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Note

Stereoselective synthesis of L-olivomycose

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The branched-chain sugar L-olivomycose (**6**) is present[1] as its 4-acetate and 4-isobutanoate in the trisaccharide moiety of several antitumor antibiotics of the aureolic acid group. The structure determination and synthesis of these antibiotics have been active areas of research since their initial isolation[2] by Grundy and co-workers in 1953. Progress toward the synthesis of the aglycon and the trisaccharide of olivomycin has recently been reported[3,4]. The synthesis of **6** from L-arabinose by Jones and co-workers[5] in 1969 confirmed the structure of L-olivomycose as 2,6-dideoxy-3-*C*-methyl-L-*arabino*-hexose. A synthesis of the methyl glycoside of **6** in eight steps from L-rhamnose (*via* L-rhamnal) has been described[6]. Although shorter than previous routes, the selectivity of the reaction sequence suffers in that the C-3 epimer is also produced during the introduction of the methyl branch. Other syntheses of **6** include a chemicoenzymic route[7], and synthesis of DL epimers from noncarbohydrate precursors[8].

Our own studies of the synthesis of branched-chain amino and nitro sugars required the preparation of methyl 2,3,6-trideoxy-3-*C*-methylene-α-L-*erythro*-hexopyranoside (**4**). During the course of these investigations a new synthesis of L-olivomycose that is short and highly stereoselective has been developed. The key step is the oxymercuration of **4**.

Commercially available 3,4-di-*O*-acetyl-L-rhamnal (**1**) was converted into methyl 2,6-dideoxy-α-L-*erythro*-hexopyranosid-3-ulose (**2**) by the method* of Thiem and Elvers[9]. The reaction of **2** with methylidenetriphenylphosphorane gave a complex mixture of products; however, Peterson alkenation, using the Grignard reagent derived from (chloromethyl)trimethylsilane[10], was successful. Addition of the Grignard reagent to **2** gave the β-hydroxysilane **3** as the only product in 86% yield. The selectivity of the addition to the β-face of the pyranosidulose **2** has precedent, and was verified by the conversion of **3** into its cyclic carbonate[9,11] **7**. Treatment of **3** with potassium hydride in oxolane gave methyl 2,3,6-trideoxy-3-*C*-

*The intermediate acetate (3 g) was deacetylated with 2:20:5 triethylamine–methanol–water (135 mL).

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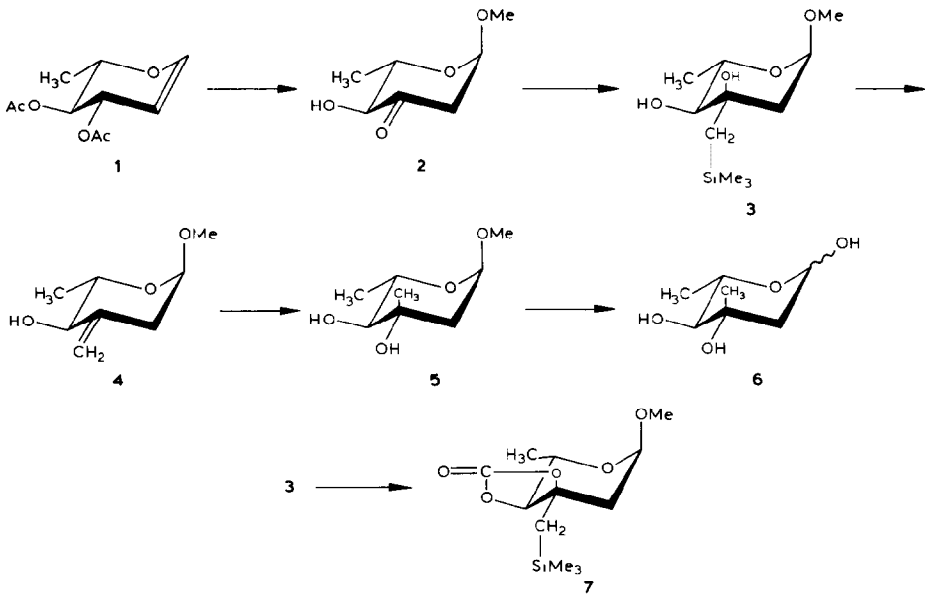
methylene-α-L-*erythro*-hexopyranoside (**4**) in 76% yield after flash chromatography. Oxymercuration–demercuration of **4** gave methyl α-L-olivomycoside (**5**) stereoselectively in 69% yield. The ^{1}H-n.m.r. spectrum of the crude reaction-product did not reveal the presence of any of the diastereomeric C-3 epimer of **5**, namely, methyl α-L-mycaroside, which exhibits different chemical shifts[9] for the 3-*C*-methyl group protons and for all of the ring protons. Stereoselective oxymercurations of other 3-*C*-methylene sugars have been reported[5,10].

