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Note

The use of aldonolactones for the synthesis of 2-*O*-methyl-L-rhamnose and 2-*O*-methyl-D-mannose

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We have previously reported the synthesis of partially substituted aldonolactones by benzoylation of L-rhamnono- and D-mannono-1,4-lactone[1] under controlled conditions. The facile chemoselective reduction of acylated lactones to the lactols[2,3] suggested their use as intermediates for the synthesis of substituted furanoid sugars, including disaccharides. To test the reactivity of the free hydroxyl group, we first tried a simple methylation reaction under various conditions.

With the aim of obtaining 3-*O*-methyl derivatives, 2,5-di-*O*-benzoyl-L-rhamnono-1,4-lactone (**1**) was methylated under conditions reported to prevent acyl migration.

Treatment of **1** with diazomethane and boron trifluoride etherate, as described by Mastronardi *et al.*[4], gave a fast-moving compound (t.l.c.) in very low proportion. The yield could not be improved after five successive treatments. It was isolated by column chromatography as a homogeneous syrup (8.6%) and identified by m.s. as 2,5-di-*O*-benzoyl-3-*O*-methyl-L-rhamnono-1,4-lactone (**2**). The fragmentation pattern showed prominent ions (105→77→51) for the aromatic series. The 3-methoxyl group promoted C-3–C-4 cleavage, giving rise to *m/z* 205 [M^+ – MeCH(OBz)CHOH; 5.1%], which subsequently loses a benzoate group (*m/z* 85, 9.6%).

When 2,5,6-tri-*O*-benzoyl-D-mannono-1,4-lactone (**3**) was methylated under the same conditions, a fast-moving component was observed (t.l.c.), but again in very low yield. Therefore, this method is unsuitable for the synthesis of the methyl derivatives.

Compound **1** was also treated with methyl trifluoromethansulfonate (methyl triflate) in the presence of 2,6-di-*tert*-butylpyridine[5], with methyl iodide–silver per-

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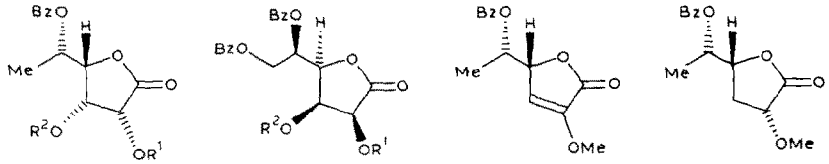

1 R^1 = Bz ; R^2 = H
2 R^1 = Bz ; R^2 = Me
4 R^1 = Me ; R^2 = Bz

3 R^1 = Bz ; R^2 = H
9 R^1 = Me ; R^2 = Bz

5

6

chlorate[6], and with methyl sulfate–aluminum oxide[7]. Chromatographic and/or spectroscopic examination indicated little or no methylation. These results might be attributable to the low acidity and steric hindrance of the 3-OH group.

Conditions more strongly alkaline would facilitate nucleophilic attack. Although acyl migrations are to be expected in basic media[8], a selective transposition of the benzoyl group might afford a monomethylated product in good yield. The synthetic applicability of Purdie's method[9] was assayed with compound **1**. Benzoyl migration was complete, and crystalline 3,5-di-*O*-benzoyl-2-*O*-methyl-L-rhamnono-1,4-lactone (**4**) was obtained in 83% yield. The 3-*O*-methyl isomer **2** could not be detected in the mixture. The structure of compound **4** was assigned from spectroscopic data.

The H-2 doublet in the ^{1}H-n.m.r. spectrum of **4** (4.29 p.p.m.) is shifted to higher field (1.36 p.p.m.) while the H-3 signal appeared downfield (1.43 p.p.m.) in comparison with the respective resonances for compound[1] **1**. This simultaneous shielding of H-2 and deshielding of H-3 is a clear evidence of benzoyl migration to O-3, and methylation at O-2. In the ^{13}C-n.m.r. spectrum (Table I), C-2 is shifted downfield (6.4 p.p.m.) on methylation, C-3 is only slightly modified, probably because of a compensation of electric and steric factors, whereas C-4 is shifted upfield (1.8 p.p.m.) because of the benzoyl group on C-3.

The m.s. of compound **4** was clearly different from that of the 3-*O*-methyl isomer **2**. The loss of benzoic acid from the molecular ion accounts for the radical cation at *m/z* 262, which underwent the typical fragmentation of furanones.

