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Note

Acetolysis of methyl (methyl 4-*O*-methyl-β-D-glucopyranosid)uronate*

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The glycosphingolipids isolated from spermatozoa of a fresh-water bivalve, *Hyriopsis schlegelii,* have a unique structure containing one or two D-mannosyl residues, novel linkages including an internal L-fucopyranosyl residue, as well as terminal D-xylosyl and 4-*O*-methyl-D-glucopyranosyluronic acid groups[2]. We previously synthesized the trisaccharide derivative which constitute the partial structure of Lipid IV. Condensation of methyl (2,3-di-*O*-acetyl-4-*O*-methyl-α-D-glucopyranosyl bromide)uronate with the appropriate OH-4-free disaccharide derivative, 2-(trimethylsilyl)ethyl 3-*O*-(2-azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-methyl-α-D-galactopyranosyl)-2-*O*-benzyl-β-L-fucopyranoside, afforded the corresponding precursor of 4-*O*-Me-β-D-Glc*p*A-(1→4)-[3-*O*-Me-α-D-Gal*p*-NAc-(1→3)]-L-Fuc[3]. In the course of the derivatization of methyl (2,3-di-*O*-acetyl-4-*O*-methyl-α-D-glucopyranosyl bromide)uronate, we prepared the acyclic compound, methyl 1,1,2,3,5-penta-*O*-acetyl-4-*O*-methyl-*aldehydo*-D-glucuronate (**9**), from methyl (methyl 4-*O*-methyl-β-D-glucopyranosid)uronate (**2**). Acetolysis of **2** with boron trifluoride etherate in acetic anhydride provided the acyclic compound **9** and a small proportion of methyl 1,2,3-tri-*O*-acetyl-4-*O*-methyl-α-D-glucopyranuronate (**5**). Kováč *et al.*[4] reported that sulfuric acid-catalyzed acetolysis of methyl (methyl 4-*O*-methyl-α-D-glucopyranosid)uronate[5] (**1**) gives, in addition to methyl (methyl 2,3-di-*O*-acetyl-4-*O*-methyl-α-D-glucopyranosid)uronate (**3**), the crystalline acyclic compound **9** in an approximate ratio of 1:1.

Treatment of the methyl α- (**1**) or β-glycoside (**2**) of the glucuronate derivative under various acetolysis conditions gave several products including the pyranose ring and open-chain compound. As summarized in Table I, every acetolysis system gave anomerization products, acetates[4,6] (**5** or **6**, or both), and the *R* and *S* acetal isomers[1], (1**R** and 1**S**)-1,2,3,5-tetra-*O*-acetyl-4-*O*-methyl-D-glucuro-

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TABLE I

YIELDS OF PRODUCTS FROM METHYL [METHYL 4-*O*-METHYL-α- (**1**) AND -β-D-GLUCOPYRANOSID]URONATE (**2**) UNDER VARIOUS EXPERIMENTAL CONDITIONS

Starting compound	*Reaction conditions*			*Relative proportions of products (%)*[a]							
	Medium	*Temp.*	*Time*	**3**	**4**	**5**	**6**	**7**	**8**	**9**	*Unknown*
2	10:1 Ac_2O–H_2SO_4	R.t.	4 d	13.3		13.3	4.1			24.0	45.3
2	10:1 Ac_2O–H_2SO_4	45°	3 h	9.8		5.7				56.9	27.6
2	100:1 Ac_2O–H_2SO_4	R.t.	6 d	20.0	68.9			6.7	4.4		
2	16:110:1 Ac_2O–AcOH–H_2SO_4	R.t.	6 d	11.4	2.9	34.3	11.4			28.6	11.4
2	10:1 Ac_2O–$BF_3 \cdot OEt_2$	0°	1 h	3.9		2.5		47.7	33.3	12.6	
2	10:1 Ac_2O–$BF_3 \cdot OEt_2$	R.t.	4 h			2.9				97.1	
2	10% Ac_2O–$AlCl_3$	R.t.	3 h			3.2				96.8	
1	10:1 Ac_2O–$BF_3 \cdot OEt_2$	0°	1 h	27.9		5.1	2.7	35.5	23.7	5.1	
1	10:1 Ac_2O–$BF_3 \cdot OEt_2$	R.t.	4 h			6.6	2.0	9.3	6.6	75.5	

[a]Yields were calculated from integration of H-1 peak of ^{1}H-n.m.r. spectra. See Table II for chemical shifts (δ) of H-1 and coupling constants $J_{1,2}$ (Hz) for each compound.

