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Synthesis of 7-Deoxy-D-*glycero*-D-*gluco*-heptose (SF-666A)

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The synthesis of 7-deoxy-D-*glycero*-D-*gluco*-heptose (1) from 3,5-O-benzylidene-1,2-O-isopropylidene-α-D-glucofuranose (2) is described. Oxidation of compound (2) afforded 3,5-O-benzylidene-1,2-O-isopropylidene-α-D-*gluco*-hexodialdo-1,4-furanose (3), which was then treated with methylmagnesium iodide to give 3,5-O-benzylidene-1,2-O-isopropylidene-7-deoxy-α-D-*glycero*-D-*gluco*-heptose (4) and its L-*glycero*-D-*gluco* isomer (5). Hydrolysis of (4) produced compound (1), which was identical with natural SF-666 A, a fermentation product of *Streptomyces setonensis* nov. sp.

Two monosaccharides, SF-666 A and SF-666 B, were isolated from the fermentation broth of *Streptomyces setonensis* nov. sp.[1] and their structures were determined to be 7-deoxy-D-*glycero*-D-*gluco*-heptose and 7-deoxy-D-*altro*-heptulose, respectively.[2] In the present paper, the synthesis of 7-deoxy-D-*glycero*-D-*gluco*-heptose (1) is described.

Several 7-deoxy-heptoses have been synthesized from their corresponding 6-deoxy-hexoses by the well-known cyanohydrin synthesis.[3] This procedure, however, is not adequate for the preparation of compound (1), because 6-deoxy-D-altrose is not readily prepared.[4] So, we tried the application of Grignard reaction[5] to suitably blocked dialdohexose.

When 3,5-O-benzylidene-1,2-O-isopropylidene-α-D-glucofuranose (2)[6] was oxidized with the Pfitzner-Moffatt reagent,[7,8] 3,5-O-benzylidene-1, 2-O-isopropylidene-α-D-*gluco*-hexodialdo-1,4-furanose (3) was obtained as a crude syrup. The product showed one major spot on thin-layer chromatograms and it gave a positive reaction with aniline hydrogen phthalate. The infra-red spectrum showed intense carbonyl peak at 1730 cm^{-1}. This compound was not stable, so attempts to purify (3), either through high-vacuum distillation or chromatography, were not successful. However, the crude aldehyde (3) gave satisfactory results in reaction with Grignard reagent.

Treatment of the aldehyde (3) with methylmagnesium iodide yielded two compounds

TABLE I. CHEMICAL SHIFTS (δ, ppm) AND COUPLING CONSTANTS (Hz) OF RING PROTONS OF COMPOUND (4) AND (5). (100 MHz)

Proton	(4)		(5)	
	Chem. shift	Coupling const.	Chem. shift	Coupling const.
H-1	6.05 (d)	$J_{1,2}=3.8$	6.01 (d)	$J_{1,2}=3.6$
H-2	4.67 (d)	$J_{2,3}=0$	4.61 (d)	$J_{2,3}=0$
H-3	4.49 (s)	$J_{3,4}=0$	4.40 (d)	$J_{3,4}=2.2$
H-4	4.49 (s)	$J_{4,5}=0$	4.2 (m)	$J_{4,5}=1.2$
H-5	3.87 (d)	$J_{5,6}=6.1$	3.8 (q)	$J_{5,6}=6.8$
H-6	4.3 (m)	$J_{6,7}=6.2$	4.1 (m)	$J_{6,7}=6.4$
H-7 (CH_3)	1.35 (d)		1.30 (d)	

s: singlet, d: doublet, q: quartet, m: multiplet.
Measured with a JEOL JNM-PFT-100 spectrometer.

that were separated by chromatography over silica gel. The product (5), which was eluted first, was subsequently shown to be 3,5-O-benzylidene-1,2-O-isopropylidene-7-deoxy-α-L-*glycero*-D-*gluco*-heptose and another product (4), which was eluted later, was determined to be its D-*glycero*-D-*gluco* isomer. The ratio of these epimers was about 1:2, with predominance of (4).

Both compound (4) and (5) gave NMR spectra that could be analyzed by first-order analysis (Table I). The coupling constant $J_{5,6}$ of (4) and (5) was 6.1 and 6.8, respectively.

