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Note

Synthesis of acetylenic derivatives of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose

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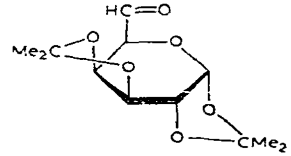
The preparation of some acetylenic derivatives of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[1–3] has been described, and we now report on the addition of organomagnesium reagents to 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**1**), and oxidation of the resulting carbinols (**2**) to ketones (**3**).

Addition of ethynylmagnesium bromide to **1**, using the method of Horton and co-workers[4,5], afforded variable yields (50–80%) of a 2:1 (n.m.r.) mixture of the D- (**4**) and L-*glycero* (**5**) epimers of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-7-ynopyranose. Crystallization from ethyl ether gave the known[4], major D-*glycero* isomer **4**.

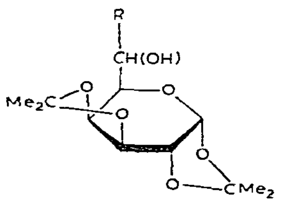
Epimeric mixtures of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-phenyl-α-D-*galacto*-oct-7-ynopyranose (**2**, R= C≡CPh), and 7,8,9-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-non-8-ynopyranose (**2**, R= $CH_2C{\equiv}CH$) were formed in 50 and 62% yields, respectively, by the addition of phenylethynyl- and propargyl-magnesium bromides to **1**. One of the isomers of **2** (R= CH≡CPh) was isolated as a syrup by column chromatography, but its configuration was not established.

When ethylmagnesium bromide reacted with **1** in tetrahydrofuran, a 3:2 (n.m.r.) mixture of the L- (**7**) and D-*glycero* (**6**) epimers of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octopyranose was obtained together with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**, R=H). The L-*glycero* epimer **7** crystallized from the epimeric mixture that had been separated from **2** (R=H) by p.l.c.

The configuration of **7** was established when catalytic hydrogenation of the D-*glycero*-ethynylcarbinol **4** gave a product (**6**) which was not identical to that (**7**) isolated from the Grignard reaction. Oxidation of **6** and **7** with chromium trioxide–pyridine–acetic acid[6] gave the same ketone (**3**, R=Et) in good yield (87 and 89%), although the D-*glycero* isomer **6** required 6 h for complete oxidation, whereas its C-6 epimer **7** was transformed in 30 min.



1



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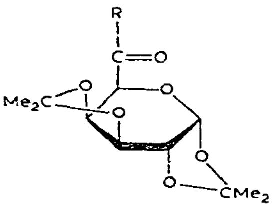

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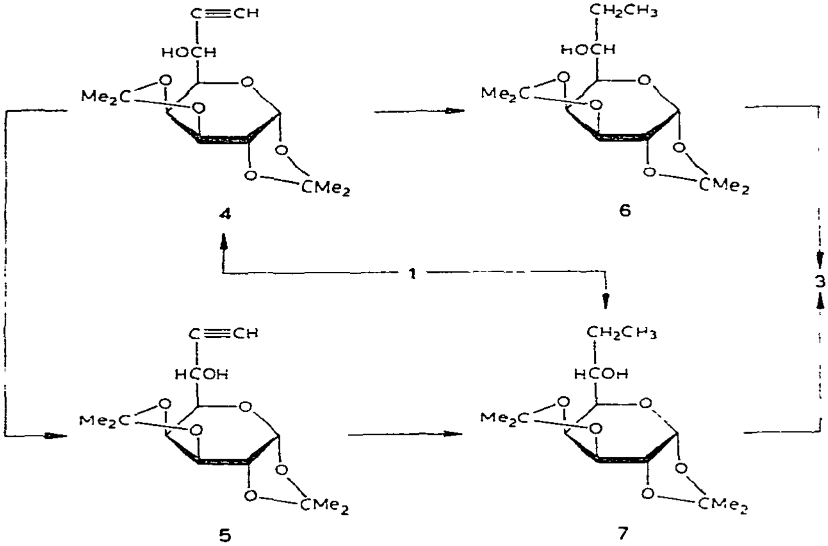

