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Preparation of dioxolane-type fluoren-9-ylidene acetals of carbohydrates and their hydrogenolysis with $AlClH_2$ to give axial fluoren-9-yl ethers*

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ABSTRACT

cis-Hydroxyl groups of hexopyranosides reacted with 9,9-dichlorofluorene to give fluoren-9-ylidene acetals, hydrogenolysis of which with $AlClH_2$ gave derivatives with axial fluoren-9-yl ether and equatorial hydroxyl groups. 1,6-Anhydro-2,3-*O*-fluoren-9-ylidene-β-D-mannopyranose (**9**) was an exception which gave a 2:3 mixture of 2- and 3-fluoren-9-yl ethers because of the marked distortion of the pyranose ring. The fluoren-9-yl ether groups could be removed easily by catalytic hydrogenation or by hydrogenolysis with the Lewis acid-type mixed hydride $AlCl_2H$.

INTRODUCTION

Three types of reagents are generally used for the hydrogenolysis of carbohydrate acetals, namely, $LiAlH_4$–$AlCl_3$[1,2], $NaCN{\cdot}BH_3$–acids[3,4], and borane–trimethylamine–$AlCl_3$[5]. For dioxolane-type acetals of pyranosides, the direction of the ring cleavage is determined by the stereochemistry at the acetal carbon atom[6]. These highly stereoselective reactions can be explained by the conformation of the dioxolane rings which depend on the *exo* or *endo* position of the bulky substituents[7,8]. The hydrogenolysis[7] of isopropylidene or phenylethylidene acetals followed the pattern of *endo* alkyl or aryl dioxolane-type acetals and gave axial ethers. The isopropyl ethers of carbohydrates are extremely stable and do not have any practical applications, and the acetophenone acetals gave mixtures of diastereomeric ethers which could not be used for preparative purposes. Hence, symmetrical acetals were sought, the hydrogenolysis of which would result in ether groups that could be removed easily. In this context, the preparation[9] and stereoselective hydrogenolysis[10] of diphenylmethylene acetals have been reported, and now we describe the synthesis of dioxolane-type fluoren-9-ylidene acetals and their hydrogenolysis to fluoren-9-yl ethers.

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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RESULTS AND DISCUSSION

Geminal dihalogeno hydrocarbons (dibromomethane[11,12], α,α-dibromotoluene[13], α,α-dichlorotoluene[14], and dichlorodiphenylmethane[9]) react with diols under basic conditions to give methylene, benzylidene, or diphenylmethylene acetals. These reagents were used also where the parent oxo-compounds or their dialkyl acetals did not provide the desired compounds. 9-Fluorenone did not react with carbohydrates, but 9,9-dichlorofluorene[15] (**1**), prepared by reaction of 9-fluorenone with phosphorus pentachloride, was suitably reactive.

Thus, **1** reacted severally in pyridine at 110° with methyl α-L-rhamnopyranoside[16], methyl 1-thio-α- and -β-L-rhamnopyranoside[9], phenyl 1-thio-α-L-rhamnopyranoside[17], benzyl β-D-arabinopyranoside[18], and 1,6-anhydro-β-D-mannopyranose[19] to give cyclic acetals. For the preparation of methyl 6-deoxy-2,3-*O*-fluoren-9-ylidene-α-L-talopyranoside (**8**), methyl 2,3-*O*-fluoren-9-ylidene-α-L-rhamnopyranoside (**2**) was oxidised[20] with pyridinium chlorochromate to give **7**, which was reduced[21] with sodium borohydride to give **8**.

^{1}H-N.m.r. spectroscopy of these cyclic acetals (Tables I and II) showed deformation of the hexopyranoside rings similar to that observed for the *endo*-phenyl isomers of dioxolane-type benzylidene acetals of rhamno-[8], talo-, and arabino-pyranosides[8]. Thus, the values of $J_{2,3}$ and $J_{3,4}$ for the rhamnopyranoside derivatives were ~6.5 Hz, as found for *endo*-phenyl benzylidene α-L-rhamnopyranoside derivatives. There was very marked deformation in the tricyclic ring system of **9**. Although the value of $J_{2,3}$ was 6.5 Hz, the values of $J_{3,4}$ and $J_{4,5}$ were ~0 Hz.

