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Note

Methyl 6-*O*-benzoyl α-D-galactopyranoside and some derivatives therefrom*

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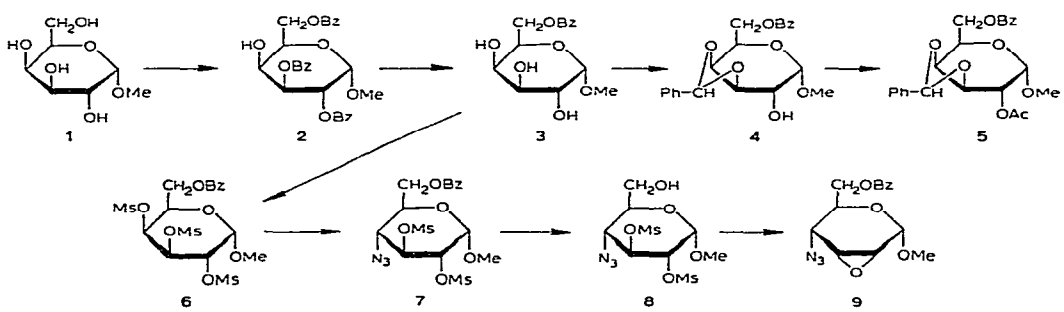
During the course of studies directed toward the synthesis of gougerotin[1–3] and blasticidin S[4–6], we prepared large quantities of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[7] (**2**) by selective benzoylation of methyl α-D-galactopyranoside (**1**). The mother liquor of crystallization of **2** from methanol contained, in addition to **2**, the tetra- and some di-*O*-benzoylated derivatives of **1**. In our attempts to recover the starting material (**1**) by saponification of the tetra- and di-*O*-benzoylated derivatives, we obtained significant amounts of a new compound, methyl 6-*O*-benzoyl-α-D-galactopyranoside (**3**), in crystalline form. A general method for the synthesis of 6-*O*-monobenzoylhexoses is the procedure of Zinner[8] which involves the benzoylation of certain hexose dithioacetals. More recently, methyl 6-*O*-benzoyl-α-D-glucopyranoside was prepared by rather complicated procedures[9–11]. In this report, we present a simple synthesis of the previously uncharacterized** methyl 6-*O*-benzoyl-α-D-galactopyranoside (**3**) from methyl α-D-galactopyranoside (**1**).

Methyl α-D-galactopyranoside (**1**) was perbenzoylated and the reaction mixture (containing **2**), without purification, was treated dropwise with sodium hydroxide in



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Methyl 6-*O*-benzoyl-α-D-galactopyranoside (3**) has been mentioned briefly in a paper on the activity of benzoyl esterases of certain fungi on 6-*O*-benzoyl sugars[12]. The synthesis, and the chemical and physical properties of this compound were not given.

methanol to afford **3** in ~30% yield. Proof of the structure of **3** rests on the following data: The elemental analysis was consistent with a methyl monobenzoylhexoside and the n.m.r. spectrum showed, in the δ 5–6 range, the absence of any proton signal other than that for the anomeric proton. The absence of such lower-field signals is indicative of the absence of benzoylation of secondary hydroxyl groups in **3**.

Several derivatives of **3** were prepared. Benzylidenation of **3** with benzaldehyde and zinc chloride afforded the 3,4-*O*-benzylidene derivative **4** which, after acetylation, gave the 2-acetate **5**. Mesylation of **3** yielded in high yield the 2,3,4-tri-*O*-mesyl derivative **6** which was converted into the 4-azide derivative **7** in 83% yield (see Experimental) after treatment with sodium azide in hexamethylphosphoric triamide at 60°. [It is noteworthy that displacement of the 4-mesyloxy group of methyl 2,6-di-*O*-benzoyl-3,4-di-*O*-mesyl-α-D-galactopyranoside (a compound analogous to **6**) with this reagent, even under more strenuous conditions, failed[5].] The selective displacement of the 4-mesyloxy group of **6** was assumed by analogy with the report of Dick and Jones[13] on poly-*O*-mesylglycopyranosides. The structure of the azido derivative, however, was fully established by elemental and spectral analyses of the de-*O*-benzoylated product **8** which was obtained by treatment of **7** with methanolic sodium methoxide at room temperature. The n.m.r. spectrum of **8** in deuterated chloroform showed the anomeric doublet at δ 5.08 ($J_{1,2} \cong 3.5$ Hz) and a quartet for H-2 at δ 4.50 ($J_{1,2} \cong 3.5$, $J_{2,3} \cong 9.7$ Hz). This clear quartet for H-2 and two sets of couplings establishes H-1, H-2, and H-3 as having equatorial, axial, and axial orientations, respectively. The third peak of the H-3 triplet (δ 4.95, $J_{2,3} \cong J_{3,4} \cong 9.7$ Hz) is hidden beneath the anomeric signal. The low chemical-shift values for the H-2 and H-3 signals indicate that the mesyloxy functions are attached to C-2 and C-3. A broad signal at δ 3.6–4.1 integrated for four protons and is attributable to H-6,6′, H-5, and H-4. Three methyl signals at δ 3.16, 3.22, and 3.45 are assigned to the two mesyloxy methyl and the glycoside methyl groups, respectively. A strong absorption band at 4.69 μm in the i.r. spectrum shows the presence of an azido function in **8**. All these data clearly established the structure of **8**, and hence of **7**.

