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STEREOSELECTIVE SYNTHESIS OF (1-ALKOXYALKYL) α- AND β-D-GLUCOPYRANOSIDURONATES (ACETAL-GLUCOPYRANOSIDURONATES): A NEW APPROACH TO SPECIFIC CYTOSTATICS FOR THE TREATMENT OF CANCER*

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ABSTRACT

The reaction of methyl 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β- (**5**) and -α-D-glucopyranuronate (**6**) severally with the dimethyl or diethyl acetals of formaldehyde, bromoacetaldehyde, propionaldehyde, 3-benzyloxypropionaldehyde, 5-carboxypentanal, and 2-bromohexanal in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate at −78° gave the corresponding (1-alkoxyalkyl) α- and β-glycosides (acetal-glucopyranosiduronates) with retention of configuration at C-1 in yields of 41–91%. Instead of the dialkyl acetals, the corresponding aldehydes and alkyl trimethylsilyl ether can be used. Deacetylation gave the corresponding methyl (acetal-β- and -α-D-glucopyranosid)uronates in good yield. De-esterification of methyl [(1*R*)-1-methoxybutyl β-D-glucopyranosid]uronate with esterase gave the acetal-β-D-glucopyranosiduronic acid which was an excellent substrate for β-D-glucuronidase.

INTRODUCTION

Such aldehydes as bromoacetaldehyde, glyoxal, and 4-hydroxypentenal are strongly cytostatic[2] but cannot usually be used in the free state since they are rapidly deactivated by metabolism in the serum. In seeking to develop new anti-cancer agents, we have investigated protected aldehydes as prodrugs[3] which should be activated preferentially in tumour cells[4]. In many animal and human malignant cell populations, a decrease in pH can be achieved depending on the concentration of extracellular glucose because of a higher rate of glycolysis in tumours compared to normal cells[5]. The rate of an enzymic hydrolysis may depend strongly on the pH in the tissue, for example, β-glucuronidase which has[6] its rate maximum between pH 4 and 5. This enzyme is more prevalent in human cancer tissue than in a normal cell population[7]. Thus, by the correlation of the β-glucuronidase activity of tumours[8]

*Glycosidation, Part 8. For Part 7, see ref. 1.
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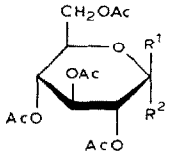
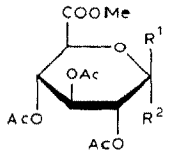
and their response to aniline mustard, it has been concluded that the extreme sensitivity of ADJ/PCS plasma cell tumours to aniline mustard is due probably to metabolic *p*-hydroxylation, glucuronide formation, and selective enzymic hydrolysis of the conjugate in the tumour[9]. Therefore, β-glucuronidase offers a means to release cytotoxic aldehydes from appropriately designed prodrugs.

We now describe the stereoselective synthesis of 1-alkoxyalkyl glycosides of methyl α- (**10**) and β-D-glucopyranuronate (**11**) as an approach to new specific cytostatics. Glycosides such as **10** and **11**, hitherto not accessible generally, can be obtained highly selectively by reaction of 1-*O*-trimethylsilyl sugar derivatives with acetals catalysed by trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate)[10]. Thus, treatment of 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-α- (**1**) and -β-D-glucopyranose (**2**) with formaldehyde dimethyl acetal in the presence of trimethylsilyl triflate gave the acetal-α- (**3**) and -β-glucosides (**4**), respectively, with high anomeric purity and in high yield. The structural element of these compounds is found, for example, in trehaloses, iridoids, and secoiridoids[11].

RESULTS AND DISCUSSION

Methyl 2,3,4-tri-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucopyranuronate (**5**) was obtained by hydrogenolysis of the benzyl β-glycoside **7** and the α anomer **6** by hydrolysis of the glycosyl bromide **8**, followed by trimethylsilation and anomerisation of the resulting mixture of **5** and **6** with trimethylsilyl triflate[12].





