Use of a Grignard reagent to lengthen a triose carbon chain

D. J. WALTON

Department of Biochemistry, Queen's University, Kingston, Ontario

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The addition of vinylmagnesium chloride to 2,3-*O*-isopropylidene-D-glyceraldehyde (I) gave a mixture of the epimeric pentene derivatives II and V, which were separated by preparative gas–liquid chromatography. Ozonolysis and subsequent deketalization of the individual epimers gave D-threose and D-erythrose, respectively, in yields of ca. 40%. This represents a method of lengthening an aldose carbon chain by one carbon atom.

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INTRODUCTION

The addition of Grignard reagents to *aldehydo* and *keto* sugars is an important method of increasing the length of glycose carbon chains. The synthesis of 2-deoxy-D-ribose by Hough (1), using allylmagnesium bromide, is a good example.

In 1961 Overend and his co-workers (2) used vinylmagnesium bromide to introduce an aldehydic function (*C*-formyl group) into a glycoside molecule. The addition of the Grignard reagent to the 2-*keto* group of a methyl pentopyranosidulose gave a 2-*C*-vinyl derivative of methyl arabinopyranoside, which, on ozonolysis, yielded a 2-*C*-formyl compound. This approach was used in the syntheses of the branched-chain sugars L-hamamelose (3) and streptose (4).

This report shows how vinylation of an *aldehydo* sugar can be used to lengthen an aldose chain by one carbon atom.

While this investigation was in progress, Horton and Tronchet (5) reported the lengthening of an arabinose carbon chain by the addition of ethynylmagnesium bromide to 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose. Lindlar reduction of the triple bond, followed by ozonolysis of the resulting vinyl group, gave derivatives of glucose and mannose.

By using a vinylmagnesium halide rather than an ethynylmagnesium halide for this type of synthesis, the Lindlar reduction step is avoided.

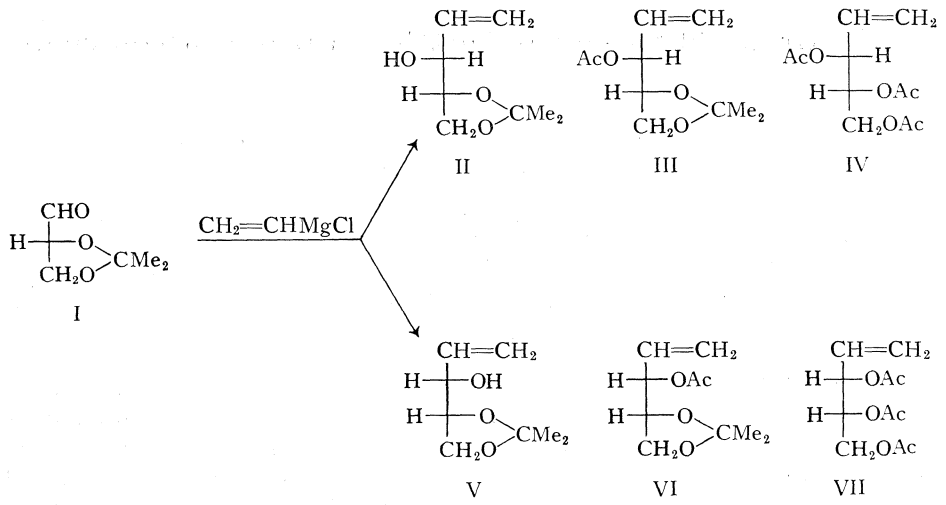
RESULTS

The reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde (I) with an excess of vinylmagnesium chloride gave, in a 65% yield, a product which was separated by preparative gas–liquid chromatography into two components. The fast-moving component (A) was identified as 1,2-*O*-isopropylidene-4-pentene-D-*threo*-1,2,3-triol (II), since ozonolysis, followed by acid hydrolysis, gave D-threose, characterized as the 2,5-dichlorophenylhydrazone. The slow-moving component (B) was likewise shown to be 1,2-*O*-isopropylidene-4-pentene-L-*erythro*-1,2,3-triol (V).

Catalytic hydrogenation and infrared spectroscopy indicated the presence of a *C*-vinyl group in compounds II and V. The product of acetylation of the mixture of II and V was shown by similar methods to be an acetate containing a *C*-vinyl group.