The L-*glycero*-ethylcarbinol **7** was also prepared by solvolysis of the 6-tosylate of the D-*glycero*-ethynylcarbinol **4** followed by catalytic hydrogenation of the product (**5**) (or of its 6-acetate followed by methanolysis). The moderate yield (56%) of the 6-tosylate of **4** obtained by Horton and co-workers[4] may have been due to partial hydrolysis.

The carbinol **4** was resistant to oxidation by chromium trioxide–pyridine–acetic acid, ruthenium tetraoxide, Jones' or Fetizon's reagents, or methyl sulphoxide–acetic anhydride[7]. The phenylethynyl and propargyl derivatives **2** ($R = C{\equiv}CPh$ or $CH_2C{\equiv}CH$) were similarly resistant to oxidation. The epimeric mixture **4**+**5** was transformed into the acetylenic ketone **3** ($R = C{\equiv}CH$) by treatment with very active manganese dioxide[8]. In contrast to the rapid oxidations (20–75 min) described by Buchanan *et al.* for other sugar hydroxyacetylenes[9], 26 h were required for complete transformation of **4**+**5**.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Kofler hot-stage apparatus. Optical rotations were determined with a Karl Zeiss Polarimeter for ~1% solutions in $CHCl_3$.

I.r. spectra were recorded for solutions in $CHCl_3$, or for KBr discs, with a Perkin–Elmer 257 spectrophotometer. N.m.r. spectra were recorded for solutions in CCl_4 or $CDCl_3$ (internal Me_4Si) at 60 or 90 MHz, with Perkin–Elmer R-24A or R-32 spectrometers. Analyses were determined by Sección de Semimicroanálisis del Instituto de Química Orgánica de Barcelona. T.l.c. was performed on Camag DSF-5 Silica gel plates with hexane–ethyl acetate (1:1) and detection with phosphomolybdic acid or 0.05% aqueous permanganate. All evaporations were carried out at $<40°/$ ~ 12 mmHg. Tetrahydrofuran was distilled over sodium and stored over 4 Å molecular sieve (Merck). The chromium trioxide–pyridine–acetic acid reagent was prepared[6] by slow addition of chromium trioxide (40 g) to a stirred solution of pyridine (32 g) in acetic acid (150 ml) at 40°, and dilution with acetic acid (to 250 ml). Active manganese dioxide was prepared[8] from manganese dichloride and potassium permanganate. 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**1**) was obtained as described by Horton and co-workers[10].

*Additions of organomagnesium reagents to 1,2:3,4-di-*O*-isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose* (**1**). — (*a*) A solution of phenylacetylene (6.4 ml) in tetrahydrofuran (10 ml) was added dropwise to a stirred solution of ethylmagnesium bromide (from 1.5 g of magnesium) in tetrahydrofuran (60 ml) at ~0° under nitrogen. The solution was stirred at room temperature for 1.5 h, and a solution of **1** (5 g) in tetrahydrofuran (20 ml) was added. The mixture was stirred for 3 h at room temperature, the solvent was partially evaporated, ethyl ether was added, and the mixture was washed with water and dried. Evaporation of the solvent and elution of the residue (3.5 g) from silica gel gave a yellow syrup of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-phenyl-α-D-*galacto*-oct-7-ynopyranose (**2**, R = C≡CPh), $[\alpha]_D^{20}$ $-30°$, R_F 0.67 (Found: C, 66.5; H, 6.7. $C_{20}H_{24}O_6$ calc.: C, 66.55; H, 6.7%).

