

CHLORODEOXY AND DEOXY SUGARS

C. R. HAYLOCK, L. D. MELTON, K. N. SLESSOR, AND A. S. TRACEY

Department of Chemistry, Simon Fraser University, Burnaby, B.C. (Canada)

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ABSTRACT

The following chlorodeoxy derivatives have been prepared in high yield by treatment of fully protected isopropylidene acetals of sugars with triphenylphosphine in carbon tetrachloride; 1-chloro-1-deoxy-2,3;4,6-di-*O*-isopropylidene-L-sorbose (1), 1-chloro-1-deoxy-2,3;4,5-di-*O*-isopropylidene-D-fructose (2), 3-chloro-3-deoxy-1,2;-5,6-di-*O*-isopropylidene- α -D-glucose (3) and - β -D-idose (4), and 6-chloro-6-deoxy-1,2;-3,5-di-*O*-isopropylidene- α -D-glucose (5). With the exception of the sorbose derivative, all of the derivatives were converted into their deoxy analogues by treatment with lithium aluminum hydride. Thus, these procedures allow preparation of 3-deoxy-D-ribo-hexose (6) and 3-deoxy-D-lyxo-hexose (7) and other deoxy sugars in good yield.

INTRODUCTION

The utility of chlorodeoxy sugars in providing synthetic intermediates has been well documented¹⁻³. Methods for introducing chloro substituents are varied and have been reviewed recently by Hanessian². A simple, mild method, which has not been extensively applied to carbohydrates is the use of triphenylphosphine in carbon tetrachloride⁴. Lee and Nolan investigated the formation of 6-chloro-6-deoxy-di-*O*-isopropylidene- α -D-galactopyranose from the parent 1,2;3,4-acetal with this reagent⁴ and subsequently 2,3;5,6-di-*O*-isopropylidene- α -D-mannofuranosyl chloride was prepared in the same way⁵ from 2,3;5,6-di-*O*-isopropylidene- α -D-mannose. In this work we describe the synthesis of a variety of chlorodeoxy and deoxy-isopropylidene acetal sugars in high yield by application of the triphenylphosphine-carbon tetrachloride chlorination procedure.

DISCUSSION

Although Lee and Nolan showed that an isolated primary hydroxyl group reacted readily with triphenylphosphine-carbon tetrachloride, it was of interest to extend this study to the more difficult case of the 1-position in a hexulose. Richardson⁶ has recently outlined the factors responsible for the unreactivity of substituents at the 1-position of 2,3;4,5-di-*O*-isopropylidene-D-fructose and 2,3;4,6-di-*O*-isopropylidene-

L-sorbose. Both of these hexulose derivatives reacted readily with triphenylphosphine-carbon tetrachloride to yield the 1-chloro-1-deoxy derivatives. Hydrolysis of the fructose derivative gave amorphous 1-chloro-1-deoxy-D-fructose, whereas the sorbose derivative was initially hydrolyzed to the crystalline 1-chloro-1-deoxy-2,3-*O*-isopropylidene-L-sorbofuranose (8), and finally to the crystalline 1-chloro-1-deoxy-L-sorbose. Reduction of the fully substituted chlorodeoxy acetal with lithium aluminum hydride in diglyme was difficult and only the fructose derivative gave a reasonably pure product in good yield. Hydrolysis of the 1-deoxy-2,3;4,5-di-*O*-isopropylidene-D-fructose (9) gave 1-deoxy-D-fructose, characterized as the phenylosazone⁷.

