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STEREOSELECTIVE SYNTHESIS OF 1,1-DIALKYL-1-METHOXYMETHYL GLUCOSIDES (ACETAL-GLUCOSIDES)*

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ABSTRACT

The synthesis is described of highly acid-sensitive 1,1-dialkyl-1-methoxymethyl glucosides (acetal-glucosides) as potential anti-cancer prodrugs. Reaction of 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucopyranose (**4**) severally with various aliphatic and alicyclic ketones and methyl trimethylsilyl ether, in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate, afforded the corresponding acetylated acetal-β-glucosides, *e.g.*, acetone gave 1-methoxy-1-methylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**7a**). Likewise the α-anomer (**8a**) of **7a** was obtained from the α-anomer of **4**. Deacetylation of the tetra-acetates then gave the acetal-α- and -β-glucosides.

INTRODUCTION

As a result of the ability of some tumours[1] to convert glucose into lactic acid in the presence of oxygen, the acid accumulates and the pH falls to 5.5–6.5 under hyperglycemic conditions (*cf.* pH 7 in many non-tumour tissues)[2]. Attempts have been made[3] to exploit this pH differential in order to design anticancer prodrugs that would be activated by acid hydrolysis in tumour tissue but would be stable and therefore non-toxic in normal tissue. In this context, we are studying 1-alkoxyalkyl glycosides (acetal-glycosides) which are highly acid-labile and from which cytotoxic aldehydes are released[4].

A rate constant of $(6.9 \pm 0.9) \times 10^{-5}$ s^{-1} was found for the hydrolysis of 1-methoxyethyl β-D-glucopyranoside at pH 3 and 28°, but little hydrolysis occurred[5] at pH 4. However, 1-ethoxyalkyl 2,3-dideoxy-D-*erythro*-hex-2-enopyranosides such as **1** were rapidly hydrolysed at pH 5 and 33° with release of the furan derivative **2**, the anticancer agent[6] aldophosphamide (**3**), and ethanol[7].

These acetal-glycosides were derived from aldehydes and we now report the synthesis of analogues derived from ketones.

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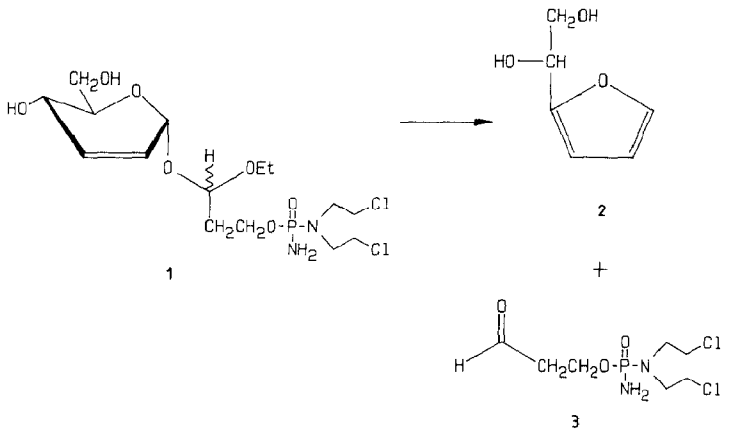
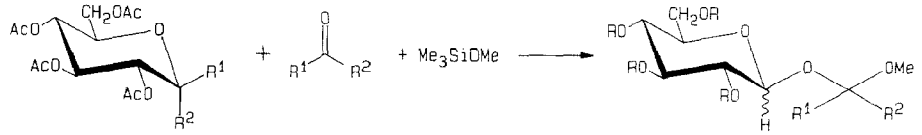


Koto *et al.*[8] have described the synthesis of acetal-glycosides derived from 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide, acetone, and various alcohols, using mercury salts and tetrabutylammonium bromide as catalysts.

RESULTS AND DISCUSSION

Reaction of 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β- (**4**) and -α-D-glucopyranose[9] (**5**) severally with the ketones **6a–e** and methyl trimethylsilyl ether (Me_3SiOMe) in the presence of 20 mol% of trimethylsilyl trifluoromethanesulfonate ($Me_3SiOSO_2CF_3$) and sodium iodide (33 mol%) in dry dichloromethane at −70° gave the acetylated acetal-glucosides **7a–e** and **8a** in yields of 27–70%.