An α,β-unsaturated lactone characterized as 5-*O*-benzoyl-2-*O*-methyl-3,6-dideoxy-L-*erythro*-hex-2-enono-1,4-lactone (**5**) was obtained as a minor product from the mixture.

The H-3 doublet at δ 6.11 p.p.m. in the ^{1}H-n.m.r. spectrum of **5**, together with signals at 147.9 p.p.m. (C-2) and 112.7 p.p.m. (C-3) in the ^{13}C-n.m.r. spectrum confirm the assigned structure. Elimination of the 3-*O*-benzoate after methylation, was observed by t.l.c. at early stages of the reaction, even when only partial addition of silver oxide had been made.

β-Elimination in aldonolactones has been extensively studied in our laboratory[3,10,11] and is considered to proceed *via* an ElcB mechanism. On this basis, a more-polar solvent, such as tetrahydrofuran, was selected in order to improve the yield of the unsaturated product **5**, and this was isolated crystalline after chromatog-

raphic purification, in 87% yield. A product of higher mobility (t.l.c.) was probably a diunsaturated derivative, as multiple elimination is a common feature in the β-elimination of aldono-1,4-lactones[10,11].

Catalytic hydrogenation of compound **5** afforded, quantitatively, 5-*O*-benzoyl-3,6-dideoxy-2-*O*-methyl-L-*arabino*-hexono-1,4-lactone (5-*O*-benzoyl-2-*O*-methyl-ascarylono-1,4-lactone, **6**), which was characterized on the basis of spectroscopic data. The appearance of high-field signals for H-3 (2.71 p.p.m.) and H-3′ (2.18 p.p.m.) in the ^{1}H-n.m.r. spectrum and for C-3 (30.4 p.p.m.) in the ^{13}C-n.m.r. (Table I), together with the observed coupling constants for H-2 and H-4, confirmed the postulated structure. Stereospecificity has always been observed upon catalytic hydrogenation over palladium of compounds with related structures[3,12]. Compound **6**, obtained in three steps from L-rhamnono-1,4-lactone, is an useful intermediate for the preparation of 2-*O*-methylascarylose. Ascarylose is a 3,6-dideoxy sugar component of glycolipids from *Parascaris equorum*[13] and has been characterized as a constituent of a specific polysaccharide from *Pasteurella pseudotuberculosis*[14].

Reduction[2] of compound **4**, by disiamylborane afforded 3,5-di-*O*-benzoyl-2-*O*-methyl-L-rhamnofuranose (**7**) as an anomeric mixture (α:β ratio 2:1) (^{13}C-n.m.r.; see Table I). Upon debenzoylation with sodium methoxide in chloroform at 0°, 2-*O*-methylrhamnose (**8**) was isolated as a chromatographically homogeneous syrup having physical constants comparable to those previously reported for this compound[15,16] (α:β ratio 3:1).

In order to determine the generality of this reaction, 2,5,6-tri-*O*-benzoyl-D-manno-1,4-lactone (**3**) was methylated under similar conditions as used with **1**. After disiamylborane reduction and debenzoylation, 2-*O*-methyl-D-mannose was obtained crystalline in 43% overall yield.

These fact suggest that benzoyl migration is complete under the conditions of Purdie methylation, making this procedure suitable for the synthesis of 2-*O*-methylrhamnose and 2-*O*-methylmannose. 2-*O*-Methyl-L-rhamnose has been reported as component of the antibiotics steffimycin[17], aranciamycin[18], and scopamycin[19]; of the oligosaccharide moiety of the antigenic glycolipid (mycoside A) from *Mycobacterium kansaii*[20], and of extracellular polysaccharides from *Rhizobium*[21]. 2-*O*-Methyl-D-mannose has been detected in the hydrolyzates from soil polysaccharides[22].

The total yield of 2-*O*-methylrhamnose from the aldonolactone is higher than the five-step synthesis reported by MacPhillamy and Elderfield[23] and is comparable to that obtained by Poszgay and Nánási[16] starting from benzyl 4-*O*-benzyl-α-L-rhamnopyranoside. Several synthesis were described for 2-*O*-methylmannose[24–27]. The procedure now described compares favorably in yield and simplicity to most of them.