Replacement of a secondary hydroxyl group by chlorine by using triphenylphosphine-carbon tetrachloride was of interest as it had not been reported in the sugar series*. 1,2;5,6-Di-*O*-isopropylidene- α -D-allose was chosen as an ideal substrate as the 3-OH group is *endo* and the 3-tosyl derivative is known to undergo nucleophilic displacement, even with chloride as the nucleophile⁸. Chlorination proceeded in very high yield and 3-chloro-3-deoxy-1,2;5,6-di-*O*-isopropylidene- α -D-glucose (3) was isolated as a liquid in 85% yield after distillation. Similar considerations led to the synthesis of 3-chloro-3-deoxy-1,2;5,6-di-*O*-isopropylidene- β -D-idose (4) from 1,2;5,6-di-*O*-isopropylidene- β -D-talose. Brimacombe, Gent and Westwood⁹ have recently published syntheses of 3-substituted L-idose derivatives by nucleophilic displacement of the *endo p*-toluenesulfonate of 1,2;5,6-di-*O*-isopropylidene-3-*O-p*-tolylsulfonyl- β -L-talose. As proof of structure of our chloro-di-*O*-isopropylidene-D-idose, X-ray crystal structure analysis was carried out on the crystalline material. 3-Chloro-3-deoxy-1,2;5,6-di-*O*-isopropylidene- β -D-idose (4) crystallizes in the orthorhombic space group P_{212121} with four molecules in the unit cell. The structure has been determined by direct methods and refined¹⁰ by full-matrix, least-squares techniques to a conventional *R* factor ($\sum |F_o| |F_c| / \sum |F_o|$) of 0.057.

Reduction of both 3-chloro-3-deoxy-1,2;5,6-di-*O*-isopropylidene-D-hexoses was carried out in tetrahydrofuran with lithium aluminum hydride. The reduction of the gluco derivative represents a convenient route to 3-deoxy-1,2;5,6-di-*O*-isopropylidene-D-ribo-hexose (6) from 1,2;5,6-di-*O*-isopropylidene-D-glucose. The deoxy derivative 6 is reported crystalline for the first time, although its melting point is low (10–12°). 3-Chloro-3-deoxy-di-*O*-isopropylidene- β -D-idose (4) gives on reduction crystalline 3-deoxy-1,2;5,6-di-*O*-isopropylidene- β -D-lyxo-hexose (8) in good yield. The latter is the final 3-deoxy-1,2;5,6-di-*O*-isopropylidene-D-hexofuranose to be described.

In order to better understand the mode and stereochemistry of the reduction of chlorodeoxy sugars with lithium aluminum hydride, 3-deuterio-1,2;5,6-di-*O*-isopropylidene- α -D-allose was prepared and converted into 3-chloro-3-deoxy-3-deuterio-1,2;5,6-di-*O*-isopropylidene- α -D-glucose. Reduction, followed by isolation

*After the preparation of this manuscript Verheyden¹¹, at the joint CIC-ACS meeting in Toronto, reported the halogenation of primary and secondary centers of some blocked and unblocked sugar nucleosides by treatment with triphenylphosphine-carbon tetrahalide.

and distillation gave 3-deoxy-3-deuterio-1,2;5,6-di-*O*-isopropylidene- α -D-*ribo*-hexose. Table I presents the $J_{2,3}$ couplings of this compound and some related compounds.

SKETCH 1

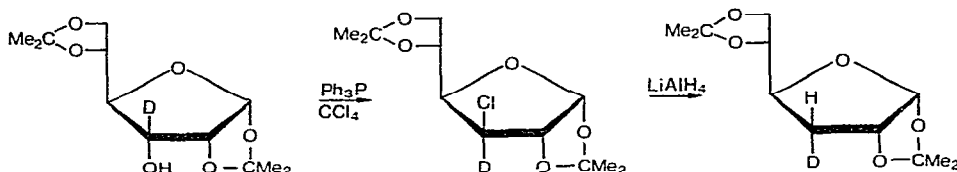


TABLE I

$J_{2,3}$ VALUES FOR SELECTED DI-*O*-ISOPROPYLIDENE-HEXOSES IN CHLOROFORM-*d*

Structure	$J_{2,3}$ (cis), Hz	$J_{2,3}$ (trans), Hz
	5.0	
		~0.5
		~0.5
	4.8	~0.5
	4.8	

From Table I the $J_{2,3}$ coupling of the 3-deoxy-3-deuterio-*ribo*-hexofuranose can be seen to be close to 5 Hz, which is indicative of a cis arrangement of H-2-H-3 as drawn. The reduction of the 3-chloro-D-glucose derivative therefore must have taken place with retention of configuration about C-3.

