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Note

Glycosylation by D-fructofuranose thio-orthoesters

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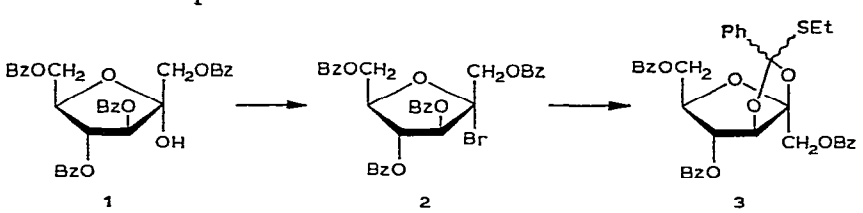
The stereospecific synthesis of complex D-fructofuranosides, especially oligosaccharides, is a difficult problem. Attempts to synthesise non-reducing, D-fructose-containing disaccharides gave[1–4] low yields (1–6%). Glycosylation by D-fructofuranose 2,3-(ethyl orthobenzoate) allowed the yields of D-fructofuranosides to be increased considerably, but β-D-fructofuranoside was formed along with the α anomer[5] (6 and 16%, respectively).

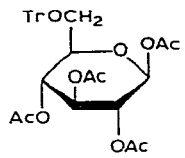
Thio-orthoesters of monosaccharides, obtainable by the reaction of acylglycosyl bromides with thiols in the presence of bases, are effective and stereospecific glycosylating agents[6–8]. We now describe the preparation of D-fructofuranose thio-orthoesters and their use for glycosylation.

1,4,6-Tri-*O*-benzoyl-2,3-*O*-(α-ethylthiobenzylidene)-β-D-fructofuranose (**3**) was obtained from 1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl bromide (**2**), which has been used[9,10] for the synthesis of D-fructofuranose 2,3-orthoesters. Compound **2** was prepared from 1,3,4,6-tetra-*O*-benzoyl-D-fructofuranose[11] (**1**). Treatment of **1** with hydrogen bromide in acetic acid in the presence of acetic anhydride afforded **2** which was treated, without purification, with ethanethiol in the presence of 2,4,6-trimethylpyridine in acetonitrile. From the resulting product mixture, the thio-orthoesters **3a** (25%) and **3b** (25%) were isolated, which were the mixtures of *exo*- and *endo*-SEt isomers in the ratios of ~3:1 and ~3:2 for **3a** and **3b** respectively, on the basis of ^{13}C-n.m.r. data (see Experimental).

Attempts to deacylate **3a** and **3b** failed. Methanolic 20% triethylamine[8] did not remove the benzoate groups and, under the conditions of Zemplén deacetylation (methanolic 0.1M sodium methoxide), ethanethiol was evolved and the products did not contain sulphur.



Glycosylation of the monosaccharide trityl ethers **4–6** by **3a** and **3b** proceeded rapidly in dichloromethane in the presence of triphenylmethylium perchlorate[7], to give high yields of the disaccharide derivatives **7–9**.



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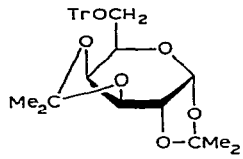

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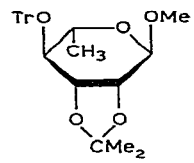

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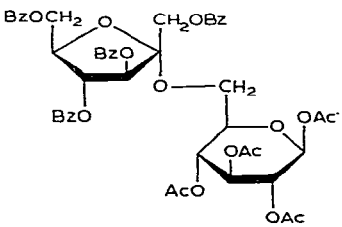

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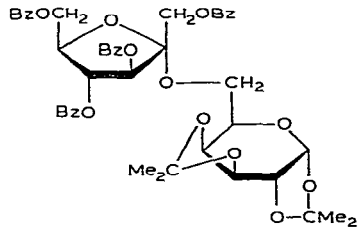

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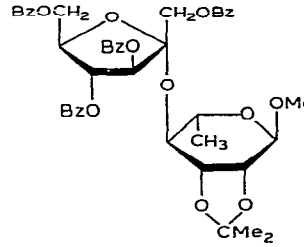

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Starting from **4** and **3a** or **3b**, 82% of **7** was obtained. The ^{13}C-n.m.r. spectrum of **7** contained only one signal for an anomeric carbon atom (δ 107.4), which was characteristic for α-D-fructofuranosides. On the other hand, an anomeric mixture[5] of 6-*O*-fructofuranosylglucose derivatives contained signals at δ 107.4 and 103.4 (see Table I). Deacylation of **7** afforded 6-*O*-α-D-fructofuranosyl-D-glucose[5].

