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Note

Synthetic routes to higher-carbon sugars. 1-*C*-Formylation of a 2-deoxyaldose *via* the anion of its diethyl dithioacetal*†

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Our laboratory has been especially interested in the development of new methods for the extension of sugar chains[1,2] in order to provide compounds of use in the synthesis of various metabolites, antimetabolites, and antiviral and antitumor compounds. In this context, the dithioacetals of sugars have been of particular value[3]. Suitably protected aldose dithioacetals are readily convertible by the action of strong bases, through abstraction of H-1, into the corresponding ketene dithioacetals[4,5], and the latter may be reduced to afford[6] the respective 2-deoxyaldose dithioacetals in high net yield.

Development of an acylanion equivalent[7] at C-1 of an aldose has provided a route to higher ketoses by C-1 alkylation of the carbanion of a 2-deoxyaldose dithioacetal derivative[8]. The principle of this reaction has also been used in the opposite sense, employing an acylanion equivalent as the reagent, reacting at an electrophilic site in a sugar derivative[3]. In this way, the 1,3-dithian-2-yl anion[9] has been used for chain extension, or branching, with various sugar substrates[10]. In particular, this reaction has been employed with protected aldonolactones, to afford 1,2-dicarbonyl sugar derivatives[1].

We now describe a new approach for sugar-chain extension, utilizing the anion generated from a dithioacetal of a 2-deoxyaldose. It is known that amides, and especially *N*,*N*-dimethylformamide, may react as acylating agents[11]. 1-*C*-Formylation of an aldose-derived anion in this way has furnished the corresponding, higher-carbon 1,2-dicarbonyl-3-deoxy sugar (a 3-deoxyhexos-2-ulose derivative) as its 2,2-dithioacetal derivative. This reaction provides a useful complement to the earlier-developed, preparative conversion of aldoses into 3-deoxyaldos-2-uloses containing the same number of carbon atoms[12,13].

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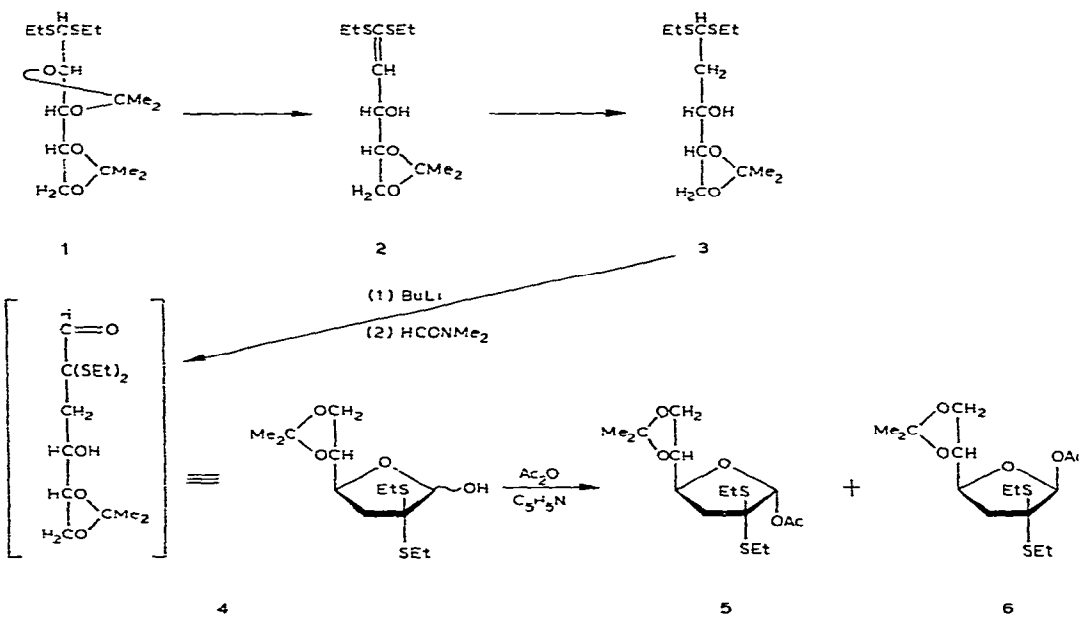
The diethyl dithioacetal (**1**) of 2,3:4,5-di-*O*-isopropylidene-D-arabinose was prepared by an adaptation of the method of Zinner *et al.*[14], and was transformed, by successive conversion into the ketene dithioacetal[4] **2** and *in situ* reduction[6] thereof with lithium aluminum hydride, into 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose diethyl dithioacetal[6] (**3**). Treatment of **3** with 3.2 equiv. of butyllithium in anhydrous oxolane (tetrahydrofuran) at −40° gave a colorless solution that became pale yellow after 2 h. The presumed dianion thereby produced was allowed to react with an excess of *N*,*N*-dimethylformamide during 1 h at −20°, at which time, complete conversion of **3** was achieved. On treatment of the mixture with water, and isolation of the product, t.l.c. showed a single component. Purification by chromatography on a column of silica gel gave a syrupy, homogeneous product, in 65% net yield, that was identified by ^{1}H-n.m.r. spectroscopy as the 1-*C*-formyl derivative of **3**, existing as a 1:3 α,β-anomeric mixture of the cyclic, furanoid tautomers **4**.

