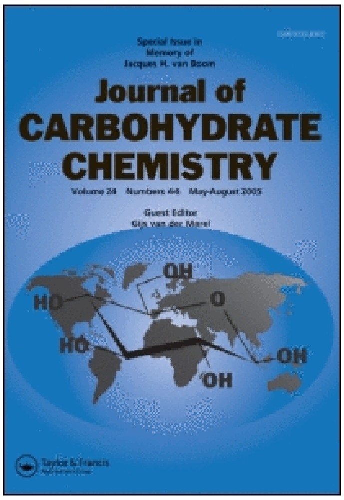

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PARTIAL BENZOYLATION OF L-RHAMNONO- AND D-MANNONO-1,4-LACTONE

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ABSTRACT

Partial benzoylation of L-rhamnono-1,4-lactone (1) gave 2,5-di-O-benzoyl-L-rhamnono-1,4-lactone (2) as the main product. In similar conditions, D-mannono-1,4-lactone (3) gave preferentially 2,5,6-tri-O-benzoyl-D-mannono-1,4-lactone (4). 2,3,5,6-Tetra-O-benzoyl- (5) and 3,6-di-O-benzoyl-D-mannono-1,4-lactone (6) were isolated in low yield from the reaction mixture. The structures of the partially benzoylated compounds 2, 4 and 6 were assigned on the basis of spectroscopic data.

INTRODUCTION

In previous papers[1-5] we have described the benzoylation of L-rhamnono-1,5- and 1,4-lactones to give, depending on the experimental conditions, either the perbenzoate or elimination products, which were used as starting materials for the synthesis of dideoxy- and trideoxysugars.

We now report the partial benzoylation of L-rhamnono-1,4-lactone (1) and D-mannono-1,4-lactone (3) to obtain in good yield 3-unsubstituted derivatives useful as intermediates for the preparation of ketosugars, amino-

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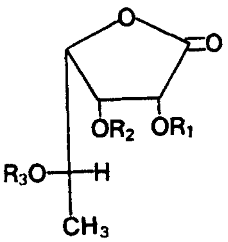
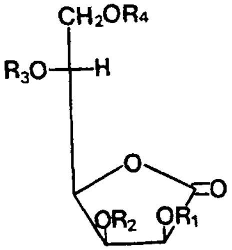
sugars and disaccharides.





1 $R_1=R_2=R_3=H$

2 $R_1=R_3=Bz;\ R_2=H$

7 $R_1=R_2=R_3=Bz$

3 $R_1=R_2=R_3=R_4=H$

4 $R_1=R_3=R_4=Bz;\ R_2=H$

5 $R_1=R_2=R_3=R_4=Bz$

6 $R_1=R_3=H;\ R_2=R_4=Bz$

RESULTS AND DISCUSSION

In our studies on the benzoylation of aldonolactones, we have found that L-rhamnono-1,4-lactone (1), under controlled conditions, gave crystalline 2,5-di-*O*-benzoyl-L-rhamnono-1,4-lactone (2) in 48% yield. In order to determine the applicability of this reaction, D-mannono-1,4-lactone (3), bearing the same relative configuration as 1, was benzoylated under similar conditions. From the reaction mixture, 2,5,6-tri-*O*-benzoyl-D-mannono-1,4-lactone (4) was isolated by column chromatography as the major product (60%). The perbenzoate 5 was also obtained and 3,6-di-*O*-benzoyl-D-mannono-1,4-lactone (6) was crystallized in very low yield from a mixture of di-*O*-benzoyl-derivatives.

The isolation of 2 and 4, respectively, as the main products, would indicate that the 3-OH group is hindered for benzoylation. No studies on the selective acylation of five-membered rings and particularly aldono-1,4-lactones, have been reported. In hexopyranoses, the 4-OH group proved to be the least reactive, and this fact was attributed to *gauche* interactions with the 5-benzoyloxymethyl group and the 3-O-benzoyl group.[6]

On the basis of ^1H NMR data, D-mannono-1,4-lactone (3) appears to exist largely in the ^3E (D)-conformation in pyridine solution,[7] and the 3-OH group would show *gauche* interactions with both the 2-OH group and the bulky substituent on C-4. Although no conformational studies have been carried out on free L-rhamnono-1,4-lactone (1), one can assume similar interactions due to the same relative configuration in both compounds.