This information, together with the results of the elemental analyses, indicated that compounds II and V were probably 1,2-*O*-isopropylidene-4-pentene-1,2,3-triols which had resulted from the addition of the Grignard reagent to the *aldehydo* group of compound I. Acetylation had yielded the mixed 3-acetates III and VI. Proof of the structures of compounds II and V was obtained by the reaction sequences described next.

Component A was treated with ozone, followed by hydrogen in the presence of Adams' catalyst. Subsequent deketalization with dilute sulfuric acid gave D-threose, in a 40% yield from component A. The D-threose was identified by chromatography and by conversion into its 2,5-dichlorophenylhydrazone. Although the small weight of the latter allowed only a single crystallization, its infrared spectrum and specific rotation were satisfactory. The



melting point of the derivative, which was 6° below the reported value (6) for the pure compound, was close to that normally obtained after a single crystallization (6, and author's observation). Since D-threose was obtained from component A, the latter was assigned the D-*threo* configuration, and was 1,2-*O*-isopropylidene-4-pentene-D-*threo*-1,2,3-triol (II). Similar treatment of component B gave, in a 45% yield, pure D-erythrose, easily convertible into its 2,5-dichlorophenylhydrazone. Component B was therefore 1,2-*O*-isopropylidene-4-pentene-L-*erythro*-1,2,3-triol (V).

The mixed epimeric 4-pentene-1,2,3-triol 1,2,3-triacetates IV and VII were prepared from compounds II and V by deketalization and subsequent acetylation. The equivalent DL-*erythro* compound had been prepared by Raphael (7) by an alternative synthesis.

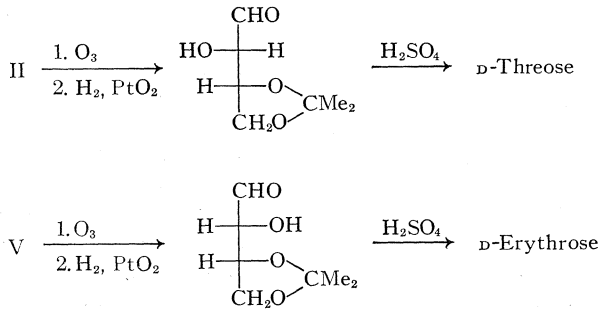
The type of synthesis described here is an alternative to the established procedures for the lengthening of aldose chains. Further work is necessary to determine the general applicability of the method. This will most probably depend on the availability of (*a*) hydroxyl-protected *aldehydo* sugars, and (*b*) procedures for separating the epimers formed in the Grignard reaction, or the compounds derived therefrom.

EXPERIMENTAL

Methods

Paper chromatography was performed by the descending technique on Whatman No. 1 paper with butan-1-ol–pyridine–water (5:3:2 v/v/v) (solvent system *a*). Glycoses were located with the alkaline silver nitrate spray (8).

Thin-layer chromatography (t.l.c.) of the glycoses was carried out on plates coated with microcrystalline cellulose (Avicel SF, purchased from American Viscose, Marcus Hook, Pennsylvania) as described by Wolfrom *et al.* (9). The plates were developed by four irrigations with water-saturated butanone (solvent system *b*), and were then sprayed with the alkaline silver nitrate reagent (8). The rates of movement on paper and on cellulose



thin-layer chromatograms are quoted relative to that of D-ribose (R_{Rib} = 1.0).

Thin-layer chromatography of other compounds was performed on plates that were coated with silica gel G (Merck, Darmstadt, Germany) and which were developed with either acetone (solvent system *c*) or benzene – ethyl acetate (4:1 v/v) (solvent system *d*). Compounds were located with the alkaline permanganate spray (10).

Analytical gas–liquid partition chromatography was performed on an Aerograph 600 instrument fitted with a flame ionization detector and an F & M 240 temperature programmer. The coiled copper column (152 × 0.155 cm internal diameter) was packed with 10% neopentyl glycol sebacate polyester on 80–100 mesh Chromosorb W. The hydrogen flow rate was 40 ml/min, and the carrier gas (nitrogen) flowed at 60 ml/min. Chloroform solutions (ca. 1% w/v) were applied to the column in the form of 1 μl injections. For chromatography of *C*-vinyl compounds the column temperature was 100° at the time of injection, rising to 205° during 14.70 min. The retention times of these compounds are quoted relative to 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (T_I = 1.0; retention time 14.24 min).