EXPERIMENTAL

General methods. — The instrumentation used has been previously described[28]. T.l.c. was performed on plates coated with 0.25-mm Silica Gel 60 (Merck 5626) and *A*, 19:1 PhMe–EtOAc; *B*, 9:1 PhMe–EtOAc; *C*, 7:1:1 1-propanol–EtOH–H_2O; *D*, 19:1 C_6H_6–EtOAc; *E*, 9:1 C_6H_6–EtOAc; and *F*, 4:1 $CHCl_3$–MeOH. Compounds were detected by spraying with 5% (v/v) H_2SO_4–EtOH followed by charring at 140° for a few min. Descending p.c. was performed on Whatman No. 1 paper with 6:4:3 (v/v) 1-butanol–C_5H_5N–H_2O; detection was effected with $AgNO_3$–NaOH[29] and aniline hydrogenphthalate[30].

G.l.c. was performed with glass columns (180 × 0.2 cm) packed with 2.5% SE-30 on Chromosorb W (AW/DMCS), 80–100 mesh, with nitrogen at a flow rate of 24 mL/min, T_i 280°; T_d 280°; T_c from 240° to 280°; rate 5°/min. 2,5-Di-*O*-benzoyl-L-rhamnono-1,4-lactone (**1**) and 2,5,6-tri-*O*-benzoyl-D-mannono-1,4-lactone (**3**) were obtained by partial benzoylation of L-rhamnono-1,4-lactone and D-mannono-1,4-lactone, respectively, as already described[1]. Compound **1** was obtained in 60% yield when the reaction was carried out at 0° with 10% BzCl excess.

Methylation of 2,5-di-O-benzoyl-L-rhamnono-1,4-lactone (**1**). — *A. With diazomethane and boron trifluoride etherate.* Methylation was performed according to the method describe by Mastronardi *et al.*[4]. To a suspension containing 200 mg (0.54 mmol) of **1** in 1.0 mL of dichloromethane cooled at −5° was added 0.02 mL $BF_3 \cdot OEt_2$. A solution of CH_2N_2 in $CH_2Cl_2$was slowly dropped in until the yellow color persisted. After 30 min at −5°, the white solid (polymethylene) formed in the reaction was filtered off, the solution was washed with saturated aq. $NaHCO_3$ and then water until neutrality, dried ($MgSO_4$) and evaporated to a syrup.

T.l.c. (solvent *A*) showed a main spot (R_F 0.36), which corresponded to the starting material, and a minor one, R_F 0.52. The mixture was remethylated five more times, by the same procedure, without considerable improvement in the yield of methylated product, as observed by t.l.c.

The fast-moving component (18 mg; 8.6%) was isolated by column chromatography (2 × 15 cm) on Silica Gel 60 (Merck, 230–400 mesh), eluting with solvent *A*. It was homogeneous by g.l.c. (T_r 5.19 min). The mass spectrum corresponded to that of 2,5-di-*O*-benzoyl-3-*O*-methyl-L-rhamnono-1,4-lactone (**2**): *m/z*(%): 384 (M^+, 3.1), 279 (3.41), 205 (5.1), 170 (1.2), 157 (4.1), 140 (4.9), 105 (100), 101 (3.3), 35 (9.6), 84 (1.1), 77 (30.1), 69 (2.5), and 51 (8.6).

B. With methyl iodide–silver oxide[9]. *3,5-Di-O-benzoyl-2-O-methyl-L-rhamnono-1,4-lactone* (**4**) *and 5-O-benzoyl-2-O-methyl-3,6-dideoxy-L-erythro-hex-2-enono-1,4-lactone* (**5**). To a solution of **1** (1.0 g, 2.70 mmol) in chloroform (20 mL) and MeI (11 mL), freshly prepared Ag_2O (0.62 g) was added portion wise in the presence of 4 Å molecular sieves.

