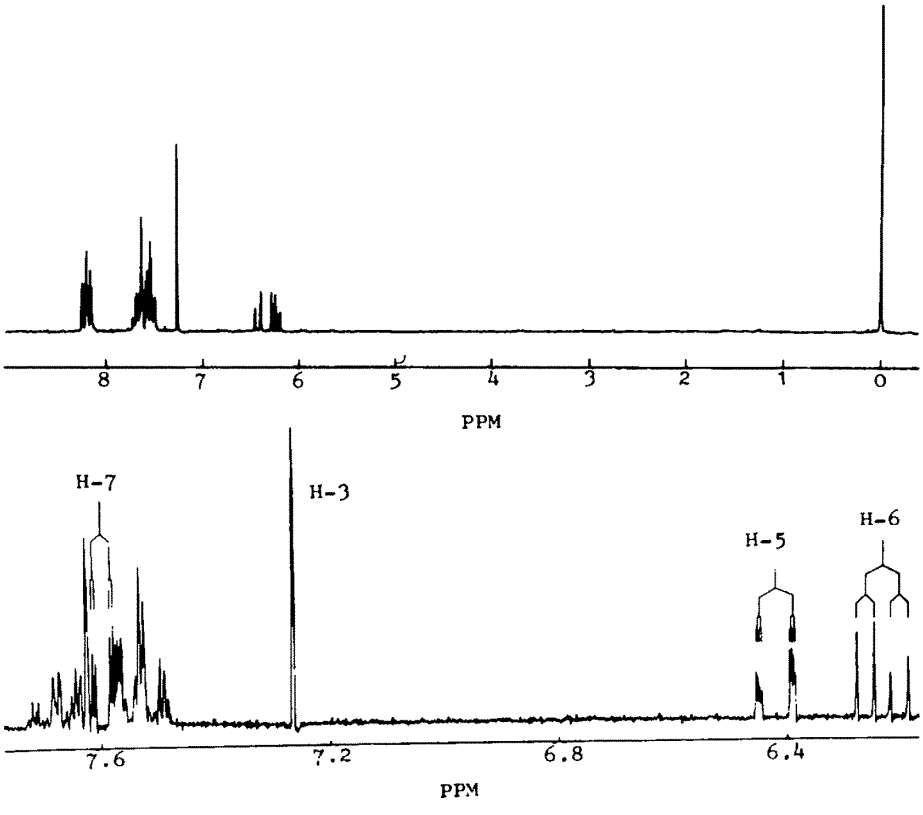

Fig. 1. ^{1}H-N.m.r. spectrum of 3-benzoyloxy-5-(3-benzoyloxyallyliden)-(5H)-furan-2-one (5). The hydrogen atoms were numbered as for the original lactone. Upper, full spectrum; lower, 6.2-7.8 p.p.m. region expansion.

In a ^{13}C-n.m.r. off-resonance decoupling experiment, the signals at 145.4 (C-4) and 138.4 p.p.m. (C-2) remained as singlets while the signals at 137.9 (C-7); 123.5 (C-3); 107.2 and 106.0 p.p.m. (C-5 and C-6) were split into doublets. In structure 3, the terminal carbon atom would appear as a triplet. Assignments were made by comparison with the data for other unsaturated aldonolactones[6].

The m.s. showed the molecular ion at 362 and the only prominent peaks were those arising from the benzoate groups (m/z 105, 77, 51). The stereochemistry of the double bonds was not established.

The benzoic acid elimination from benzoylated aldonolactones takes place in successive steps. The relative extent of breaking of the C-H bond and the C-OBz bond depends on the ease of removal of the hydrogen as a proton and the fact that the benzoate is a poor leaving-group.

The H-2 proton in aldonolactones is acidic due to the stabilization of the intermediate carbanion and it is likely that an E_{1cb} mechanism operates in the first elimination step. A similar reasoning could explain the elimination of the second molecule of benzoic acid but not further elimination to give 5. In the unsaturated lactone 2, H-6 is more acidic than H-7, and its removal should lead to the formation of 3. The fact that 5 is the real product of the reaction would indicate that the driving force in this case is the stability of the resulting olefin, and the orientation in the elimination reaction is not the expected one on the basis of the intermediate carbanion. Furthermore, compound 5 was the only one observable in the reaction mixture.

