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SYNTHESIS OF 6,6′-DIDEOXY-6,6′-DIFLUOROSUCROSE*

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ABSTRACT

The chemical synthesis of 6,6′-dideoxy-6,6′-difluorosucrose was accomplished in five steps: (*a*) tritylation of C-6,-1′ and -6′ of sucrose; (*b*) benzoylation of 6,1′,6′-tri-*O*-tritylsucrose; (*c*) detritylation with mild acid; (*d*) fluorination at C-6 and -6′ with diethylaminosulfur trifluoride (DAST); and (*e*) debenzoylation. The resulting compound was chromatographically pure. The structure was established by ^{13}C- and ^{19}F-n.m.r. spectrometry and by elemental analysis.

INTRODUCTION

The replacement of a hydroxyl group by a fluoro group in sucrose would provide a sucrose analogue whose steric features and electronic structure are little altered, but whose chemical character is changed. The covalent radius of fluorine bonded to carbon is 138.1 ±0.5 pm, which is very close[1] to the radius (143 ±1 pm) of a hydroxyl group bonded to carbon. In addition, the fluoro group has six nonbonded electrons which are approximately equivalent to the four nonbonded electrons of the hydroxyl group and hence may participate in hydrogen bonding as the oxygen of the hydroxyl group does. Fluorine, however, is monovalent and when bonded to carbon, it does not have a hydrogen atom that it can donate for hydrogen bonding and it cannot form glycosidic linkages as the hydroxyl group can. For these reasons, the replacement of a hydroxyl group by a fluoro group at C-6 and -6′ in sucrose provides an analogue that should be quite useful in studying biochemical systems involving sucrose.

Several sucrose derivatives have been synthesized by Hough *et al.*[2,3] and by Khan *et al.*[4,5]. Fluoro sugars have been synthesized by Kent *et al.*[6–8], Foster *et al.*[9], and Pacák *et al.*[10], but the synthesis of fluorosucroses has never been reported.

We report here the synthesis of 6,6′-dideoxy-6,6′-difluorosucrose by fluorinating 2,3,4,3′,4′-penta-*O*-benzoylsucrose with diethylaminosulfur trifluoride (DAST) followed by debenzoylation.

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TABLE I

SYNTHESIS OF 6,6′-DIDEOXY-6,6′-DIFLUOROSUCROSE (6)

Compound	*Reaction*	*Product*	*Starting material*		*Product*		*Individual reaction yield (%)*	*Cumulative yield (%)*
			(g)	*(mmol)*	*(g)*	*(mmol)*		
1	Tritylation	2	102.6	300	172.2	161	54	54
2	Benzoylation	3	172.0	161	201.1	126	78	42
3	Detritylation	4	201.1	126	98.2	111	88	37
4	Fluorination	5	98.2	111	28	31	28	10
5	Debenzoylation	6	28	31	9.0	25	80	8.3

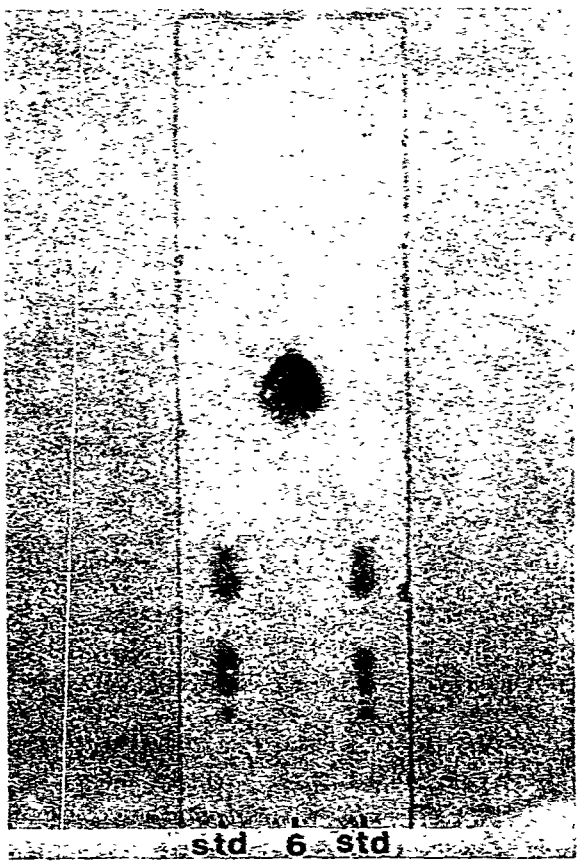

Fig. 1. T.l.c. of compound 6 on 0.25-mm Merck Silica Gel 60 with two ascents of 9:1 (v/v) acetonitrile–water. Standards in descending order were D-fructose, D-glucose, sucrose, nigerose, and isomaltose.