Treatment of compound **7** with excess sodium methoxide for a prolonged reaction time led to the isolation of **8** and did not produce an anhydro derivative. When **8** was allowed to react with potassium *tert*-butoxide or *tert*-pentoxide, a mixture of products was formed which gave a positive test on a t.l.c. plate when sprayed with Methyl Red–sodium iodide reagent. The mixture was benzoylated and subjected to column chromatography (silica gel) from which the major component was eluted. This major component was shown to be the known[5] methyl 2,3-anhydro-4-azido-6-*O*-benzoyl-4-deoxy-α-D-allopyranoside by comparison of its i.r. and n.m.r. spectra with those of authentic material.

Attempts to prepare **3** by benzoylation of **1** with limited amounts of benzoyl chloride in pyridine were not successful. Rather, a mixture of several benzoylated galactosides was formed (as shown by t.l.c.) which rendered the preparation of **3** by this route impractical.

EXPERIMENTAL

General. — Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. T.l.c. was performed on microscope slides coated with Silica Gel GF_{254} (Merck), and developed in 9:1 chloroform–methanol.

Methyl 6-O-benzoyl-α-D-galactopyranoside (**3**). — Methyl α-D-galactopyranoside (**1**, 8.9 g, 46 mmoles) was dissolved in pyridine (90 ml) and the solution was stirred and cooled in an ice-bath. Benzoyl chloride (19.5 ml) was added slowly, and the solution was kept overnight at room temperature. The mixture was poured onto ice and saturated sodium hydrogen carbonate (600 ml) with vigorous stirring. After 1 h, the aqueous phase was decanted from the gummy precipitate. The residue was triturated with water (3 × 50 ml) to remove pyridine, dissolved in methanol (~250 ml) and M sodium hydroxide (6 ml) was added with stirring. The reaction was monitored by t.l.c.. After 20 min, the solution was neutralized with M hydrochloric acid, and evaporated *in vacuo* to a thin paste. The residue was boiled with benzene (2 × 25 ml), which was decanted, and then boiled with ethyl acetate (3 × 100 ml), followed by filtration through glass wool. The filtrate was evaporated to a paste that was triturated with ether and filtered off to yield **3** (3.2 g), m.p. 147–148°. The ethyl acetate extracts were evaporated and the residue was dissolved in water that was then saturated with sodium chloride; extraction with ethyl acetate, and work-up of the organic layer yielded an additional amount (0.62 g) of the monobenzoate. The benzene extracts were washed with water (2 × 50 ml), and the aqueous solution was saturated with sodium chloride, extracted with ethyl acetate (2 × 100 ml), and worked-up to yield more **3** (0.3 g; total yield, 4.12 g, 30%), m.p. (after recrystallization from 2-propanol) 150–151°, $[\alpha]_D^{27}$ +122° (*c* 0.96, pyridine).

Anal. Calc. for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.56; H, 5.99.

Methyl 6-O-benzoyl-3,4-O-benzylidene-α-D-galactopyranoside (**4**). — Compound **3** (29.8 g, 0.1 mole) was shaken with benzaldehyde (50 ml) and fused zinc chloride (20 g) for 48 h. Water (250 ml) and petroleum ether (b.p. 30–60°, 250 ml) were added to the clear solution and the mixture was shaken for 10 min. The petroleum ether was discarded and the aqueous suspension was shaken with additional petroleum ether (150 ml). Crystallization of the product occurred, and this was filtered off and washed with water and petroleum ether to yield **4** (11.0 g, 28.5%), m.p. 135–145° (sintering at 129°); recrystallization from ethanol raised the m.p. to 154–155.5°, $[\alpha]_D^{27}$ +128° (*c* 1.25, pyridine).