The mixture was stirred at 40° in the dark, under N_2, until starting material could no longer be detected by t.l.c. (3–6 h). After filtration, the solution was evaporated to a syrup; t.l.c. (solvent *B*) showed a main product (R_F 0.38) and a

TABLE I

^{13}C-N.M.R. CHEMICAL SHIFTS[a] (δ) OF COMPOUNDS **1** AND **3–9**

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OCH_3*
1[b]		71.1	68.2	81.2	67.2	17.3	
4	171.4	77.5	68.8	79.4	67.4	17.3	59.8
7α	100.3	86.1	71.7	80.0	68.9	17.1	58.9
7β	95.3	80.3[c]	70.0	80.1[c]	69.5	17.4	58.9
8α	91.6	81.7	70.8	73.5	69.0	17.7	59.5
8β	94.8	82.5	74.2	70.2	73.1	17.7	62.7
3[b]		70.8	68.5	77.1	68.2	62.8	
5	166.9	147.9	112.7	79.5	70.4	14.6	58.3
6	173.6	75.5	30.4	77.2	70.4	14.9	58.2
9	170.9	77.3	68.5	75.0	68.1	62.7	59.8

[a]In chloroform-*d*, except for compound **8** (D_2O–H_2O). [b]Under the recording conditions, carbonyl carbon was not observed. [c]The assignments may be interchanged.

minor one (R_F 0.27), which were separated by column chromatography (3.5 × 20 cm) on Silica Gel H (Merck) using solvent *B*. The product of higher mobility was isolated as a homogeneous syrup (0.86 g, 83%), that crystallized from MeOH–water; m.p. 87–88°; $[\alpha]_D^{25}$ +106.5° (*c* 1, $CHCl_3$) and was characterized as 3,5-di-*O*-benzoyl-2-*O*-methyl-L-rhamnono-1,4-lactone (**4**); ν_{max}^{Nujol} 1795 (1,4-lactone CO), 1730 cm^{-1} (benzoate CO); ^{1}H-n.m.r.: δ 8.07–7.30 (m, 10 aromatic H), 6.15 (dd, $J_{2,3}$ 5.0, $J_{3,4}$ 3.5 Hz, H-3), 5.48 (m, H-5), 4.67 (dd, $J_{3,4}$ 3.5, $J_{4,5}$ 8.0 Hz, H-4), 4.29 (d, H-2), 3.58 (s, MeO), 1.57 (d, $J_{5,6}$ 6.0 Hz, 3 H-6); ^{13}C-n.m.r.: δ 164.8 (benzoate CO); 133.4–128.2 (aromatic C) (for other carbon resonances, see Table I), *m/z* (%): 384 (M^+, 5.5), 354 (3.8), 262 (1.6), 234 (5.1), 230 (2.3), 219 (7.0), 218 (11.7), 191 (6.1), 178 (5.8), 158 (2.8), 149 (1.8), 140 (18.6), 137 (3.3), 122 (3.5), 113 (2.7); 111 (2.8), 106 (33.5), 105 (100), 92 (11.2), 91 (21), 85 (7.0), 84 (5.0), 83 (9.0), 77 (79.4), 57 (7.3), and 51 (12.9).

Anal. Calc. for $C_{21}H_{20}O_7$: C, 65.60; H, 5.25. Found: C, 65.72; H, 5.37.

The compound of R_F 0.27 was later eluted with the same solvent (0.041 g, 6%). It crystallized from 2-propanol; m.p. 79–81°, $[\alpha]_D^{25}$ +3.1° (*c* 1.3, $CHCl_3$) and was characterized as 5-*O*-benzoyl-2-*O*-methyl-3,6-dideoxy-L-*erythro*-hex-2-enono-1,4-lactone (**5**); ν_{max}^{Nujol} 1770 (α,β-unsaturated 1,4-lactone CO); 1705 (benzoate CO); 1655 cm^{-1} (conjugated C=C); λ_{max}^{MeOH} 224 (ε 36000) and 273 nm (ε 75000); ^{1}H-n.m.r.: δ 8.10–7.36 (m, 5 aromatic H), 6.11 (d, $J_{3,4}$ 2.0 Hz, H-3), 5.29 (m, H-5), 5.11 (dd, $J_{4,5}$ 4.5 Hz, H-4), 3.83 (s, MeO), 1.39 (d, $J_{5,6}$ 6.4 Hz, 3 H-6); ^{13}C-n.m.r.: δ 165.3 (benzoate CO), 133.2, 129.4, 128.3 (aromatic C), (for other carbon resonances, see Table I).

Anal. Calc. for $C_{14}H_{15}O_5$: C, 64.12; H, 5.38. Found: C, 64.10; H, 5.47.

Compound **5** was obtained in 87% yield when methylation was performed using tetrahydrofuran as solvent. After 6 h, no starting material was observed by t.l.c. and the main product (R_F 0.27) was isolated and purified as described.