Likewise, **8** (71%) and **9** (73%) were obtained from **3a** and **5** and **6**, respectively. The α-fructofuranoside configuration in **8** and **9** followed unequivocally from the presence of a single C-2 signal for the fructose moiety at δ 107.4 and 107.8 in the

TABLE I

^{13}C-N.M.R. DATA FOR DISACCHARIDE DERIVATIVES **7–9**

Compound	*Anomer*[a]	*Chemical shifts (p.p.m.)*					
		C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
7	α′	59.7	107.4	81.2	78.9	81.4	63.6
	β	91.8	70.4	73.0	68.7	73.6	60.3
7-β	β′	64.8	103.4	78.0	77.8	79.3	64.8
	β	91.8	70.4	73.0	68.7	73.6	68.0
8	α′	59.7	107.4	81.2	79.1	81.5	63.8
	α	96.5	70.7	70.6	71.2	67.1	60.8
9	α′	62.6	107.8	81.2	78.4	81.5	64.4
	α	98.2	76.1	77.9	75.8	64.2	17.6

[a]Anomers marked with a prime refer to non-reducing residues.

^{13}C-n.m.r. spectra. Thus, the thio-orthoesters can be regarded as more effective and stereospecific D-fructofuranosylating agents than the corresponding orthoesters.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 141 polarimeter at 20 ±2° (for solutions in chloroform unless otherwise stated). ^{13}C-N.m.r. spectra were recorded at ambient temperature with a Bruker WP-60 instrument operating at 15.08 MHz in the deuterio-lock mode for ~20% solutions in $CDCl_3$ (internal Me_4Si) with 3,000–9,000 transitions. Pyridine was distilled from potassium hydroxide, and acetonitrile from calcium chloride and then from calcium hydride. Dichloromethane was washed with concentrated sulphuric acid and water, dried ($CaCl_2$), and distilled from calcium hydride. T.l.c. was performed on Silica Gel L 5/40 μm (C.S.S.R.) with toluene–ethyl acetate (*A*, 10:1; *B*, 3:1), and detection with aqueous potassium permanganate (sulfur-containing products) and/or by charring with sulfuric acid. Column chromatography was performed on Silica Gel L 100/250 μm (C.S.S.R.). P.c. was conducted on Filtrak FN-11 paper with *C* 1-butanol–pyridine–water (6:4:3), and detection with potassium periodate–silver nitrate–potassium hydroxide[12]. Solutions were concentrated *in vacuo* at 40°.

1,3,4,6-Tetra-O-benzoyl-α-D-fructofuranose (**1**). — To a solution of D-fructose (36 g, 0.2 mol) in pyridine (600 mL) was added benzoyl chloride (116 mL, 1 mol) at such a rate that the temperature of the mixture did not exceed 65°. The solution was then kept for 15 min, water (20 mL) was added, and the mixture was cooled to room temperature, diluted with chloroform (1 L), washed successively with water (3 × 1 L), 3% sulfuric acid (3 × 1 L), water (1 L), saturated aqueous sodium hydrogencarbonate (1 L), and water (1 L), dried ($CaCl_2$), and concentrated. The residue was crystallised from methanol (1 L), to give **1** (83 g, 69%), m.p. 121–123°, $[\alpha]_D$ −3° (*c* 1); lit.[11] m.p. 122–123°, $[\alpha]_D$ −4° (*c* 2.4).