The anomers of **4** were separated as their acetates. Conventional acetylation of **4** with acetic anhydride–pyridine gave a mixture of two products, readily separated (as oils) by column chromatography. The major, dextrorotatory product (64%) was identified as the β anomer **6**, and the minor, levorotatory one (22%) as the α anomer **5**, by ^{1}H- and ^{13}C-n.m.r. spectroscopy. Full details of the structural attributions are recorded in the Experimental section.

EXPERIMENTAL

General methods. — T.l.c. was performed with glass plates (0.25 mm) precoated with Silica Gel 60F-254 (E. Merck, Darmstadt, G.F.R.); components were



detected by u.v. light, and by spraying the plates with sulfuric acid. Column chromatography was conducted with Silica Gel 60 (230–400 mesh, E. Merck, Darmstadt). Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. ^{1}H-N.m.r. spectra were recorded by Dr. O. Mols at 200 MHz with a Bruker WP-200 spectrometer, which was also used for ^{13}C spectra (at 50.72 MHz); chloroform-*d* was used as the solvent. The ^{13}C-n.m.r. attributions were verified by off-resonance decoupling. Chemical shifts refer to an internal standard of tetramethylsilane (δ 0.00). Elemental analyses were performed by Dr. O. Mols.

*Preparation of 2,3:4,5-di-*O*-isopropylidene-*D*-arabinose diethyl dithioacetal*[14] (**1**). — The procedure used was a minor modification of that of Zinner *et al.*[14]. A solution of D-arabinose diethyl dithioacetal (**1**; 25.6 g, 100 mmol) in dry acetone (1 L) and 96% sulfuric acid (5 mL) was stirred with anhydrous copper(II) sulfate (200 g, predried for 1 week at 120°) for 2 days at ~25°. The mixture was processed as described in ref. 14, to give a pale-yellow syrup, yield 29 g (87%), that was purified by vacuum distillation to give an almost colorless syrup; yield 26.2 g (78%), b.p. 142–143°/40 Pa (0.3 mmHg); $[\alpha]_D^{25}$ +82.5° (*c* 1.0, methanol) (lit.[14] $[\alpha]_D$ +83.3°); R_F 0.67 (1:4 ethyl acetate–hexane); ^{1}H-n.m.r.: δ 3.93–4.31 (m, 6 H, H-1,2,3,4,5,5′), 2.73, 2.74 (2 q, 4 H, *J* 7.0 Hz, 2 SCH_2CH$_3$), 1.34, 1.38, 1.42, 1.45 (4 s, 12 H, 2 CMe$_2$), and 1.25, 1.30 (2 t, 6 H, 2 SCH$_2$CH_3): ^{13}C-n.m.r.: δ 109.6, 110.1 (*C*Me$_2$), 77.2, 79.2, 84.5 (C-2,3,4), 67.7 (C-5), 52.5 (C-1), 25.2, 26.6, 27.0, 27.3 (C*M*e$_2$ and SCH$_2$CH$_3$), and 14.3 (SCH_2CH$_3$); calc. for $C_{15}H_{28}O_4S_2$: *m/z* 336.1429, obs. *m/z* 336.1438, base peak *m/z* 143, 135 (95%).

Compound **1** was directly converted, under the experimental conditions described by Wong and Gray[6], by way of compound **2** (not isolated), into 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (**3**), isolated as a chromatographically homogeneous oil in ~55% overall yield, having ^{1}H- and ^{13}C-n.m.r. spectra in close agreement with data published[6] for **3**.

*3-Deoxy-5,6-*O*-isopropylidene-α,β-*D*-*erythro*-hexofuranos-2-ulose 2,2-diethyl dithioacetal* (**4**). — A solution of the deoxy sugar derivative **3** (522 mg, 1.86 mmol) in dry oxolane (20 mL) was purged with dry nitrogen, and cooled to −40°. A 2.2M solution of butyllithium in hexane (Alfa Products, Danvers, MA; 2.7 mL, 5.94 mmol) was slowly added, with stirring. The mixture was stirred for 2 h at −35 to −40°, an excess of *N,N*-dimethylformamide (0.5 mL, 11.8 mmol) was slowly added, the temperature was allowed to rise to −20°, and stirring was continued for 1 h at this temperature. Water (2 mL) was added, the solution was allowed to attain room temperature, poured into water (50 mL), the mixture extracted with chloroform, and the extract washed with water, dried (sodium sulfate), and evaporated. The resultant product, **4**, was purified on a column of silica gel with 3:1 petroleum ether–ethyl acetate, to afford pure **4** as a colorless, syrupy mixture of the furanose anomers; yield 360 mg (65%); $[\alpha]_D^{25}$ −14° (*c* 2.4, chloroform); R_F 0.33; ^{1}H-n.m.r.: δ 5.19 (d, 0.25 H, $J_{1\alpha,OH}$ 5 Hz, H-1α), 5.07 (d, 0.75 H, $J_{1\beta,OH}$ 7.4 Hz, H-1β), 4.36–3.71 (m, 5 H, H-4,5,6,6′ and OH-1), 2.73, 2.72, 2.71, 2.70 (4 overlapping q, 2 weak at 2.73, 2.72, and 2 strong at 2.71, 2.70, 4 H, 2 SCH_2CH$_3$ of α and β anomers), 2.40 (q,