RESULTS AND DISCUSSION

The synthesis of 6,6′-dideoxy-6,6′-difluorosucrose (**6**) was accomplished in five steps: sucrose (**1**) was tritylated to give 6,1′,6′-tri-*O*-tritylsucrose[13] (**2**) followed by benzoylation to give 2,3,4,3′,4′-penta-*O*-benzoyl-6,1′,6′-tri-*O*-tritylsucrose[13] (**3**); this was detritylated by mild acid treatment to give 2,3,4,3′,4′-penta-*O*-benzoylsucrose[14] (**4**), which was fluorinated with diethylaminosulfur trifluoride[11] (DAST) to give 6,6′-dideoxy-6,6′-difluoro-2,3,4,3′,4′-penta-*O*-benzoylsucrose (**5**); compound **6** was obtained by debenzoylation of **5** with sodium methoxide in methanol[12]. The amounts of starting compound and product yields, obtained for the five reactions, are given in Table I.

The structure and purity of **6** was demonstrated by thin-layer and high pressure liquid chromatography, and by ^{13}C- and ^{19}F-n.m.r. spectrometry. T.l.c. showed the presence of a single component (Fig. 1). L.c. analysis of a 15-min hydrolysis by M trifluoroacetic acid at 25° showed three components: the starting material and two hydrolysis products, presumably 6-deoxy-6-fluoroglucose and 6-deoxy-6-fluorofructose (see Fig. 2).

Comparison of the ^{13}C-n.m.r. spectra of sucrose and of **6** (Fig. 3) showed that **6** had a sucrose-like structure that was substituted at C-6 and -6′ in that **6** showed peaks at 104.73, 93.09, and 61.94 p.p.m. corresponding to C-2′, -1, and -1′, respectively, but peaks at 63.17 and 62.33 p.p.m., which correspond to C-6 and -6′ of sucrose, were conspicuously absent from the spectrum. Further assignment of peaks in the ^{13}C-n.m.r. spectrum of **6** was complicated by a complexity of carbon–fluorine couplings. The ^{19}F-n.m.r. spectrum, however, provided confirmatory evidence for the

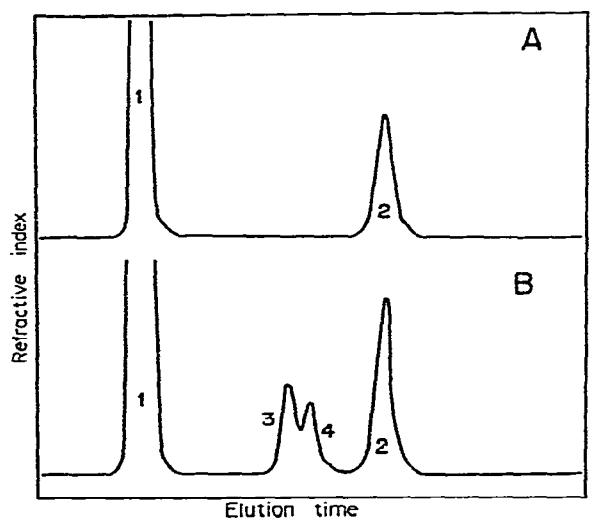

Fig. 2. High-pressure liquid chromatography of compound **6**. A, peak No. 2, compound **6**. B, partial acid hydrolysis of compound **6**. Peaks Nos. 3 and 4 are products. Peak No. 1 is the solvent. The elution solvent was 4:1 (v/v) acetonitrile–water.

