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# UNSATURATED SUGARS I. DECARBOXYLATIVE ELIMINATION OF METHYL 2,3-DI-*O*-BENZYL-α-D-GLUCOPYRANOSIDURONIC ACID TO METHYL 2,3-DI-*O*-BENZYL-4-DEOXY-β-L-*threo*-PENT-4-ENOPYRANOSIDE*

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ABSTRACT

Decarboxylative elimination of methyl 2,3-di-*O*-benzyl-α-D-glucopyranosiduronic acid (**1**) with *N*,*N*-dimethylformamide dineopentyl acetal in *N*,*N*-dimethylformamide gave methyl 2,3-di-*O*-benzyl-4-deoxy-β-L-*threo*-pent-4-enopyranoside (**3**). Debenzylation of **3** was effected with sodium in liquid ammonia to give methyl 4-deoxy-β-L-*threo*-pent-4-enopyranoside (**4**). Hydrogenation of **3** catalyzed by palladium-on-barium sulfate afforded methyl 2,3-di-*O*-benzyl-4-deoxy-β-L-*threo*-pentopyranoside (**5**), whereas hydrogenation of **3** over palladium-on-carbon gave methyl 4-deoxy-β-L-*threo*-pentopyranoside (**6**). An improved preparation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside is also described.

## INTRODUCTION

A recent report from this laboratory described the facile conversion of 2′-deoxynucleoside uronic (5′-carboxylic)† acids into 2,3-dihydrofuryl derivatives of pyrimidines and purines *via* a single-step "decarboxylative elimination" reaction[1]. The reaction, employing *N*,*N*-dimethylformamide dineopentyl acetal in *N*,*N*-dimethylformamide, has now been extended to methyl 2,3-di-*O*-benzyl-α-D-glucopyranosiduronic acid[2] (**1**) to afford the corresponding unsaturated sugar, methyl 2,3-di-*O*-benzyl-4-deoxy-β-L-*threo*-pent-4-enopyranoside (**3**), in high yield.

The reaction sequence constitutes a convenient synthetic approach to hitherto undescribed 4,5-unsaturated pentopyranosides, as well as a potentially useful degradation of C-6 from a pyranoside.

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†See Ref. 1 for the basis of this terminology.

RESULTS AND DISCUSSION

Treatment of methyl 2,3-di-*O*-benzyl-α-D-glucopyranosiduronic acid* (**1**) with *N,N*-dimethylformamide dineopentyl acetal in *N,N*-dimethylformamide for 3 h at 50° gave a syrupy product, formulated as methyl 2,3-di-*O*-benzyl-4-deoxy-β-L-*threo*-pent-4-enopyranoside (**3**), in 79% yield. The n.m.r. spectrum of **3** (*cf.* Fig. 1) showed, *inter alia*, two vinyl-proton resonances whose chemical shifts and coupling constants were consistent with a vinyl ether (glycal) structure[4]. The entire spectrum was amenable to first-order analysis, and the assignments were verified by spin-decoupling experiments. Further evidence for the assigned structure (**3**) was derived from the i.r. spectrum, which showed a sharp absorption band at 1655 $cm^{-1}$ indicative of a vinyl ether[5].