TABLE II

CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS $J_{1,2}$ (Hz)

Compound	*H-1*	$J_{1,2}$
3	4.933	3.67
4	4.445	7.70
5	6.306	3.67
6	5.732	7.69
7	5.843	4.58
8	5.775	5.86
9	6.947	4.58

nate methyl acetal (**7** and **8**) or the acyclic compound[3,4] (**9**). The reaction of **2** with acetic anhydride and sulfuric acid was slow yielding the anomerization product **3**, the 1,2,3-triacetates **5** and **6**, and the acyclic compound **9**. When the reaction temperature was raised, the acyclic compound **9** was the main product. When the sulfuric acid concentration was lowered, small amount of acetals (**7** and **8**) and a mixture of α- and β-glycosides **3** and **4** were obtained, even when the reaction was kept for 6 days. Compound **2** was acetolyzed by boron trifluoride etherate–acetic anhydride at room temperature, as well as by aluminium chloride–acetic anhydride to give the acyclic compound **9** in quantitative yield. When the reaction temperature was kept at 0°, a mixture of the acetals isomers **7** and **8** was obtained in a 5:3 ratio, in addition to **9**; the acetals could not be distinguished by ^{1}H-n.m.r. spectroscopy. The orientation of **7** was confirmed by X-ray analysis of a single crystal obtained by crystallization from 2-propanol[1].

When the α-D anomer **1** was used as starting material, the acetolysis reaction afforded almost the same results, except for the formation of **4**. They showed that both acetal bonds (C-1–O–C-5 and C-1–O–Me) are more reactive in the β-D-glycoside than in the α-D-glycoside[7]. The ratios of final products (Table I) were determined, in all cases, by ^{1}H-n.m.r. spectroscopy (Table II). The good selectivity observed for the formation of **5** and **6** (45.7%), **7** and **8** (81.0%), and **9** (97.1%) was considered to be the result of thermodynamic or kinetic control. Few experiments giving cyclic or acyclic products (or both) were clearly regulated by the reaction conditions[8]. In the case of the reaction of the β-D-glycoside **2**, anomerization was observed in all cases. Two possible mechanisms have been proposed by Lindberg[9] and Lemieux[10] for the anomerization of *O*-acetylated alkyl glycosides. With 100:1 acetic anhydride–sulfuric acid, no acetate **5** or **6** could be obtained, but the anomerization product **3** and the acetals **7** and **8**. This result is in agreement with the anomerization mechanism proposed by Lindberg[9] (Scheme 1).

In order to determine the reactivity of the starting material or the reaction products (or both), compound **2** was acetolyzed with boron trifluoride etherate. The reaction was monitored by h.p.l.c. using a column of ODS-Hypersil with acetonitrile–water as eluent and detection of absorbance at 220 nm. The starting material was rapidly acetylated, and then transformed into the corresponding β-D-