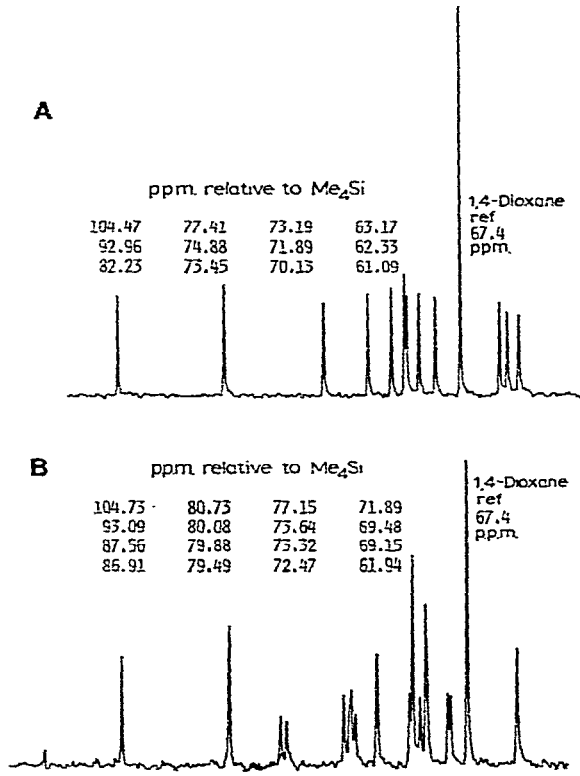

Fig. 3. ^{13}C-N.m.r. spectra of A, sucrose and B, compound 6.

structure. The ^{19}F spectrum (Fig. 4) shows two distinct sextets centered at 235.21 and 227.74 p.p.m. that are due to signals arising from a fluorine atom on C-6 coupled to the two hydrogen atoms on C-6 giving a triplet, each of which is further split by H-5, resulting in a sextet. Similarly, the signals arising from fluorine on C-6′ is a triplet that is split by H-5′, giving a sextet. Substitution on no other carbon atoms would give these sextets. For example, if substitution had occurred at C-1′, a unique triplet would have resulted and it would not have been split into a sextet as the requisite hydrogen atom on C-2′ is not present. Substitution for any of the secondary hydroxyl groups would have given a higher order of peaks with a different pattern of intensities. The synthesized compound **6**, therefore, is considered to be substituted at C-6 and -6′ by fluorine.

The fluorination reaction with DAST might have been expected to cause the replacement of all three of the primary hydroxyl groups by fluorine to give 6,1′,6′-trideoxy-5,1′,6′-trifluorosucrose (**7**). Under our conditions, fluorination of **4** at positions 6 and 6′ was the major product, which follows the pattern of substitution in sucrose observed by Hough *et al.*[15–17], Lemieux and Barette[18], Bragg and Jones[19], and Suami *et al.*[20], in which it was found that C-1′ was the last and most difficult to

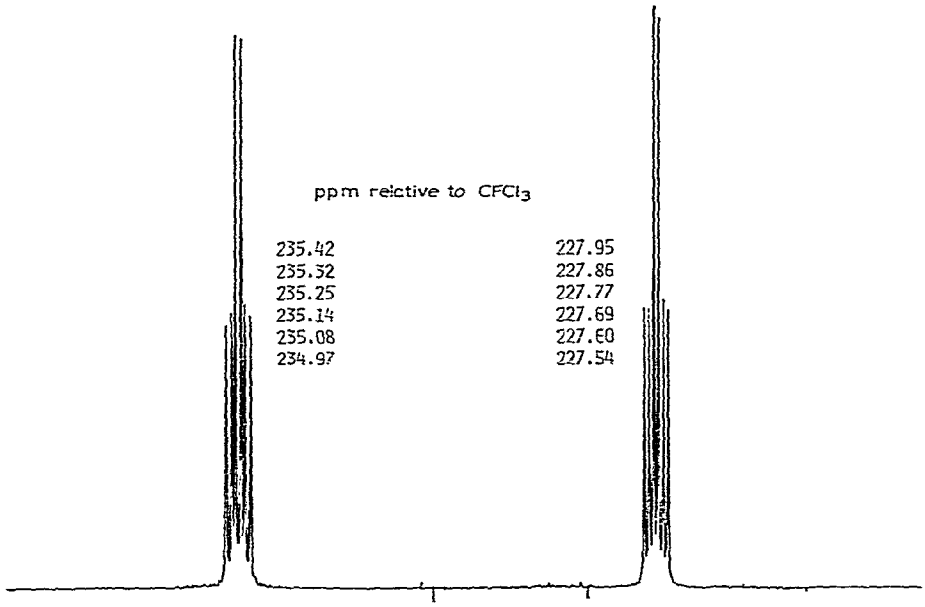

Fig. 4. ^{19}F-N.m.r. spectrum of compound **6**.

substitute of the three primary hydroxyl-bearing atoms. Guthrie *et al.*[21] recently reported the failure to prepare 1′-deoxy-1′-fluorosucrose.