(*b*) A solution of **1** (5 g) in tetrahydrofuran (10 ml) was added dropwise to a stirred solution of propargylmagnesium bromide (from 0.72 g of magnesium, 3.75 g of propargyl bromide, and 0.03 g of $HgCl_2$) in ethyl ether (20 ml) at ~0° under nitrogen. The mixture was stirred for 0.5 h, 10% ammonium chloride was added, the mixture was extracted with ethyl ether, and the combined extracts were dried and concentrated. P.l.c. of the residue (3.56 g) gave 7,8,9-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-non-8-ynopyranose (**2**, R = $CH_2C{\equiv}CH$, 3.56 g) as a syrup, R_F 0.52; ν_{max}^{KBr} 3490 (OH), 3280 (C≡H), and 2120 cm^{-1} (C≡C) (Found: C, 60.5; H, 7.4. $C_{15}H_{22}O_6$ calc.: C, 60.4; H, 7.4%).

(*c*) A solution of **1** (3 g) in tetrahydrofuran (25 ml) was added to a stirred solution of ethylmagnesium bromide (from 0.36 g of magnesium) in tetrahydrofuran (15 ml) under nitrogen at ~0°. The solution was stirred for 5 h at room temperature and then for 1.5 h at 55°. 10% Aqueous ammonium chloride was added, the mixture was extracted with ethyl ether, and the combined extracts were dried and concentrated. P.l.c. of the residue (2.33 g) gave syrupy 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**, R = H) and a mixture (0.96 g) of isomeric ethyl derivatives **2** (R = Et). Crystallization from ethyl ether–hexane afforded white prisms of 7,8-dideoxy-1,2:3,4-

di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-octopyranose (7), m.p. 80–82°, $[\alpha]_D -50°$, R_F 0.45 (Found: C, 58.3; H, 8.4. $C_{14}H_{24}O_6$ calc.: C, 58.3; H, 8.4%).

*Conversion of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-*D-glycero-α-D-galacto-*oct-7-ynopyranose* (**4**) *into the* L-glycero *isomer* **5**. — A mixture of **4** (0.63 g), toluene-*p*-sulphonyl chloride (0.58 g), and pyridine (10 ml) was stirred for 64 h at room temperature. Water (0.5 ml) was added, the mixture was stirred for 1 h, ice-water (100 ml) was added, and stirring was continued for 3 h. The mixture was extracted with ethyl ether, the combined extracts were washed with 2M HCl and saturated aqueous sodium hydrogen carbonate, dried, and concentrated. The syrupy residue (0.45 g) was crystallized from ethyl ether–hexane to give **5**, m.p. 135–136°, R_F 0.4; lit.[4] m.p. 136–137°.

Conventional treatment of **5** with acetic anhydride–pyridine gave the 6-acetate, m.p. 123–124° (from ethanol); lit.[4] m.p. 122°.

Hydrogenation of ethynyl derivatives. — (*a*) A mixture of **4** (0.4 g), ethyl acetate (20 ml), and 10% palladium-on-charcoal (0.4 g) was shaken under hydrogen at room temperature and atmospheric pressure for 1 h, and then filtered through Celite. Concentration of the solvent and crystallization of the resulting syrup from ethyl ether–hexane afforded white prisms (0.18 g) of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-octopyranose (**6**), m.p. 70–71°, $[\alpha]_D^{20}$ −81°, R_F 0.45 (Found: C, 58.1; H, 8.25. $C_{14}H_{24}O_6$ calc.: C, 58.3; H, 8.4%).

(*b*) A mixture of the 6-acetate of **5** (0.3 g), 10% palladium-on-charcoal (0.25 g), and ethyl acetate was shaken under hydrogen at room temperature and atmospheric pressure for 0.5 h, and then filtered through Celite and concentrated. A solution of the syrupy residue (0.30 g) in 0.2M methanolic sodium methoxide (2 ml) in methanol (5 ml) was heated at 35° for 12 h. Water was then added, and the solution was stirred with Amberlite IR-120(H^+) resin, filtered, and concentrated. Crystallization of the residue from ethyl ether–hexane gave **7** as white prisms (0.20 g), m.p. and mixture m.p. 80–82°.