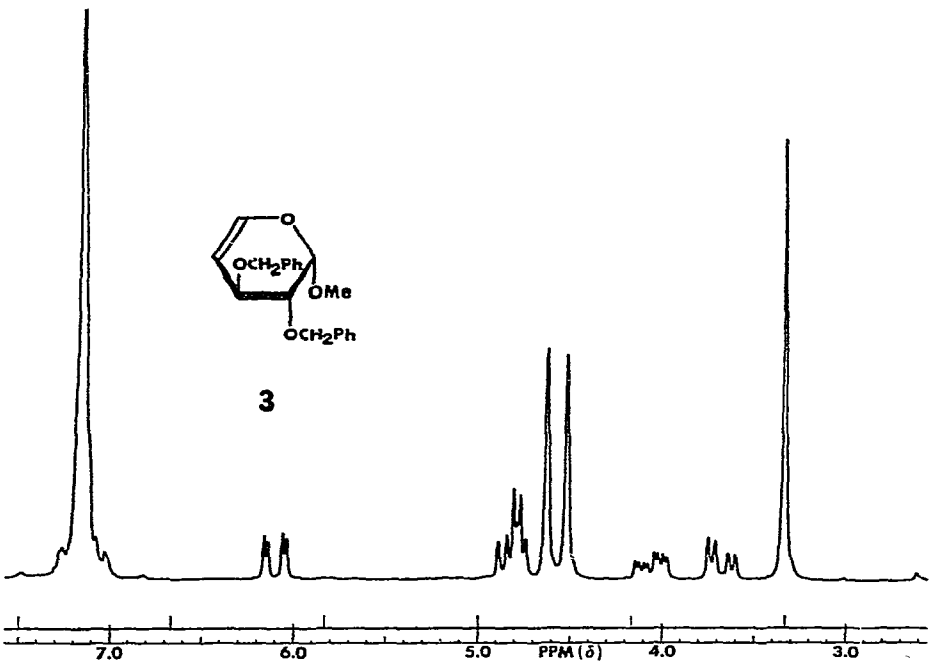
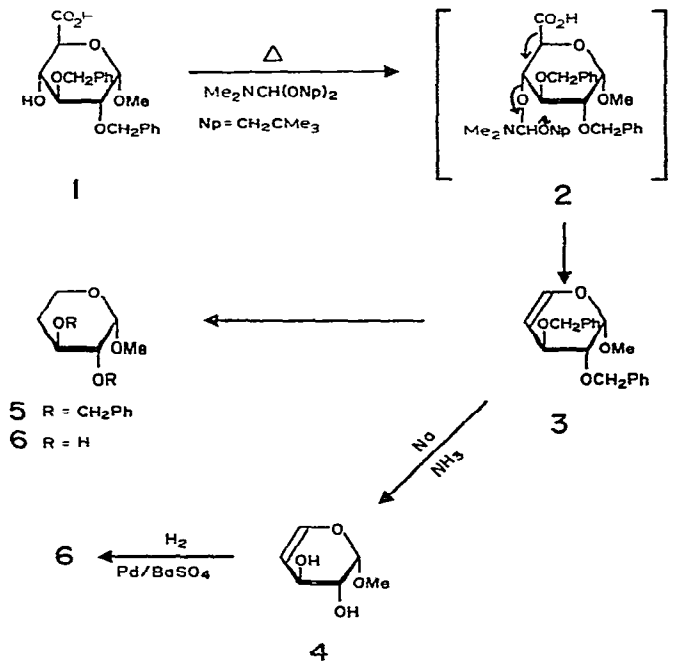



Fig. 1. The 60-MHz n.m.r. spectrum of methyl 2,3-di-*O*-benzyl-4-deoxy-β-L-*threo*-pent-4-enopyranoside (**3**) in acetone-$d_6$.

Selective removal of the benzyl groups in **3** was effected by sodium in liquid ammonia to give a new unsaturated derivative (**4**), in 83% yield, as a syrup that was readily purified by sublimation *in vacuo* onto a cold finger. The colorless, crystalline compound melted below room temperature to a viscous, colorless oil. The n.m.r. and i.r. spectra of **4** were in complete accord with the proposed structure.

*The present work includes a more-convenient preparation[3] of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, an intermediate in the synthesis of **1** (see Refs. 8 and 9).

Catalytic hydrogenation of the double bond in **3** over palladium-on-barium sulfate gave a syrupy product, methyl 2,3-di-*O*-benzyl-4-deoxy-*β*-L-*threo*-pentopyranoside (**5**), in 83% yield. Both the n.m.r. and i.r. spectra were characterized by the absence of the vinyl ether absorption. By contrast, the presence of the benzyl groups was readily ascertained. Hydrogenolysis of the benzyl groups in **5** with palladium-on-carbon afforded methyl 4-deoxy-*β*-L-*threo*-pentopyranoside (**6**) as a crystalline solid in 76% yield. Alternatively, debenzylation and saturation of the double bond in **3** were readily accomplished in one step with palladium-on-carbon to give **6** directly in 84% yield. To complete the study, hydrogenation of **4** was performed with palladium-on-barium sulfate to give the crystalline dihydro derivative **6** in 67% yield.




Thus far, decarboxylative elimination has been applied to nucleoside uronic and glycopyranosiduronic acids in which the carboxyl group at C-4 (C-5) and the adjacent hydroxyl group are *trans* disposed. Studies are currently in progress to determine both the specific geometrical requirements of the glycosiduronic acid and the scope of the reaction.

Attempts to apply the decarboxylative elimination transformation to (unprotected) methyl α-D-glucopyranosiduronic acid[6] were unsuccessful. Presumably, preferential generation of a 3,4-dimethylaminomethylene cyclic acetal in the latter case precludes the intermediate formation of the requisite mixed acetal (**2**) that comprises the effective leaving group.