An Aerograph 1520 instrument was used for preparative gas–liquid chromatography. It was equipped with a thermal conductivity detector and a coiled copper column (600 × 0.30 cm internal diameter) containing the same packing as the analytical column, and kept at 135°. The flow rate of the carrier gas (helium) was 210 ml/min (measured at the column outlet). Samples were collected in two glass tubes which were changed manually.

Optical rotations were measured at 22°. Infrared spectra were recorded with a Perkin–Elmer Infracord spectrophotometer. Melting points were determined on a Fisher block, and are uncorrected. Acetic anhydride was evaporated at diminished pressure on a water bath at 55°. Solvents were evaporated with the water bath at 40°.

Materials

Reference D-erythrose was prepared by lead tetraacetate oxidation of D-glucose by the method of Perlin (11). Paper chromatography (system *a*) gave a single spot, R_{Rib} 1.15. Cellulose t.l.c. (system *b*) showed a single spot, R_{Rib} 2.51, with a tail extending to the origin. The standard used for the reducing power determinations was dried to constant weight at 50° *in vacuo* over phosphorus pentoxide.

Reference D-threose was prepared by a similar oxidation of D-galactose (12). On paper chromatography (system *a*) it had R_{Rib} 1.24. An impurity, R_{Rib} 0.92, was also present. Cellulose t.l.c. (system *b*) showed a single spot, R_{Rib} 2.71, with a tail extending to the origin.

2,3-*O*-Isopropylidene-D-glyceraldehyde (I) was prepared by the method of Baer and Fisher (13), and had b.p. 38–43° at 7 mm (lit. (13) b.p. 35–42° at 8–11 mm).

Vinylmagnesium chloride was obtained from Peninsular ChemResearch, Gainesville, Florida, in cans which contained 1 mole of reagent dissolved in ca. 500 ml of tetrahydrofuran. In the Grignard reaction described, the whole contents of a can were quickly emptied into the reaction flask, which was gassed with nitrogen. To minimize contact with air, the exact volume of the reagent solution was not measured.

1,2-O-Isopropylidene-4-pentene-D-threo (and L-erythro)-1,2,3-triol (II and V)

A solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (I, 17.0 g, 0.131 mole) in 38 ml of dry tetrahydrofuran was added, over 30 min, to a solution (ca. 500 ml) of vinylmagnesium chloride (1 mole) in tetrahydrofuran, which was vigorously stirred under dry nitrogen. During the addition the temperature rose from 21 to 60°. The solution was heated under reflux for 3.5 h, and was then cooled to 20° with an ice bath. Ether[1] (60 ml) was added, followed by saturated ammonium chloride solution (200 ml), the temperature of the mixture being kept below 30° with an ice bath. After half of the ammonium chloride solution had been added, the mixture was a thick paste, but the magnesium salts coagulated and settled after complete addition. The resulting clear supernatant solution was decanted, and the salts were washed with ether (4 × 100 ml) by alternate stirring and decantation. The main solution and the ethereal extracts were combined, stirred with anhydrous potassium carbonate (150 g) for 30 min, and filtered. Removal of the solvents and distillation gave 13.4 g (65%) of the product, which was a colorless, mobile liquid, b.p. 41–42° at 0.1 mm, $[\alpha]_D$ +7° (*c*, 3.2 in chloroform). Silica gel t.l.c. (system *d*) gave a single spot, R_f 0.18. Infrared spectrum (liquid film): 3 350 (OH), 3 040 (alkene CH), 1 845 (vinyl CH overtone), 1 640 (vinyl C=C), and 920 cm^{-1} (vinyl CH).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.52; H, 8.73.

Analytical gas–liquid chromatography gave two peaks: component A, T_I 0.242, and component B, T_I 0.283, in a ratio of areas of 1:1.51, respectively.