4 R^1 = $OSiMe_3$, R^2 = H
5 R^1 = H , R^2 = $OSiMe_3$

6

7a-e R = Ac , β-anomer
8a R = Ac , α-anomer
9a-d R = H , β-anomer
10a R = H , α-anomer

6 – 10	R^1	R^2
a	Me	Me
b	Et	Et
c	— $(CH_2)_4$ —	
d	— $(CH_2)_5$ —	
e	Me	CH_2CH_2Ph
f	^iPr	^iPr
g	Me	^tBu
h	Me	CH_2Cl
i	CH_2Cl	CH_2Cl

Instead of Me_3SiOMe and the ketones, the corresponding dimethyl acetals could also be used, but the yields were sometimes lower. The reaction times varied from 24 to 54 h and the reactions were monitored by t.l.c. In contrast to the synthesis of acetal-glycosides of aldehydes, where $Me_3SiOSO_2CF_3$ alone was the catalyst, the addition of sodium iodide in the preparation of the acetal-glucosides of ketones usually improved the yields and reduced the times of reaction. Presumably, Me_3SiI is formed and acts as a catalyst. The use of pure Me_3SiI is unsuitable because of its instability and its high cost. An increase in the amount of catalyst, prolongation of the times of reaction, or higher temperatures of reaction did not enhance the yields, but often led to the formation of such side products as trehaloses[9] and methyl glucosides.

As described for the acetal-glucosides of aldehydes[4], the above reactions proceeded with retention of configuration at C-1, so that there was no neighboring-group effect[10]. The unsymmetrical ketone **6e** gave **7e** as a ~1:1 mixture of diastereomers. At temperatures higher than −30°, the anomerization **4** → **5** occurred[9] and an α,β-mixture of acetal-glucosides was formed. The best yields of acetylated acetal-glucosides were obtained with acetone, 3-pentanone, and cyclohexanone. Branching at the α position, as in 2,4-dimethyl-3-pentanone (**6f**) and *tert*-butyl methyl ketone (**6g**), prevented reaction from occurring, as did electron-withdrawing groups at the α-position, as in **6h** and **6i**, probably because of steric effects and destabilization of the intermediate carboxonium ion[11] $R^1R^2C = O^+Me$. The formation of the carboxonium ion occurs rapidly in comparison to that of the acetylated acetal-glycosides **7** or **8**, since enantiomerically pure acetals racemized within a few minutes under the reaction conditions[12].

The carboxonium ion $R^1R^2C = O^+Me$, formed from the ketone and Me_3SiOMe, can react either with Me_3SiOMe to give the acetal $R^1R^2C(OMe)_2$ or with **4** and **5** to give the acetylated acetal-glucosides **7** or **8**. The best results with **4** were obtained by employing **4, 6**, and Me_3SiOMe in ratios of 1:10:3. However, in the reaction of **5** with acetone and Me_3SiOMe, ratios of 1:2:2.5 gave the best result.

Since the acetylated acetal-glucosides **7** and **8** were highly acid-labile, appropriate precautions were necessary for their isolation, purification, and spectroscopic identification. The n.m.r. data showed that 20–40% cleavage of **7** and **8** occurred during conventional column chromatography on silica gel or aluminium oxide. Therefore, flash-chromatography was necessary with a minimum of adsorbent and dry, acid-free solvents to which the addition of a small proportion of triethylamine slowed down the decomposition. *tert*-Butyl methyl ether was an excellent solvent for chromatography. Sometimes the substrates **4** and **5** had R_F values similar to those of the products, as found for **7b** and **7d**. Phase-transfer catalyzed desilylations, using tetrabutylammonium fluoride after quenching with triethylamine, were appropriate for these compounds. The products **7a,h,d** and **8a** were crystalline.