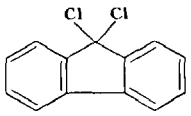
The ^{13}C-n.m.r. spectra of the cyclic acetals, (Table III) contained resonances for the acetal carbons at ~113 p.p.m. The formation of the acetal ring causes strong positive α-shifts at the bridgehead carbons (equatorial oxygens ~+7 p.p.m., axial oxygens ~+5.5 p.p.m.).

Hydrogenolysis of the cyclic acetals with $AlClH_2$ gave axial ether derivatives (**10**–**15**); the only exception was 1,6-anhydro-2,3-*O*-fluoren-9-ylidene-β-D-mannopyranose (**9**), which gave a 2:3 mixture of 1,6-anhydro-2- (**16**) and -3-*O*-fluoren-9-yl-β-D-mannopyranose (**15**). This anomalous ring cleavage is due probably to the marked distortion of the mannopyranose ring system in **9**, so that there is no axial or equatorial oxygen and the selectivity of the reagent is reduced.

The structure of the ring-opened products was determined easily by periodate oxidation and ^{13}C-n.m.r. spectroscopy. Each L-rhamnopyranoside and D-arabinopyranoside ether could be oxidised with periodate and therefore contained vicinal hydroxyl groups. Likewise, **16** was cleaved by periodate but **15** was stable.

The ^{13}C-n.m.r. spectra showed that the fluoren-9-yl moiety caused an ~+6 p.p.m. α-shift, and a large negative β-shift in the pyranosyl skeleton. These β-shifts are especially strong (up to ~−2 p.p.m.) for the 2-ethers, on the resonance of C-1.

The fluoren-9-yl ethers are stable under basic and acidic conditions, but they can be removed by hydrogenolysis either with $AlCl_2H$ or H_2–Pd/C, and may prove to be useful protecting groups in carbohydrate chemistry.



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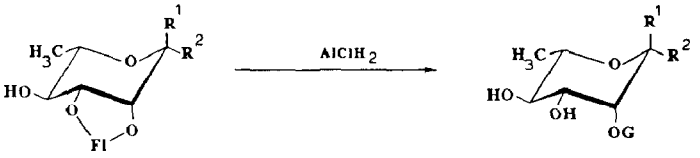
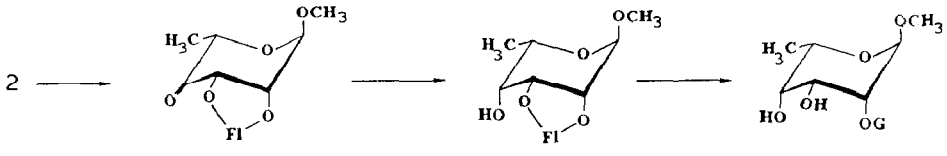


2	$R^1 = OCH_3$, $R^2 = H$	10
3	$R^1 = SCH_3$, $R^2 = H$	11
4	$R^1 = H$, $R^2 = SCH_3$	–
5	$R^1 = SPh$, $R^2 = H$	12

6 13



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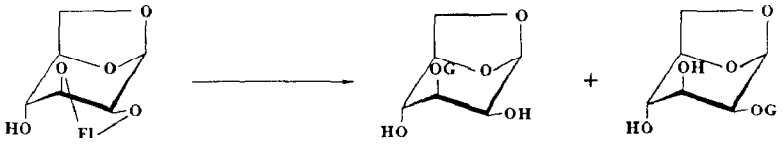
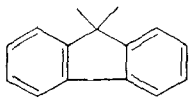


9 15 16



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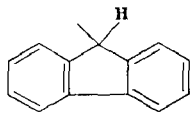

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TABLE I

^{1}H-N.m.r. chemical shifts (p.p.m.)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*Other signals*
2	4.94	4.70	4.62	3.80	3.80	1.39	3.45 (OCH_3)
3	5.45	4.71	4.49	4.06	3.79	1.33	2.12 (SCH_3)
4	4.66	4.75	4.42	3.73	3.31	1.34	2.20 (SCH_3)
5	5.85	4.94	4.59	3.88	4.27	1.35	
6	5.10	4.21	4.84	4.77			4.01 (H-5a), 4.19 (H-5b)
							4.65, 4.89 (OC*H*$_2$Ph)
8	5.03	4.65	4.70	3.89	4.01	1.44	3.45 (OCH_3)
9	5.62	4.52	4.60	4.02	3.91		4.17 (H-6a), 4.76 (H-6b)

