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## Note

# Selective substitution at the 3-position in a 3,4-*O*-dibutylstannylene-D-galactopyranose derivative. An improved synthesis of 2,4,6-tri-*O*-benzyl-D-galactose

MINA A. NASHED* AND LAURENS ANDERSON†

*Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin–Madison, Madison WI 53706 (U. S. A.)*

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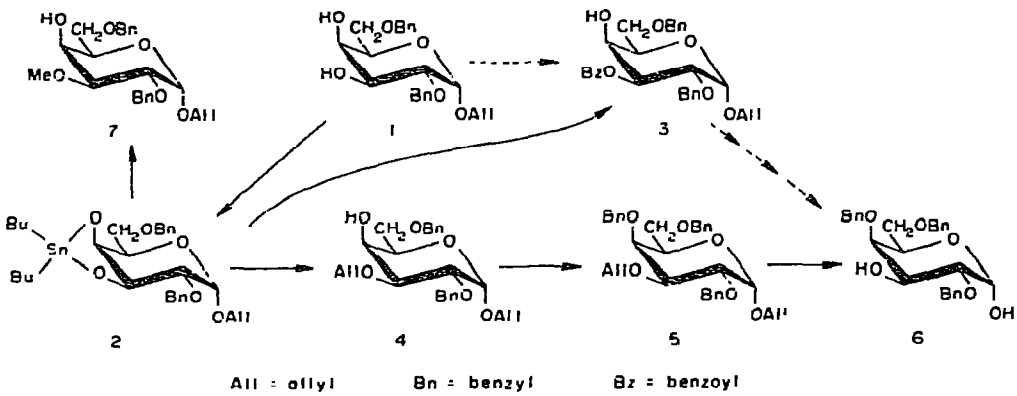
A synthesis of 2,4,6-tri-*O*-benzyl-D-galactopyranose (**6**) and the derived 2,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranose was the subject of a recent paper from this laboratory[1]. The key step in the synthesis was the selective benzoylation, in pyridine at low temperature, of allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**1**). Further elaboration of the resulting 3-benzoate **3** provided a usable route to the desired end-product, but the method was not fully satisfactory. There was interference from the ~15% of 2,3-dibenzoate formed in the benzoylation step, and danger of benzoyl migration in the Purdie benzylation of **3**. Migration was in fact observed in one instance, when silver oxide a month old was used.

As described in a preliminary communication[2], our search for a better route from **1** to **6** led us to investigate the acylation and alkylation of the cyclic dibutylstannylene derivatives of **1** and related, partially substituted sugars having an axial–equatorial, vicinal diol group. These reactions had been studied in the nucleoside series by Wagner, Verheyden, and Moffatt[3], and the ready formation of dibutylstannylene compounds from pyranoid glycols had been demonstrated by David and Thieffry[4]. When our work was nearing completion, Augé, David, and Veyrières[5] reported that a close analog of the stannylene compound **2**, namely benzyl 6-*O*-allyl-2-*O*-benzyl-3,4-*O*-dibutylstannylene-α-D-galactopyranoside, was alkylated by benzyl bromide exclusively at position 3. Our results[2] confirmed and extended the findings of the French workers: in all cases the cyclic dibutylstannylene derivatives we studied gave high yields of monobenzoylated or monoalkylated products when treated with benzoyl chloride or an active alkyl halide. In every instance but one substitution occurred essentially exclusively at the equatorial oxygen.