O-Deacetylation of the tetra-acetates **7a–d** and **8a** to give the acetal-glucosides **9a–d** and **10a**, respectively, was best performed using Lewatit ML 500 (OH^-)

TABLE I

SELECTED ^{1}H- (200 MHz) AND ^{13}C-N.M.R. (50.3 MHz) PARAMETERS FOR **7–10**[a]

Compound	*Chemical shifts, δ (coupling constants, Hz)*				
	H-1 ($J_{1,2}$)	OCH_3	*C-1*	*C-1'*	OCH_3
7a	4.86 (8.0)	3.26	93.41	102.39	49.38
7b	4.84 (8.0)	3.22	92.92	106.96	48.73
7c	4.87 (8.0)	3.29	94.53	114.22	50.57
7d	4.90 (7.75)	3.24	93.03	102.91	48.43
7e	4.86, 4.88 (8.0)	3.26, 3.28	93.15, 93.27	103.79, 104.04	49.11, 49.22
8a	5.39 (3.75)	3.24	88.98	101.93	49.16
9a	4.58 (8.0)	3.24	97.14	102.98	49.80
9b	4.54 (8.0)	3.18	96.62	107.43	49.01
9c	4.55 (8.0)	3.22	98.36	114.66	50.68
9d	4.57 (8.0)	3.19	96.57	103.31	48.79
10a	5.10 (4.0)	3.19	93.22	102.52	49.67

[a]Series **7** and **8** in $CDCl_3$, **9** and **10** in D_2O.

resin in methanol. The use of pure **7a–d** and **8** avoided the need for chromatography of the products.

The acetal-glucosides **9** and **10** had higher rates of hydrolysis than acetal-glycosides derived from aldehydes, which accords with the increased acid-lability of acetals of ketones compared to those of aldehydes[13]. Rate constants of 11.4–3.7 × 10^{-4} s^{-1} for acetal-β-glycosides **9a–d** and 0.88 × 10^{-4} s^{-1} for the acetal-α-glycoside **10a** were found at pD 6.0 and 35.0° in 67mM phosphate buffer (I = 0.20M, KCl).

The structures of the new compounds were determined mainly by ^{1}H- and ^{13}C-n.m.r. spectroscopy (Table I). As expected, signals at δ 4.84–4.90 and 4.54–4.58 with a $J_{1,2}$ value of 8.0 Hz were observed for the resonance of H-1 in the β-glucosides **7a–e** and **9a–d**, respectively. In the corresponding α-glucosides **8a** and **10a**, H-1 resonated at δ 5.39 and 5.10, respectively, with a $J_{1,2}$ value of 3.75 Hz.

EXPERIMENTAL

General. — Melting points were determined with a Kofler melting-point apparatus and are corrected. Elemental analyses were performed at the Micro-

analytical Laboratory, University of Göttingen. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. The ^{1}H- and ^{13}C-n.m.r. spectra (200 MHz, internal Me_4Si) were recorded with Varian XL-200 and VXR-200 instruments. The progress of all reactions was monitored by t.l.c. on SIL G/UV_{254} (Macherey Nagel). Aliquots were removed from reaction mixtures under anhydrous conditions and without any change in temperature. Column chromatography was performed on Kieselgel 0.032–0.063 (ICN, Biomedicals). Solvents used for chromatography were *A*, 2:1 light petroleum–ethyl acetate; *B*, 1:1 light petroleum–*tert*-butyl methyl ether; *C*, 15:1 ethyl acetate–methanol; *D*, 1:1 hexane–ethyl acetate; *E*, 1:1 light petroleum–ethyl acetate.

All reactions were carried out under argon in anhydrous media. It was essential to use pure compounds and the stated reaction temperatures, otherwise colouration and loss of selectivity occurred.

Synthesis of acetal-β- (**7**) *and -α-glucosides* (**8**) *from 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-* (**4**) *and -α-*D*-glucopyranose* (**5**). — To a solution of **4** or **5** (420 mg, 1.0 mmol), ketone **6** (10.0 mmol), Me_3SiOMe (410 μL, 3.0 mmol), and NaI (50.0 mg, 0.33 mmol) in dry dichloromethane (3 mL) at −70° was added $Me_3SiOSO_2CF_3$ (36 μL, 0.2 mmol). The mixture was stirred at −70° until the reaction was complete (24–60 h, t.l.c., solvent *E*), then quenched with triethylamine (0.1 mL), warmed to room temperature, and immediately filtered through silica gel (2 g) with ethyl acetate or *tert*-butyl methyl ether as solvent. The eluate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica gel (60 g, solvent *A* or *B*) to afford **7** and **8**, respectively.