	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-9'*	*Other signals*
10	4.76	3.95	3.69	3.42	3.61	1.34	5.62	3.29 (OCH_3)
11	5.25	4.07	3.70	3.41	3.90	1.30	5.60	2.05 (SCH_3)
12	5.42	4.26	3.76	3.55	3.99	1.30	5.72	
13	5.00	3.92	3.85	3.97			5.69	3.66 (H-5a), 3.67 (H-5b)
								4.52, 4.73 (OC*H*$_2$Ph)
14	4.80	3.95	3.80	3.52	3.87	1.30	5.58	3.30 (OCH_3)
15	5.31	3.66	3.96	3.88	4.43		5.64	3.75 (H-6a), 4.33 (H-6b)
16	5.07	3.06	3.50	3.72	4.32		5.76	3.68 (H-6a), 4.28 (H-6b)

TABLE II

^{1}H-N.m.r. coupling constants (Hz)

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{4,OH}$	$J_{3,OH}$	$J_{2,OH}$
2	0	6.5	6.5	8.5	6.0		5.0		
3	0	6.5	6.5	9.5	6.0		4.0		
4	2.5	6.5	6.5	8.0	6.5		0		
5	0	6.5	6.5	9.0	6.0		4.0		
6	5.0	5.5	7.0	2.5					4.5
8	1.0	7.0	5.0	1.5	7.0		0		
9	3.0	6.5	0	0	7.0		8.0		
10	1.5	4.0	9.5	9.5	6.5		0	0	
11	0	4.0	9.5	9.5	6.0		3.0	10.0	
12	0	3.5	9.5	9.5	6.0		0	0	
13	3.4	9.3	3.4	2.4				6.8	7.5
14	1.5	2.5	4.0	1.5	6.0		1.5	11.0	
15	2.0	5.8	1.9	2.0	5.8	1.0	9.5		11.5
16	2.0	5.2	2.0	1.6	5.8	1.0	1.0	0.5	

TABLE III

^{13}C-N.m.r. data[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-9'*	*Other signals*
2	98.43	76.49	78.39	74.31	66.43	17.92	113.10	55.00 (OCH_3)
3	81.29	77.70	78.73	75.94	66.15	17.60	113.23	13.40 (SCH_3)
4	82.12	77.63	79.90	77.54	75.29	18.04	113.70	14.63 (SCH_3)
5	83.89	76.77	78.52	76.01	67.03	17.37	113.33	–
6	95.72	68.90	75.40	73.82	61.14	–	113.08	69.75 (OCH_2Ph)
8	99.02	73.71	74.57	66.69	64.93	16.72	113.04	55.32 (OCH_3)
9	99.54	69.90	75.90	72.16	76.99	64.54	113.07	–
10	99.15	76.90	71.33	73.89	67.55	17.63	81.10	54.86 (OCH_3)
11	83.91	78.51	71.83	74.00	68.39	17.55	80.61	13.76 (SCH_3)
12	86.63	78.38	71.06	72.31	69.18	16.84	80.54	–
13	98.01	70.30	74.37	77.63	61.34	–	80.56	69.76 (OCH_2Ph)
14	99.64	77.44	66.65	72.95	66.25	16.44	81.85	55.02 (OCH_3)
15	102.05	64.65	77.19	70.63	75.80	65.77	82.49	–
16	101.16	68.54	71.20	71.24	76.03	64.77	80.49	–

[a] Chemical shifts in p.p.m.

EXPERIMENTAL

General methods. — Solutions were concentrated at 40° (bath) under diminished pressure. Chromatography was performed on Kieselgel 60. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter at room temperature. The ^{1}H- (200 and 400 MHz) and ^{13}C-n.m.r. (50.3 MHz) spectra were recorded with Bruker WP-200 SY and Varian XLA-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). Melting points were determined on a Kofler apparatus and are uncorrected. T.l.c. was performed on Kieselgel 60 F_{254} (Merck) with *A*, 98:2; *B*, 95:5; *C*, 9:1; *D*, 8:2 dichloromethane–acetone; and *E*, 9:1 hexane–ethyl acetate, with detection by charring with sulfuric acid.