TABLE II

CHEMICAL SHIFTS (τ) IN CHLOROFORM-*d*

Compound	H-1	H-2	H-3	H-4	H-5	H-6	CH ₃
1	\longleftrightarrow		5.5 \longleftrightarrow 6.3	\longrightarrow			3.54, (8.65 \times 2), 8.70
2	6.4		5.61	5.40	5.81	6.2	8.46, (8.57 \times 2), 8.71
3	4.10	5.34	5.66	\longleftarrow	5.8	\longrightarrow	8.53, 8.61, 8.68, 8.73
4	3.89	5.23	5.6	5.7	6.23	5.7	8.43, 8.50, 8.55, 8.63
5	4.10	5.49	6.81	6.4	5.66	6.38	8.52, (8.66 \times 3)
6	4.21	5.27	7.83, 8.26	5.88	6.18	5.9	8.52, 8.59, 8.66, 8.70
7	4.20	5.28	8.01, 8.29	5.75	6.18	5.87	8.55, 8.64, 8.71, 8.77
8	\longleftrightarrow		5.5 \longleftrightarrow 6.2	\longrightarrow			8.48, 8.60
9	8.67		5.95	5.38	5.88	6.3	8.47, 8.52, 8.54, 8.67
10	4.11	5.50	5.89	5.92	6.41	8.73	8.52, (8.88 \times 3)

It was of interest to investigate the reaction of 1,2;5,6-di-*O*-isopropylidene- α -D-glucose with triphenylphosphine-carbon tetrachloride, to determine whether displacement or rearrangement of acetals followed by chlorination at C-6 would occur, as has been observed with various other chlorinating agents under similar conditions¹¹. A product was obtained that distilled under similar conditions reported for 6-chloro-6-deoxy-1,2;3,5-di-*O*-isopropylidene- α -D-glucose¹¹ (5). Hydrolysis of the product gave a crystalline chlorodeoxy sugar having properties identical with those reported for 6-chloro-6-deoxy-D-glucose^{11,12}. Interestingly, upon reduction of 5, two products were evident after distillation. T.l.c. in 5:1 toluene-ethyl ether indicated a major component (R_F 0.4) (10) and a minor component ($\sim 10\%$, R_F 0.1). The minor component was identical in chromatographic mobility with compound 6 and this leads us to suspect that a small amount of the 3-chloro sugar was formed in addition to the 6-chloro derivative. The 3-chloro sugar would probably have had the *allo* configuration, which is not too surprising considering the recent report of sulfonate displacements at C-3 of 1,2;5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl- α -D-glucofuranose¹³.

Although triphenylphosphine-carbon tetrachloride has been used with acetals, esters, and ethers⁴, the rearrangement of the acetal linkage in 1,2;5,6-di-*O*-isopropylidene- α -D-glucofuranose indicates that indiscriminate application of this chlorination procedure is unwise. Attempts to chlorinate methyl 4,6-*O*-benzylidene- α -D-glucoside, 1,2;4,5-di-*O*-isopropylidene-D-fructose, 1,2;4,5-di-*O*-isopropylidene-D-ribo-hexulose and 1,2;5,6-di-*O*-isopropylidene-D-mannitol by this method have not been successful. The glucoside, fructose, and psicose derivatives appear to decompose in refluxing carbon tetrachloride containing triphenylphosphine, whereas the mannitol derivative seems to rearrange in low yield during the chlorination. Thus, the chlorination procedure is applicable to derivatives whose blocking groups do not rearrange and whose expected sites for chlorination are sufficiently accessible. The yields of chlorinated products from such reactions are excellent.

EXPERIMENTAL

General. — Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Evaporations were carried out on Buchi rotary evaporators at bath temperatures not exceeding 45°. Optical rotations were measured on a Perkin-Elmer Model P22 spectropolarimeter at 24°. T.l.c. was effected on Silica gel G by using 10% sulfuric acid and heat for development. N.m.r. spectra were obtained with a Varian A56-60 or¹⁴ HA-100 spectrometer with tetramethylsilane as an internal reference. The petroleum ether used had b.p. 30–60°.