1 R^1 = H, R^2 = $OSiMe_3$
2 R^1 = $OSiMe_3$, R^2 = H
3 R^1 = H, R^2 = OCH_2OMe
4 R^1 = OCH_2OMe, R^2 = H

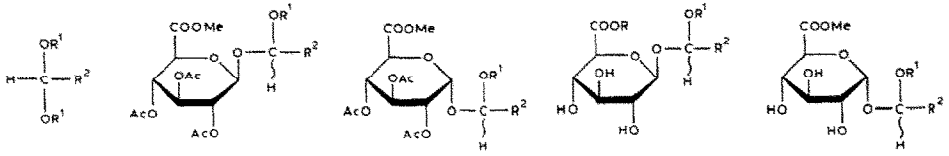
5 R^1 = $OSiMe_3$, R^2 = H
6 R^1 = H, R^2 = $OSiMe_3$
7 R^1 = OBzl, R^2 = H
8 R^1 = H, R^2 = Br

Reaction of the β anomer of **5** with the acetals **9a–e** in the presence of catalytic amounts of trimethylsilyl triflate in dichloromethane at −78° gave good yields of the acetal-β-D-glycosides **10a–e**. The efficiency of the glucuronidation could be increased by the addition of 0.5–5 mol of acetone or the corresponding aldehyde of the acetal.

In a similar manner, reaction of the α anomer **6** and **9a–e** in the presence of trimethylsilyl triflate at −78° to −20° gave the α-glycosides **11a–f**. Thus, the configuration at C-1 of the glycosides **10** and **11** is determined by the configuration at C-1 in **5** and **6**, respectively. However, at −50°, rapid anomerisation of **5**→**6** occurred. This reaction can be utilised for the selective synthesis of the α-glycosides

11 starting from a mixture of **5** and **6**. For the selective synthesis of the β-glycosides **10** from **5**, the temperature of the reaction must be kept at −78°, when anomerisation did not occur. However, **5** did not react with the less reactive acetals such as **9f** at −78° and, at −45°, reaction yielded a 9:1 mixture of the α- (**10f**) and β-glycosides (**11f**). Although isomerisation of the α-1-*O*-trimethylsilyl derivative **6** to the β anomer **5** does not occur, the temperature of the reaction with acetals should not be allowed to rise above −20° since side reactions (formation of disaccharides) or decomposition may occur.

The reaction of **5** and **6** severally with formaldehyde dimethyl acetal (**9a**) gave a single product **10a** and **11a**, respectively. However, with each of the prochiral acetals **9b–e**, a mixture of diastereomers at C-1′ was formed. The selectivity was much higher in the formation of the α-glycosides **11**. The ratios of diastereoisomers varied from 1.3:1 to 2.6:1 for **10** and from 1.3:1 to 8.1:1 for **11**, which probably reflects the influence of anomeric effects in the formation of the transition states[1]. The mixtures of 1′*S*/1′*R*-isomers could not be resolved by chromatography but, for **10c**, they could be isolated by fractional crystallisation.



a R^1 = Me, R^2 = H
b R^1 = Et, R^2 = CH_2Br
c R^1 = Me, R^2 = Pr
d R^1 = Et, R^2 = CH_2CH_2OBzl
e R^1 = Me, R^2 = $(CH_2)_4COOMe$
f R^1 = Me, R^2 = CH(Br)Bu

O-Deacetylation of the triacetates **10a–e** and **11a–f** with sodium methoxide or potassium carbonate in methanol at room temperature gave the methyl acetal-β- (**12a–e**) and -α-D-glucopyranosiduronates (**13a–f**) in excellent yield.