The structure of 2 was assigned by comparison of its ^1H NMR spectrum with that of 2,3,5-tri-O-benzoyl-L-rhamnono-1,4-lactone (7).[4] Both spectra were performed in DMSO-d_6, and the chemical shifts and coupling constants observed are shown in Table 1. An upfield shift of 0.57, 1.53 and 0.39 p.p.m., respectively, was observed for H-2, H-3 and H-4, whereas H-5 was only slightly displaced. On deuteration, the H-3 signal in the spectrum of 2 was simplified, and the doublet at δ 6.15 corresponding to the hydroxylic proton disappeared.

The spectra for compounds 4 and 5, recorded in chloroform-d, showed similar upfield shifts for H-2, H-3 and H-4 in 4, which resulted in the superposition of the H-2 and H-5 signals, and the H-3, H-4 and H-6,6' signals, respectively (Table 1). When the spectrum was measured in DMSO-d_6, better resolution was achieved, and upon deuteration the signal assigned to H-3 was simplified.

Compound 6 has two free hydroxyl groups and was characterized as 3,6-di-O-benzoyl-D-mannono-1,4-lactone by its ^1H NMR spectrum (Table 1). In comparison with 5, the more shielded hydrogens are H-2 and H-5 ($\Delta\delta$ 1.31 and 1.72 p.p.m., respectively), while H-3,

TABLE 1

^1H NMR Chemical Shifts and Coupling Constants (J,Hz) of Compounds 2,4,5,6 and 7.

Compound	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$;$J_{5,6'}$)	H-6	H-6' ($J_{6,6'}$)	Other
7[a]	6.57(d) (5.2)	6.28(q) (3.0)	5.27(q) (8.0)	5.56(m) (6.0)	1.56(d)[d]		Aromatic H 7.3-8.1(m, 15H)
2[a]	6.00(d) (5.0)	4.75(q)[c] (3.0)	4.88(q) (8.0)	5.42(m) (6.0)	1.45(d)[d]		Aromatic H 7.4-8.2(m, 10H) OH: 6.15 $J_{H-3,OH}$=5.0 Hz
4[b]	5.74(d) (4.0)	4.6-5.1(m)		5.76(m)	4.6-5.1(m)		Aromatic H 7.3-8.2(m, 15H) OH: 3.8
4[a]	6.04(d) (4.5)	4.78(q)[c] (3.5)	5.25(q) (8.0)	5.70(m) (2.0,5.0)	4.98(q)	4.57(q) (-12.0)	Aromatic H 7.3-8.2(m, 15H) OH: 6.32 $J_{H-3,OH}$=4.0 Hz
5[b]	6.17(d) (6.0)	6.28(q) (3.5)	5.28(q) (9.0)	5.92(o) (3.0,5.0)	5.28(q)	4.71(q) (-14.0)	Aromatic H 7.2-8.2(m, 20H)
6[b]	4.86(d) (6.0)	6.05(q) (3.0)	4.4-4.8(m)	4.2(m)	4.4-4.8(m)		Aromatic H 7.3-8.2(m, 10H) OH: 5.3

a. In DMSO-d_6. b. In chloroform-d. c. The signal multiplicity corresponds to the spectrum with added D_2O. d. 3H.

H-6 and H-6' showed only small shifts.

If we compare the coupling constants for compounds 4, 5 and 6 (Table 1) with those reported for D-mannono-1,4-lactone,[7] we can assign the same conformational equilibrium for the benzoylated products. The larger value observed for $J_{3,4}$ in 4 and 5 should indicate some contribution of the E_3 D-conformation[8] which accords with the fact that in the free lactones intramolecular hydrogen bonding between the 2-OH and the lactone carbonyl takes part in the stabilization of the favored conformation.[9] This additional stabilization is no longer possible in the protected compounds 4 and 5 but still operates in 6, adding further evidence for its bearing a free 2-OH group.