Acid-catalyzed hydrolysis of **5** gave L-olivomycose (**6**) in 55% yield after recrystallization. The melting point, optical rotation, and ^{1}H-n.m.r. spectrum of the product matched those reported[12]. This efficient synthesis of L-olivomycose demonstrates the utility of the 3-*C*-methylene sugar **4**, a compound that should also be a valuable intermediate in the synthesis of other branched-chain carbohydrates of the L configuration.



EXPERIMENTAL

General procedures. — Melting points were determined on a Thomas–Hoover melting-point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 299 infrared spectrometer, and ^{1}H-n.m.r. spectra with a Perkin–Elmer R-32 90-MHz spectrometer. The 200-MHz, ^{1}H-n.m.r.spectrum of methyl α-L-olivomycoside (**5**) was recorded with a Varian XL-200 spectrometer. Chemical shifts for proton resonances are given relative to tetramethylsilane (δ 0.0 p.p.m.). Thin-layer chromatography was performed on aluminum-supported plates of silica gel 60 (0.2 mm, F-254, E. Merck). Flash chromatography was con-

ducted on silica gel 60 (230–400 mesh, Merck 9385). Chloroform was dried by passing it through a column of basic alumina (Woelm, activity 1). Oxolane (tetrahydrofuran, THF) was distilled from calcium hydride before use. Elemental analyses were performed by Galbraith Laboratories. Optical rotations were measured with Perkin–Elmer 241 and Rudolph Autopol III polarimeters.

*Methyl 2,6-dideoxy-3-C-(trimethylsilyl)methyl-α-*L-ribo-*hexopyranoside* (**3**). — (Trimethylsilyl)methylmagnesium chloride was prepared from (chloromethyl)trimethylsilane (3.34 g, 27.2 mmol) and magnesium turnings (0.653 g, 27.2 mmol) in anhydrous ether (30 mL). Preparation of the Grignard reagent required refluxing for 30 min after addition of the reagents. To the cooled solution was added a solution of **2** (0.87 g, 5.44 mmol) in dry benzene (10 mL) dropwise, with stirring, at 0°. After 1.75 h, saturated ammonium chloride solution was added slowly. The mixture was diluted with ether (100 mL), and the organic phase was separated, and successively washed with saturated ammonium chloride solution, water, and saturated sodium chloride solution, dried (sodium sulfate), and evaporated, to give **3** (1.16 g, 86%) as a yellow liquid. An analytical sample was prepared by flash chromatography with 1:4 ethyl acetate–petroleum ether; $[\alpha]_D^{20}$ −47.2° (CH_2Cl_2); ν_{max}^{film} 3500, 3000–2900, 1450, 1405, 1375, 1360, and 1330 cm^{-1}; ^{1}H-n.m.r. data (90 MHz, $CDCl_3$): δ 4.68 (m, 1 H, H-1, $J_{1,2a}$ 3.4, $J_{1,2e}$ 1.5 Hz), 3.74 (bs, 1 H, OH-3), 3.52 (m, 1 H, H-5, $J_{4,5}$ 9 Hz), 3.38 (s, 3 H, OCH_3), 2.84 (t, 1 H, H-4, $J_{4,OH-4}$ 9 Hz), 2.25 (d, 1 H, OH-4), 2.10 (dd, 1 H, H-2*e*, $J_{2a,2e}$ 14 Hz), 1.71 (dd, 1 H, H-2*a*), 1.34 (d, 1 H, SiCH), 1.28 (d, 3 H, H-6, $J_{5,6}$ 6 Hz), 0.65 (d, 1 H, SiCH), and 0.1 (s, 9 H, Me_3Si).

Anal. Calc. for $C_{11}H_{24}O_4Si$: C, 53.19; H, 9.74. Found: C, 53.24; H, 9.93.

*Methyl 2,3,6-trideoxy-3-C-methylene-α-*L-erythro-*hexopyranoside* (**4**). — Potassium hydride (0.6 g of a 50% dispersion in oil, 7.5 mmol of KH) was washed with dry hexane under nitrogen in a round-bottomed flask equipped with a magnetic stirrer. The washings were removed by means of a pipet, and THF (10 mL) was added, followed, dropwise with stirring, by a solution of β-hydroxysilane **3** (0.62 g, 2.5 mmol) in THF (5 mL) at room temperature. Progress of the reaction was monitored by thin-layer chromatography on silica gel with 1:4 ethyl acetate–petroleum ether. The starting material was consumed within 50 min, and the mixture was poured into cold, saturated ammonium chloride solution layered with ether. The aqueous layer was extracted with ether, and the extracts were combined, and evaporated to give a yellow residue. Purification by flash chromatography on a column of silica gel with 1:4 ethyl acetate–petroleum ether gave 0.3 g (76%) of crystalline product; m.p. 65–66°, $[\alpha]_D^{20}$ −204.7° (CH_2Cl_2); ν_{max}^{film} 3450, 3000–2900, 1660, and 1450 cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 5.12 (s, 1 H, vinyl), 4.91 (s, 1 H, vinyl), 4.72 (dd, 1 H, H-1), 3.85–3.4 (m, 3 H, H-4,5, OH), 3.34 (s, 3 H, OCH_3), 2.53 (m, 2 H, H-2*a*,2*e*), and 1.34 (d, 3 H, H-6, $J_{5,6}$ 6 Hz).