*5-O-Benzoyl-2-O-methyl-3,6-dideoxy-*L-arabino-*hexono-1,4-lactone. (5-O-benzoyl-2-O-methyl-ascarylono-1,4-lactone)* (**6**). — Compound **5** (1.05 g; 4.0 mmol) was dissolved in EtOAc (12 mL) and hydrogenated over 10% palladium–charcoal at room temperature and atmospheric pressure until no further absorption of hydrogen was observed (~18 h). T.l.c. (solvent *B*) showed only one spot (R_F 0.28), which was characterized as **6** after recrystallization from EtOH; m.p. 58–59°, $[\alpha]_D^{25}$ +31.5° (*c* 2.2, $CHCl_3$); yield: 95%; ν_{max}^{Nujol} 1785 (1,4-lactone CO); 1715 (benzoate CO); ^{1}H-n.m.r.: δ 8.12–7.36 (m, 5 aromatic H), 5.34 (m, $J_{4,5}$ 4.4, $J_{5,6}$ 6.5 Hz, H-5), 4.52 (m, $J_{3,4}$ 6.2, $J_{3',4}$ 9.9 Hz, H-4), 4.17 (dd, $J_{2,3}$ 8.5, $J_{2,3'}$ 9.9 Hz, H-2), 3.60 (s, MeO), 2.71 (ddd, $J_{3,3'}$ 12.9 Hz, H-3), 2.18 (m, H-3'), 1.41 (d, 3 H-6), ^{13}C-n.m.r.: δ 165.2 (benzoate CO), 133.3, 126.6, 129.4 and 128.2 (aromatic C) (for other carbon resonances, see Table I).

Anal. Calc. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.66; H, 6.17.

*3,5-Di-O-benzoyl-2-O-methyl-*L-*rhamnofuranose* (**7**). — To a freshly prepared solution containing 8.8 mmol of bis(2-butyl-3-methyl)borane (disiamylborane) in tetrahydrofuran (4 mL), compound **2** (0.682 g, 1.78 mmol) in 2 mL of tetrahydrofuran was added. After stirring for 20 h at room temperature, the mixture was processed as already described[31]. Compound **3** was obtained as a chromatographically homogeneous syrup (0.665 g, 97%); $[\alpha]_D^{25}$ +62° (*c* 1.1, $CHCl_3$); ν_{max}^{film} 3500 (OH), 1715 cm^{-1} (benzoate CO); ^{1}H-n.m.r.: δ 8.00–7.24 (m, 10 aromatic H), 6.00–5.83 (m, H-3α,3β), 5.56–5.28 (m, H-1α,1β,5α,5β), 4.55 (dd, $J_{3,4}$ 4.1, $J_{4,5}$ 8.0 Hz, H-4α), 4.27 (dd, $J_{3,4}$ 4.8, $J_{4,5}$ 8.6 Hz, H-4β), 4.00–3.82 (m, H-2α,2β), 3.70 (s, broad, disappeared on deuteration, OH), 3.47 (s, MeO-α), 3.41 (s, MeO-β), 1.52 (d, $J_{5,6}$ 6.0 Hz, 3H-6β), 1.48 (d, $J_{5,6}$ 6.0 Hz, 3 H-6α); ^{13}C-n.m.r.: δ 165.4, 165.2, and 165.0 (benzoate CO), 133.2, 127.9 (aromatic C) (for other carbon resonances, see Table I). The composition of the anomeric mixture was estimated from the intensities of the resonances for C-1 in the ^{13}C-n.m.r. spectrum).

Anal. Calc. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.34; H, 5.83.

*2-O-Methyl-*L-*rhamnose* (**8**). — A solution of **7** (0.389 g) in anhydrous $CHCl_3$ (8 mL) was cooled to 0° and 0.5M NaOMe in anhydrous MeOH was added. After stirring for 2 h, the solution showed no starting material by t.l.c. (solvent *B*).

