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Note

Reactions of partially acylated aldohexopyranosides*: a contribution to the preparation and chemistry of 3,2-enolones

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Regioselective oxidation of methyl 3,6-di-*O*-benzoyl- and methyl 3,6-di-*O*-pivaloyl-α-D-mannopyranoside by pyridinium chlorochromate leads to methyl 3,6-di-*O*-benzoyl- (**1**) and methyl 3,6-di-*O*-pivaloyl-α-D-*arabino*-hexopyranosid-2-ulose (**2**), respectively, which are useful intermediates in chemical syntheses[1]. Methyl 3,4,6-tri-*O*-acyl-α-D-*arabino*-hexopyranosid-2-uloses easily undergo elimination reactions to 3,2-enolones[2], which are also of interest in the field of synthesis[3]. We now report on the use of **1** and **2** as synthons for a more convenient preparation of 3,2-enolones and on some new reactions of the latter compounds.

Treatment of **1** or **2** with mesyl chloride in pyridine–dichloromethane at room temperature gave high yields of the 3,6-di-*O*-benzoyl (**5**) and 3,6-di-*O*-pivaloyl (**6**) derivatives, respectively, of methyl 4-deoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose, *via* the intermediate mesylates **3** and **4**. Although **5** but not **6** is known[3], the procedure used here is a new and easier approach to these compounds.

3,2-Enolones are relatively stable towards acid, but tend to undergo base-catalysed elimination reactions leading to γ-pyrone systems[4,5]. Thus, **5** readily loses benzoic acid, and the product adds methanol with 3→2 acyl migration on treatment[6] with methanol–sodium carbonate–dimethyl sulfoxide to give methyl 2-*O*-benzoyl-4,6-dideoxy-2-*C*-methoxy-α-D-*glycero*-hex-4-enopyranosid-3-ulose (**7**). However, when **6** was treated at 0° with methanol containing a catalytic amount of sodium methoxide, a rapid addition of 1 mol of methanol took place and gave **8** (major product), $[\alpha]_D$ +58° (ethanol), and **9**, $[\alpha]_D$ +8° (ethanol), in the ratio 95:5, which had different mobilities in chromatography but similar ^1H- and ^{13}C-n.m.r. spectra. The n.m.r. data were not helpful in establishing the configuration of C-2 in **8** and **9**. By analogy with comparable results[6], the first step of the reaction **6**→**8** + **9** is the addition of methoxide to the carbonyl group at position 2, mainly from the sterically less-hindered side, *i.e.*, *trans* to MeO-1. Initial 5,6-elimination, as

*Part III. For Part II, see ref. 1.
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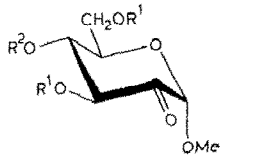

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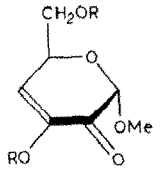

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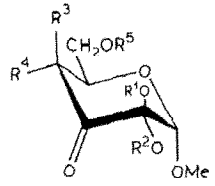
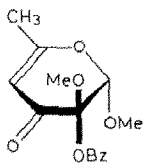
6 R = Piv



8 R^1 = Me, R^2 = R^5 = Piv, R^3 = R^4 = H
9 R^1 = R^5 = Piv, R^2 = Me, R^3 = R^4 = H
10 R^1 = CD_3, R^2 = R^5 = Piv, R^3 = D, R^4 = H
11 R^1 = CD_3, R^2 = R^5 = Piv, R^3 = H, R^4 = D
12 R^1 = Et, R^2 = R^5 = Piv, R^3 = R^4 = H
13 R^1 = Me, R^2 = R^5 = Bz, R^3 = R^4 = H



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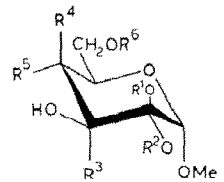