The present note records the experimental details of the stereospecific benzoylation, methylation, and allylation of allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**1**)

*On leave of absence from the Department of Chemistry, Alexandria University, Alexandria, Egypt.
†Please address correspondence to this author.

via its dibutylstannylene derivative **2**. The evidence that the products are the 3-substituted derivatives is summarized in our initial communication[2]. In addition, an improved procedure for the preparation of 2,4,6-tri-*O*-benzyl-D-galactopyranose (**6**) is given. This consists in the benzylation of the 3-allyl ether **4** to give **5**, which can be deallylated to **6** as earlier described by Gent, Gigg, and Conant[6]. Even though the availability of a "clean" preparation of the benzoate **3** eliminates one of the disadvantages of our earlier synthesis of **6**, the new route is superior because the benzylation step can be achieved by an efficient method, without fear of causing a migration of the group used to protect O-3. Moreover, when this group is allyl, one step (debenzoylation) is saved. We isolated the fully benzylated intermediate **5** pure in order to determine its physical properties, as these had not been recorded by Gent, Gigg, and Conant[6], who in their original synthesis of **6** obtained **5** by a route different from ours. However, when **6** is prepared by our method, the yields are improved ($\geq$ 50% from **1**) if intermediates **4** and **5** are used without purification.




## EXPERIMENTAL

*General.* — Instrumental and chromatographic procedures were as described in earlier papers of this series[7]. The following solvent combinations (v/v) were utilized for thin-layer and column chromatography: A, 19:1 chloroform–acetone; B, 97:3 chloroform–ethyl acetate; and C, 4:1 chloroform–acetone.

*Allyl 3-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranoside* (**3**). — Pure allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[6] (**1**) (0.8 g, 2 mmol) and dibutyltin oxide (0.5 g, 2 mmol) in methanol (100 ml) were heated for ~ 1 h under reflux.

The resulting clear solution was concentrated in a rotary evaporator, then the residue was dried under oil-pump vacuum (Dry Ice trap). The p.m.r. spectrum of the syrupy product (**2**) showed no O*H* signal. This product was dissolved in 50 ml of 1,4-dioxane, and then triethylamine (2.6 ml, 19 mmol) and benzoyl chloride (2.2 ml, 19 mmol) were added, and the mixture was stirred for 1 h at room temperature. At this point, t.l.c. in solvent A showed no starting material and only one major product-spot. Water was added, the product was extracted into chloroform, and the extract was

washed with 5% hydrochloric acid, water, 5% sodium hydrogencarbonate solution, and again with water. Evaporation of the dried chloroform solution left a colorless syrup, which was purified by chromatography on silica gel (50 g, solvent A). The yield of the syrupy title compound was 0.82 g (81%); $[\alpha]_D^{25}$ +94.3° (*c* 2.1, chloroform); previously recorded[1] $[\alpha]_D^{25}$ +95°. The mobility on t.l.c. and the p.m.r. spectrum of the product were identical with those of our previous sample.

*Allyl 3-O-allyl-2,6-di-O-benzyl-α-D-galactopyranoside* (**4**). — The dibutylstannylene derivative from 2.54 g (6.3 mmol) of **1** was dissolved in *N,N*-dimethylformamide (25 ml) and allyl iodide (2.0 g, 11.9 mmol) was added. The solution was heated for 1 h at 100°, at which time t.l.c. (solvent A) showed that only traces of **1** were present (the stannylene compound decomposes on silica gel). Most of the solvent was removed by evaporation under diminished pressure, the product was extracted into chloroform, and the extract was washed with 10% sodium thiosulfate, and then with water. Following evaporation of the chloroform, the residue was chromatographed on silica gel (200 g, column diameter 2.7 cm, solvent A). This afforded 2.2 g (79%) of the syrupy title compound **4**; $[\alpha]_D^{25}$ +68.5°, $[\alpha]_{436}^{25}$ +131.4° (*c* 0.85, chloroform); p.m.r. ($CDCl_3$): $\delta$ 7.53–7.03 (m, 10, Ph–H), 6.35–5.62 (m, 2, –CH=), 5.48–5.00 (m, 4, =C$H_2$), 5.00–4.43 (m, 5, H-1 and PhC$H_2$), 4.33–3.57 (m, 10, H-2,3,4,5,6,6', OC$H_2$CH=), and 2.58 (bs, 1, exchangeable, O*H*). Found: C, 70.52; H, 7.37. $C_{26}H_{32}O_6$ (440.52) requires C, 70.89; H, 7.32.