The structures of **10–13** were confirmed by ^{1}H- and ^{13}C-n.m.r. spectroscopy. Thus, each of the β-glycosides **10a–e** and **12a–e** gave a signal for H-1 at δ 4.86 (d, $J_{1,2}$ 7.5 Hz), whereas those for H-1 in the α-glycosides **11a–f** and **13a–f** occurred at δ 5.41 (d, $J_{1,2}$ 3.5 Hz). The decoupled ^{13}C-n.m.r. spectra of **10** and **11** contained singlets for C-1 at δ 95.9 and 92.9. The configuration at C-1′ can be determined by the chemical shifts of the signals for C-1′ and H-1′. In the compounds with a (1*S*,1′*S*) or (1*R*,1′*R*) configuration, the ring oxygen compresses the C-1′–H-1′ bond, but this effect is absent in compounds with a (1*S*,1′*R*) or (1*R*,1′*S*) configuration[1,13]. Thus, for the β-glycosides **10a–e** with the (1′*S*)-configuration, a downfield shift of Δδ 0.02–0.20 for H-1′ and an upfield shift of Δδ 1.32–3.53 for C-1′ was found compared to the (1′*R*)-isomers. Similarly, compression of the C-1′–H-1′-bond in the (1′*R*)-α-glycosides **11a–f** caused an upfield shift of the C-1′ resonance by

TABLE I

PRODUCTS OF THE REACTION OF **5** AND **6** WITH **9a–f** (SEE EXPERIMENTAL)

Product	*Yield (%)*	*M.p. (degrees)*	*Reaction time (h)*	*Reaction temp. (degrees)*	*Ratio of 1'S/1'R and 2'S/2'R forms*[a]	$[\alpha]_D^{20}$ *(chloroform) (degrees)*
10a	83	139	18	−78		−90 (*c* 1)
10b	47	121	48	−78	1.3:1	−25 (*c* 0.5)
10c	65	75	24	−78	2.6:1	−38 (*c* 1)
10c$_R$		88				−54 (*c* 1)
10c$_S$		98				−49 (*c* 1)
10d	74		48	−78	1.3:1	−30 (*c* 1)
10e	52		24	−78	1.9:1	−34 (*c* 1)
11a	76	96	12	−78		+128 (*c* 0.5)
11b	52	101	4	−35	1:4.1	+139 (*c* 0.5)
11c	91	95	6	−40	1:4.6	+122 (*c* 1)
11d	85		8	−50	1:1.3	+95 (*c* 1)
11e	66	62	48	−78	1:8.1	
					1:11.7[b]	+101 (*c* 1)
11f	63		12	−45	1:1.1:1.1:1.2	+86 (*c* 1)

[a]Determined by ^{13}C-n.m.r. spectroscopy. [b]After repeated crystallisation (ether–light petroleum).

TABLE II

ANALYTICAL AND SELECTED N.M.R. DATA FOR **10** AND **11**

Compound	*Formula*	*Calc.*	*Found*	*Chemical shifts (200 MHz)*			
				H-1'		*C-1'*	
				1'-R	*1'*-S	*1'*R	*1'*S
10a	$C_{15}H_{22}O_{11}$	C, 47.62; H, 5.86	C, 47.82; H, 5.97				
10b	$C_{17}H_{25}BrO_{11}$	C, 42.08; H, 5.19; Br, 16.47	C, 42.24; H, 5.35; Br, 16.31	4.96 (dd)	4.98 (dd)	101.90	100.58
10c	$C_{18}H_{28}O_{11}$	C, 51.42; H, 6.71	C, 51.50; H, 6.80	4.60 (t)	4.83 (t)	105.42	101.89
10d	$C_{25}H_{34}O_{12}$	C, 57.03; H, 6.51	C, 57.21; H, 6.49	4.89 (t)	5.04 (t)	101.60	100.11
10e	$C_{21}H_{32}O_{13}$	C, 51.22; H, 6.55	C, 51.04; H, 6.45	4.60 (t)	4.72(t)	105.58	102.34
11a	$C_{15}H_{22}O_{11}$	C, 47.62; H, 5.86	C, 47.72; H, 5.80				
11b	$C_{17}H_{25}BrO_{11}$	C, 42.08; H, 5.19; Br, 16.47	C, 42.31; H, 5.20; Br, 16.50	5.06 (t)	4.90 (t)	100.12	102.81
11c	$C_{18}H_{28}O_{11}$	C, 51.42; H, 6.71	C, 51.60; H, 6.87	4.98 (t)	4.71 (t)	102.19	106.25
11d	$C_{25}H_{34}O_{12}$	C, 57.03; H, 6.51	C, 57.23; H, 6.47	[a]		100.35	102.62
11e	$C_{21}H_{32}O_{13}$	C, 51.22; H, 6.55	C, 51.09; H, 6.45	4.64 (t)	[a]	102.52	106.16
11f	$C_{20}H_{31}BrO_{11}$	C, 45.55; H, 5.93; Br, 15.15	C, 45.59; H, 5.98; Br, 15.20				

[a]Superimposed by other signals.