1-Chloro-1-deoxy-2,3;4,6-di-O-isopropylidene-L-sorbose (1). — 2,3;4,6-Di-O-isopropylidene-L-sorbose (5 g) and triphenylphosphine (15 g) were dissolved in carbon tetrachloride (400 ml) and the solution was refluxed for 48 h during which time white crystals precipitated. The solution was cooled and diluted with petroleum ether (1 liter). The resulting mixture was kept at –20° overnight, filtered and evaporated to give a syrup, which was dissolved in petroleum ether (200 ml). This solution was kept for 3 h at 5°, filtered, and evaporated to give a thick syrup that was vacuum distilled through a 10-cm Vigreux column; $b_{0.05}$ 83–86°, to give a syrup (3.6 g) that crystallized spontaneously. Recrystallization from petroleum ether (12 ml) gave material (3 g) melting at 56–58°, $[\alpha]_D -22.3^\circ$ (c 0.71, chloroform).

Anal. Calc. for $C_{12}H_{19}ClO_5$: C, 51.71; H, 6.82; Cl, 12.75. Found: C, 51.62; H, 6.96; Cl, 12.85.

1-Chloro-1-deoxy-2,3-O-isopropylidene-L-sorbofuranose (8). — To a solution of compound 1 (25 g) in acetone (250 ml) was added 5M hydrochloric acid (375 ml) and the solution was kept for 4.5 h at 50°. Sufficient solid sodium hydrogen carbonate was added to make the solution slightly basic and the solution was evaporated. An aqueous solution of the resulting syrup was extracted twice with hexane (100 ml) and then five times with ethyl acetate (150 ml). The combined ethyl acetate fractions were dried over K_2CO_3 and evaporated. The product was crystallized from ethyl acetate–petroleum ether to give fine crystalline material (14.5 g). Recrystallization from ethyl acetate–petroleum ether gave material melting at 71–72°, $[\alpha]_D +1.9^\circ$ (c 1.56, water).

Anal. Calc. for $C_9H_{15}ClO_5$: C, 45.28; H, 6.29; Cl, 14.88. Found: C, 45.40; H, 6.43; Cl, 15.07.

1-Chloro-1-deoxy-L-sorbose. — Compound 8 (6 g) was dissolved in water (50 ml) and (20 ml) of Dowex-50 (H^+) was added. The mixture was heated for 3 h on a steam bath with intermittent shaking. Filtration and evaporation gave a syrup that crystallized after a few weeks. Recrystallization from ethyl acetate–petroleum ether gave material (1.25 g) melting at 95.5–97.0°, $[\alpha]_D -34.5^\circ$ (c 1.20, water).

Anal. Calc. for $C_6H_{11}ClO_5$: C, 36.27; H, 5.54; Cl, 17.88. Found: C, 36.16; H, 5.56; Cl, 17.77.

1-Chloro-1-deoxy-2,3;4,5-di-O-isopropylidene-D-fructose (2). — 2,3;4,5-Di-O-isopropylidene-D-fructose (5 g) was dissolved in a solution of triphenylphosphine (10 g) in carbon tetrachloride (60 ml). The solution was refluxed for 4 h and after

cooling was worked up as described for compound 1. Vacuum distillation gave a syrup, $b_{0.005}$ 80–85°, which crystallized and was recrystallized from petroleum ether to yield material (3.1 g) melting at 53.0–53.5°, $[\alpha]_D -34.2^\circ$ (c 0.292, cyclohexane).

Anal. Calc. for $C_{12}H_{19}ClO_5$: C, 51.71; H, 6.82; Cl, 12.75. Found: C, 51.74; H, 6.71; Cl, 12.66.

1-Deoxy-2,3,4,5-di-O-isopropylidene-D-fructose (9). — Compound 2 (4 g) was dissolved in diglyme (20 ml) and lithium aluminum hydride (2 g) was added. The mixture was refluxed overnight. The excess hydride was destroyed with 10% aqueous ammonium chloride, the suspension filtered through a Celite pad, and the residue thoroughly washed with acetone. The combined filtrate and washings were evaporated to a residual liquid that was subjected to fractionation by vacuum distillation. A chromatographically pure material (3.0 g) was obtained, $b_{0.007}$ 55–57°, as a thick syrup that failed to crystallize; $[\alpha]_D -8.9^\circ$ (c 1.16, chloroform).

