Formation and Structures of (*E*)- and (*Z*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-4-enofuranoses

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Thr reactions of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-α-D-gluco- and β-L-idofuranoses (1 and 2) with tetrabutylammonium fluoride in *N*,*N*-dimethylformamide gave (*E*)- and (*Z*)-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-4-enofuranoses (3 and 4), respectively, as the major products. The structure of the (*E*)-isomer 3 was determined by single-crystal X-ray analysis. 3-*O*-Benzyl-5,6-dideoxy-5-fluoro-1,2-*O*-isopropylidene-β-L-ido- and α-D-glucofuranoses (6 and 7) were formed as minor products in the respective reactions.

Keywords 5,6-dideoxyhex-4-enofuranose; X-ray analysis; fluorination; 5,6-dideoxy-5-fluorohexofuranose; tetrabutylammonium fluoride

As an extension of our studies on fluorination of 6-deoxyhexopyranoses,[1,2] we attempted to conduct fluorination at C-5 of 6-deoxyhexofuranoses by using the displacement of a sulfonyloxyl group with fluoride anion. However, the reaction of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-α-D-glucofuranose (**1**)[3] with an excess of tetrabutylammonium fluoride (TBAF) in *N*,*N*-dimethylformamide (DMF) gave the crystalline 4,5-unsaturated compound **3** as the major product (54% yield) along with 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**5**)[4,5] in 37% yield, and the yield of 3-*O*-benzyl-5,6-dideoxy-5-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose (**6**) was only 5% (Chart 1).

When 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-L-idofuranose (**2**)[6] was treated with TBAF under the same reaction conditions as those for **1**, the eliminated products, **4**[7] and **5**, were formed in 43 and 32% yields, respectively, along with 3-*O*-benzyl-5,6-dideoxy-5-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**) in 8% yield (Chart 1).

The structure of **3** was determined by single-crystal X-ray analysis. Figure 1 shows a perspective drawing of the molecular structure of **3**, which has the *E*-configuration around the 4,5-unsaturated bond.

The ^{1}H- and ^{13}C-NMR spectral data for **3** and **4**, listed in Tables I and II, are suggestive of 4,5-unsaturated 6-deoxyhexofuranose structures. The NOE experiments on **3** and **4** revealed the presence of the NOE between H-3 and H-6 only for **3** and between H-3 and H-5 only for **4**. These results are in agreement with the X-ray-analyzed structure of **3** and indicate that **4** has the *Z*-configuration. Compound **4** was first reported by Inokawa *et al.*[7] without definition of the configuration. Thus, we have identified **4** as the (*Z*)-isomer.[8]

The NMR spectral data including the F–H and C–F coupling constants observed for the fluorinated compounds, **6** and **7** (Tables I and II), are consistent with 5-fluorinated structures. The ^{19}F-NMR spectral data for each compound are given in Experimental. The F–H five-bond coupling observed for **7** (2.7 Hz for $J_{F,H\text{-}1}$) may suggest the conformation in which the H-5–F and H-1–C-1 bonds are in *trans*-coplanar relationship[9] to the C-4–O-4 bond. Elucidation of the absolute configuration at C-5 of **6** and **7** was based on the close similarity of the ^{1}H- and ^{13}C-NMR parameters to those of 5-deoxy-5-fluoro-1,2-*O*-isopropylidene-β-L-ido- and α-D-glucofuranoses,[10] respectively.