Catalytic hydrogenation of 5 on palladium-charcoal yielded crystalline 2,7-di-O-benzoyl-3,5,6-trideoxy-(DL)-threo-heptono-1,4-lactone (6). Compound 6 was homogeneous by t.l.c. and h.p.l.c. under different conditions; this fact together with the spectral data, indicate that we are dealing with only one pair of enantiomers of the two theoretically possible from 5. After hydrogenation of the exocyclic double bond, the 3- benzoyloxypropyl group attached to the ring would prevent attack from the same side, resulting in the formation of only one pair of enantiomers, in which the two chiral centers bear a threo relationship. We have already reported[2,4,7] stereoselectivity in the hydrogenation of enono-1,4-lactones over palladium.

In the ^{1}H-n.m.r. spectrum of 6 (Table I) the chemical shifts and coupling constants for the ring protons are similar to the values for 2,5-di-O-benzoyl-3,6-dideoxy-L-arabino-hexono-1,4-lactone[8] (7) and 2-O-benzoyl-3,5,6-trideoxy-(DL)-threo-hexono-1,4-lactone[4] (8), in accordance with the proposed configuration.

The large values for $J_{2,3}$ (8.60 Hz), $J_{2,3'}$ (10.70 Hz) and $J_{3',4}$ (10.40 Hz) confirm the postulated threo relationship for the two chiral centers. In the erythro configuration H-2 (or H-4) would lie outside the angle formed by H-3 and H-3' and H-4 (or H-2) would bisect it, resulting in smaller coupling constants.

If the structure 3 were the correct one, hydrogenation should give more than one pair of enantiomers due to the introduction of another chiral center at C-6. Furthermore, the terminal methyl group would appear as a doublet at high fields in the ^{1}H-n.m.r. spectrum and at about 15 p.p.m.[6] in the ^{13}C-n.m.r. spectrum.

The conformation of 6 was analysed on the basis of its ^{1}H-n.m.r. spectrum. The dihedral angles between H-2, H-3, H-3' and H-4 were estimated by the DAERM method (dihedral angle estimation by the ratio method)[9], which has been originally used for furanoses[10,11]. We have extended its application to establish the favored

Table I. Chemical shifts and coupling constants of compounds 6-8

Compound	H-2 ($J_{2,3}$)	H-3 ($J_{2,3'}$)	H-3' ($J_{3',4}$)	($J_{3,3'}$)	H-4 ($J_{3,4}$)	H-5 ($J_{4,5}$)	H-6 ($J_{5,6}$)	H-7
6	5.73(q) (8.60)	2.95(m) (10.70)	2.06(m) (10.40)	(12.63)	4.58(m) (5.47)	1.94(m)		4.40(m)
7	5.68(q) (8.4)	2.96(m) (10.2)	2.34(m) (10.0)	(12.5)	4.63(m) (6.5)	5.37(m) (5.0)	1.49(d) (6.4)	
8	5.66(q) (8.5)	2.87(m) (10.4)	2.05(m) (10.1)	(12.5)	4.41(m) (6.2)	1.80(m) (5.5)	1.08(t) (6.8)	

conformation of 3-deoxy-aldonolactones[4,8]. The results obtained (Table II) accord with those reported for 7 and 8 . Cases a, c, e, and g may be rejected, because of the large values of the Karplus constants calculated. The solution d/h appears as the more probable and indicates a conformation in which C-3 (in the D-isomer) lies above the plane determined by C-2, C-1, and the ring oxygen whereas C-4 lies slightly below it, minimizing the interactions between the substituents.

Table II. DAERM analysis[a] of couplings in compound 6

Protons coupled	Case	J_1[b]	J_2	θ_1[b]	θ_2	k_1	k_2
H-2 and H-3,3'	a	10.70	8.60	60	64	42.88	47.56
	b	10.70	8.60	20	144	12.36	13.74
	c	8.60	10.70	63	61	42.50	47.31
	d	8.60	10.70	31	155	12.06	13.39
H-4 and H-3,3'	e	10.40	5.47	57	67	35.24	38.93
	f	10.40	5.47	9	133	10.97	12.18
	g	5.47	10.40	66	58	34.49	38.25
	h	5.47	10.40	42	166	10.25	11.39

[a] ω=124º ; $k_1/k_2 = 0.9$

[b] J_1 cis-coupling; θ_1, the corresponding angle.

The trideoxyheptono-1,4-lactone 6 is a valuable intermediate for the synthesis of deoxy sugars.