14 R^1 = Me, R^2 = R^6 = Piv, R^3 = R^4 = R^5 = H
15 R^1 = Me, R^2 = R^6 = Piv, R^3 = D, R^4 = R^5 = H
16 R^1 = CD_3, R^2 = R^6 = Piv, R^3 = R^5 = H, R^4 = D
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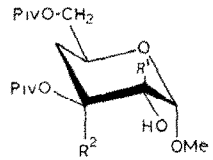

18 R^1 = R^2 = H
19 R^1 = R^2 = D
20 R^1 = D, R^2 = H

stated by Lichtenthaler *et al.*[6], was *not* observed. Subsequently, 3→2 acyl migration[6] occurs during the formation of **7**. The chiral centre at C-5 is not affected under these conditions. Only a small quantity of the isomeric product **9** was formed as a consequence of the addition of methoxide from the more-hindered side of the substrate.

When the base-catalysed reaction of **6** was carried out in methanol-d_4, a 9:1 mixture of **10** and **11** was obtained; when ethanol was used, the product was **12** and no diastereoisomer of the type **9** was isolated. These compounds allowed assignment of the two methoxyl signals in the ^{1}H-n.m.r. spectrum of **8**, since the chemical shifts of the signals for MeO-1 for **8, 10, 11,** and **12** were in good agreement (Table I). Treatment of **5** with methanolic sodium methoxide gave **13**.

Borohydride reduction of **8** gave a good yield of **14**, the structure of which was confirmed by ^{1}H-n.m.r. spectroscopy; the $J_{3,4}$ and $J_{3,4'}$ values indicated H-3 to be axial. Reduction of **8** with borodeuteride gave 3-d_1 the derivative **15**; no H/D-exchange was observed in this reaction. Thus, it is clear that MeO-2*a* prevents hydride transfer from the same side. Oxidation of **14** with pyridinium chlorochromate regenerated **8**, indicating that the substituents at C-2 had not been affected. Treatment of the mixture of **10** and **11** with sodium borohydride gave a mixture of **16** and **17**, the ^{1}H-n.m.r. spectra of which allowed assignment of the signal for MeO-1 in **14** and **15**.

Reduction of **8** with sodium borohydride in ethanol gave methyl 4-deoxy-3,6-di-*O*-pivaloyl-α-D-*xylo*-hexopyranoside (**18**) in contrast to the results described above, and **19** was obtained when borodeuteride was used. The formation of **18** involves the intermediate **14**, since **14** also gives **18** on treatment with ethanolic borohydride and **20** with ethanolic borodeuteride. As with **15**, neither of the deuterated compounds **19** and **20** showed any H/D-exchange, indicating that the isolated products arise by two hydride-transfer reactions without involvement of base-catalysed equilibrations.

Reductions using complex hydrides can be influenced greatly by the solvent[7]. Thus, borohydride decomposes more rapidly in methanol than in ethanol. It is assumed that, after the formation of **14**, HO-3 is deprotonated followed by 2→3 migration of the pivaloyl group and irreversible elimination of a methoxide anion. The carbonyl group generated at C-2 is then stereoselectively reduced from the less-hindered side. The *trans*-rearrangements observed here are generally less favoured than *cis*-rearrangements, but they can occur under basic conditions[8] and may be facilated by MeO-2*a* in **8**→**17**, leading to destabilisation of the $^4C_1$ conformation.

The reactions described above allow an easy preparation and isotopic labelling of several 4-deoxy sugar derivatives.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi Model 510 melting-point apparatus and are uncorrected. Optical rotations were measured

TABLE I

^{1}H-NMR DATA ($CDCl_3$, INTERNAL Me_4Si)