In the reactions of **1** and **2** with TBAF, fluorination

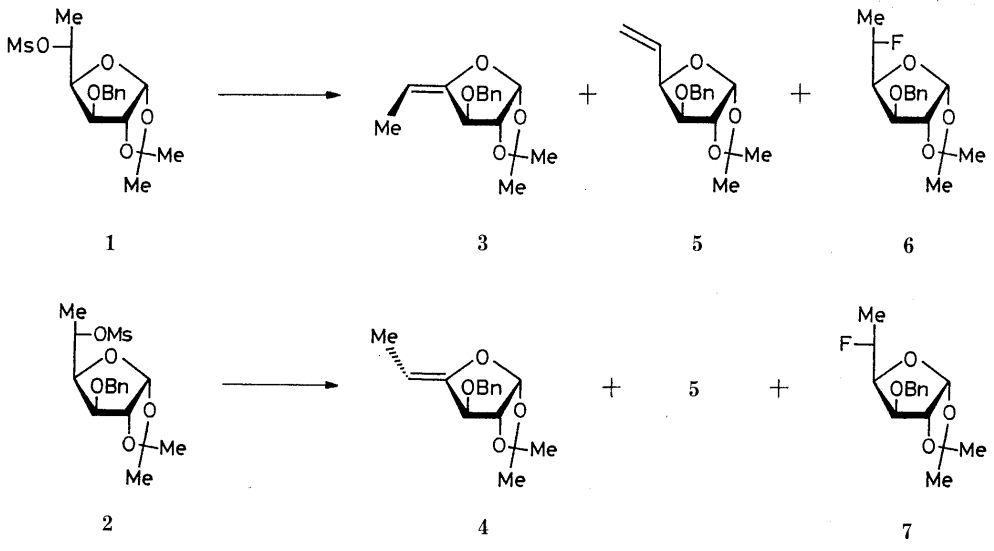

Chart 1

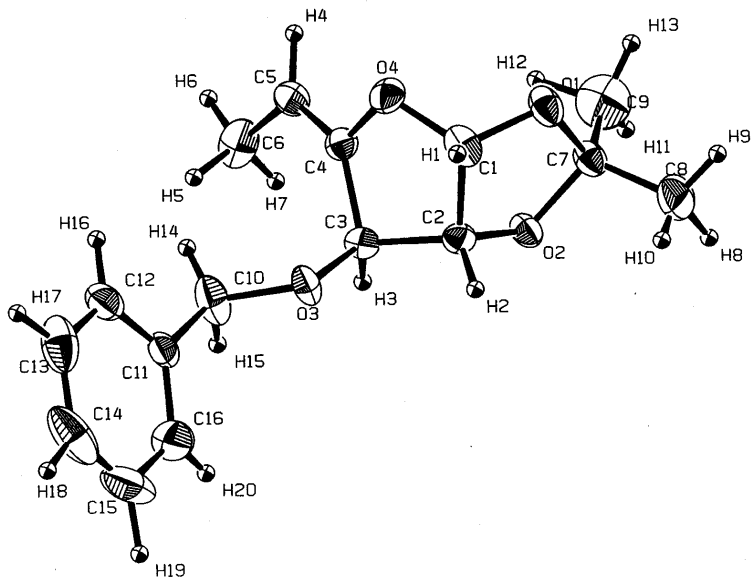

Fig. 1. Perspective Drawing of the Structure of **3**

TABLE I. ^{1}H-NMR Spectral Data for **3**—**7**

Compd.	δ (ppm) $J_{H,H}$ (Hz) ($J_{F,H}$ (Hz))									
	H-1	H-2	H-3	H-4	H-5	H-6(6')	Me_2C	$PhCH_2$	Ph
3	6.02	4.64	4.56		5.20	1.63	1.38, 1.42	4.46, 4.65	7.27—7.38
	3.5	0			7.2			J_{AB}=11.7	
4	6.10	4.57	4.19		4.67	1.70	1.38, 1.44	4.56, 4.65	7.27—7.37
	3.3	0.5			6.8			J_{AB}=11.6	
5	5.97	4.63	3.89	4.63	6.02	5.33, 5.44	1.33, 1.51	4.55, 4.66	7.27—7.38
	3.8	0	3.1	7.0	10.3, 17.2			J_{AB}=12.0	
					$J_{6,6'}$=1.8				
6	6.00	4.64	3.91	4.18	4.89	1.24	1.34, 1.51	4.42, 4.68	7.26—7.40
	3.8	0.5	3.5	8.0	6.3			J_{AB}=11.7	
			(0.7)	(13.5)	(50.2)	(23.8)			
7	5.91	4.61	4.06	4.09	4.96	1.49	1.32, 1.51	4.61, 4.68	7.28—7.40
	3.8	0	3.1	8.3	6.2			J_{AB}=11.6	
	(2.7)		(0.4)	(8.2)	(46.2)	(25.5)			

proceeds to a limited extent with inversion of configuration at C-5 and the elimination predominates over the fluorination, probably because attack of the fluoride anion at C-5 is significantly hindered by the bulky benzyloxyl group at C-3.