EXPERIMENTAL

Melting points were determined with a Fischer-Johns apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 710 B spectrophotometer. ^{1}H- and ^{13}C-n.m.r. spectra were recorded with a Bruker 200 MHz instrument for solutions in chloroform-d with tetramethylsilane as internal reference. Mass spectra were performed with a Varian MAT CH7A spectrometer coupled to a Varian MAT data-system 166. T.l.c. was effected on Silicagel 60 (Merck) precoated-plates with benzene-ethyl acetate (19:1) as eluent and iodine detection. H.p.l.c. was performed with a Hewlett Packard 1084 B chromatograph with variable UV detector, on a 10 μ-Lichrosorb Si-100 (Merck) column.

3-Benzoyloxy-5-(3-benzoyloxyallylidene)-(5H)-furan-2-one (5). To a solution of 2,3,5,6,7-penta-O-benzoyl-D-glycero-D-gulo-heptono-1,4-lactone[5] (4) (2.2 g) in chloroform (12 mL), 3 mL of triethylamine were added and the reaction mixture was kept in the dark with stirring at room temperature. It was monitored by t.l.c. and the best yield of 5 was achieved after 6 h . The solution was evaporated to dryness with successive additions of toluene. The brownish syrup was purified on a Silicagel H (Merck) column using benzene with increasing amounts of ethyl acetate as the solvent. Compound 5 (0.66 g, 59% yield) was homogeneous by t.l.c. (R_F 0.45) and crystallized as light yellow needles upon addition of ethanol, m.p. 151-152º. H.p.l.c. using 0.1% methanol-chloroform for elution afforded a single peak (retention volume 6.3). I.r. $\nu_{max.}^{nujol}$ 1780 (lactone C=O); 1740 cm^{-1} (benzoate C=O). ^{1}H-N.m.r.: δ 7.60 (H-7, dd, $J_{6,7}$ 6.21 Hz; $J_{5,7}$ 1 Hz); 7.26 (H-3, d, $J_{3,5}$ 0.5 Hz); 6.42 (H-5, m, $J_{5,6}$ 11.75 Hz); 6.23 (H-6, dd). ^{13}C-N.m.r.: δ 145.4 (C-4); 138.4 (C-2); 137.9 (C-7); 134.6, 134.0, 130.6, 130.1, 129.2, 128.8, 128.7, 128.5 (aromatic C); 123.5 (C-3); 107.2 and 106.0 p.p.m. (C-5 and C-6). M.s.: m/z 362 (M^+, 3.9%); 105 ($C_6H_5CO^+$, 100%); 77 ($C_6H_5^+$, 78%); 51 ($C_4H_3^+$, 18%).

2,7-Di-O-benzoyl-3,5,6-trideoxy-(DL)-threo-heptono-1,4-lactone (6). A solution of 5 (0.53 g) in ethyl acetate was hydrogenated over 5% palladium-charcoal until no more starting material was observed by t.l.c.. The catalyst was removed by filtration and the solution was evaporated to a syrup, which was purified on a Silicagel H column using chloroform-methanol (99:1) as eluent. Compound 6 (0.48 g, 89%) crystallyzed on standing and was recrystallyzed from isopropyl ether; m.p. 61-62º ; R_F 0.18 ; h.p.l.c. in the conditions described above using 0.5% methanol-chloroform for elution afforded a single peak (retention volume 7.32). I.r. $\nu_{max.}^{nujol}$ 1790 (lactone C=O); 1720 cm^{-1} (benzoate C=O). ^{1}H-N.m.r. data are shown in Table I. ^{13}C-N.m.r.: δ 171.9 (lactone C=O); 166.5, 165.4 (benzoate C=O); 133.7, 133.0, 130.2, 130.0, 129.6, 128.8, 128.5, 128.4 (aromatic C); 76.5 (C-4); 69.1 (C-2); 64.0 (C-7); 35.3 (C-3); 32.4* (C-6); 24.7* (C-5) (* The assignments may be interchanged). M.s.: m/z 368 (M^+, 0.6); 247 (M - PhCOO•, 3.4%); 246 (M - PhCOOH, 6.3%); 219 (247 - CO, 1.1%); 218 (246 - CO, 1.1%); 205 (M - $BzO(CH_2)_2$-CH_2•, 4.2%); 105 ($C_6H_5CO^+$, 100%); 77 ($C_6H_5^+$, 83%); 51 ($C_4H_3^+$, 18.7%). Anal. Calc. for $C_{21}H_{20}O_6$: C, 68.48%; H, 5.43%. Found: C, 68.62%; H, 5.67%.

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