Compound	*H-1*	*H-2*	*H-3*	*H-4a*	*H-4e*	*H-5*	*H-6*	*H-6'*	*Bu^t, Piv*	*H^{ar}, Bz*	*OMe (C-1)*	*OMe (C-2)*	*OEt*	*OH*
8	5.64 (s)	—	—	2.78 (dd)	2.47 (dd)		4.1–4.4 (m)		1.23/1.27 (2 s)	—	3.38 (s)	3.28 (s)	—	—
	$J_{4a,4e}$ −14.0 Hz, $J_{4a,5}$ 10.5 Hz, $J_{4e,5}$ 3.0 Hz													
9	5.17 (s)	—	—	2.45–2.65 (m)			4.0–4.3 (m)		1.22/1.24 (2 s)	—	3.47[a] (s)	3.52[a] (s)	—	—
10/11	5.64 (s)	—	—	2.74[b] (m)	2.46[b] (m)		4.1–4.4 (m)		1.22/1.26 (2 s)	—	3.38 (s)	—	—	—
12	5.66 (s)	—	—	2.81 (m)	2.45 (m)		4.1–4.4 (m)		1.23/1.25 (2 s)	—	3.37 (s)		1.20 (t) 3.37–3.60 (2 dq)	—
13	5.91 (s)	—	—	2.96 (m)	2.65 (m)		4.4–4.6 (m)		—	7.3–7.6, 8.0–8.3 (2 m)	3.36[a] (s)	3.40[a] (s)	—	—
	$J_{4a,4e}$ −13.5 Hz, $J_{4a,5}$ 11.1 Hz, $J_{4e,5}$ 2.7 Hz													
14	5.33 (s)	—	4.20 (m)	1.80 (m)	1.86 (m)	3.79 (m)	4.1 (m)			—	3.35 (s)	3.58 (s)	—	3.10 (bs)
14[c]	5.81 (s)	—	4.53 (dd)	1.9–2.3 (m)		4.10 (m)	4.3 (m)		1.23/1.26 (2s)	—	3.37 (s)	3.83 (s)		6.50 (bs)

	$J_{3,4a}$ 10.0 Hz, $J_{3,4e}$ 6.5 Hz												
15	5.34	—	—	1.7–2.0		3.97	4.1	1.22/1.23	—	3.35	3.58	—	3.08
	(s)			(m)		(m)	(m)	(2 s)		(s)	(s)		(bs)
16/17	5.33	—	4.20	1.86			3.9–4.2	1.22/1.23	—	3.36	—	—	3.12
	(s)		(m)	(m)			(m)	(2 s)		(s)			(m)
18	4.79	3.55	5.08	1.44	2.02		3.9–4.2	1.21/1.22	—	3.43	—	—	2.43
	(d)	(dd)	(ddd)	(q)	(ddd)		(m)	(2 s)		(s)			(bs)
	$J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.8 Hz, $J_{3,4a}$ 11.3 Hz, $J_{3,4e}$ 5.1 Hz, $J_{4a,4e}$ −12.2 Hz, $J_{4a,5}$ 12.0 Hz, $J_{4e,5}$ 1.9 Hz												
19	4.78	—	—	1.44	2.01		3.9–4.2	1.21/1.22	—	3.42	—	—	2.33
	(s)			(t)	(dd)		(m)	(2 s)		(s)			(bs)
20	4.79	—	5.07	1.45	2.02		3.9–4.2	1.21/1.22	—	3.43	—	—	2.27
	(s)		(dd)	(q)	(ddd)		(m)	(2 s)		(s)			(bs)

[a]These values may be interchanged. [b]The ratio of intensities for the signals of H-4*a* and H-4*e* was 1:9. [c]Pyridine-d_5.

with a Perkin–Elmer Model 241 polarimeter. T.l.c. was performed on silica gel 60 (Merck) with benzene–ethyl acetate (5:1) and detection with 0.2% anthrone in sulfuric acid. Column chromatography was carried out on Silica Woelm 100–200. N.m.r. spectra were recorded with Varian EM 390 (^{1}H, 90 MHz) and CFT-20 (^{13}C, 20 MHz) spectrometers, for solutions (50 mg/mL) in $CDCl_3$ or pyridine-d_5 with internal Me_4Si. N.m.r. data are given in Tables I and II.