Compound 2 shows similar coupling constant values as those reported for the perbenzoate 7,[4] indicating a favored E_3 (L)-conformation.

The ^{13}C NMR chemical shift assignments for the benzoylated aldonolactones 2, 4, 5 and 6 were substantiated by selective decoupling experiments and are shown in Table 2 together with data for compound 7 included for comparison. As we already reported,[10] C-4 was more deshielded than the other saturated carbons. The debenzoylated carbon atom in 2 and 4 (C-3) showed a negligible shift. This fact can be explained taking into account that the upfield shift observed for the α-carbon on deacylation of cyclohexanols[11] is cancelled out by the downfield shift caused by less steric hindrance. On the other hand, the β-carbon atoms (C-2 and C-4) suffered a downfield shift ranging from 1.47 to 1.85 p.p.m.

If we compare the ^{13}C NMR spectrum of 6 with that of 5, the debenzoylated carbons, C-2 and C-5, showed only slight variation (0.61 and 0.60 p.p.m., respectively), while the β-carbon atoms were shifted downfield (4.25

TABLE 2

^{13}C NMR Chemical Shifts of Compounds **2**, **4**, **5**, **6** and **7**

Compound	C-1	C-2	C-3	C-4	C-5	C-6
7[a]	169.53	69.58	68.79	79.89	67.33	17.51
2[a,b]	--	71.31	68.47	81.46	67.45	17.46
5[a]	168.83	69.31	68.51	75.26	67.93	62.60
4[a,b]	--	70.78	68.53	77.11	68.19	62.75
6[c]	175.84	69.92	72.76	77.20	67.33	66.43

a. In chloroform-d. b. In the recording conditions carbonyl carbons were not observed. c. In DMSO-d_6.

p.p.m. for C-3; 1.94 p.p.m. for C-4 and 3.83 p.p.m. for C-6).

These are the first studies on ^{13}C NMR spectra of partially benzoylated aldonolactones, but a similar behavior has been reported for partially acetylated D-glucopyranoses[12] and L-rhamnoses.[13]

The isolation of **6** is not contradictory with the fact that the 3-OH group is the less reactive. This compound was crystallized in very low yield (4.6%) from a mixture of dibenzoylated products with similar mobility in TLC, which was not further analysed. The very good yields obtained for **2** and **4** make them potentially useful intermediates.

EXPERIMENTAL

General procedures. The instrumentation used has been described previously.[4] TLC was performed on Silica Gel G (Merck). The following solvent systems were used: (a) benzene-ethyl acetate (19:1); (b) chloroform-methanol (19:1). Detection was effected with iodine vapor. GLC was performed with glass columns (180 x 0.2 cm) packed with 2.5% SE-30 on Chrom W (AW/DMCS 80-100 mesh) with nitrogen at a flow-rate of 28 mL/min; T_i 280°C; T_d 280°C. Trimethylsilyl derivatives were prepared with hexamethyldisilazane and trimethylchlorosilane.[14] L-rhamnono-1,4-lactone and D-mannono-1,4-lactone were obtained by bromine oxidation of L-rhamnose and D-mannose, respectively.[15,16]

2,5-Di-O-benzoyl-L-rhamnono-1,4-lactone (2). L-rhamnono-1,4-lactone (1, 0.5 g) was dissolved in 2 mL of anhydrous pyridine, and 0.9 mL of freshly distilled benzoyl chloride was added dropwise with external cooling. The solution was shaken for two hours at room temperature, poured into 30 mL of ice-water and treated as previously described.[1-4] TLC of the reaction mixture showed a main product (R_f 0.54, solvent a) and a minor one (R_f 0.73, solvent a), which were separated by column chromatography on Silica Gel H (Merck) using benzene with increasing concentrations of ethyl acetate as eluent. The product of greater mobility was characterized as 2,3,5-tri-O-benzoyl-L-rhamnono-1,4-lactone (7)[4] (0.200 g, 13.7%).