The replacement of hydroxyl groups by fluorine is usually difficult, because of the low nucleophilicity and high basicity of the fluoride ion. The latter frequently gives rise to elimination reactions instead of substitution, or to deacylation and *O*-alkylation reactions of the acetate or benzoate protective groups. The use of DAST with a properly substituted sucrose intermediate has provided a means of circumventing these problems of fluorination.

EXPERIMENTAL

General methods. — Thin-layer chromatography was carried out on 0.25-mm Merck Silica gel 60 with 2 ascents of 9:1 (v/v) acetonitrile–H_2O, and detection by charring with 20% sulfuric acid in methanol. L.c. was performed with a Waters Associates Model ALC/GPC-201 Liquid Chromatograph and a Waters Associates carbohydrate column. ^{13}C-N.m.r. spectra were obtained with a JEOL FX-90 Q spectrometer and ^{19}F-n.m.r. spectra with a Bruker WM-300 spectrometer. Optical rotations were recorded with a Rudolph polarimeter and a sodium light source.

2,3,4,3′,4′-penta-O-benzoylsucrose. — 6,1′,6′-Tri-*O*-tritylsucrose (**2**) and 2,3,4,3′,4′-penta-*O*-benzoyl-6,1′,6′-tri-*O*-tritylsucrose (**3**) were synthesized and purified by the methods of Hough *et al.*[13]; **3** was detritylated to give **4** as described by Khan[14].

2,3,4,3',4'-Penta-O-benzoyl-6,6'-dideoxy-6,6'-difluorosucrose. — 2,3,4,3',4'-Penta-*O*-benzoyl-6,6'-dideoxy-6,6'-difluorosucrose (**5**) was synthesized by fluorinating **4** with DAST, which was prepared as described by Middleton[20]: 27 g (30 mmol) of **4** in 75 mL of diglyme was added dropwise to 84 mL (180 mmol) of DAST in 150 mL of diglyme at −5° under a flow of nitrogen. After the addition, the solution was heated for 1 h to 90° in an oil bath; t.l.c. [Analtech HETLC-F silica gel plates irrigated with 97:3 (v/v) benzene–methanol] showed a major product having R_F 0.6. The mixture was slowly added to 1500 mL of saturated sodium hydrogencarbonate with 100 mL of dichloromethane. The organic phase was washed 5 times with an equal volume of water to remove diglyme; it was then dried over Drierite and evaporated to a syrup. The syrup was chromatographed with benzene on a column (2.5 × 60 cm) of silica gel; **5** was eluted in 1200 mL; $[\alpha]_D$ +35.1° (*c* 2.61, chloroform).

Anal. Calc. for $C_{47}H_{40}F_2O_{14}$: C, 65.19; H, 4.66; F, 4.39. Found: C, 65.35; H, 4.83; F, 4.19.

6,6'-Dideoxy-6,6'-difluorosucrose (**6**). — The title compound (**6**) was obtained by debenzoylation of **5** with sodium methoxide in methanol[12]: ~8 g of **5** was dissolved in 100 mL of methanol and 0.5 g sodium methoxide was added. After 35 min at room temperature, t.l.c. [45:5:3 (v/v) ethyl acetate–ethanol–water] showed that debenzoylation was complete. The mixture was made neutral with 8 g (12–16 meq) of Amberlite IRC-50 carboxylate resin (H^+ form); 100 mL of water was added, and the mixture was filtered, evaporated to a syrup, dissolved in a minimum volume of methanol, and applied to a column (2.4 × 52 cm) of silica gel. The column was eluted with 45:5:3 (v/v) ethyl acetate–ethanol–water. The first 200 mL of eluate contained impurities and **6**; the next 500 mL contained pure **6** as judged by t.l.c.; $[\alpha]_D$ +53.7° (*c* 2.45, water).

Anal. Calc. for $C_{12}H_{20}F_2O_9$: C, 41.62; H, 5.82; F, 10.97. Found: C, 42.30; H, 5.88; F, 11.10.

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