*Methyl 3,6-di-*O*-benzoyl-4-deoxy-α-*D*-glycero-hex-3-enopyranosid-2-ulose* (**5**). — To a stirred solution of **1** (2.0 g, 5 mmol) in dichloromethane (20 mL) were added pyridine (2.0 g, 25.28 mmol) and mesyl chloride (1.38 g, 12.05 mmol). The mixture was kept at 30° for 24 h with occasional shaking and then cooled, dichloromethane (50 mL) was added, and the solution was washed with saturated aqueous sodium hydrogencarbonate and water, and then dried (Na_2SO_4). Removal of the solvent and drying of the residue at 10^{-3} mmHg gave a syrup, which crystallised after elution from a short column of silica gel with benzene, to yield **5** (1.87 g, 97.8%), m.p. 124–125° (from hexane), $[\alpha]_D^{20}$ +32° (*c* 1.1, chloroform), R_F 0.47; lit.[4] m.p. 124–125°, $[\alpha]_D^{20}$ +33° (chloroform).

*Methyl 4-deoxy-3,6-di-*O*-pivaloyl-α-*D*-glycero-hex-3-enopyranosid-2-ulose* (**6**). — Using essentially the above method, **2** (1.80 g, 5 mmol) was converted into **6**. The crude product was purified by column chromatography (hexane–ethyl acetate, 1:10), to yield **6** (1.68 g, 98.1%) as a syrup, $[\alpha]_D^{23}$ +28° (*c* 1.1, chloroform), R_F 0.47. N.m.r. data ($CDCl_3$): ^{1}H, δ 1.22 (s, 9 H, ^{t}Bu), 1.30 (s, 9 H, ^{t}Bu), 3.53 (s, 3 H, OMe), 4.23 (dd, 1 H, H-6), 4.40 (dd, 1 H, H-6′), 4.86 (s, 1 H, H-1), 5.93 (dt, 1 H, H-5), and 6.53 (d, 1 H, H-4); $J_{4,5}$ 1.8, $J_{5,6}$ 5.2, $J_{5,6'}$ 5.2, $J_{6,6'}$ −11.4 Hz; ^{13}C, δ 27.15 (Me_3C), 38.88 (Me_3C), 39.04 (Me_3C), 56.25 (OMe), 64.50 (C-6), 67.91 (C-5), 99.52 (C-1), 132.25 (C-4, $^1J_{C,H}$ 160 Hz), 142.64 (C-3), 175.25 (Me_3CC), 177.50 (Me_3CC), and 182.51 (C-2).

Anal. Calc. for $C_{17}H_{26}O_7$: C, 59.63; H, 7.65. Found: C, 59.33; H, 7.87.

Base-catalysed addition of methanol to **6**. — To a stirred solution of **6** (1.0 g, 2.92 mmol) in methanol (20 mL) at 0° was added sodium methoxide (50 mg, 0.56 mmol). The reaction was monitored by t.l.c.; after 15–20 min, all **6** had disappeared. The mixture was neutralised with 2.5% acetic acid in methanol, concentrated at 8 mmHg to 2 mL, and subjected to column chromatography (hexane–ethyl acetate, 1:5) to yield, first, methyl 4-deoxy-2-*C*-methoxy-2,6-di-*O*-pivaloyl-α-*D*-*erythro*-hexapyranosid-3-ulose (**8**; 0.938 g, 85.8%) as a syrup, $[\alpha]_D^{25}$ +58° (*c* 1, chloroform; *c* 1.4, ethanol), R_F 0.44.

Anal. Calc. for $C_{18}H_{30}O_8$: C, 57.74; H, 8.08. Found: C, 57.63; H, 8.28.

Eluted second was methyl 4-deoxy-2-*C*-methoxy-2,6-di-*O*-pivaloyl-α-*D*-*threo*-hexopyranosid-3-ulose (**9**; 0.049 g, 4.5%) as a syrup, $[\alpha]_D^{25}$ +8° (*c* 0.8, ethanol), R_F 0.22.

Anal. Found: C, 57.67; H, 8.22.