The compound of R_f 0.54 crystallized upon addition of ethanol (0.550 g, 48.2%); mp 195-197°C; $[\alpha]_D^{20}$ +13.5° (*c* 1.0, chloroform). ν_{max}^{Film} 3480 (OH); 1790 (1,4-lactone carbonyl); 1700 cm^{-1} (benzoate carbonyl) T_R of the O-trimethylsilyl derivative 6.10 min (T_c 230°C). ^{1}H NMR data are shown in Table 1. ^{13}C NMR data are shown in Table 2.

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.86. Found: C, 64.57; H, 5.07.

2,3,5,6-Tetra-O-benzoyl-D-mannono-1,4-lactone (5). D-mannono-1,4-lactone (3, 1.0 g) was dissolved in 5.0 mL of anhydrous pyridine and benzoylated with 4.5 mL of benzoyl chloride. The mixture was shaken for 2 h at room temperature, poured into 100 mL of ice-water and treated as previously described.[1-4] TLC showed only one product (R_f 0.70, solvent a), which was purified by treatment with ethanol but could not be induced to crystallize (3.0 g, 89%). It was characterized as 2,3,5,6-tetra-O-benzoyl-D-mannono-1,4-lactone; $[\alpha]_D^{20}$ -99.0° (*c* 1.0, chloroform); ν_{max}^{Nujol} 1800 (1,4-lactone carbonyl), 1720 cm^{-1} (benzoate carbonyl). ^1H NMR data are shown in Table 1. ^{13}C NMR data are shown in Table 2.

Anal. Calcd for $C_{34}H_{26}O_{10}$: C,68.68; H, 4.39. Found: C, 68.55; H, 4.40.

2,5,6-Tri-O-benzoyl-D-mannono-1,4-lactone (4). D-mannono-1,4-lactone (3, 1.0 g) was benzoylated with 7.5 mL of anhydrous pyridine and 2.5 mL of freshly distilled benzoyl chloride. The solution was shaken for 2 h at room temperature, poured into 100 mL of ice-water and treated as previously described.[1-4] TLC showed a major product of R_f 0.50 (solvent a), together with two minor ones (R_f 0.70 and R_f 0.80, solvent a). The mixture (3.0 g) was separated by column chromatography on Silica Gel H (Merck) using chloroform-methanol (99:1) as eluent.

The faster moving component was characterized as compound 3 (0.83 g, 25%).

The product of R_f 0.50 could be crystallized either from benzene or methanol (1.65 g, 60%). The melting points obtained were 88-90°C and 136-138°C, respectively; $[\alpha]_D^{20}$ -20.0° (*c* 1.0, chloroform); ν_{max}^{Nujol} 3400 (OH); 1820 (1,4-lactone carbonyl) and 1730 cm^{-1} (benzoate carbonyl). Its O-trimethylsilyl derivative showed T 5.16 min (T_c programmed from 230° to 280°C, 10°C/min). ^1H NMR data are shown in Table 1. ^{13}C NMR data are shown in Table 2.

Anal. Calcd for $C_{27}H_{22}O_9$: C, 66.12; H, 4.52. Found: C, 66.12; H, 4.68.

The last fractions from the column were eluted with chloroform-methanol (1:1) and concentrated to a syrup (0.51 g). Upon addition of ethanol 3,6-di-O-benzoyl-D-mannono-1,4-lactone (6) crystallized (0.1 g, 4.6%) and was recrystallized from the same solvent to give mp 204-208°C; $[\alpha]_D^{20}$ +8.7° (*c* 1.0, acetone); ν_{max}^{Nujol} 3400 (OH); 1820 (1,4-lactone carbonyl); 1740 and 1700 cm^{-1} (benzoate carbonyl). Its di-O-trimethylsilyl derivative showed T_R 1.96 min (T_C programmed from 230 to 280 °C, 10°C/min). ^1H NMR data are shown in Table 1. ^{13}C NMR data are shown in Table 2.

Anal. Calcd for $C_{20}H_{18}O_8$: C, 62.18: H, 4.70. Found: C, 62.37: H, 4.95.

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