TABLE III

PRODUCTS OF DEACETYLATION OF **10** AND **11**

Product	*Yield (%)*	*M.p. (degrees)*	$[\alpha]_D^{20}$ *(methanol) (degrees)*	*Formula*	*Calc.*	*Found*
12a	91 (A)[a]		−133 (*c* 0.7)	$C_9H_{16}O_8$	C, 42.86; H, 6.39	C, 42.90; H, 6.48
12b	79 (B)	116	−27 (*c* 1)	$C_{11}H_{19}BrO_8$	C, 36.78; H, 5.33	C, 36.88; H, 5.19
12c	91 (A)		−16 (*c* 1)	$C_{12}H_{22}O_8$	C, 48.97; H, 7.53	C, 48.67; H, 7.51
(1′*R*)-**12c**	62 (B)	125	−70 (c 0.6)	$C_{12}H_{22}O_8$	C, 48.97; H, 7.53	C, 48.65; H, 7.51
12d	86 (A)		−24 (*c* 1)	$C_{19}H_{28}O_9$	C, 56.99; H, 7.05	C, 57.16; H, 7.03
12e	82 (A)		−48 (*c* 1)	$C_{15}H_{26}O_{10}$	C, 49.18; H, 7.15	C, 49.36; H, 7.29
13a	88 (A)	126	+114 (*c* 1)	$C_9H_{16}O_8$	C, 42.86; H, 6.39	C, 42.88; H, 6.38
13b	74 (B)		+84 (*c* 1)	$C_{11}H_{19}BrO_8$	C, 36.78; H, 5.33	C, 36.58; H, 5.52
13c	82 (A)	96	+35 (*c* 1)	$C_{12}H_{22}O_8$	C, 48.97; H, 7.53	C, 49.32; H, 7.36
13d	72 (A)		+46 (*c* 1)	$C_{19}H_{28}O_9$	C, 56.99; H, 7.05	C, 56.84; H, 7.05
13e	78 (A)	52	+20 (*c* 1)	$C_{15}H_{26}O_{10}$	C, 49.18; H, 7.15	C, 49.33; H, 7.34
13f	93 (B)		+126 (*c* 1)	$C_{14}H_{25}BrO_8$	C, 41.91; H, 6.28	C, 42.02; H, 6.24

[a]A, Methanolic sodium methoxide; B, methanol–potassium carbonate.

TABLE IV

N.M.R. DATA FOR **10a,b** AND **11a,b** ($CDCl_3$, INTERNAL Me_4Si)