Treatment of **6** (0.30 g, 0.88 mmol) as described above, but using methanol-d_4

TABLE II

^{13}C-N M.R DATA ($CDCl_3$, INTERNAL Me_4Si)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*CH_3,Bu^t,Piv*	*C^q,Bu^t,Piv*	*OMe (C-1)*	*OMe (C-2)*	*COO,Piv/Bz*
8	101.35	98.96	196.59	42.29	67.19	65.22	26.94/27.16	38.88/39.70	55.56[a]	51.58[b]	176.13/177.94
9	100.94	97.84	195.25	42.88	68.50	65.62	26.89/27.18	38.84/39.12	55.46[c]	51.84[d]	176.61/177.99
10/11	101.34	98.96	196.69	—	67.14	65.21	26.94/27.17	38.87/39.70	55.59	—	176.18/177.94
12	101.55	98.88	197.00	42.30	67.20	65.24	26.93/27.18	38.86/39.67	55.54	—	176.08/177.94[e]
13	101.52	99.92	196.86	42.50	67.25	65.82	—	—	55.70	52.02	163.87/166.13[f]
14	97.40	101.59	68.79	33.43	65.93	65.79	27.12/27.21	38.82/39.64	55.49	52.57	177.75/178.19
15	97.51	101.47	—	33.34	65.94	65.81	27.10/27.20	38.81/39.60	55.42	52.58	177.63/178.13
16/17	97.39	101.54	68.68	—	65.84	65.76	27.10/27.18	38.81/39.63	55.45	—	177.74/178.19
18	100.13	71.93	70.57	32.61	65.90	65.76	27.17/27.25	38.88	55.24	—	178.13/179.59
19	100.10	—	—	32.45	65.78	65.73	27.11/27.19	38.79	55.14	—	178.03/178.42
20	100.07	—	70.44	32.54	65.78	65.72	27.11/27.20	38.81	55.15	—	178.08/178.45

[a]dd, $^1J_{C,H}$ 144, $^3J_{C,H}$ 4 Hz. [b]d, $^1J_{C,H}$ 144 Hz. [c]dd, $^1J_{C,H}$ 144, $^3J_{C,H}$ 4 Hz. [d]d, $^1J_{C,H}$ 144 Hz. [e]Additional signals: δ 15.15 (CH_3CH_2) and 60.15 (CH_3CH_2). [f]Additional signals: δ 128.33 (C-1′, Bz at C-2), 128.52 (C^m, 2 Bz, overlapping), 129.66 (C-1′, Bz at C-6), 129.77 (C^o, Bz at C-6), 130.23 (C^o, Bz at C-2), 133.31 (C^p, Bz at C-6) and 133.61 (C^p, Bz at C-2).

(6 mL) and sodium hydride (10 mg), gave, after chromatography, a mixture of **10** and **11** (0.274 g, 81.8%)*.

Treatment of the foregoing mixture (0.25 g, 0.66 mmol) with borodeuteride, as described below for **14**, gave a mixture of **16** and **17** (0.198 g, 78.8%).

*Methyl 4-deoxy-2-C-ethoxy-2,6-di-O-pivaloyl-α-*D-erythro-*hexopyranosid-3-ulose* (**12**). — Treatment of **6** (1.0 g, 2.92 mmol) as described above, but using ethanol and sodium ethoxide (30 mg), gave, after chromatography, **12** as the sole syrupy product (0.769 g, 67.8%), $[\alpha]_D^{24}$ +49.5° (*c* 1.1, chloroform), R_F 0.49.

Anal. Calc. for $C_{19}H_{32}O_8$: C, 58.75; H, 8.30. Found: C, 58.90; H, 8.35.

*Methyl 2,6-di-O-benzoyl-4-deoxy-2-C-methoxy-α-*D-erythro-*hexopyranosid-3-ulose* (**13**). — To a solution of **5** (0.50 g, 1.31 mmol) in dichloromethane–methanol (1:1, 20 mL) was added sodium methoxide (30 mg) at 0°. After stirring for 20 min, the reaction was stopped and the mixture was worked-up as described above. The product was subjected to column chromatography (benzene–ethyl acetate, 1:5), to give **13** (0.399 g, 73.5%) as a syrup, $[\alpha]_D^{24}$ +46° (*c* 0.9, chloroform), R_F 0.48.

Anal. Calc. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.87; H, 5.52.