1-Deoxy-D-fructose. — Compound 9 (600 mg) was dissolved in 50% aqueous acetic acid (5 ml) and kept overnight at room temperature. The solution was evaporated with water until no further acetic acid was present. The amorphous material (240 mg) had $[\alpha]_D -82^\circ$ (c 4.4, water), [lit.⁷ $[\alpha]_D -90^\circ$ (c 1.5, water)]. The phenylosazone, prepared by the method of Ishizu *et al.*⁷ had m.p. 136–139°, $[\alpha]_D -18.5^\circ$ (c 0.6, pyridine) [lit.⁷ m.p. 137–140°, $[\alpha]_{5780} -28^\circ$ (c 1.3, pyridine)].

1-Chloro-1-deoxy-D-fructose. — Compound 2 (2 g) was kept in 90% trifluoroacetic acid¹⁵ (10 ml) for four h at room temperature. Water was evaporated several times from the solution and finally the aqueous solution was treated with charcoal, filtered, and evaporated to a syrup (1.2 g), $[\alpha]_D -53.3^\circ$ (c 1.38, water). Treatment of the product with phenylhydrazine hydrochloride and sodium acetate in water on a steam bath gave a good yield of D-arabino-hexulose phenylosazone, m.p. 194–197°, $[\alpha]_D -89.5^\circ$ (c 0.67, pyridine); lit.¹⁶, m.p. 207°, $[\alpha]_D -90^\circ$ (c 1.0, pyridine). The facile loss of the chloro group during osazone formation is not surprising since the methoxyl group in 1-O-methyl-D-fructose is readily lost under identical conditions¹⁷. Attempts to prepare the *p*-nitrophenylhydrazone failed, presumably because of this ready loss of the chloro substituent.

3-Chloro-3-deoxy-1,2;5,6-di-O-isopropylidene- α -D-glucose (3). — 1,2;5,6-Di-O-isopropylidene- α -D-allose¹⁸ (5 g) and triphenylphosphine (10 g) were dissolved in carbon tetrachloride (400 ml) and the solution was refluxed for 96 h. Workup as described for compound 1 gave a syrup (4.56 g) after vacuum distillation; $b_{0.004}$ 76°, $[\alpha]_D -16.5^\circ$ (c 0.4, chloroform) (lit.⁸, $b_{0.05}$ 84–88°. Hydrolysis⁸ gave 3-chloro-3-deoxy-D-glucose, m.p. 147–149°, $[\alpha]_D 66.5 \rightarrow 60.9^\circ$ (c 0.6, water, 24 h), lit.⁸, m.p. 150–152°, $[\alpha]_D^{22} +66^\circ$ (c 0.18, water).

Anal. Calc. for $C_{12}H_{19}ClO_5$: C, 51.71; H, 6.82; Cl, 12.75. Found: C, 51.86; H, 6.87; Cl, 12.94.

3-Deoxy-1,2;5,6-di-O-isopropylidene- α -D-ribo-hexose (6). — Compound 3 (10 g) and lithium aluminum hydride (5 g) were dissolved in dry tetrahydrofuran (40 ml) and the mixture was refluxed for 24 h. The deoxy sugar was isolated as described for compound 9 and distillation ($b_{0.005}$ 70–72°) gave a syrup (5.71 g) that

crystallized at low temperature; m.p. 10–12°, $[\alpha]_D -2.75^\circ$ (c 0.4, chloroform) [lit.¹⁹ $b_{0.3}$ 74–78°, $[\alpha]_D^{18} -5.78^\circ$ (c 4.2, ethanol)]. Partial hydrolysis.¹⁷ gave 3-deoxy-1,2-*O*-isopropylidene- α -D-ribo-hexose, m.p. 82°, $[\alpha]_D -15.0^\circ$ (c 1.3, water) (lit.¹⁹, m.p. 84°).

3-Deoxy-3-deuterio-1,2;5,6-di-O-isopropylidene- α -D-ribo-hexose. — 3-Deuterio-1,2;5,6-di-*O*-isopropylidene- α -D-allose (3.2 g), prepared by reduction of 1,2;5,6-di-*O*-isopropylidene- α -D-ribo-hexofurano-3-ulose with sodium borodeuteride, was dissolved in carbon tetrachloride (200 ml) and triphenylphosphine (9 g) was added. After 40 h the reaction was worked up in the same way as the non-deuterated material to give 2.7 g of doubly distilled product. The chlorodeuterio sugar (500 mg) was then refluxed in tetrahydrofuran (35 ml) containing lithium aluminum hydride (500 mg) for 40 h. The 3-deoxy- α -D-ribo-hexose derivative was isolated as previously described to yield 430 mg of product. N.m.r. spectroscopy (see Discussion) indicated that reduction had taken place from the *exo* side with retention of configuration.

