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SYNTHESIS OF HIGHER-CARBON SUGARS* *via* VINYLTIN DERIVATIVES OF SIMPLE MONOSACCHARIDES

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ABSTRACT

6-*O*-Benzyl-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-ynopyranose reacted with tributyltin hydride to afford (*Z*)-6-*O*-benzyl-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-(tributylstannyl)-L-*glycero*-α-D-*galacto*-oct-7-enopyranose, which was subsequently isomerised to the *E*-olefin **4**. Replacement of the tributyltin moiety with lithium in **4** afforded the vinyl anion which reacted with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose, furnishing 3-*O*-benzyl-6-*C*-[(*E*)-6-*O*-benzyl-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranos-7-ylidene]-6-deoxy-1,2-*O*-isopropylidene-α-D-gluco- (**6**) and -β-L-ido-furanose (**7**) in yields of ~70 or ~87% (depending on the temperature of the reaction). The configurations of the new chiral centres in **6** and **7** were determined by their conversion into 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-gluco- and -β-L-ido-furanose, respectively. Oxidation of **6** and **7** gave the same enone, 3-*O*-benzyl-6-*C*-[(*E*)-6-*O*-benzyl-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranos-7-ylidene]-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose.

INTRODUCTION

The synthesis of optically pure natural compounds from carbohydrates is now a well-established method in organic chemistry[1]. For the synthesis of such ionophoric antibiotics as boromycin[2], higher-carbon sugars seemed to be the best starting materials. There are two general routes for the preparation of these chiral synthons, involving (*a*) the condensation of a sugar unit with an achiral molecule[3,4] and further conversion into a polyhydroxylated system as, for example, in the synthesis of tunicamin[4], and (*b*) the coupling of two sugar sub-units[5–11]. Method (*b*) is probably the more convenient since most, if not all, of the chiral centres of the target molecule are present in the sub-units.

*Strictly speaking, these compounds are C_{13} sugar derivatives but, because of their resemblance to disaccharides and for easier comprehension, they are named as *x*-deoxy-*x*-(*C*-glycosyl)glycose derivatives.

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Acetylene is a suitable substrate for the synthesis of higher sugars by reaction, for example, with aldehydes[9], but the semi-reduction of the triple bond can be troublesome. A solution to the problem would be a direct synthesis of higher sugar allylic alcohols *via* vinyl anions of simple monosaccharides.

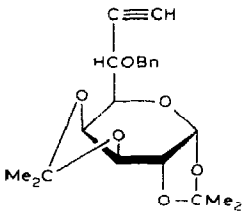
RESULTS AND DISCUSSION

Addition of tributyltin hydride to acetylene affords *cis*-(tributylstannyl)-olefins that are readily isomerised to the more stable *trans* products[12]. After the addition of butyl-lithium to this derivative, a facile replacement of the tributylstannyl moiety with lithium is observed so that these derivatives can serve as vinyl-anion equivalents **1** (R–CH=CH–Li). Addition of **1** to an aldehyde affords the allylic alcohol in good yields[13].

Sugar-derived vinyl anions should be stable and yield higher sugar allylic alcohols on reaction with the formyl derivatives of simple carbohydrates. Readily available 6-*O*-benzyl-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-ynopyranose (**2**) was selected as the model compound for the preparation of higher sugars.

The addition (3 h, 143°) of tributyltin hydride to the acetylene group in **2** gave the *Z* and *E* olefins, in the ratio 2:1, in almost quantitative yield. The configurations of the double bonds in **3** and **4** were determined readily from their ^{1}H-n.m.r. spectra, since the *J* values for the olefinic protons were ~13 and 20 Hz, respectively. Prolonged heating (in boiling xylene) of **3** effected *cis*→*trans* isomerisation to give **4**. This isomerisation occurred *only* when catalytic amounts of tributyltin hydride and azobis(isobutyronitrile) were present; chromatographically pure **3** did not isomerise on heating at 143° for 24 h.