1 H, $J_{3\beta,3'\beta}$ 13.4, $J_{3\beta,4\beta}$ 6.2 Hz, H-3β overlapping H-3α signal), 2.20 (q, 1 H, $J_{3'\beta,4}$ 8 Hz, H-3'β overlapping H-3'α signal), and 1.42–1.21 (12 H, CMe_2 and 2 SCH_2CH_3). The H-1 signals became singlets after D_2O exchange.

*1-O-Acetyl-3-deoxy-5,6-O-isopropylidene-α-*D-erythro-*hexofuranos-2-ulose 2,2-diethyl dithioacetal* (**5**) *and its β anomer* (**6**). — The mixture of anomers (**4**) obtained in the preceding experiment (320 mg, 0.91 mmol) was acetylated with acetic anhydride (5 mL) in pyridine (10 mL) at ~25°. The reaction was complete after 30 min (t.l.c., 8:1 petroleum ether–ethyl acetate). The mixture was poured onto ice (50 g), and extracted with ether, and the two products formed (**5**, R_F 0.19, and **6**, R_F 0.15) were separated by chromatography on a column of silica gel with 8:1 petroleum ether–ethyl acetate.

The α anomer **5** was obtained as an oil; yield 81 mg (22%): $[\alpha]_D^{25}$ +106° (*c* 1.2, chloroform); ^{1}H-n.m.r.: δ 6.27 (s, 1 H, H-1), 3.87–4.27 (m, 4 H, H-4,5,6,6'), 2.58–2.75 (m, 5 H, 2 SCH_2CH$_3$ and H-3'), 2.27 (q, 1 H, $J_{3,4}$ 4.6, $J_{3,3'}$ 13.8 Hz, H-3), 2.11 (s, 3 H, OAc), 1.40, 1.34 (2 s, 6 H, CMe_2), and 1.25, 1.26 (2 t, 6 H, *J* 7.5 Hz, 2 SCH_2CH_3); ^{13}C-n.m.r.: δ 169.5 (C=O), 109.4 (*C*Me$_2$), 101.2 (C-1), 80.2, 77.4 (C-4,5), 67.4 (2 C, C-2,6), 42.2 (C-3), 26.8, 25.2 (or 25.1) (CMe$_2$), 25.1 (or 25.2), 24.5 (SCH_2CH$_3$), 21.0 (OAc), 14.1, and 13.6 (SCH_2CH_3).

Anal. Calc. for $C_{15}H_{26}O_5S_2$: C, 51.40; H, 7.48; S, 18.29. Found: C, 51.79; H, 7.46; S, 18.17.

The β anomer (**6**) was likewise obtained as an oil; yield 228 mg (64%): $[\alpha]_D^{25}$ −64° (*c* 1.7, chloroform); ^{1}H-n.m.r.: δ 6.18 (s, 1 H, H-1), 4.23–4.34 (m, 1 H, H-4), 3.88–4.13 (m, 3 H, H-5,6,6'), 2.61–2.73 (m, 4 H, 2 SCH_2CH$_3$), 2.45 (q, 1 H, $J_{3,3'}$ 13.0, $J_{3,4}$ 6.4 Hz, H-3), 2.32 (q, 1 H, $J_{3',4}$ 8.7 Hz, H-3'), 2.10 (s, 3 H, OAc), 1.37, 1.34 (2 s, 6 H, CMe_2), and 1.23 and 1.28 (2 t, 6 H, *J* 7.5 Hz, 2 SCH_2CH_3); ^{13}C-n.m.r.: δ 169.3 (C=O), 109.5 (*C*Me$_2$), 100.2 (C-1), 81.2, 78.6 (C-4,5), 67.4, 67.3 (C-2,6), 41.7 (C-3), 26.7, 25.2 (CMe_2), 24.4, 24.1 (SCH_2CH$_3$), 21.1 (OAc), 14.2, and 13.8 (SCH_2CH_3).

Anal. Calc. for $C_{15}H_{26}O_5S_2$: C, 51.40; H, 7.48; S, 18.29. Found: C, 51.50; H, 7.46; S, 18.10.

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