Oxidations. — (*a*) Chromium trioxide–pyridine–acetic acid reagent (4 ml) was added dropwise to a stirred solution of **7** (0.54 g) in acetic acid (5 ml) at 0°. Stirring was continued for 0.5 h at room temperature, water (50 ml) was added, and the mixture was extracted with ethyl ether (3 × 20 ml). The combined extracts were washed with 2M hydrochloric acid (3 × 20 ml), aqueous sodium hydrogen carbonate, and water, dried, and concentrated. Crystallization of the residue from ethyl ether–hexane (1:1) gave white prisms of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octopyranos-6-ulose (**3**, R = Et), m.p. 70–72°, $[\alpha]_D^{20}$ −136°, R_F 0.61, ν_{max}^{KBr} 1718 cm^{-1} (C=O) (Found: C, 58.69; H, 8.1. $C_{14}H_{22}O_6$ calc.: C, 58.73; H, 7.74%).

A product identical with **3** (R = Et) was obtained from **6** by reaction for 6 h using the above procedure.

(*b*) A mixture of the epimers **4**+**5** (0.3 g), active manganese dioxide (6 g), and dichloromethane (20 ml) was stirred at room temperature for 26 h, and then filtered through Celite and concentrated. Crystallization of the resulting syrup (0.23 g) from ether–hexane gave small prisms of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-

TABLE I

N.M.R. DATA

Compound	*Chemical shifts and multiplicities*								
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*CMe_2*	*OH*	*Other*
2, R = $C\equiv CPh$	4.37d	5.65dd	5.17dd	5.85dd	6.1dd	5.35d	8.45, 8.5, 8.6	6.5	2.7 (Ph)
2, R = $CH_2C\equiv CH$	4.5d	5.7dd	5.45m	5.65m	6.15dd	6.05m	8.45, 8.55, 8.65	5.5	7.4m, 8.0t ($CH_2C\equiv CH$)
3, R = $C\equiv CH$	4.31d	– – – – – – 5.26sb, 5.7sb – – – – – –				—	8.46, 8.55, 8.65	—	6.55 ($C\equiv CH$)
3, R = Et	4.35d	5.65dd	5.45sb	5.81sb	5.45sb	—	8.5, 8.64, 8.67	—	7.35dq, 8.97t (Et)
6	4.45d	5.7dd	5.37dd	5.45dd	6.3m	6.45dd	8.5, 8.53, 8.65	7.45	8.2–8.5m, 9.0t (Et)
7	4.4d	5.65dd	5.37dd	5.72dd	6.18dd	6.4dt	8.5, 8.53, 8.65	7.0	8.2–8.5m, 9.0t (Et)

Compound	*Coupling constants (Hz)*							
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{7,9}$
2, R = $C\equiv CPh$	5.2	1.8	7.1	1.6	6.3	—	—	—
2, R = $CH_2C\equiv CH$	5.2	2.0		1.5	6.0	4.8	—	2.6
3, R = $C\equiv CH$	5.0				—	—	—	—
3, R = Et	5.1	1.9		1.4	—	—	7.8	—
6	4.9	2.0	7.9	1.35	3.6		6.8	—
7	4.9	2.2	8.0	1.6	6.0	1.6	6.8	—

D-*galacto*-oct-7-ynopyranos-6-ulose (3, R = C≡CH), m.p. 123.5–125°, $[\alpha]_D^{27}$ −97°, R_F 0.76; $\nu_{max}^{CHCl_3}$ 3290 (C≡CH). 2100 (C≡C), and 1680 cm^{-1} (C=O) (Found: C, 59.65; H, 6.55. $C_{14}H_{18}O_6$ calc.: C, 59.57; H, 6.43%).

The n.m.r. data for these compounds are given in Table I, and those not included are in agreement with published data[4].

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