Compound	*^{1}H-N.m.r. data*
10a	δ 5.36–5.19 (m, 2 H, H-3,4), 5.16–5.04 (m, 1 H, H-2), 5.01 (d, 1 H, *J* 7 Hz, H-1′), 4.86 (d, 1 H, *J* 7.5 Hz, H-1), 4.61 (d, 1 H, *J* 7 Hz, H-1′), 4.16–4.01 (m, 1 H, H-5), 3.77 (s, 3 H, COOMe), 3.39 (s, 3 H, OMe), 2.07, 2.04, 2.03 (3 s, 9 H, 3 Ac).
10b	δ 5.36–4.84 (m, 5 H, H-1,2,3,4,1′), 4.09–4.02 (m, 1 H, H-5), 3.77 (s, 3 H, COOMe), 3.73–3.35 (m, 4 H, H-2′,1″), 2.06, 2.04, 2.03 (3 s, 9 H, 3 Ac), 1.29–1.17 (m, 3 H, H-2″).
11a	δ 5.60 (t, 1 H, *J* 10 Hz, H-4), 5.41 (d, 1 H, *J* 4 Hz, H-1), 5.22 (t, 1 H, *J* 10 Hz, H-3), 4.99 (dd, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 10 Hz, H-2), 4.92 (d, 1 H, *J* 7 Hz, H-1′), 4.64 (d, 1 H, *J* 7 Hz, H-1′), 4.43 (d, 1 H, *J* 10 Hz, H-5), 3.78 (s, 3 H, COOMe), 3.42 (s, 3 H, OMe), 2.09, 2.06, 2.05 (3 s, 9 H, 3 Ac).
11b	δ 5.56 (t, 1 H, *J* 10 Hz, H-4), 5.45 (d, 1 H, *J* 4 Hz, H-1), 5.20 (t, 1 H, *J* 10 Hz, H-3), 4.96 (dd, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 10 Hz, H-2), 4.90 (t, 1 H, *J* 5.5 Hz, H-1′), 4.59 (d, 1 H, *J* 10 Hz, H-5), 3.78 (s, 3 H, COOMe), 3.74–3.55 (m, 2 H, H-1″), 3.44, 3.33 (2 d, 2 H, *J* 5.5 Hz, H-2′), 2.06, 2.04 (3 s, 9 H, 3 Ac), 1.10 (t, 3 H, *J* 7 Hz, H-2″).
	^{13}C-N.m.r. data
10a	δ 170.09, 169.40, 169.18, 167.15 ($COCH_3$), 95.93 (C-1), 93.63 (C-1′), 72.58, 72.14, 71.08, 69.31 (C-2/5), 55.86 (OCH_3), 52.91 ($COOCH_3$), 20.62, 20.50 ($COCH_3$).
10b	δ 170.01, 169.86, 169.34, 169.04, 167.06, 166.92 ($COCH_3$), 101.90, 100.58 (C-1′), 96.61, 96.29 (C-1), 72.40, 72.22, 72.12, 71.06, 70.98, 70.81, 69.24, 68.97 (C-2/5), 64.09, 62.71 (C-1″), 52.88, 52.83 ($COOCH_3$), 32.35, 31.37 (C-2′), 20.65, 20.54, 20.45 ($COCH_3$), 14.95, 14.74 (C-2″).
11a	δ 169.96, 169.75, 169.51, 168.02 ($COCH_3$), 93.83 (C-1′), 92.85 (C-1), 70.13, 69.64, 69.31, 68.86 (C-2/5), 56.11 (OCH_3), 52.87 ($COOCH_3$), 20.68, 20.52 ($COCH_3$).
11b	δ 169.90, 169.55, 167.94, 167.87 ($COCH_3$), 102.81, 100.12 (C-1′), 92.74, 92.48 (C-1), 70.17, 70.13, 69.51, 69.41, 69.09, 69.03, 68.98, 68.77 (C-2/5), 64.58, 62.83 (C-1″), 52.92, 52.87 ($COOCH_3$), 31.90, 31.41 (C-2′), 20.68, 20.61, 20.55, 20.51 ($COCH_3$), 15.05, 14.83 (C-2″).

TABLE V

^{1}H-N.M.R. DATA (200 MHz) FOR **12a,b** AND **13a,b** (D_2O/ACETONE-d_6, INTERNAL Me_4Si)