Preparation of fluoren-9-ylidene acetals (**2–6** *and* **9**). To a solution of the substrate sugar in dry pyridine (15 mL/g) were added 2 equiv. of 9,9-dichlorofluorene (**1**). The mixture was stirred for 4 days at 110° (monitoring by t.l.c., solvent *A* or *B*). The dark-red solution was then poured onto crushed ice, and, after 1 h, the residue was diluted with dichloromethane, washed with 0.5M sulfuric acid and then with water until neutral, dried (Na_2SO_4), and concentrated. The dark-red residue was passed through a short column of silica gel (solvent *A*). The appropriate fractions were combined and concentrated to give the product (58–76%).

*Methyl 2,3-O-fluoren-9-ylidene-α-*L*-rhamnopyranoside* (**2**). — Compound **2** (76%), R_F 0.42 (solvent *B*), had m.p. 166–167° (from ethanol), $[\alpha]_D^{20}$ +6° (*c* 0.85, chloroform).

Anal. Calc. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.48; H, 5.91.

*Methyl 2,3-O-fluoren-9-ylidene-1-thio-α-*L*-rhamnopyranoside* (**3**). — Compound **3** (71%), R_F 0.49 (solvent *B*), had m.p. 178–179° (from ethanol), $[\alpha]_D^{20}$ −76° (*c* 0.4, chloroform).

Anal. Calc. for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.65. Found: C, 67.45; H, 5.64.

Methyl 2,3-O-fluoren-9-ylidene-1-thio-β-L-rhamnopyranoside (**4**). — Column chromatography (solvent *E*) of the crude product gave amorphous **4** (58%), R_f 0.36 (solvent *B*), $[\alpha]_D^{20}$ +8° (*c* 1.15, chloroform).

Anal. Calc. for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.65. Found: C, 67.40; H, 5.70.

Phenyl 2,3-O-fluoren-9-ylidene-1-thio-α-L-rhamnopyranoside (**5**). — Column chromatography (solvent *E*) of the crude product gave amorphous **5** (68%), R_f 0.56 (solvent *B*), $[\alpha]_D^{20}$ −74° (*c* 0.2, chloroform).

Anal. Calc. for $C_{25}H_{22}O_4S$: C, 71.74; H, 5.29. Found: C, 72.05; H, 5.21.

Benzyl 3,4-O-fluoren-9-ylidene-β-D-arabinopyranoside (**6**). — Compound **6** (72%), R_f 0.57 (solvent *B*), had m.p. 90–91° (from ethanol), $[\alpha]_D^{20}$ −126° (*c* 0.45, chloroform).

Anal. Calc. for $C_{25}H_{22}O_5$: C, 74.61; H, 5.50. Found: C, 74.58; H, 5.52.

1,6-Anhydro-2,3-O-fluoren-9-ylidene-β-D-mannopyranose (**9**). — Compound **9** (73%), R_f 0.28 (solvent *B*), had m.p. 186–188° (from ethanol), $[\alpha]_D^{20}$ −59° (*c* 1.2, chloroform).

Anal. Calc. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.41; H, 5.00.

Methyl 6-deoxy-2,3-O-fluoren-9-ylidene-α-L-talopyranoside (**8**). — To a solution of **2** (500 mg, 1.47 mmol) in dry dichloromethane (15 mL) were added 4Å molecular sieves (500 mg) and pyridinium chlorochromate (2.5 g). The mixture was stirred in the dark at room temperature overnight, then filtered through a short column of silica gel (solvent *E*), and concentrated *in vacuo*. The yellow residue (**7**: 450 mg, 90%) was used for the next step without any purification. To a solution of **7** (400 mg) in methanol (10 mL) were added 2 equiv. of $NaBH_4$ (90 mg), and the solution was stirred for 2 h at room temperature. The excess of $NaBH_4$ was decomposed with aqueous acetic acid, and the mixture was concentrated. Column chromatography (solvent *A*) of the residue gave amorphous **8** (360 mg, 88% from **7**), R_f 0.55 (solvent *A*), $[\alpha]_D^{20}$ +27° (*c* 0.5, chloroform).

Anal. Calc. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.43; H, 5.88.

Preparation of the axial fluoren-9-yl ethers (**10**–**15**). — To a solution (100 mg/10 mL) of the fluoren-9-ylidene acetal in dry 1:1 dichloromethane–ether were added $LiAlH_4$ (2 equiv./1 equiv. of substrate) and $AlCl_3$ (2 equiv./1 equiv. of substrate). The solution was heated under reflux and the reaction was monitored by t.l.c. (solvent *C*). After complete conversion of starting material (0.5–3.5 h), the mixture was diluted with ether, the excess of $LiAlH_4$ was decomposed by successive addition of ethyl acetate and water, and the organic layer was washed twice with water, dried (Na_2SO_4), and concentrated. The products (**10**–**14**) were crystallised from ethanol and the yields were quantitative. For the reaction of **9**, the ratio of the products **15**:**16** was 3:2, and they were isolated by column chromatography (solvent *C*) and crystallised from ethanol.