*Allyl 3-O-allyl-2,4,6-tri-O-benzyl-α-D-galactopyranoside* (**5**). — To a solution of allyl 3-*O*-allyl-2,6-di-*O*-benzyl-α-D-galactopyranoside (**4**) (2.2 g, 5 mmol) in 25 ml of dry benzene was added sodium hydride (1.5 g, 50% dispersion in oil) and benzyl chloride (2 g, 15.8 mmol), and the solution was boiled under reflux. The benzylation was monitored by t.l.c. (solvent B), which indicated disappearance of the starting material after 4 h. Methanol was added to the cooled solution, and the product was isolated by conventional extraction. Chromatography on silica gel (300 g, column diameter 3.3 cm, solvent B) afforded 2.31 g (87%) of the syrupy title compound **5**; $[\alpha]_D^{25}$ +36.2°, $[\alpha]_{436}^{25}$ +64.9° (*c* 1, chloroform); p.m.r. ($CDCl_3$): $\delta$ 7.60–6.97 now 15 H and 5.53–4.35 now 12 H (addition of PhC$H_2$ and the downfield shift of 1 sugar ring H), no O*H* signal. Found: C, 74.59; H, 7.24. $C_{33}H_{36}O_6$ (530.63) requires C, 74.69; H, 7.22.

*2,4,6-Tri-O-benzyl-D-galactopyranose* (**6**). — Compound **5** (2.31 g, 4.4 mmol) was converted into **6** as described by Gent, Gigg, and Conant[6]. Crystallization of the product from benzene–Skellysolve B, and recrystallization from methanol yielded 1.27 g (65%) of material melting at 122–123°, $[\alpha]_D^{25}$ +39.9 (5 min) → +33.7° (20 h), $[\alpha]_{436}^{25}$ +76.7 (5 min) → +66.2° (20 h) (*c* 0.98, chloroform). Gent, Gigg and Conant[6] recorded m.p. 123–124°; $[\alpha]_D$ +40.4 → +37.6° (24 h) (chloroform). We[1] previously found m.p. 126–128°; $[\alpha]_D^{25}$ +40.3 (2 min) → +36.6° (20 h) (chloroform). The p.m.r. spectrum was identical with that of our previous sample.

*Conversion of* **1** *into* **6** *without purification of intermediates.* — Allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**1**, 2.24 g) was treated with dibutyltin oxide and allylated to **4**, as already described. The crude **4** was benzylated to **5** with benzyl

chloride and potassium hydroxide[8], and the allyl groups were removed[6] from the crude **5**. Crystallization of the product gave 1.0 g of **6** melting at 120–122°. An additional 0.3 g of pure material was recovered by chromatography of the mother liquors (50 g silica gel, column diameter 1.3 cm, solvent C). Thus the total yield of **6** was 1.3 g (52%). When the intermediates **4** and **5** were subjected to chromatographic purification, the overall yield of **6** from **1** was 45%.

*Allyl 2,6-di-O-benzyl-3-O-methyl-α-D-galactopyranoside* (**7**). — The dibutylstannylene derivative from 0.4 g (1 mmol) of **1** was dissolved in *N,N*-dimethylformamide (5 ml), and methyl iodide (0.5 g, 3.5 mmol) was added. The solution was kept for 10 h at 45°, at which time t.l.c. (solvent A) showed that only traces of **1** were present. The mixture was processed as described for compound **4**. The yield of syrupy title compound, purified by chromatography (50 g silica gel, solvent A), was 0.32 g (77%); $[\alpha]_D^{25}$ +74°, $[\alpha]_{436}^{25}$ +141° (*c* 2, chloroform); p.m.r. ($CDCl_3$): $\delta$ 3.48 (s, 3, $OCH_3$). Found: C, 69.55; H. 7.34. $C_{24}H_{30}O_6$ (414.48) requires C, 69.54; H, 7.30.

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