1,4,6-Tri-O-benzoyl-2,3-O-(α-ethylthiobenzylidiene)-β-D-fructofuranose (**3**). — A solution of **1** (24 g, 40 mmol) in chloroform (80 mL) was treated with 40% hydrogen bromide in glacial acetic acid (60 mL) and acetic anhydride (20 mL) for 1.5 h at room temperature. The mixture was concentrated to dryness, and toluene (3 × 60 mL) was evaporated from the residue which was then dried *in vacuo*. A solution of the resulting bromide **2** in acetonitrile (80 mL) was treated with 2,4,6-trimethylpyridine (8 mL) and ethanethiol (40 mL). The mixture was stored overnight at room temperature, concentrated to half volume, diluted with chloroform (100 mL), and washed with water (2 × 100 mL). The organic layer was concentrated and the dry residue was crystallised from ether (200 mL) and pentane (200 mL). The crystalline product was collected, washed with a small amount of ether, and dried *in vacuo*, to give **3a** (6.5 g, 25%), m.p. 111–113°, $[\alpha]_D$ −11° (*c* 2.2), R_F 0.73 (solvent *A*).

Anal. Calc. for $C_{36}H_{32}O_9S$: C, 67.48; H, 5.04; S, 5.00. Found: C, 67.37; H, 5.17; S, 5.04.

The mother liquor was concentrated, and the residue was subjected to column chromatography with light petroleum–ether. From the appropriate fractions, **3b** (6.5 g, 25%) crystallised on cooling; m.p. 107–109°, $[\alpha]_D$ −15° (*c* 0.85), R_F 0.73 (solvent *A*).

Anal. Found: C, 67.68; H, 5.00; S, 4.78.

In the ^{13}C-n.m.r. spectra of both products (**3a** and **3b**) four high-field signals were present at δ 14.7 and 14.1 (CH_3CH_2S-*exo* and -*endo*) and at δ 24.5 and 24.6 (CH_3CH_2S-*exo* and -*endo*).

Glycosylation of the trityl ethers **4–6** *by the thio-orthoesters* **3**. — To a stirred solution of trityl ether (1.1 mmol) and triphenylmethylium perchlorate (0.4 mmol) in dichloromethane (5 mL) containing 2,4,6-trimethylpyridine (0.2 mmol) was added a solution of thio-orthoester (1 mmol) in dichloromethane (10 mL) dropwise during 30 min. The mixture was then treated with 3:1 pyridine–methanol (0.5 mL), diluted with chloroform (20 mL), and washed with water (2 × 20 mL). The organic layer was concentrated and the residue was subjected to column chromatography by using gradient elution (benzene→benzene–ether, 4:1).

In this way, amorphous 1,2,3,4-tetra-*O*-acetyl-6-*O*-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-β-D-glucopyranose (**7**, 82%) was obtained from **3a** and **4**, and had $[\alpha]_D$ +24° (*c* 1.1), R_F 0.43 (solvent *B*).

Anal. Calc. for $C_{48}H_{46}O_{19}$: C, 62.20; H, 5.00. Found: C, 62.11; H, 5.31.

Compound **7** (82%), obtained from **3b** and **4**, had $[\alpha]_D$ +26° (*c* 1.8).

Likewise, amorphous 1,2:3,4-di-*O*-isopropylidene-6-*O*-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-α-D-galactopyranose (**8**, 71%) was obtained from **3a** and **5**, and had $[\alpha]_D$ −1° (*c* 1), R_F 0.33 (solvent *A*).

Anal. Calc. for $C_{46}H_{46}O_{15}$: C, 65.86; H, 5.53. Found: C, 65.76; H, 5.43.

Likewise, amorphous methyl 2,3-*O*-isopropylidene-4-*O*-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-α-L-rhamnopyranoside (**9**, 73%) was obtained from **3a** and **6**, and had $[\alpha]_D$ −11° (*c* 1).

Anal. Calc. for $C_{44}H_{44}O_{14}$: C, 66.31; H, 5.57. Found: C, 66.04; H, 5.50.

6-O-α-D-Fructofuranosyl-D-glucose. — Compound **7** (300 mg) was treated with methanolic 0.1M sodium methoxide (10 mL) for 4 h. The solution was neutralised with KU-2 (PyH^+) resin, filtered, and concentrated. The residue was washed with hexane (3 × 5 mL) and dried *in vacuo* over phosphorus pentaoxide, to give the title disaccharide (110 mg, 100%), $[\alpha]_D$ +62.5° (*c* 1, water), R_{Glc} 0.73 (solvent *C*), R_{Fru} 0.60 (solvent *C*); lit.[5] $[\alpha]_D$ +64° (*c* 0.5, water).

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