Compound	
12a	δ 4.95 (d, 1 H, *J* 7 Hz, H-1), 4.69, 4.65 (2 d, 2 H, *J* 8 Hz, H-1′), 3.98 (d, 1 H, *J* 10 Hz, H-5), 3.79 (s, 3 H, COOMe), 3.71–3.34 (m, 3 H, H-2,3,4), 3.43 (s, OMe).
12b	δ 4.99 (dd, 0.5 H, J_1 4, J_2 5 Hz, H-1′), 4.96 (dd, 0.5 H, J_1 5, J_2 5.5 Hz, H-1′), 4.75, 4.71 (2 d, 1 H, *J* 8 Hz, H-1), 3.78 (s, 3 H, COOMe), 4.04–3.26 (m, 8 H, H-2/5, 2′,1″), 1.19, 1.16 (2 t, 3 H, *J* 7 Hz, H-2″).
13a	δ 5.11 (d, 1 H, *J* 4 Hz, H-1), 4.90, 4.69 (2 d, 1 H, *J* 8 Hz, H-1′), 4.18 (d, 1 H, *J* 9.5 Hz, H-5), 3.77 (s, 3 H, COOMe), 3.84–3.60 (m, 2 H, H-3,4), 3.57 (dd, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 9.5 Hz, H-2), 3.44 (s, 3 H, OMe).
13b	δ 5.20, 5.19 (2 d, 1 H, *J* 4 Hz, H-1), 4.95, 4.94 (2 t, 1 H, *J* 5.5 Hz, H-1′), 4.29 (d, 1 H, *J* 9.5 Hz, H-5), 3.76 (s, 3 H, COOMe), 3.98–3.26 (m, 7 H, H-2,3,4,2′,1″), 1.19, 1.18 (2 t, 3 H, *J* 7 Hz, H-2″).

2.69–4.06 p.p.m. and a downfield shift of the H-1′ resonance by 0.04–0.17 p.p.m. in relation to the (1′*S*)-α-glycosides. The correctness of the assignment and of the empirically stated rule was confirmed by an X-ray analysis of the (1′*S*)-acetal-β-D-glucopyranosiduronate **10c**.

Treatment of the (1*R*)-1-methoxybutyl glycoside **12c** with β-D-glucuronidase *(Escherichia coli)* did not cleave the glycosidic bond significantly because of the blocked carboxylic acid function. Hydrolysis of the methyl ester group in **12a** by an esterase from porcine liver in potassium phosphate buffer could be followed by ^{1}H-n.m.r. spectroscopy, using the COOMe resonance at δ 3.72, and was almost complete after 5 h at 33°. The resulting (1*R*)-1-methoxybutyl β-D-glucopyranosiduronic acid (**14**) was unstable and difficult to obtain in a salt-free form, but could be freed from the esterase by filtration through a membrane filter. When β-D-glucuronidase was added to the filtrate, monitoring by ^{1}H-n.m.r. spectroscopy showed that, after 15 min, 50% of **14** had been cleaved to give glucuronic acid and butanal and, after 3 h, the hydrolysis was complete. Although methyl β-D-glucopyranuronate **12c** is not a good substrate for the β-D-glucuronidase, it may be feasible to use the methyl esters in the development of cytostatic agents since these compounds will be de-esterified enzymically to the glucopyranosiduronic acids *in vivo*.

EXPERIMENTAL

General. — Melting points were determined with a Mettler FP 61 or a Kofler apparatus and are uncorrected. Elemental analyses were performed by Mr. Beller (Microanalytical Laboratory, University of Göttingen). Optical rotations were determined with a Perkin–Elmer 241 polarimeter. ^{1}H- and ^{13}C-n.m.r. spectra were recorded with a Varian XL-200 instrument (200 MHz, internal Me_4Si). The progress of all reactions was monitored by t.l.c. on SIL G/UV_{254} (Macherey, Nagel & Co., 0.25 mm).

All reactions were carried out under an inert gas and in anhydrous media. It was essential to use pure materials and to maintain the stated reaction temperatures.

Preparation of the acetal-glucopyranosiduronates **10** *and* **11**. — (*a*) 0.10M Trimethylsilyl trifluoromethanesulfonate in dichloromethane (0.2 mL) was added to a solution of **5** or **6** (0.25 mmol) and **9** (0.38 mmol) in anhydrous dichloromethane (3 mL) under N_2 at −78°. The mixture was stirred at −78° until the reaction was complete (t.l.c.). The reaction was then quenched with triethylamine (0.1 mL), the cold solution was washed through silica gel with ether, and the eluate was concentrated *in vacuo*. Column chromatography (silica gel; hexane–ethyl acetate, 1:1) of the residue afforded **10** and **11**, respectively. Addition of 0.5–5 mmol of acetone, or the aldehyde which corresponds to **9**, to the reaction mixture improved the yield and shortened the reaction time. For the synthesis of the acetal-α-D-glucopyranosiduronates **11a–f**, the reaction temperature can be raised up to −20° according to the reactivity of the acetal **9** used (Table I).