When **3** was treated with butyl-lithium in tetrahydrofuran at room temperature, no exchange of the tributylstannyl moiety with lithium was observed, probably due to steric hindrance. However, **4** reacted readily with butyl-lithium at −78°, affording the vinyl anion, which was treated with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[14] (**5**) to give the diastereoisomeric allylic alcohols, 3-*O*-benzyl-6-*C*-[(*E*)-6-*O*-benzyl-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-



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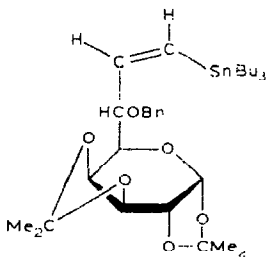

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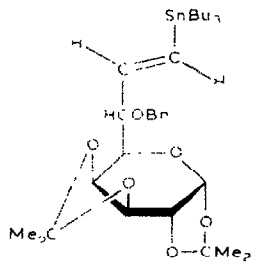

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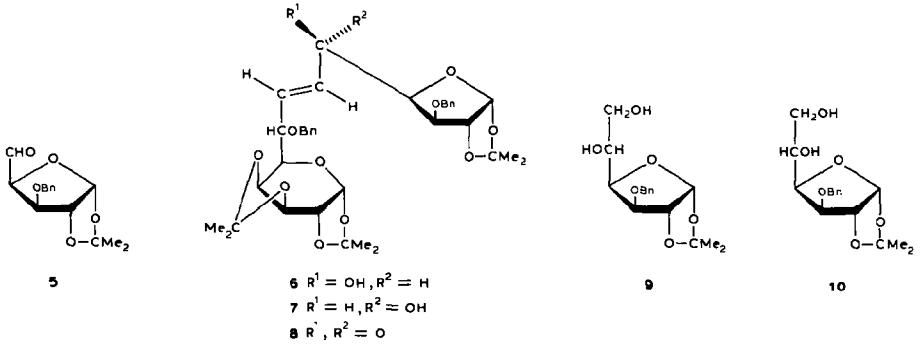


5 6 $R^1 = OH, R^2 = H$ 7 $R^1 = H, R^2 = OH$ 8 $R^1, R^2 = O$ 9 10

glycero-α-D-*galacto*-heptopyranos-7-ylidene]-6-deoxy-1,2-*O*-isopropylidene-α-D-gluco- (**6**) and -β-L-ido-furanose (**7**). The diastereoselectivity of this process was temperature-dependent. Thus, when the reaction was quenched at −78°, the ratio of **6** and **7** was ~3:1 (74% yield), whereas, at 0°, the ratio was ~3:2 and the yield was higher (87%). Oxidation of **6** or **7** with the Jones reagent gave the same enone **8**, proving that they were diastereoisomers.

The configurations of the new chiral centres in **6** and **7** were established by the following chemical correlations. Ozonolysis of the double bond in **6** followed by reduction of the crude ozonide afforded 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[15] (**9**). Likewise, **7** afforded the L-*ido* isomer[16] (**10**) of **9**. Thus, the configuration of the new chiral centre in **6** is *R* and that in **7** is *S*.

The method reported allows the preparation of the higher sugar allylic alcohols (as mixtures of diastereoisomers) in high overall yield from readily available derivatives of simple monosaccharides.

EXPERIMENTAL

General. — Melting points were determined with a Kofler apparatus and were not corrected. Optical rotations were measured with a Perkin–Elmer 141 spectropolarimeter on solutions in ethyl acetate at 20 ±2°. ^{1}H-N.m.r. spectra (the data for **6–8** are recorded in Table I) were recorded with a JEOL JNM-4H-100, Bruker WM-250, or Bruker A-400 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Mass spectra were recorded with a Finningan 8200 instrument. Column chromatography was performed on silica gel (Merck 230–400 mesh). Organic solutions were dried over anhydrous magnesium sulfate.

6-O-Benzyl-7,8-dideoxy-1,2:3,4-di-O-isopropylidene-L-glycero-α-D-galacto-*oct-7-ynopyranose* (**2**). — 7,8-Dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-ynopyranose[17] (7.1 g, 25 mmol) in dry *N,N*-dimethylformamide (30 mL) was added dropwise to a slurry of sodium hydride (3.0 g of a 50% suspension in oil, 60 mmol) in *N,N*-dimethylformamide (30 mL). A solution of benzyl bromide (3.1 mL, 26 mmol) in *N,N*-dimethylformamide (10 mL) was then added dropwise.

The mixture was stirred overnight at room temperature and then diluted with ether (100 mL), the excess of hydride was decomposed with water, and the organic layer was washed thrice with water, dried, and concentrated. Column chromatography (light petroleum–ether, 7:1) of the crude product afforded **2** (7.45 g, 19.92 mmol; 79.7%), isolated as an oil, $[\alpha]_D$ −22° (*c* 0.9). ^{1}H-N.m.r. data: *inter alia*, δ 5.51 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 2.40 (d, 1 H, $J_{8,8}$ 2.0 Hz, H-8).