EXPERIMENTAL

*General methods.* — Evaporations were conducted in a Büchi rotary evaporator *in vacuo* at a bath temperature below 40° unless stated otherwise. Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are uncorrected. Samples for analysis were dried at $10^{-3}$ torr over $P_2O_5$ for 8 h at room temperature. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois and M-H-W Laboratories, Garden City, Michigan. Thin-layer chromatography (t.l.c.) was performed on 6 × 2-cm, precoated, silica gel F-254 aluminum foils (Merck, Darmstadt, Germany) in solvents $S_1$ (19:1 dichloromethane–methanol) and $S_2$ (9:1 dichloromethane–methanol). Preparative t.l.c. was performed on 2-mm thick, 40 × 20 cm loose (non-adhering) layers of silica gel (70–325 Mesh ASTM, Merck, Darmstadt, Germany) containing 1% of fluorescent indicator (Leuchtpigment ZS Super, Riedel-De Haën, Hannover, Germany). Non-specific detection of products was accomplished with iodine vapor; u.v.-absorbing compounds were detected with a Mineralight lamp; unsaturated compounds were detected with potassium permanganate spray. Paper chromatography in solvent $S_3$ (7:1:2 isopropyl alcohol–concentrated ammonium hydroxide–water) was performed by the descending method on Whatman 3 MM paper; detection was by silver nitrate–sodium hydroxide[7]. Optical rotations were determined with a Perkin–Elmer Model 141 polarimeter. I.r. spectra were measured in a Perkin–Elmer Model 21 spectrometer. N.m.r. spectra were obtained with a Varian A-60A spectrometer; tetramethylsilane was used as internal standard with acetone-$d_6$ as solvent. *N,N*-Dimethylformamide was dried with Linde Molecular Sieves, 4A. *N,N*-Dimethylformamide dineopentyl acetal was obtained from Aldrich, Milwaukee, Wisconsin.

*Improved preparation of methyl 4,6-O-benzylidene-α-D-glucopyranoside.* — A solution of powdered, anhydrous methyl α-D-glucopyranoside (38.0 g, 0.20 mole), ethyl orthoformate (63 ml, 0.38 mole), freshly distilled benzaldehyde (61 ml, 0.60 mole), and anhydrous hydrogen chloride in *N,N*-dimethylformamide (39 ml of 2.99M hydrogen chloride in *N,N*-dimethylformamide, 0.12 mole) in *N,N*-dimethylformamide (400 ml) was stirred at room temperature for 3 days. The acid was neutralized by stirring with excess powdered sodium carbonate. The salts were removed by filtration through a Celite pad and the solid was washed with *N,N*-dimethylformamide (2 × 40 ml). The combined filtrates were evaporated *in vacuo* (80°, bath temperature), and the syrup was poured into ice–water (800 ml). The crystalline product was filtered off, washed with petroleum ether (b.p. 30–60°, ~500 ml), and dried *in vacuo*; yield 48.8 g (88%), m.p. 165–166°, $[\alpha]_D^{24}$ +109° (*c* 2, chloroform) [lit.[8,9] m.p. 166–167°, $[\alpha]_D^{20}$ +110° (chloroform)].

*Decarboxylative elimination of methyl 2,3-di-O-benzyl-α-D-glucopyranosiduronic acid*[2] (**1**). — *N,N*-Dimethylformamide (15 ml) was evaporated twice at 0.1 torr and a bath temperature of 50° from syrupy **1** (690 mg). The residue was then heated for 3 h at 50° with *N,N*-dimethylformamide (10 ml) and *N,N*-dimethylformamide dineopentyl acetal (2.0 ml), at which time t.l.c. (solvent $S_1$) indicated the absence of **1**. The

solution was evaporated as already described, and the crude product, dissolved in dichloromethane, was applied to three plates of loose-layer silica gel (solvent $S_2$). The wide band ($R_F$ ~0.9) was eluted (solvent $S_2$) to afford chromatographically homogeneous (solvent $S_1$) syrupy methyl 2,3-di-*O*-benzyl-4-deoxy-β-L-*threo*-pent-4-enopyranoside (**3**), which rapidly decolorized permanganate; yield 460 mg (79%); $[\alpha]_D^{24}$ +194.2° (*c* 0.5, chloroform); $\nu_{max}^{film}$ 1655 $cm^{-1}$ (C=C–O); n.m.r. data: τ 2.66 (aromatic protons), 3.74 (q, $J_{4,5}$ 6.3 Hz, $J_{3,5}$ 1.3 Hz, H-5), 5.06 (q, H-4) 5.08 (d, $J_{1,2}$ 2.2 Hz, H-1), 5.23 and 5.34 (s, $-CH_2Ph$), 5.82 (o, $J_{3,4}$ 2.9 Hz, H-3, 6.22 (q. $J_{2,3}$ 6.5 Hz, H-2), and 6.55 (s, $-OCH_3$).