(*b*) 0.10M Trimethylsilyl trifluoromethanesulfonate in dichloromethane (0.10 mL) was added to a solution of **5** and **6** (0.25 mmol) in anhydrous dichloromethane (3 mL) under N_2 at −30°. The reaction was stirred for 2 h at −30°, then cooled to −78°. A solution of **9** (0.38 mmol) in anhydrous dichloromethane (2 mL) and then 0.10M trimethylsilyl trifluoromethanesulfonate (0.1 mL) were added. The mixture was stirred at −78° until reaction was complete, then quenched with triethylamine (0.1 mL), and worked-up as described in (*a*). The following compounds were prepared (see Tables I, II, and IV).

Methyl (methoxymethyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**10a**), methyl (2-bromo-1-ethoxyethyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**10b**), methyl (1-methoxybutyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**10c**), methyl [(1*R*)-1-methoxybutyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid]uronate (1′*R*)-(**10c**), methyl [(1*S*)-1-methoxybutyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid]-uronate (1′*S*)-(**10c**), methyl (3-benzyloxy-1-ethoxypropyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**10d**), methyl (1-methoxy-5-methoxycarbonylpentyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**10e**), methyl (methoxymethyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate (**11a**), methyl (2-bromo-1-ethoxyethyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate (**11b**), methyl (1-methoxybutyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate (**11c**), methyl (3-benzyloxy-1-ethoxypropyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate (**11d**), methyl (1-methoxy-5-methoxycarbonylpentyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate (**11e**), and methyl (2-bromo-1-methoxyhexyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate (**11f**).

Deacetylation of **10a–e** *and* **11a–f**. — To a solution of **10** or **11** (0.50 mmol) in dry methanol (10 mL) was added methanolic 0.1% sodium methoxide (3.0 mL) or, for sensitive compounds such as **10b, 11b,** and **11f**, potassium carbonate (0.5 g, 5 mmol), and the mixture was stirred for 1–2 h at room temperature, then filtered, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel or crystallisated from ethyl acetate. The following compounds were prepared (see Tables III and V).

Methyl (methoxymethyl β-D-glucopyranosid)uronate (**12a**), methyl (2-bromo-1-ethoxyethyl β-D-glucopyranosid)uronate (**12b**), methyl (1-methoxybutyl β-D-glucopyranosid)uronate (**12c**), methyl (1*R*)-1-methoxybutyl β-D-glucopyranosid)uronate (1′*R*)-(**12c**), methyl (3-benzyloxy-1-ethoxypropyl β-D-glucopyranosid)uronate (**12d**), methyl (1-methoxy-5-methoxycarbonylpentyl β-D-glucopyranosid)uronate (**12e**), methyl (methoxymethyl α-D-glucopyranosid)uronate (**13a**), methyl (2-bromo-1-ethoxyethyl α-D-glucopyranosid)uronate (**13b**), methyl (1-methoxybutyl α-D-glucopyranosid)uronate (**13c**), methyl (3-benzyloxy-1-ethoxypropyl α-D-glucopyranosid)uronate (**13d**), methyl (1-methoxy-5-methoxycarbonylpentyl α-D-glucopyranosid)uronate (**13e**), and methyl (2-bromo-1-methoxyhexyl α-D-glucopyranosid)uronate (**13f**).