Anal. Calc. for $C_{21}H_{22}O_7 \cdot 2H_2O$: C, 59.71; H, 6.20. Found: C, 59.46; H, 6.06.

Methyl 2-O-acetyl-6-O-benzoyl-3,4-O-benzylidene-α-D-galactopyranoside (**5**). — Compound **4** (7 g, 181 mmoles) was dissolved in anhydrous pyridine (30 ml) and acetic anhydride (15 ml) was added with stirring. After 5 h at room temperature, the solution was poured into ice–water (300 ml). A thick gummy precipitate formed, the water was decanted, and the residue dissolved in hot ethanol. The cooled solution yielded 1.85 g of colorless crystals of **5**, m.p. 127.5–129°. Concentration of the mother

liquor yielded an additional 0.2 g (total yield, 2.05 g, 26.2%). Recrystallization gave crystals with m.p. 128–129°, $[\alpha]_D^{27}$ +110° (*c* 1.19, acetone).

Anal. Calc. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.46; H, 5.70.

Methyl 6-O-benzoyl-2,3,4-tri-O-mesyl-α-D-galactopyranoside (**6**). — Compound **3** (15.0 g, 0.05 mole) was dissolved in pyridine (200 ml) and the solution cooled in an ice-bath. Methanesulfonyl chloride (16 ml, ~0.2 mole) was added and the solution was kept overnight at room temperature. Additional methanesulfonyl chloride (2 ml) was added and the solution was stirred for 1 h. The reaction mixture was then poured into ice–water (1200 ml) with vigorous stirring. The solid precipitate was filtered off and washed with ice-cold water. The residue was recrystallized from methanol to yield long needles of **6** (25.5 g, 95%), m.p. 126–128°. $[\alpha]_D^{27}$ +94° (*c* 1.37, pyridine).

Anal. Calc. for $C_{17}H_{24}O_{13}S_3$: C, 38.34; H, 4.54; S, 18.06. Found: C, 38.47; H, 4.80; S, 18.30.

Methyl 4-azido-6-O-benzoyl-4-deoxy-2,3-di-O-mesyl-α-D-galactopyranoside (**7**). — A mixture of compound **6** (5.2 g, 0.01 mole) and sodium azide (0.78 g, 0.102 mole) in hexamethylphosphorotriamide (23 ml) was stirred and heated to 60°. After 2 h, an additional amount of sodium azide (0.1 g) was added and allowed to react for 2 h. The reaction mixture was cooled to room temperature and poured into chloroform (400 ml). The mixture was washed with water (10 × 100 ml), and the organic layer was dried (sodium sulfate) and evaporated to an oil. The residue was triturated with petroleum ether (200 ml) to a thick, sticky syrup. The petroleum ether was decanted and the residue was dissolved in chloroform and applied to a column of Silica Gel G (200 g). The column was developed with 1:9 ethyl acetate–chloroform. Compound **7** having $[\alpha]_D^{27}$ +126° (*c* 1.35, acetone) was obtained as a colorless oil (3.35 g, 71%) which was sufficiently pure for the next step. Some of the starting material **6** was also recovered (0.730 g, raising the effective yield to 83%).

Reaction of **6** with sodium azide for 1 h at 90° gave a dark-brown mixture from which the slightly discolored compound **7** was isolated in 95% yield.

Methyl 4-azido-4-deoxy-2,3-di-O-mesyl-α-D-galactopyranoside (**8**). — Compound **7** (0.6 g, 1.26 mmoles) was dissolved in anhydrous methanol (35 ml) and freshly prepared sodium methoxide (0.205 g of sodium in 5 ml of methanol) was added. The solution was stirred for 28 h at room temperature. T.l.c. showed only one spot. The solution was neutralized with acetic acid and evaporated to dryness. The residue was washed repeatedly with benzene, and the washings were evaporated to give a yellow oil. This was chromatographed on a Silica Gel G column (12.5 × 2 cm) with 1:9 methanol–chloroform as eluant. Pure compound **8** (0.44 g, 96%) was obtained as an oil, $[\alpha]_D^{27}$ +128° (*c* 0.98, acetone).

Anal. Calc. for $C_9H_{17}N_3O_9S_2$: C, 28.78; H, 4.57; S, 17.08. Found: C, 28.98; H, 4.81; S, 17.37.

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