A solution of the mixture of compounds II and V (290.3 mg) in 25 ml of ethanol at 22° was stirred under hydrogen (atmospheric pressure) in the presence of platinum oxide (15.0 mg). The absorption of hydrogen, complete in 10 min, was 42.7 ml (96.5% of theory). The reaction product showed a complete absence of the infrared absorption frequencies attributed to the vinyl group of compounds II and V.

1,2-O-Isopropylidene-4-pentene-D-threo (and L-erythro)-1,2,3-triol 3-Acetate (III and VI)

The mixture of compounds II and V (2.0 g) was heated under reflux for 1.5 h with acetic anhydride (40 ml) and anhydrous sodium acetate (2 g). The reaction mixture was cooled and most of the acetic anhydride was removed by evaporation. The

[1]Ether prevented solidification of the reaction mixture during the addition of the ammonium chloride solution.

residue was stirred with 100 ml of water, the resulting acetic acid was neutralized with solid potassium bicarbonate, and the aqueous solution was extracted with chloroform. The chloroform extract was washed with dilute potassium bicarbonate solution and then with water, dried with anhydrous sodium sulfate, and concentrated. Distillation gave 1.9 g (75%) of a colorless mobile liquid, b.p. 55° at 0.2 mm, $[\alpha]_D$ 0° (*c*, 4.1 in chloroform). Silica gel t.l.c. (system *d*) gave a main spot, R_f 0.40, with a minor spot, R_f 0.74; gas–liquid chromatography showed a single peak, T_I 0.316. Infrared spectrum (liquid film): no peak at 3 000 – 4 000 cm^{-1} (OH absent); peaks at 1 730 (CO of OAc), 1 630 (vinyl C=C), and 1 220 cm^{-1} (OAc).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.05. Found: C, 60.11; H, 8.07.

On catalytic hydrogenation with PtO_2, 98.6% of the theoretical volume of hydrogen was absorbed.

Preparative Gas–Liquid Chromatography of Compounds II and V

One hundred and seventy-five samples (each 6 μl) of a chloroform solution (33.3% w/v) of the Grignard reaction product (II and V) were injected into the preparative gas–liquid chromatographic column. Two completely separate peaks were recorded at retention times of 9.83 (component A) and 11.28 min (component B). Pure samples of component A (65 mg) and component B (162 mg) were obtained as colorless liquids in separate collection vessels. The total recovery was 63%. Component A had values of $[\alpha]_D$ +9° (*c*, 2.9 in chloroform), R_f 0.18 (single spot, silica gel t.l.c., system *d*), and T_I 0.242 (single peak, gas–liquid partition chromatography). Component B had $[\alpha]_D$ +6° (*c*, 2.2 in chloroform), R_f 0.18 (single spot, silica gel t.l.c., system *d*), and T_I 0.283 (single peak, gas–liquid partition chromatography). The infrared spectra (liquid films) of the two components differed in the 1 200 – 1 100 cm^{-1} region. Here, each component gave an identical peak at 1 144 cm^{-1}, but in the spectrum of component A this peak had a pronounced shoulder at 1 130 cm^{-1}.

D-*Threose from Component A*

Ozonolysis

A slow stream of ozonized oxygen was passed through a solution of component A (50 mg) in ethyl acetate (15 ml) for 20 min at 0°, and then for 20 min at room temperature. The ozonide was hydrogenated for 15 min at atmospheric pressure in the presence of platinum oxide (7 mg). The resulting solution, which smelled strongly of formaldehyde, was filtered and concentrated to dryness.

Cleavage of the Isopropylidene Group To Give D-*Threose*

The main part of the ozonolysis product was heated on the steam bath for 1 h with 5 ml of 0.2 *N* sulfuric acid. The solution was cooled, neutralized by the addition of Dowex 1 (carbonate) resin, and then diluted to 250 ml with water. Estimation of the reducing power of the solution by the Nelson method (14), with D-erythrose as a standard, gave a value of 61 μg/ml. Hence the total weight of tetrose was 15.3 mg (40% from component A). The solution was concentrated to a syrup for chromatographic examination; paper chromatography (system *a*) gave a single spot, R_{Rib} 1.22, corresponding to D-threose; cellulose t.l.c. (system *b*) showed a main component, R_{Rib} 2.71 (with a tail extending to the origin), corresponding to D-threose, together with a minor component, R_{Rib} 0.55.