Anal. Calc. for $C_{21}H_{26}O_6$: C, 67.4; H, 7.0. Found: C, 67.0; H, 7.3.

*3-O-Benzyl-6-C-[(E)-6-O-benzyl-7-deoxy-1,2:3,4-di-O-isopropylidene-*L-glycero-*α*-D-galacto-*heptopyranos-7-ylidene]-6-deoxy-1,2-O-isopropylidene-α-*D-*gluco-* (**6**) *and -β-*L-*ido-furanose* (**7**). — A mixture of **2** (2.22 g, 5.93 mmol), tributyltin hydride (1.75 mL, 6.5 mmol), azobis(isobutyronitrile) (10 mg), and xylene (20 mL) was boiled under reflux for 3 h. T.l.c. (light petroleum–ether, 3:1, 2 developments) then showed the disappearance of **2** and the formation of two less polar products. The mixture was concentrated to dryness under reduced pressure. Column chromatography (light petroleum–ether, 95:5) of the residue gave, first, (*Z*)-6-*O*-benzyl-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-(tributylstannyl)-L-*glycero*-*α*-D-*galacto*-oct-7-enopyranose (**3**; 2.61 g, 3.93 mmol; 66.3%), isolated as an oil. ^{1}H-N.m.r. data: *inter alia*, δ 6.67 (1 H, $J_{6,7}$ 6.0, $J_{7,8}$ 13.2 Hz, H-7), 6.20 (1 H, H-8), 5.61 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1). Isolated second was the 7-*E* isomer **4** (1.26 g, 1.90 mmol; 32%), isolated as an oil. ^{1}H-N.m.r. data: *inter alia*, δ 6.45 (1 H, $J_{8,7}$ 20 Hz, H-8), 6.13 (1 H, $J_{7,6}$ 4.4 Hz, H-7), 5.60 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1).

When a solution of **3** (2.5 g) in dry xylene (20 mL) was boiled under reflux, t.l.c. (light petroleum–ether, 3:1; 2 developments) showed no change after 24 h. When a catalytic amount (10 mg) of azobis(isobutyronitrile) and tributyltin hydride (0.1 mL) were added and the solution was boiled under reflux, t.l.c. after 8 h showed the complete conversion of **3** into **4**, which was isolated (2.3 g, 92%) by column chromatography.

To a solution of **4** (0.9 g, 1.35 mmol) in tetrahydrofuran (3 mL) at −78° was added butyl-lithium (0.94 mL of 1.6M solution in hexane; 1.5 mmol, 1.1 equiv.), and the mixture was stirred at −78° for 1 h. T.l.c. (light petroleum–ether, 2:1) then showed disappearance of **4**. A solution of **5** (460 mg, 1.65 mmol, dried by evaporation thrice with xylene) in tetrahydrofuran (2 mL) was added dropwise and the mixture was kept for 2 h at −78°. Ether (10 mL) was then added followed by saturated aqueous ammonium chloride (1 mL), and the organic layer was washed with water, dried, and concentrated. Column chromatography (light petroleum–ethyl acetate, 7:3) of the residue afforded, first, **6** (465 mg, 0.71 mmol; 52.3%), isolated as an oil, $[\alpha]_D$ −34° (*c* 1.3). Mass spectrum: *m/z* 639 (M^+ − 15), 596, 581, 249.

Anal. Calc. for $C_{36}H_{46}O_{11}$: C, 66.0; H, 7.1. Found: C, 65.9; H, 7.1.

Eluted second was a mixture (32 mg, 0.05 mmol; 3.7%) of **6** and **7**. Eluted third was **7** (154 mg, 0.24 mmol); 17.8%), isolated as an oil, $[\alpha]_D$ −86° (*c* 0.7). Mass spectrum: *m/z* 639 (M^+ − 15), 596, 581, 249.

Anal. Found: C, 65.7; H, 6.9.