*Methyl 4-deoxy-2-C-methoxy-2,6-di-O-pivaloyl-α-*D-xylo-*hexopyranoside* (**14**). — To a stirred solution of **8** (0.63 g, 1.68 mmol) in methanol (15 mL) at 0° was added sodium borohydride (90 mg). Stirring was continued for 20 min at 0°, the reaction was stopped by the addition of 10% acetic acid in methanol (6 mL), and the solution was concentrated to 5 mL, diluted with dichloromethane (80 mL), washed with saturated aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. The resulting syrup was subjected to column chromatography (hexane–ethyl acetate, 1:5), to give **14** (0.532 g, 84.1%), m.p. 96° (from hexane), $[\alpha]_D^{23}$ +92° (*c* 0.5, chloroform), R_F 0.23.

Anal. Calc. for $C_{18}H_{32}O_8$: C, 57.43; H, 8.57. Found: C, 57.58; H, 8.51.

When the procedure was repeated, but using sodium borodeuteride, **8** (0.21 g, 0.56 mmol) gave crystalline **15** (0.177 g, 83.5%).

To a solution of **14** (0.51 g, 1.35 mmol) in dichloromethane (30 mL) were added molecular sieve (4 Å, 2.00 g), dry sodium acetate (0.20 g), and pyridinium chlorochromate (1.00 g). After stirring for 8 h at ambient temperature under nitrogen, the mixture was concentrated to dryness, the residue was extracted with ether, and the combined extracts were treated with charcoal, filtered, and concentrated. Column chromatography (hexane–ethyl acetate, 1:5) of the residue gave **8** (0.405 g, 80.2%).

*Methyl 4-deoxy-3,6-di-O-pivaloyl-α-*D-xylo-*hexopyranoside* (**18**). — Using the procedure described for the preparation of **14**, but replacing methanol by ethanol, **8** was converted into syrupy **18** (0.477 g, 82.0%), $[\alpha]_D^{26}$ +124° (*c* 1.1, chloroform), R_F 0.24.

Anal. Calc. for $C_{17}H_{30}O_7$: C, 58.94; H, 8.73. Found: C, 59.13; H, 8.94.

To a solution of **14** (0.30 g, 0.80 mmol) in ethanol (8 mL) at 0° was added

*Melting points, optical rotations, and R_F values of the deuterated species were not significantly different from those for the proton analogues.

sodium borohydride (45 mg). After stirring for 20 min, the mixture was worked-up as described above, to give **18** (0.210 g, 75.8%). Treatment of **8** (0.21 g, 0.56 mmol) with sodium borodeuteride (30 mg), as described for **18**, gave **19** (0.162 g, 83.1%).

Treatment of **14** (0.30 g, 0.80 mmol) with sodium borodeuteride 845 mg), as described above for **14**, gave **20** (0.219 g, 78.8%).

REFERENCES

1 A. KLAUSENER, J. RUNSINK, AND H.-D. SCHARF, *Justus Liebigs Ann. Chem.*, (1984) 783–790.
2 F. W. LICHTENTHALER AND P. HEIDEL, *Angew. Chem.*, 81 (1969) 998–999; F. W. LICHTENTHALER, *Methods Carbohydr. Chem.*, 6 (1972) 348–350.
3 F. W. LICHTENTHALER, *Pure Appl. Chem.*, 50 (1978) 1343–1362.
4 F. W. LICHTENTHALER, K. STROBEL, AND G. REIDEL, *Carbohydr. Res.*, 49 (1976) 57–67.
5 F. W. LICHTENTHALER AND U. KRASKA, *Carbohydr. Res.*, 58 (1977) 363–377.
6 F. W. LICHTENTHALER, S. NISHIYAMA, AND P. JARGLIS, *Angew. Chem.*, 91 (1979) 1001–1002.
7 H. C. BROWN AND S. KRISHNAMURTHY, *Tetrahedron*, 35 (1979) 567–607.
8 A. H. HAINES, *Adv. Carbohydr. Chem. Biochem.*, 33 (1976) 11–109.