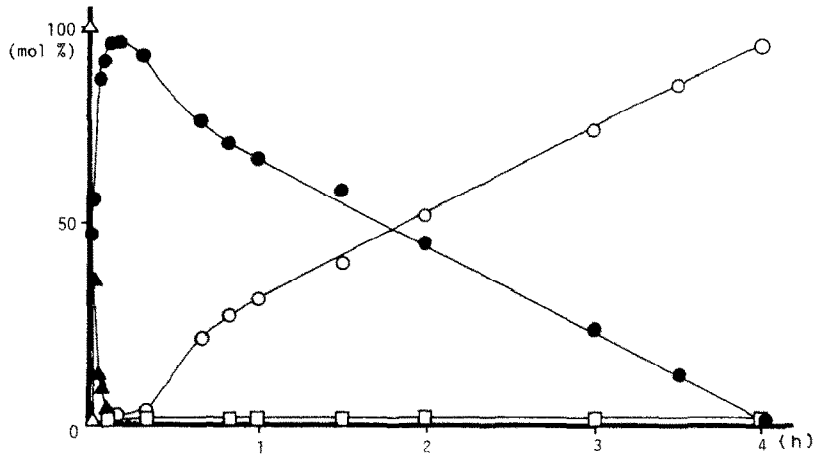
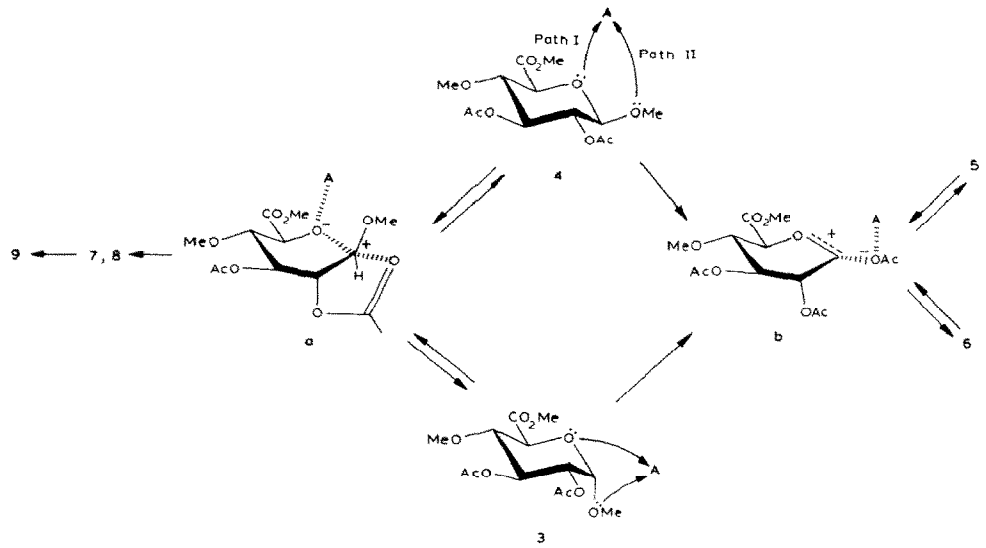
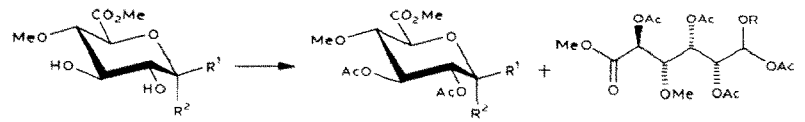


Fig. 1. Proportions of compounds **2** (—△—), **3** and **4** (—▲—), **5** (—□—), **7** and **8** (—●—), and **9** (—○—) during acetolysis with 10:1 acetic anhydride–boron trifluoride etherate at room temperature. See also Table I.





1 R^1 = H, R^2 = OMe
2 R^1 = OMe, R^2 = H

3 R^1 = H, R^2 = OMe
4 R^1 = OMe, R^2 = H
5 R^1 = H, R^2 = OAc
6 R^1 = OAc, R^2 = H

7 R = Me *(R)*
8 R = Me *(S)*
9 R = Ac

Scheme 1A + 1B.

glycoside **4**, which was immediately converted into the acetal derivatives **7** and **8**; later, the proportion of acylal derivative **9** increased and that of acetals **7** and **8** decreased. There was no equilibrium between acetates **5** and **6** and acyclic compound **9**, because the total yield of **5** and **6** was almost constant. Furthermore, for the reaction of the α-D anomer, the total yield of **5** and **6** remained constant through the reaction, though anomerization was in progress. This result is in agreement with the anomerization mechanism proposed by Lemieux[10] which involves a cyclic ion **b** as intermediate (Scheme 1).