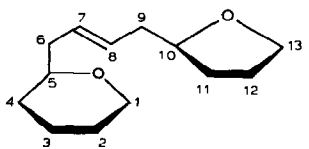
Alternatively, to a solution of **4** (820 mg, 1.23 mmol) in dry tetrahydrofuran (2

TABLE I

^{1}H-N.M.R. DATA FOR **6–8**[a]

Compound	*Chemical shifts (δ, p.p.m.)*												
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-8*	*H-9*	*H-10*	*H-11*	*H-12*	*H-13*	*CMe$_2$*
6	5.60	4.30	4.54	4.20	3.78	4.14	5.85	5.97	4.59	4.05	4.05	4.63	6.02	1.54, 1.50, 1.45, 1.31, 1.35 2x
7	5.60	4.29	4.53	4.16	3.79	4.08	5.89	5.85	4.57	4.04	3.89	4.65	6.00	1.55, 1.51, 1.44, 1.29, 1.35 2x
8	5.61	4.28	4.53	4.11	3.80	4.27	7.10	6.90	—	4.83	4.32	4.61	6.15	1.51 2x, 1.44, 1.30, 1.35 2x
	Coupling constants (Hz)												
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$	$J_{10,11}$	$J_{11,12}$	$J_{12,13}$		
6	5.0	2.25	7.8	1.7	8.2	5.5	15.0	4.2	6.0	n.d.	0	3.5		
7	5.0	2.25	7.8	1.7	8.0	5.0	15.0	4.5	6.5	3.2	0	3.7		
8	5.0	2.0	8.0	~1.0	8.0	5.0	15.0	—	—	3.5	0	3.5		

[a]The numbering is as follows:



mL) at −78° was added butyl-lithium (0.86 mL of 1.6M solution in hexane; 1.37 mmol, 1.2 equiv.), and the anion was generated for 1 h at −78°. A solution of dry **5** (360 mg, 1.29 mmol) in tetrahydrofuran (2 mL) was added, and the solution was kept for 15 min at −78° and then allowed to warm to 25°. The reaction was quenched by the addition of saturated aqueous ammonium chloride and the products were extracted with ether. Column chromatography of the crude material afforded **6** (410 mg, 0.63 mmol; 51.2%) and **7** (290 mg, 0.44 mmol; 35.8%).

*3-O-Benzyl-6-C-[(E)-6-O-benzyl-7-deoxy-1,2:3,4-di-O-isopropylidene-*L-glycero-*α*-D-galacto-*heptopyranos-7-ylidene]-6-deoxy-1,2-O-isopropylidene-α-*D-xylo-*hexofuranos-5-ulose* (**8**). — (*a*) A solution of **6** (420 mg, 0.64 mmol) in acetone (10 mL) was titrated with the Jones reagent[18] (1 mL of a 0.7M solution of the oxidant) until t.l.c. (light petroleum–ethyl acetate, 1:1) indicated disappearance of **6** and the formation of a less polar product visible in u.v. light. Ether (20 mL) was added, the mixture was washed twice with water, and the organic layer was concentrated. Column chromatography (light petroleum–ethyl acetate, 4:1) of the residue gave **8** (334 mg, 0.51 mmol; 79%), isolated as an oil, $[\alpha]_D$ −70° (*c* 0.9). Mass spectrum: *m/z* 652 (M^+), 637.2649 [(M^+ − 15); calc. 637.2649], 561, 546, 503, 488, 424, 403, 249, 229.

Anal. Calc. for $C_{36}H_{44}O_{11}$: C, 66.2; H, 6.8. Found: C, 66.5; H, 6.8.

(*b*) Alcohol **7** (120 mg, 0.183 mmol) was oxidised as described for **6**, to afford **8** (93 mg, 77.5%).

Determination of the configuration at the new chiral centre in **6** *and* **7**. — Ozone was passed through a solution of **6** (102 mg, 0.15 mmol) in dichloromethane (30 mL) at −78°, and the reaction was monitored by t.l.c. (light petroleum–ethyl acetate, 1:1). After 10 min, the mixture was poured into a solution of triphenylphosphine (30 mg) in dichloromethane (10 mL). After 1 h at 0°, the mixture was concentrated to dryness and a solution of the residue in dry tetrahydrofuran (5 mL) was reduced with lithium aluminium hydride (15 mg) under standard conditions[19], to give 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**9**; 30.5 mg, 61%), which was isolated by column chromatography (light petroleum–ethyl acetate, 1:1) and shown to be identical with authentic material[15].

Treatment of **7** (97 mg, 0.15 mmol), as described above for **6**, gave 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (**10**; 27 mg, 56.8%), which was identical (t.l.c., ^{1}H-n.m.r., i.r.) with authentic material[16].

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