Phase-transfer catalyzed desilylation of unreacted **4** *and* **5**. — The crude product (1 g) obtained above, potassium fluoride (170 mg, 3.00 mmol), tetrabutylammonium fluoride dihydrate (940 mg, 3.00 mmol), and aqueous 10% $NaHCO_3$ (10 mL) were stirred with ether (10 mL) until desilylation was complete (45 min; t.l.c., solvent *E*). Then the organic layer was separated, the aqueous phase was extracted with ether (4 × 10 mL), and the combined organic solutions were washed with brine, dried (K_2CO_3/Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography of the residue on silica gel (70 g, solvent *A* or *B*) afforded pure **7** and **8**, respectively.

O-*Deacetylation of the tetra-acetates* **7** *and* **8**. — A solution of **7** and **8** (1.0 mmol) in dry methanol (10 mL) was stirred with Lewatit ML 500 (OH^-) resin (5.0 g, type I) for 5 h at room temperature. The reaction was monitored by t.l.c. (solvent *C*). The mixture was washed through Celite (1 g; column diameter, <2 cm) with methanol (100 mL) and the eluate was concentrated *in vacuo* to afford **9** and **10**, respectively.

*1-Methoxy-1-methylethyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**7a**). — The reaction of **4** (420 mg, 1.0 mmol), acetone (580 μL, 10.0 mmol), and Me_3SiOMe (410 μL, 3.0 mmol) for 24 h yielded **7a** (291 mg, 70%), m.p. 102° (from ether–light petroleum), $[\alpha]_D^{20}$ −33° (*c* 1, chloroform); R_F 0.42 (solvent *E*). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.36, 1.42 (2 s, 6 H, 2 Me), 2.02, 2.04, 2.05, 2.07 (4 s, 12 H, 4

Ac), 3.26 (s, 3 H, OMe), 3.73 (ddd, 1 H, $J_{5,6a}$ 2.75, $J_{5,6b}$ 5.5, $J_{5,4}$ 10.0 Hz, H-5), 4.13 (dd, 1 H, $J_{6a,5}$ 2.75, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.24 (dd, 1 H, $J_{6b,5}$ 5.5 Hz, $J_{6b,6a}$ 12.0 Hz, H-6b), 4.86 (d, 1 H, J 8.0 Hz, H-1), 5.04 (dd, 1 H, $J_{2,1}$ 8.0, $J_{2,3}$ 9.5 Hz, H-2), 5.07 (dd, 1 H, $J_{4,3}$ 9.5, $J_{4,5}$ 10.0 Hz, H-4), and 5.26 (t, 1 H, J 9.5 Hz, H-3); ^{13}C, δ 20.62, 20.72 (4 CH_3CO), 24.73, 26.27 (2 CH_3), 49.38 (OCH_3), 62.30 (C-6), 68.66 (C-4), 71.38 (C-2), 71.78 (C-5), 73.34 (C-3), 93.41 (C-1), 102.39 (C-1'), 169.11, 169.48, 170.30, and 170.57 (4 CO).

Anal. Calc. for $C_{18}H_{28}O_{11}$ (420.4): C, 51.43; H, 6.71. Found: C, 51.56; H, 6.75.

1-Ethyl-1-methoxypropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**7b**). — The reaction of **4** (820 mg, 1.95 mmol), diethyl ketone (2.10 mL, 20.0 mmol), and Me_3SiOMe (820 μL, 6.0 mmol) for 48 h followed by phase-transfer catalyzed desilylation afforded **7b** (446 mg, 51%), m.p. 94–94.5° (from ether–light petroleum), $[\alpha]_D^{20}$ −13° (*c* 1, chloroform); R_F 0.48 (solvent *E*).

Anal. Calc. for $C_{20}H_{32}O_{11}$ (448.5): C, 53.56; H, 7.19. Found: C, 53.68; H, 7.16.

1-Methoxycyclopentyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**7c**). — The reaction of **4** (800 mg, 1.90 mmol), cyclopentanone (1.72 mL, 19.0 mmol), and Me_3SiOMe (800 μL, 5.7 mmol) for 48 h yielded **7c** (404 mg, 47%), as a colourless oil, $[\alpha]_D^{20}$ −18° (*c* 1, chloroform); R_F 0.40 (solvent *E*).