Compound **8** was recovered by water extraction (4 × 10 mL). The aqueous phase was neutralized with Dowex 50W (H^+) resin and evaporated to a syrup which was purified by column chromatography (1.5 × 12 cm) on Silica Gel 60 (Merck, 230–400 mesh) using 4:1 $CHCl_3$–MeOH as eluent. It could not be induced to crystallize. Yield 0.128 g (72%); $R_{Rhamnose}$ 1.79 (solvent *C*); $[\alpha]_D^{25}$ +26° (*c* 0.7, H_2O); lit.[15] $[\alpha]_D$ +24° (*c* 3.8, H_2O); lit.[16] $[\alpha]_D$ +25° (*c* 0.3, H_2O); ^{1}H-n.m.r.: δ 5.19 (d, $J_{1,2}$ 1.5 Hz, H-1α), 4.77 (s, broad, H-1β), 3.97–3.27 (m, H-2α,2β,3α,3β,4α,4β,5α,5β, MeO-β), 3.45 (s, MeO-α), 1.25 (d, $J_{5,6}$ 6.0 Hz, 3 H-6β), 1.22 (d, $J_{5,6}$ 6.3 Hz, 3 H-6α); ^{13}C-n.m.r., see Table I.

On demethylation with BBr_3 in CH_2Cl_2 at −78°, only rhamnose was observed by paper chromatography.

*3,5,6-Tri-O-benzoyl-2-O-methyl-*D-*mannono-1,4-lactone* (**9**). — To a solution

of 2,5,6-tri-*O*-benzoyl-D-mannono-1,4-lactone (**3**, 0.17 g) in $CHCl_3$ (3 mL) and MeI (5 mL), freshly prepared Ag_2O (89 mg) was slowly added. After stirring for 24 h at 40°, no starting material could be detected by t.l.c. After filtration, the solution was concentrated to a syrup, which on t.l.c. (solvent *D*) showed a main spot (R_F 0.40). The product was purified by column chromatography on Silica Gel H (Merck, 20 × 1.5 cm) using 49:1 $CHCl_3$–EtOAc as eluent, and isolated as a homogeneous syrup which was characterised as **9** (0.15 g, 86%). It could not be induced to crystallize; $[\alpha]_D^{20}$ −97.8° (*c* 1, $CHCl_3$) ν_{max}^{film} 1800 (1,4-lactone CO); 1720 cm^{-1} (benzoyl CO); ^{1}H-n.m.r.: δ 8.2–7.2 (m, 15 aromatic H); 6.19 (dd; $J_{2,3}$ 5.0, $J_{3,4}$ 3.5 Hz, H-3), 5.80 (m, $J_{4,5}$ 9.0, $J_{5,6}$ 3.0, $J_{5,6'}$ 5.0 Hz, H-5), 5.05 (dd, H-4), 5.00 (dd, $J_{6,6'}$ 13.0 Hz, H-6), 4.67 (dd, H-6'), 4.35 (d, H-2), and 3.60 (s, MeO); ^{13}C-n.m.r.: δ 165.7, 164.8, and 164.6 (benzoyl CO), 133.5–128.3 (aromatic C) (for other carbon resonances, see Table I).

Anal. Calc. for $C_{28}H_{24}O_9$: C, 66.66; H, 4.79. Found: C, 66.85; H, 5.07.

2-O-Methyl-D-mannose (**10**). — To a freshly prepared solution containing 1.4 mmol of bis(2-butyl-3-methyl)borane (disiamylborane) in tetrahydrofuran (0.7 mL), compound **9** (0.14 g, 0.28 mmol) in tetrahydrofuran (2 mL) was added. After stirring for 20 h at room temperature, the mixture was processed as already described[31]. The organic layer was evaporated to a syrup, which on t.l.c. showed a main product (R_F 0.30, solvent *E*; R_F 0.25, solvent *D*). The crude product (0.12 g) was dissolved in $CHCl_3$ (4 mL) and 0.5M NaOMe in MeOH (4 mL) was added with external cooling. After stirring for 1 h at 0°, the solution showed no starting material by t.l.c. (solvent *E*). The free sugar was recovered by water extraction (3 × 5 mL) and the aqueous phase was neutralized with Dowex 50W (H^+) resin. Evaporation gave a syrup that crystallized upon addition of EtOH (26 mg, 48% yield). It was characterised as **10** by comparison with an authentic sample; R_F 0.42 (solvent *F*); m.p. and mixed m.p. 135–137°; lit.[27] 138–139°; $[\alpha]_D^{20}$ 8.8 →5.0 (24 h, *c* 2, H_2O); lit.[27] 6.6 →4.8 (24 h, H_2O).

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