3-Chloro-3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-idose (4). — 1,2;5,6-Di-*O*-isopropylidene- β -D-talose²⁰ (1.6 g) was refluxed in carbon tetrachloride (120 ml) containing triphenylphosphine (3.2 g) for 7 days. The reaction mixture was diluted with petroleum ether (400 ml), cooled to 0°, filtered and evaporated to a syrup. The syrup was dissolved in ethyl acetate (200 ml), washed once with water (100 ml), and twice with 2% aqueous potassium permanganate. The organic phase was dried over potassium carbonate, filtered, and evaporated to give crystals. Recrystallization from petroleum ether (40 ml) yielded the pure product (1.0 g), m.p. 108.5–110°, $[\alpha]_D +24.7^\circ$ (c 0.65, cyclohexane).

Anal. Calc. for $C_{12}H_{19}ClO_5$: C, 51.71; H, 6.82; Cl, 12.75. Found: C, 51.71; H, 6.86; Cl, 12.62.

3-Deoxy-1,2;5,6-di-O-isopropylidene- β -D-lyxo-hexose (7). — To a solution of compound 4 (960 mg) in dry tetrahydrofuran (25 ml) was added lithium aluminum hydride (1 g) and the mixture was refluxed for 20 h. Isolation was as described for 9, except that the product did not need distillation and crystallized readily on evaporation. Recrystallization from petroleum ether gave chunky needles (500 mg) melting at 57.5–58.5°, $[\alpha]_D 21.9^\circ$ (c 1.47, chloroform).

Anal. Calc. for $C_{12}H_{20}O_5$: C, 59.02; H, 8.20. Found: C, 59.04; H, 8.29.

6-Chloro-6-deoxy-1,2;3,5-di-O-isopropylidene- α -D-glucose (5). — 1,2;5,6-Di-*O*-isopropylidene- α -D-glucose (20 g) was dissolved in carbon tetrachloride (2 liters) in which triphenylphosphine (45 g) has been dissolved. After 31 h of refluxing, the solution was worked up as previously described for 3. Distillation ($b_{0.01}$ 95–96°) gave material (17.0 g) that was homogeneous by t.l.c. (5:1 toluene–ethyl ether), but which showed an impurity by n.m.r. spectroscopy, $[\alpha]_D 35.9^\circ$ (c 1.07, $CHCl_3$). [Lit.¹¹ $b_{0.05}$ 84–85°, $[\alpha]_D 36^\circ$ (c 2.64, $CHCl_3$)]. Hydrolysis of this chloro sugar derivative (5 g) in 50% aqueous methanol (50 ml) with 30 ml of Dowex 50 (H^+) for 3 h at reflux with stirring yielded 6-chloro-6-deoxy-D-glucose (1.7 g), m.p. 137–139° after recrystallization from ethanol–ethyl ether; $[\alpha]_D 98.8 \rightarrow 51.5^\circ$ (c 1.6, water, 18 h). [Lit.¹¹, m.p. 135–136° $[\alpha]_D 95.6 \rightarrow 51.1^\circ$ (18 h, water)].

6-Deoxy-1,2;3,5-di-O-isopropylidene- α -D-glucose (10). — Compound 5 (900 mg)

in dry tetrahydrofuran (10 ml) was refluxed with lithium aluminum hydride (500 mg) for 14 h. Isolation in the usual manner gave a product which upon distillation ($b_{0.005}$ 46°) gave mobile liquid (290 mg); $[\alpha]_D$ 34.8° (c 1.25, chloroform). T.l.c. indicated a slow-running component ($\sim 10\%$) to be present. [lit.²¹, $b_{0.07}$ 58°, $[\alpha]_D^{19}$ 38.9° (c 1.955, chloroform)].

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