Our results are consistent with the mechanism shown in Scheme 1. The acid catalyst **A** may coordinate with the ring oxygen atom (O-5) of the D-glucuronic acid derivative, as suggested by Lindberg[9]. Participation of CH_3CO_2-2, as shown in **a**, may help open the ring and stabilize the charge. Ring closure followed by a loss of **A** would yield **3** or **4** (anomerization). Alternatively, the C-1 of intermediate **a** may be subjected to nucleophilic attack by acetic anhydride to give the acetals **7** and **8**, and subsequent loss of a methoxyl group by acetolysis would yield the acylal **9** (Path I). If fission occurs before the ring is opened (Path II), the product would be the acetate as proposed by Lemieux[10]. It should be mentioned that these deductions may not be applicable to other uronic acid derivatives[11].

EXPERIMENTAL

Methods. — ^{1}H-N.m.r. spectra were recorded with a JEOL GSX-400 MHz spectrometer.

Materials. — Methyl (methyl 4-*O*-methyl-β-D-glucopyranosid)uronate (**2**) was prepared according to our previous report[3], and the α-D anomer (**1**) by the procedure of Wacek *et al.*[5].

General acetolysis procedure. — The uronate **1** or **2** was added to a solution of the corresponding acid catalyst maintained for the desired time period at the required temperature. The solution was then extracted with chloroform, and washed successively with aqueous $NaHCO_3$ solution and water. The dried extract was concentrated to dryness under reduced pressure. For monitoring the reaction, aliquots of the reaction mixture were withdrawn at intervals, processed as just described, and analyzed by h.p.l.c. under the following conditions: column of ODS-Hypersil 5 μm (4.6 mm I.D. × 250 mm; Shandon), eluted with 1:3 acetonitrile–water at a flow rate of 0.8 mL/min, a temperature of 25°, and detection at 220 nm. The retetntion times observed were: **3** and **4**, 13.7; **5** and **6**, 17.8; **7** and **8**, 20.1; and **9**, 24.4 min.

*(1R and 1S)-1,2,3,5-Tetra-*O*-acetyl-4-*O*-methyl-*D*-glucuronate methyl acetal* (**7** *and* **8**). — The acetolysis mixture obtained by the action of 10:1 acetic anhydride–boron trifluoride etherate was purified by h.p.l.c. on a column of LiChrosorb 7 μm (10 mm I.D. × 250 mm) (Daisel, Osaka, Japan), eluted with 1:3 acetonitrile–water at a flow rate of 3.1 mL/min, and a temperature of 25°, and detection at 220 nm; the retention times observed were: **3** and **4**, 32.3; **5** and **6**, 42.3; **7** and **8**, 46.5; and **9** 57.8 min.

Compounds **7** and **8**. T.l.c. (3:2 hexane–ethyl acetate) R_F 0.38.

Anal. Calc. for $C_{17}H_{26}O_{12}$: C, 48.34; H, 6.20. Found: C, 48.17; H, 5.84.

Compound **7**. Crystallization of the crude acetolysis mixture from 2-propanol gave pure **7**, m.p. 114–115°, $[\alpha]_D^{20}$ −17.6° (*c* 0.9, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.843 (d, 1 H, $J_{1,2}$ 4.58 Hz, H-1), 5.530 (t, 1 H, $J_{2,3}$ 5.31, $J_{3,4}$ 5.13 Hz, H-3), 5.382 (dd, 1 H, H-2), 5.261 (d, 1 H, $J_{4,5}$ 4.77 Hz, H-5), 3.825 (t, 1 H, H-4), 3.795, 3.460, 3.447 (s, each 3 H, 3 OMe), 2.149, 2.115 (2), and 2.073 (s, each 3 H, 4 OAc).

Compound **8**. ^{1}H-N.m.r. ($CDCl_3$): δ 5.775 (d, 1 H, $J_{1,2}$ 5.86 Hz, H-1), 5.525 (dd, 1 H, $J_{2,3}$ 4.40, $J_{3,4}$ 5.32 Hz, H-3), 5.303 (dd, 1 H, H-2), 5.278 (d, 1 H, $J_{4,5}$ 4.58 Hz, H-5), 3.790 (t and s, 4 H, H-4 and CO_2Me), 3.460, 3.447 (s, each 3 H, 2 OMe), 2.149, 2.121, 2.115, and 2.108 (s, each 3 H, 4 OAc).

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