Methyl 2-O-(fluoren-9-yl)-α-L-rhamnopyranoside (**10**). — Prepared from **2**. **10** had m.p. 168–170°, $[\alpha]_D^{20}$ −2° (*c* 0.4, chloroform), R_f 0.20 (solvent *C*).

Anal. Calc. for $C_{20}H_{22}O_5$: C, 70.15; H, 6.47. Found: C, 70.10; H, 6.45.

Methyl 2-O-(fluoren-9-yl)-1-thio-α-L-rhamnopyranoside (**11**). — Prepared from **3**. **11** had m.p. 149–151°, $[\alpha]_D^{20}$ −53° (*c* 0.5, chloroform), R_f 0.28 (solvent *C*).

Anal. Calc. for $C_{20}H_{22}O_4S$: C, 67.01; H, 6.18. Found: C, 66.97; H, 6.20.

Phenyl 2-O-(fluoren-9-yl)-1-thio-α-L-rhamnopyranoside (**12**). — Prepared from **5**, **12** had m.p. 213–216°, $[\alpha]_D^{20}$ −47° (*c* 0.4, chloroform), R_t 0.58 (solvent *D*).

Anal. Calc. for $C_{25}H_{24}O_4S$: C, 71.40; H, 5.75. Found: C, 71.46; H, 5.73.

Benzyl 4-O-(fluoren-9-yl)-β-D-arabinopyranoside (**13**). — Prepared from **6**, **13** had m.p. 166–168°, $[\alpha]_D^{20}$ −119.5° (*c* 0.3, chloroform), R_F 0.49 (solvent *D*).

Anal. Calc. for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.30; H, 6.01.

Methyl 6-deoxy-2-O-(fluoren-9-yl)-α-L-talopyranoside (**14**). — Prepared from **8**, **14** had m.p. 169–170°, $[\alpha]_D^{20}$ −15° (*c* 0.5, chloroform), R_t 0.69 (solvent *D*).

Anal. Calc. for $C_{20}H_{22}O_5$: C, 70.15: H, 6.47. Found: C, 70.12: H, 6.51.

1,6-Anhydro-3-O-(fluoren-9-yl)-β-D-mannopyranose (**15**). — Prepared from **9**, **15** (47%) had m.p. 176–178°, $[\alpha]_D^{20}$ −68° (*c* 0.6, chloroform), R_F 0.46 (solvent *D*).

Anal. Calc. for $C_{19}H_{18}O_5$: C, 70.80: H, 5.62. Found: C, 70.84; H, 5.68.

1,6-Anhydro-2-O-(fluoren-9-yl)-β-D-mannopyranose (**16**). — Prepared from **9**, **16** (33%) had m.p. 144–145°, $[\alpha]_D^{20}$ −62.5° (*c* 0.2, chloroform), R_F 0.36 (solvent *D*).

Anal. Calc. for $C_{19}H_{18}O_5$: C, 70.80; H, 5.62. Found: C, 70.76; H, 5.66.

Removal of the fluoren-9-yl ether by catalytic hydrogenolysis. — To a solution of **10** (300 mg, 0.87 mmol) in ethanol (30 mL) were added 10% Pd/C (30 mg) and 3 drops of acetic acid, and the mixture was stirred under H_2. After 12 h, the only product was methyl α-L-rhamnopyranoside (140 mg, 90%).

Removal of the fluoren-9-yl ether by hydrogenolysis with $AlCl_2H$. — To a solution of **10** (100 mg, 0.30 mmol) in dry 1:1 dichloromethane–ether (10 mL) were added 3 equiv. of $LiAlH_4$ (34 mg) and 9 equiv. of $AlCl_3$ (350 mg), and the mixture was heated under reflux. After 2 h, t.l.c. (solvent *B*) indicated complete reaction. The mixture was diluted with ether, the excess of $LiAlH_4$ was decomposed by successive addition of ethyl acetate and water, the organic layer was concentrated, and the residue was crystallised from ethyl acetate to give methyl α-L-rhamnopyranoside (40 mg, 74%).

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