Experimental

Melting points were determined with a Yanagimoto MP-500D melting point apparatus and are uncorrected. Optical rotations were measured with a Horiba SEPA-200 polarimeter at 20 °C. NMR spectra were recorded with a Varian VXR-300 spectrometer at 300 MHz for ^{1}H-NMR and at 75.4 MHz for ^{13}C-NMR in $CDCl_3$. Assignment of all proton and carbon signals was performed by H–H and C–H COSY measurements. Chemical shifts of protons were calculated from that of the satellite peak of $CDCl_3$ at δ 7.26, and those of carbons are relative to the central peak of $CDCl_3$ at δ 77.0. Chemical shifts for ^{19}F-NMR are relative to hexafluorobenzene as an internal standard. For column chromatography, silica gel (Wakogel C-300) was used.

(*E*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-4-enofuranose (3), 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (5), and 3-*O*-Benzyl-5,6-dideoxy-5-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose (6) A solution of **1** (470 mg, 1.26 mmol) and TBAF trihydrate (1.99 g, 6.31 mmol) in DMF (3.8 ml) was stirred for 18 h at 120 °C. DMF was removed by evaporation and the residue was taken up in chloroform; this solution was washed with water, dried over anhydrous sodium sulfate, and concentrated to a syrup. The syrup was chromatographed using a gradient mixed-solvent system of toluene–ethyl acetate (30 : 1→8 : 1) to give crystalline **3** (188 mg, 54%), and then **5** (130 mg, 37%).

3: Recrystallization from cyclohexane furnished an analytical sample as colorless needles, mp 77—78 °C, $[\alpha]_D$ −58.0° (c=1.0, chloroform). *Anal.* Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.76; H, 7.29.

5: A colorless syrup, $[\alpha]_D$ −66.4° (c=3.4, ethanol) (lit. $[\alpha]_D$ −66± 0.5° (c=3, ethanol)[5]; $[\alpha]_D$ −56.4° (c=3.22, chloroform)[4]). *Anal.* Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.44; H, 7.26.

Further elution afforded **6** (18.2 mg, 5%) as a colorless syrup, $[\alpha]_D$ −51.2° (c=0.7, chloroform). *Anal.* Calcd for $C_{16}H_{21}FO_4$: C, 64.85; H, 7.14. Found: C, 65.10; H, 7.32. ^{19}F-NMR ($CDCl_3$) δ: −21.08 (ddq, $J_{F,H-4}$=13.5 Hz, $J_{F,H-5}$=50 Hz, $J_{F,H-6}$=24 Hz, F-5).

(*Z*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-4-enofuranose (4), 3-*O*-Benzyl-5,6-dideoxy-5-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (7), and 5 A solution of **2** (472 mg, 1.27 mmol) and TBAF trihydrate (2.01 g, 6.37 mmol) in DMF (3.8 ml) was stirred for 18 h at 120 °C. The mixture was worked-up in the same manner as described for the reaction of **1**. Chromatographic separation using a gradient mixed-solvent system of toluene–ethyl acetate (30 : 1→5 : 1) afforded **4** (151 mg, 43%) as a colorless syrup, and then **7** (28.6 mg, 8%).

4: $[\alpha]_D$ −35.8° (c=0.9, chloroform) (lit. $[\alpha]_D$ −36.0° (c=2.5, chloroform)[7]; $[\alpha]_D$ −53.2° (c=1.2, methanol)[11]). *Anal.* Calcd for $C_{16}H_{20}O_4$:

TABLE II. ^{13}C-NMR Spectral Data for **3**—**7**

Compd.	δ (ppm) $J_{C,F}$ (Hz)									
	C-1	C-2	C-3	C-4	C-5	C-6	$\underline{Me}_2C$	$Me_2\underline{C}$	$Ph\underline{C}H_2$	Ph
3	105.6	83.0	77.4	152.9	100.4	12.2	27.3 27.9	113.3	70.8	127.8 127.9 128.5 137.5
4	106.4	83.3	80.5	152.0	100.4	10.4	27.3 27.9	113.6	70.0	127.8 127.9 128.5 137.5
5	104.8	82.9	83.4	81.6	132.3	119.0	26.2 26.8	111.5	72.1	127.5 127.8 128.4 137.5
6	105.4	81.6	82.0 (8.2)	82.8 (18.6)	89.2 (167.5)	16.8 (22.0)	26.2 26.8	111.9	71.7	127.8 128.1 128.5 136.8
7	105.2	82.6	81.2	82.0 (32.1)	86.5 (162.7)	18.7 (21.0)	26.2 26.8	111.9	72.5	127.6 127.9 128.4 137.4