D-*Threose 2,5-Dichlorophenylhydrazone*

The tetrose-containing syrup was kept overnight *in vacuo* over phosphorus pentoxide, and was then dissolved in 0.5 ml of methanol. The 2,5-dichlorophenylhydrazone was prepared by the method of Perlin (6), using 15 mg of 2,5-dichlorophenylhydrazine. The crystallization solvent, which differed from that described by Perlin (6), consisted of ethyl acetate (0.07 ml), benzene (0.07 ml), and *n*-hexane (0.07 ml). No seeding was necessary. The product (11 mg) had m.p. 101–104° and $[\alpha]_D$ +12° (7 min) → +2° (3 h) (*c*, 1.8 in methanol) (lit. (6) $[\alpha]_D$ +14° (in methanol), m.p. 103–106° after a single crystallization, and m.p. 108–110° for the pure compound). The infrared spectrum (Nujol mull) was identical in all significant absorptions with that of authentic material. The peaks at 1 044, 1 012, 892, and 856 cm^{-1} were characteristic of the threose derivative. The behavior on silica gel t.l.c. (system *c*) was identical with that of an authentic sample. A single spot, R_f 0.81, was detected with the alkaline permanganate spray.

D-*Erythrose from Component B*

Ozonolysis and ketal cleavage of component B (140 mg) by the above methods gave D-erythrose (48 mg, 45% from component B), $[\alpha]_D$ −34° (*c*, 2.4 in water) (based on the reducing power) (lit. $[\alpha]_D$ −41° (11), −32° (11), and −30° (15)). Paper chromatography (system *a*) revealed a single spot, R_{Rib} 1.15, corresponding to D-erythrose. Cellulose t.l.c. (system *b*) gave a single spot, R_{Rib} 2.49, corresponding to D-erythrose, with a tail extending to the origin.

D-*Erythrose 2,5-Dichlorophenylhydrazone*

This compound was prepared by Perlin's method (11). The product was crystallized twice from ethyl acetate – benzene (1:1 v/v) to give the pure derivative (20 mg), m.p. 111–113°, $[\alpha]_D$ −12° (16 min) → −8° (6 h) → +2° (52 h) (*c*, 3.3 in methanol) (lit. (11) $[\alpha]_D$ −12.5° (in methanol) and m.p. 110–112°). The infrared spectrum (Nujol mull) was identical with that of the authentic compound. Peaks characteristic of this compound were present at 1 052, 1 000, 882, 860, and 842 cm^{-1}. Silica gel t.l.c. gave a single spot, R_f 0.85, corresponding to the authentic compound.

*4-Pentene-*D-*threo (and* L-*erythro)-1,2,3-triol 1,2,3-Triacetate (IV and VII)*

The mixture of compounds II and V (3.0 g) obtained from the Grignard reaction was heated under reflux for 1.5 h with 70% aqueous acetic acid (100 ml). The solution was concentrated to dryness and the resulting syrup was dissolved in water (30 ml). Brown substances were removed from the

aqueous solution by extraction with chloroform (2 × 20 ml). Concentration of the aqueous solution gave a syrup, which was treated with acetic anhydride (30 ml) and anhydrous sodium acetate (1.5 g) as described for the previous acetylations. The final product was a colorless mobile liquid (3.1 g, 67%), b.p. 80–82° at 0.08 mm, $[\alpha]_D$ +16° (*c*, 8.0 in chloroform). Raphael (7) reported that 4-pentene-DL-*erythro*-1,2,3-triol 1,2,3-triacetate had b.p. 86–88° at 0.2 mm. Silica gel t.l.c. (system *d*) gave a single spot, R_f 0.35. Infrared spectrum (liquid film): no OH peak; peaks at 3 040 (alkene CH), 1 730 (CO of OAc), 1 630 (vinyl C=C), and 1 212 cm^{-1} (OAc). The hydrogen absorption was 99% of the theoretical (atmospheric pressure, PtO_2).

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.28; H, 6.48.

Two peaks were recorded by gas–liquid chromatography, having T_I 0.655 and T_I 0.697 in a ratio of areas of 1.4:1.

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