*Anal.* Calc. for $C_{20}H_{22}O_4$: C, 73.60. H, 6.80. Found: C, 73.52; H, 6.86.

*Methyl 4-deoxy-β-*L-threo-*pent-4-enopyranoside* (**4**). — A 300 ml flask, fitted with a Dry Ice condenser and a magnetic stirrer, was charged with anhydrous ammonia (~100 ml), and sodium was added until the blue color of the solution persisted. A sample of **3** (1.0 g) in 1,4-dioxane (2 ml) was added dropwise over a period of 5 min. After an additional 10 min, ammonium chloride was added to the solution until the blue color disappeared. The ammonia was allowed to evaporate, and the residue was extracted twice with hot ethyl acetate (2 × 15 ml). The combined extracts were evaporated, and the yellow syrup was purified by sublimation at 45° *in vacuo* onto a cold finger. The white, crystalline material that was collected melted below room temperature to give a colorless, viscous syrup; yield 370 mg (83%), $R_F$ 0.83 (solvent $S_3$); $[\alpha]_D^{25}$ +340° (*c* 1.1, water); $\nu_{max}^{film}$ 1650 $cm^{-1}$ (C=C–O); n.m.r. data: τ 4.10 (q, $J_{4,5}$ 6.0 Hz, $J_{3,5}$ 1.0 Hz, H-5), 5.40 (overlapping multiplets, H-1, H-4), 6.04 (o, $J_{2,3}$ 6.5 Hz, $J_{3,4}$ 3.0 Hz, H-3), 6.31 (broad s, disappeared upon deuteration, OH), 6.52 (q, $J_{1,2}$ 2.2 Hz, H-2), and 6.71 (s, –OMe).

*Anal.* Calc. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.22; H, 6.88.

*Methyl 2,3-di-*O*-benzyl-4-deoxy-β-*L-threo-*pentopyranoside* (**5**). — A solution of the alkene (**3**, 582 mg) in 95% ethanol (30 ml) was hydrogenated under one atmosphere of hydrogen in a Parr apparatus in the presence of 5% palladium-on-barium sulfate (1 g) for 30 min at room temperature. The catalyst was removed by filtration through a Celite pad, and the filtrate was evaporated to a pale-yellow syrup. T.l.c. (solvent $S_1$) showed a single spot, having the same mobility as **3**, that was not decolorized by permanganate spray. The syrup was taken up in dichloromethane and the solution, after passage through a short column of silica gel, was evaporated and dried to give analytically pure **5** as a colorless syrup; yield 490 mg (83%) $[\alpha]_D^{24}$ +136.5° (*c* 0.5, chloroform); n.m.r. data: τ 2.70 (s, aromatic protons), 5.33 (m, H-1, $-CH_2Ph$), 6.22–6.82 (overlapping multiplets, H-2,3,4,4′,5,5′), and 6.68 (s, $-OCH_3$).

*Anal.* Calc. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.34; H, 7.23.

*Methyl 4-deoxy-β-*L-threo-*pentopyranoside* (**6**). — *A. From* **3**. The alkene **3** (780 mg) in 95% ethanol (30 ml) was reduced (hydrogen, 1 atm) in a Parr apparatus in the presence of 10% palladium-on-carbon (1 g) for 2 h at room temperature. The catalyst was removed by filtration, washed with ethanol, and the filtrate was evaporated to a powder that crystallized from water–acetone to give **6** as colorless crystals; yield 302 mg (84%), m.p. 109–110°, $[\alpha]_D^{25}$ +177.2° (*c* 0.5, water); $R_F$ 0.75 (solvent $S_3$);

n.m.r. data: $\tau$ 5.55 (d, $J_{1,2}$ 3.2 Hz, H-1), 6.16–6.72 (overlapping multiplets, H-2,3,4,4′,5,5′, OH), and 6.83 (s, $-OCH_3$).

*Anal.* Calc. for $C_6H_{12}O_4$: C, 48.64; H, 8.17. Found: C, 48.32; H, 7.93.

B. *From* **4**. Catalytic reduction of **4** (100 mg) with hydrogen and 5% palladium-on-barium sulfate (100 mg) as just described gave crystalline material (68 mg, 67%) that was identical with **6**.

C. *From* **5**. Catalytic reduction of **5** (310 mg) over 10% palladium-on-carbon (350 mg) as already described gave crystalline material (106 mg, 76%) that was identical with **6**.

*Attempted decarboxylative elimination of methyl α-D-glucopyranosiduronic acid.* — A sample of methyl α-D-glucopyranosiduronic acid (**6**) was subjected to the conditions described for the decarboxylative elimination of **1**. No alkene (**4**) could be detected by n.m.r. spectroscopy.

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