TABLE III. Positional Parameters and Equivalent Isotropic Thermal Parameters for **3**

Atom	x	y	z	B_{eq}
O1	1.2620 (4)	1.0424	0.4195 (4)	5.1 (3)
O2	1.1331 (4)	0.709 (1)	0.4368 (3)	3.9 (2)
O3	0.8763 (4)	0.945 (1)	0.2670 (3)	4.3 (2)
O4	1.1602 (4)	1.057 (2)	0.2618 (4)	4.6 (3)
C1	1.1463 (7)	1.088 (2)	0.3615 (6)	4.4 (4)
C2	1.0516 (6)	0.895 (2)	0.3889 (5)	3.6 (3)
C3	0.9890 (6)	0.796 (2)	0.2900 (5)	3.4 (3)
C4	1.0932 (6)	0.846 (2)	0.2256 (5)	3.7 (3)
C5	1.1295 (6)	0.734 (2)	0.1477 (6)	4.7 (4)
C6	1.0634 (7)	0.508 (2)	0.1019 (6)	6.2 (5)
C7	1.2554 (7)	0.822 (2)	0.4720 (6)	4.1 (4)
C8	1.2606 (8)	0.881 (2)	0.5779 (6)	8.7 (5)
C9	1.3583 (8)	0.653 (2)	0.4457 (8)	10.5 (6)
C10	0.8005 (7)	0.865 (2)	0.1781 (6)	6.0 (4)
C11	0.6816 (7)	1.031 (2)	0.1657 (5)	4.2 (4)
C12	0.6764 (7)	1.219 (2)	0.0988 (6)	5.2 (5)
C13	0.571 (1)	1.372 (2)	0.0868 (7)	7.5 (5)
C14	0.471 (1)	1.330 (3)	0.1409 (9)	8.6 (6)
C15	0.4709 (9)	1.150 (3)	0.2053 (8)	8.3 (7)
C16	0.5788 (9)	0.994 (2)	0.2160 (6)	6.2 (5)

C, 69.55; H, 7.30. Found: C, 69.55; H, 7.35.

7: A colorless syrup, $[\alpha]_D$ −26.8° (c=2.1, chloroform). *Anal.* Calcd for $C_{16}H_{21}FO_4$: C, 64.85; H, 7.14. Found: C, 64.80; H, 7.24. ^{19}F-NMR ($CDCl_3$) δ: −21.30 (ddq, $J_{F,H-4}$=8 Hz, $J_{F,H-5}$=46 Hz, $J_{F,H-6}$=25 Hz, F-5).

Further elution gave **5** (111 mg, 32%).

X-Ray Analysis of 3 A colorless needle crystal of approximately 0.2×0.2×0.6 mm was mounted on a Rigaku AFC-5R diffractometer and the cell parameters and the intensity data were measured with graphite-monochromated CuK_α radiation. Crystal data: (*E*)-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-4-enofuranose, $C_{16}H_{20}O_4$, M.W.=276.33, monoclinic, a=10.325(1) Å, b=5.432(1) Å, c=13.6736(6) Å, β=96.223(7)°, V=762.4(2) Å^3, space group $P2_1$, Z=2, D_{cal}=1.204 g·cm^{-3}, μ for CuK_α=6.64 cm^{-1}. Of the total of 1637 reflections within the 2θ range of 6° through 140.3°, 920 were measured as about the 3σ (I) level and were used for the structure determination. Approximate atomic coordinates were obtained by the direct method using the program MITHRIL[12] and refined by the full-matrix least-squares method. The final R value was 0.065. The positional parameters and selected torsion angles for **3** are listed in Tables III and IV, respectively.

TABLE IV. Selected Torsion Angles for **3**

A–X–Y–B	Torsion angle (ϕ/°) along X–Y
C1–C2–C3–C4	26.1 (7)
O4–C4–C3–C2	−30.7 (7)
C1–O4–C4–C3	23.9 (7)
C2–C1–O4–C4	−5.9 (7)
O4–C1–C2–C3	−13.5 (7)
C1–O4–C4–C5	−155.7 (7)
C2–C3–C4–C5	148.9 (8)
C3–C4–C5–C6	1.0 (1)
O4–C4–C5–C6	−179.2 (6)

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References and Notes

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