Anal. Calc. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.53; H, 9.10.

*Methyl 3,4-O-carbonyl-2,6-dideoxy-3-C-(trimethylsilyl)methyl-α-*L-ribo-

hexopyranoside (**7**). — A solution of β-hydroxysilane **3** (0.126 g, 0.5 mmol), and 1,1-carbonyldiimidazole (0.090 g, 1.1 equiv.) in benzene (3 mL) was stirred and boiled under reflux for 1 h. Additional 1,1-carbonyldiimidazole (25 mg) was added and the mixture was boiled under reflux for 1 h; t.l.c. on silica gel with 1:4 ethyl acetate–petroleum ether then indicated that no starting material remained. The mixture was cooled to room temperature, diluted with ether (40 mL), washed with water (3 × 10 mL), dried (sodium sulfate), and evaporated to give syrupy product **7** (0.123 g, 88%) which was purified by chromatography on a column of silica gel with 1:4 ethyl acetate–petroleum ether. There was obtained 0.105 g which crystallized from petroleum ether–dichloromethane, m.p. 81–82°, $[\alpha]_D^{20}$ −115.5° (CH_2Cl_2); ν_{max}^{film} 3000–2900, 1800, 1545, and 1455 cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 4.55 (t, 1 H, H-1, $J_{1,2}$ 6 Hz), 3.9–3.68 (m, 2 H, H-4,5), 3.23 (s, 3 H, OCH_3), 2.05 (m, 2 H, H-2*a*,2*e*), 1.22 (d, 3 H, H-6), 1.20 (d, 1 H, SiCH, J_{vic} 12, ^4J 1 Hz), 0.90 (d, 1 H, SiCH), and 0.1 (s, 9 H, Me_3Si).

*Methyl 2,6-dideoxy-3-*C*-methyl-α-*L-arabino-*hexopyranoside (methyl α-*L-*olivomycoside,* **5**). — To a stirred solution of mercuric acetate (0.525 g, 1.1 equiv.) in 1:1 THF–water (5 mL) at room temperature was added **4** (0.237 g, 1.5 mmol), the mixture stirred for 30 min at room temperature, and then cooled to 0°. Aqueous 3M sodium hydroxide solution (3.5 mL) was added, followed by sodium borohydride (0.038 g, 0.6 equiv.) in 3M sodium hydroxide (2 mL), dropwise, at 0°. Mercury was deposited, and the aqueous layer was saturated with sodium chloride, and then extracted with dichloromethane. The extracts were combined, and kept at 0° until the rest of the mercury had settled. The solution was decanted, dried (sodium sulfate), and the suspension filtered through a 2-cm pad of silica gel. The filtrate was evaporated, giving colorless, syrupy **5** (0.183 g, 69%), which was used directly for hydrolysis. Purification of **5** by flash chromatography with 1:1 ethyl acetate–petroleum ether gave a syrup whose 200-MHz, ^{1}H-n.m.r. spectrum was identical with that reported[6] at 270 MHz. It had $[\alpha]_D^{22}$ −145° (EtOH); lit.[6] $[\alpha]_D$ −9.7°, lit.[12] −137°.

*2,6-Dideoxy-3-*C*-methyl-*L-arabino-*hexose (*L*-olivomycose,* **6**). — Compound **5** (0.183 g, 1.04 mmol) in 0.1M sulfuric acid (10 mL) was stirred overnight at room temperature, and then for 4 h at 40°. The acid was neutralized with barium carbonate, the mixture filtered through Celite–charcoal, and the filtrate evaporated, to give L-olivomycose as an off-white solid (0.162 g). Crystallization from ethyl acetate–petroleum ether gave white crystals of **6** (0.092 g, 55%); m.p. 101–102° (lit.[5] m.p. 102–103°), $[\alpha]_D^{25}$ −14.9° (H_2O, initial), lit.[12] $[\alpha]_D^{22}$ −15.0° (H_2O, initial). The 90-MHz, ^{1}H-n.m.r. spectrum was identical with that reported[12] at 100 MHz.

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