Anal. Calc. for $C_{20}H_{30}O_{11}$ (446.5): C, 53.81; H, 6.77. Found: C, 54.00; H, 6.94.

1-Methoxycyclohexyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**7d**). — The reaction of **4** (420 mg, 1.0 mmol), cyclohexanone (1.20 mL, 10.0 mmol), and Me_3SiOMe (500 μL, 3.65 mmol) for 48 h followed by phase-transfer catalyzed desilylation afforded **7d** (235 mg, 51%), m.p. 76–78° (from ether–light petroleum), $[\alpha]_D^{20}$ −20° (*c* 1, chloroform); R_F 0.43 (solvent *E*).

Anal. Calc. for $C_{21}H_{32}O_{11}$ (460.5): C, 55.19; H, 7.00. Found: C, 54.78; H, 7.14.

(1RS)-1-Methoxy-1-methyl-3-phenylpropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**7e**). — The reaction of **4** (400 mg, 0.95 mmol), benzyl acetone (1.4 mL, 9.5 mmol), and Me_3SiOMe (400 μL, 2.9 mmol) for 54 h yielded **7e** (329 mg, 45%), as a colourless oil after removal of excess of ketone by distillation (60°, 1 Torr), having a 1:1.2 ratio of diastereomers; $[\alpha]_D^{20}$ −11° (*c* 1, chloroform); R_F 0.44 (solvent *D*).

Anal. Calc. for $C_{25}H_{34}O_{11}$ (510.5): C, 58.82; H, 6.71. Found: C, 58.71; H, 6.71.

1-Methoxy-1-methylethyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (**8a**). — The reaction of **5** (950 mg, 2.26 mmol), acetone (1.3 mL, 23 mmol), and Me_3SiOMe (930 μL, 6.8 mmol) for 32 h at −30° yielded **8a** (243 mg, 27%), m.p. 116° (from ether–light petroleum), $[\alpha]_D^{20}$ +132° (*c* 1, chloroform); R_F 0.41 (solvent *E*).

Anal. Calc. for $C_{18}H_{28}O_{11}$ (420.4): C, 51.43; H, 6.71. Found: C, 51.51; H, 6.70.

1-Methoxy-1-methylethyl β-D-glucopyranoside (**9a**). — *O*-Deacetylation of **7a** (570 mg, 1.24 mmol) for 6 h yielded **9a** (329 mg, 96%), m.p. 119–122° (from methanol), $[\alpha]_D^{20}$ −53° (*c* 1, methanol).

Anal. Calc. for $C_{10}H_{20}O_7$ (252.3): C, 47.61; H, 7.99. Found: C, 47.52; H, 7.96.

1-Ethyl-1-methoxypropyl β-D-glucopyranoside (**9b**). — *O*-Deacetylation of **7b** (240 mg, 0.53 mmol) for 5 h yielded **9b** (139 mg, 94%), m.p. 118° (from methanol), $[\alpha]_D^{20}$ −42° (*c* 1, methanol). Instability precluded elemental analysis.

1-Methoxycyclopentyl β-D-glucopyranoside (**9c**). — *O*-Deacetylation of **7c** (240 mg, 0.54 mmol) for 5 h yielded **9c** (139 mg, 93%), as a colourless oil, $[\alpha]_D^{20}$ −30° (*c* 1, methanol). Instability precluded elemental analysis.

1-Methoxycyclohexyl β-D-glucopyranoside (**9d**). — *O*-Deacetylation of **7d** (460 mg, 1.00 mmol) for 6 h yielded **9d** (204 mg, 77%), m.p. 138° (from methanol–ether), $[\alpha]_D^{20}$ −40° (*c* 1, methanol).

Anal. Calc. for $C_{13}H_{24}O_7$ (292.3): C, 53.41; H, 8.28. Found: C, 53.24; H, 8.22.

1-Methoxy-1-methylethyl α-D-glucopyranoside (**10a**). — *O*-Deacetylation of **8a** (200 mg, 0.48 mmol) for 5 h yielded **10a** (106 mg, 88%), m.p. 133° (from methanol), $[\alpha]_D^{20}$ +164° (*c* 1, methanol).

Anal. Calc. for $C_{10}H_{20}O_7$ (252.3): C, 47.61; H, 7.99. Found: C, 47.79; H, 7.78.

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