*Cleavage of the ester function in (1′*R*)-***12c*** and hydrolysis of the resulting (1*R*)-1-methoxybutyl β-D-glucopyranosiduronic acid* (**14**) *with β-D-glucuronidase*. — To

a solution of (1′*R*)-**12c** (12.3 mg, 0.044 mmol) in 0.5 mL of deuterated 0.1M potassium phosphate buffer (pH 7.5) were added 130 U of esterase from porcine liver. The reaction was followed by ^{1}H-n.m.r. spectroscopy at 33° and the methyl ester was almost completely hydrolysed within 5 h to give **14**. The mixture was filtered through a membrane filter, β-D-glucuronidase (0.044 U, 840 Fishman units) from *Escherichia coli* was added, and the reaction was followed by ^{1}H-n.m.r. spectroscopy. The glycosidic bond was cleaved within 15 min to 50% at 29°, and after 3 h the reaction was quantitative.

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REFERENCES

1 L. F. TIETZE, R. FISCHER, H. J. GUDER, AND M. NEUMANN, *Justus Liebigs Ann. Chem.*, (1987) 847–856.
2 E. SCHAUENSTEIN, H. ESTERBAUER, AND H. ZOLLNER, *Aldehydes in Biological Systems*, Pion/Academic, London, 1977; G. G. GUIDOTTI, L. LORETI, AND E. CIARANFI, *Eur. J. Cancer*, 1 (1965) 23–32; E. CIARANFI, L. LORETI, A. BORGHETTI, AND G. G. GUIDOTTI, *ibid.*, 1 (1965) 147–151.
3 M. L. SINNOTT, in M. I. PAGE (Ed.), *The Chemistry of Enzyme Action*, Elsevier, Amsterdam, 1984.
4 N. BROCK, in D. N. REINHOUDT, T. A. CONNORS, H. M. PINEDO, AND K. W. VAN DE POLL (Eds.), *Structure–Activity Relationships of Anti-Tumor Agents*, Martinus Nijhoff, London, 1983.
5 F. SCHNEIDER, *Naturwissenschaften*, 68 (1981) 20–21.
6 G. A. LEVVY AND C. A. MARSH, *Adv. Carbohydr. Chem.*, 14 (1959) 381–429.
7 E. DOHRMANN, *β-Glucuronidase in Experimentelle Medizin, Pathologie und Klinik*, Springer Verlag, Berlin, 1969; J. CONCHIE, J. FINDLAY, AND G. A. LEVVY, *Biochem. J.*, 71 (1959) 318–325; J. TOMASIC AND D. KEGLEVIC, *ibid.*, 133 (1973) 789–795.
8 J. CONCHIE AND G. A. LEVVY, *Br. J. Cancer*, 11 (1957) 487–493; U. BICKER, *Nature (London)*, 252 (1974) 726–727; M. J. SWEENEX, D. A. HOFFMAN, AND G. A. POORE, *Cancer Res.*, 31 (1971) 477–478; K. A. WATANABE, A. MATSUDA, M. J. HALAT, D. H. HOLLENBERG, J. S. NISSELBAUM, AND J. J. FOX, *J. Med. Chem.*, 24 (1981) 893–897; A. PARKER AND L. FEDOR, *ibid.*, 25 (1982) 1505–1507.
9 T. A. CONNORS AND M. WHISSON, *Nature (London)*, 210 (1966) 866–867.
10 L. F. TIETZE AND R. FISCHER, *Tetrahedron Lett.*, 22 (1981) 3239–3242; *Angew. Chem. Int. Ed. Engl.*, 20 (1981) 969–970; L. F. TIETZE, R. FISCHER, AND H.-J. GUDER, *Synthesis*, (1982) 946–948.
11 L. F. TIETZE, *Angew. Chem.*, 95 (1983) 840–854; L. F. TIETZE, U. NIEMEYER, P. MARX, AND K.-H. GLÜSENKAMP, *Tetrahedron*, 36 (1980) 735–740, 1231–1237; L. F. TIETZE AND R. FISCHER, *Angew. Chem.*, 95 (1983) 902–908.
12 L. F. TIETZE AND R. SEELE, *Carbohydr. Res.*, 148 (1986) 349–352.
13 L. F. TIETZE, R. FISCHER, H. J. GUDER, A. GOERLACH, M. NEUMANN, AND T. KRACH, *Carbohydr. Res.*, 164 (1987) 177–194.