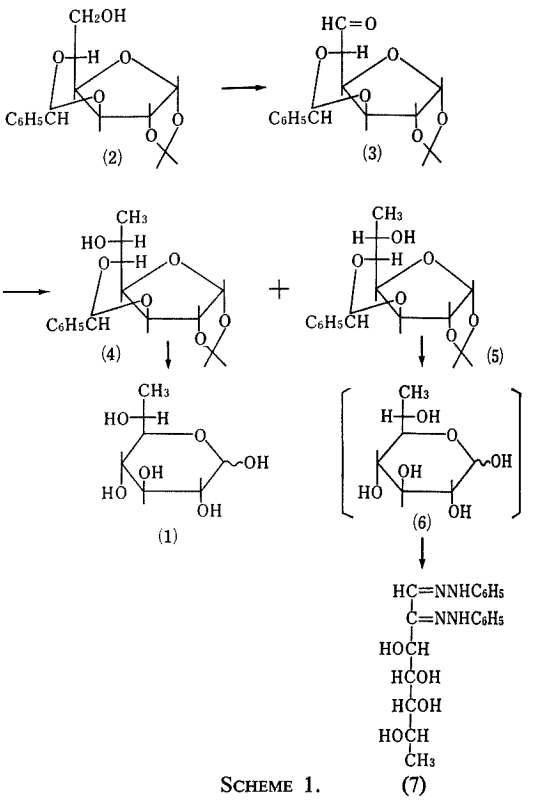
Hydrolysis of compound (4) with dilute sulfuric acid produced 7-deoxy-D-*glycero*-D-*gluco*-heptose (1), which was identical with natural SF-666 A in paper chromatographic behavior and in optical rotation, infra-red and NMR spectrum. As reported in the previous report,[1] SF-666 A exhibited a moderate antibacterial activity against *Gluconobacter suboxydans* and some strains of *Staphylococcus aureus*. By testing with paper disc method, natural SF-666 A and synthetic compound (1) showed the similar inhibition zones on the plate of *Gluconobacter suboxydans*.

When compound (5) was hydrolyzed and treated with phenylhydrazine, a crystalline phenylosazone (7) was obtained. Compound (7) was identical with 7-deoxy-L-*galacto*-heptulose phenylosazone.[2] This fact indicates that C-6 of (5) has L-*glycero* configuration.

EXPERIMENTAL

Melting points were uncorrected. NMR spectra were recorded with a Varian T-60 spectrometer and a JEOL JNM-PFT-100 spectrometer at 60 MHz and 100 MHz, respectively, in $CDCl_3$ with TMS as an internal standard (compound 3, 4 and 5) and in D_2O (compound 1).[2] Mass spectra were measured with a JEOL JMS-01SG spectrometer. The ionizing energy was 75 eV and the sample temperature of (4) and (5) was 120°C and that of (7) was 170°C. Column chromatography was performed with silicic acid, Mallinckrodt Chemicals Works, 100 mesh. TLC was carried out on silica gel, E. Merck,

3, 5-O-Benzylidene-1,2-O-isopropylidene-α-D-gluco-hexodialdo-1,4-furanose (3)



SCHEME 1.

3, 5-O-Benzylidene-1, 2-O-isopropylidene-α-D-glucofuranose (2) was prepared by the method described by Schmidt.[6] The oxidation technique devised by Pfizner and Moffatt[7] was used as described by Horton, Nakadate and Tronchet.[8a]

To a solution of compound (2) (2.8 g) in dimethyl sulfoxide (9 ml) and benzene (2.5 ml) were added anhydrous pyridine (0.5 ml), phosphoric acid (0.25 ml), and, finally N,N'-dicyclohexylcarbodiimide (6.2 g). The mixture was stirred for 5 hr at room temperature and then was filtered to remove N,N'-dicyclohexylurea. A solution of oxalic acid monohydrate (5 g) in methanol (12 ml) was added to the filtrate and the mixture was stirred for 1 hr, and then filtered. The filtrate was dilute with benzene and washed with aqueous sodium hydrogen carbonate solution. The aqueous extracts were extracted with benzene and organic solvent phases were combined, dried thoroughly and evaporated. The residual syrup was dissolved in absolute benzene, whereupon a small amount of N,N'-dicyclohexylurea crystallized. The mixture was filtered and the filtrate was evaporated under high-vacuum in a rotary evaporater below 80°C to give a dense syrup. Yield, 2.6 g. IR ν_{max}^{liq} cm^{-1}: 1730 (C=O). The thin-layer chromatogram (solvent system, benzene-MeOH, 9:1) gave one major spot at *Rf* 0.74, when it was visibilized by spraying with 10% H_2SO_4

or aniline hydrogen phthalate. This compound was not stable, so, without further purification, was condensed with Grignard reagent.

3,5-O-Benzylidene-1, 2-O-isopropylidene-7-deoxy-α-D-glycero-D-gluco-heptose (4) and 3,5-O-benzylidene-1,2-O-isopropylidene-7-deoxy-α-L-glycero-D-gluco-heptose(5) A solution of newly prepared aldehyde (3) (2.6 g) in absolute benzene (15 ml) was added to an ethereal solution of methylmagnesium iodide (30 g of methylmagnesium iodide in 60 ml of absolute ether). The mixture was allowed to stand for 2 days at room temperature and was poured into ice-water containing 20 g of ammonium chloride. The organic layer was separated and the aqueous layer was extracted twice with ether. The organic solvent extracts were combined, dried and evaporated to give a syrup (1.4 g). The thin-layer chromatogram on silica gel with benzene-MeOH (15: 1) showed that the syrup consisted of a component (4) (*Rf* 0.41), another component (5) (*Rf* 0.55) and the other minor products. The mixture was applied to a column (16×1.5 cm) of silicic acid and the components were eluted with benzene-MeOH (15: 1). Fractions (3 ml each) were collected, examined by TLC and the fractions 9~11 were evaporated to give compound (5) (280 mg, yield 9.5% from compound 2) and from fractions 14~19, the needle crystals of (4) (570 mg, yield 19.6% from compound 2) were obtained. They were recrystallized from chloroform-ether. The physical properties of (4) and (5) were as follows:

(4), mp 165~166°C, $[\alpha]_D^{24}$ +10° (*c*=1, $CHCl_3$); IR $\nu_{max}^{KBr}cm^{-1}$: 3510(OH), weak band 3360, $\nu_{max}^{nujol}cm^{-1}$: 3520 (OH), shoulder 3360. NMR $\delta_{Me_4Si}^{CDCl_3}$ (100 MHz): see Table I and 7.38 (5H, benzene), 1.34 and 1.54 (2×3 H, isopropylidene) and 5.85 (1H, –CH of benzylidene). MS *m/e* (relative intensity): 322 (M^+) (15), 307 (6), 277 (18), 129 (18), 113 (11) 100 (100). *Anal.* Found: C, 62.99; H, 7.12. Calcd. for $C_{17}H_{22}O_6$: C, 63,34; H, 6.88%.

(5), mp 176~177°C, $[\alpha]_D^{24}$ +11° (*c*=0.7, $CHCl_3$); IR $\nu_{max}^{KBr}cm^{-1}$: 3340(OH), $\nu_{max}^{nujol}cm^{-1}$:3375 (OH) NMR $\delta_{Me_4Si}^{CDCl_3}$ (100 MHz): see Table I and 7.40 (5H, benzene), 1.33 and 1.51 (2×3 H, isopropylidene) and 5.5 (1H, –CH of benzylidene). MS *m/e* (relative intensity): 322 (M^+) (1), 307 (3), 278 (5), 277 (5), 220 (10), 160 (23), 141 (17), 129 (41), 113 (69), 107 (61), 105 (80), 100 (100). *Anal.* Found: C, 62.61; H, 7.29. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%.

7-Deoxy-D-glycero-D-gluco-heptose (1). 3,5-O-Benzylidene-1,2-O-isopropylidene-7-deoxy-α-D-*glycero*-D-*gluco*-heptose (4) (215 mg) was boiled for 4 hr with 5 ml of 1% sulfuric acid. The cooled solution was extracted with ether to remove benzaldehyde and benzoic acid. Then, sulfate ions were removed from the aqueous solution by use of barium hydroxide. After barium sulfate was removed by filtration, the filtrate was concentrated *in vacuo* to give a hygroscopic powder (80 mg, yield 59%). The thin-layer chromatogram (solvent system: *n*-butanol-acetic acid-H_2O, 4: 1: 2) showed a spot at *Rf* 0.3. $[\alpha]_D^{24}$ +38° (*c*=4, H_2O), SF-666 A showed $[\alpha]_D^{24}$ +38° (*c*=1, H_2O). The NMR and IR spectra were identical with the spectra[1,2] of SF-666 A. The *Rf* value (0.32) on paper chromatogram (solvent system: *n*-butanol-acetic acid-H_2O, 4: 1: 5 upper layer) was identical with that of SF-666 A. *Anal.* Found: C, 40.61; H, 7.35. Calcd. for $C_7H_{14}O_6 \cdot 1/2\ H_2O$: C, 41.37; H, 7.44%. Bioassay: paper disc method, *Gluconobacter suboxydans*, medium, see Reference 1). Incubation, 18 hr at 28°C. Diameter of inhibition zone: synthetic (1) (concentration, 8 mg/ml) 23.05 mm, SF-666 A (8 mg/ml) 22.15 mm.

7-Deoxy-L-galacto-heptulose phenylosazone (7). 3,5-O-Benzylidene-1, 2-O-isopropylidene-7-deoxy-α-L-*glycero*-D-*gluco*-heptose (5) (70 mg) was hydrolyzed by boiling with 1% sulfuric acid for 5 hr and the cooled solution was extracted with ether to remove benzaldehyde and benzoic acid. After sulfate ions were removed by use of barium hydroxide, the filtrate was concentrated to a syrup, which was then treated with phenylhydrazine by the usual procedure to give 7-deoxy-L-*galacto*-heptulose phenylosazone (7) (10 mg). mp 178~180°C, MS *m/e* 372 (M^+), 354 ($M-H_2O$), 336 ($M-2H_2O$). IR spectrum was identical with that of 7-deoxy-L-*galacto*-heptulose phenylosazone (mp 180°C).[2]

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