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Note

A facile synthesis of α-D-galactopyranosyl-(1 → 1)-α-D-galactopyranoside and its analogues

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In a previous paper [1] we reported the synthesis of trehalose esters of corynomycolic acid, the simplest of the mycolic acids, for studies of trehalose:mycoloyl transferase [2]. We have also reported [3] the synthesis of the gluco–galacto analogue of trehalose for the same purpose. Trehalosamines have been isolated from microorganisms [4] or synthesized [5] and found to have antimicrobial activity [6]. In the present study, we describe the synthesis of trehalose analogues having various sugar residues, such as D-galactose and 4,4′-diazido-D-galactose, which represents a potential, preparative precursor for the corresponding 4,4′-diaminotrehalose.

Synthetic routes to the galacto–galacto trehalose analogue have been investigated by several groups [7–10]. Birch and Richardson [7] and Goren and co-workers [10] prepared galacto–galacto trehalose from dibenzylidene trehalose by multistep reactions. Also, Pavia et al. [9] prepared the same compound from the monosaccharide building blocks. The disadvantage of this procedure was in the lack of stereoselectivity. Our results, presented herein, reveal some unanticipated advantages of this latter approach.

Symmetrical trehalose hexabenzoate [3] (**1**) was prepared from the tributylstannyl derivative as described by Ogawa and Matsui [11]. The ready availability of the key intermediate **1** permitted the synthesis of symmetrically substituted galacto-trehalose. Acylation of the OH-4,4′ groups of **1** with trifluoromethanesulfonic anhydride (triflic

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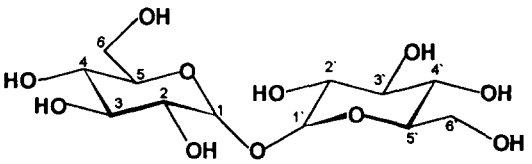
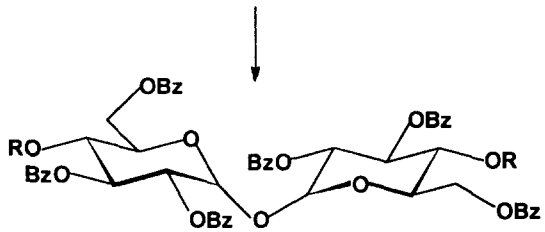
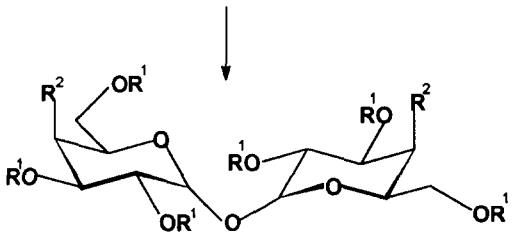


Trehalose



1 R = H Bz = benzoyl

2 R = trifluoromethylsulfonyl



3 R^1 = Bz R^2 = OH
4 R^1 = H R^2 = OH
5 R^1 = Bz R^2 = N_3
6 R^1 = H R^2 = N_3

anhydride) gave the 4,4′-ditriflate derivative **2** in almost quantitative yield. Compound **2** was readily characterized by its ^{1}H NMR spectrum, which showed a new signal shifted downfield to δ 6.35 as a triplet having a spacing of 9.5 Hz, identifiable by decoupling experiments as the signal for H-4,4′, and by its ^{13}C NMR spectrum, showing a downfield shift (δ 78.64) for C-4,4′. Displacement of the ditriflate **2** from O-4,4′ with sodium nitrite in *N*,*N*-dimethylformamide [12,13] at room temperature afforded the hexabenzoate **3** (72%) with inversion of configuration at C-4,4′. The characterization of compound **3** was based on its ^{1}H NMR spectrum, in which the signal for H-3,3′ showed a large coupling ($J_{2,3}$ 10.6 Hz) and a small coupling ($J_{3,4}$ 2.8 Hz) typical of the galacto configuration. Zemplén *O*-deacylation of **3** furnished α-D-galactopyranosyl-(1 → 1)-α-D-galactopyranoside (**4**) in almost quantitative yield. Compound **4** has been reported by

Birch and Richardson [7] as a crystalline product having mp 267–272°C, $[\alpha]_D$ +244°, which is in agreement with our findings.

Treatment of **2** with sodium azide in *N,N*-dimethylformamide in the presence of dicyclopentano-15-crown-5 [3,14] at ambient temperature gave the 4,4′-diazidogalacto analogue **5** (75%). The combination of triflate as leaving group and azide as the nucleophile in the presence of crown ether provided an excellent yield of the displacement product **5**. The structure of **5** was confirmed by ^{1}H and ^{13}C NMR spectra in which the signal of H-3,3′ showed a large ($J_{2,3}$ 10.6 Hz) and a small ($J_{3,4}$ 3.5 Hz) coupling, and a high-field ^{13}C shift (δ 61.36) of the signal for C-4,4′. *O*-Debenzoylation of compound **5** afforded 4,4′-diazido-galacto-trehalose **6** in almost quantitative yield. The structure of **6** was confirmed by ^{1}H and ^{13}C NMR spectra, indicating a symmetrical structure where the signal for H-1,1′ showed a doublet with a small coupling (J 3.9 Hz), and a singlet at δ 63.67 characteristic of a C–N signal. Preliminary experiments showed that the diazido derivative **6** has antimicrobial activity.

1. Experimental

General methods.—Melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were determined at 22°C with a Perkin–Elmer model 241 polarimeter. NMR spectra were recorded at Glycomed, Inc. (Alameda, CA) with a Varian Gemini 300 MHz spectrometer at ambient temperature. ^{13}C NMR spectra were recorded at 75.50 MHz. Chemical shifts are referenced to Me_4Si as the internal standard. Liquid secondary-ion mass spectrometry (LSIMS) was performed on a Finnigan MATTSQ-70, triple-stage quadrupole mass spectrometer equipped with an Antek cesium ion gun. Glycerol or 3-nitrobenzyl alcohol (Aldrich) was employed as the sample matrix. Separations were accomplished by open-column chromatography on silica gel 60 (70–230 mesh, E. Merck). TLC was performed on silica gel plates (250 μm, Merck). The following solvent combinations (v/v) were utilized for thin-layer and column chromatography: A, 9:1, toluene–EtOAc; B, 19:1, toluene–EtOAc; C, 19:1, $CHCl_3$–acetone; D, 1:8:6, H_2O–MeOH–EtOAc. Elemental analyses were performed at Galbraith Laboratories, Inc., Knoxville, TN.

*2,3,6-Tri-*O*-benzoyl-4-*O*-trifluoromethylsulfonyl-α-*D*-glucopyranosyl-(1 → 1)-2,3,6-tri-*O*-benzoyl-4-*O*-trifluoromethylsulfonyl-α-*D*-glucopyranoside* (**2**).—A solution of 2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl-(1 → 1)-2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside [3,9] (**1**) (3 g, 3.1 mmol) in dry CH_2Cl_2 (50 mL) and pyridine (0.8 mL, 15 mmol) was cooled to 0°C, triflic anhydride (1.2 mL, 9 mmol) was added dropwise with stirring, and the reaction was allowed to warm to room temperature and left for a further 30 min, after which TLC (solvent A) indicated complete conversion of **1** into the more mobile ditriflate **2**. The mixture was diluted with CH_2Cl_2, washed successively with cold aq HCl (1%), $NaHCO_3$ (5%), and water, dried, and evaporated, to give an amorphous solid **2** in almost quantitative yield. ^{1}H NMR ($CDCl_3$): similar to that of **1** except for the downfield shift of H-4,4′ to δ 6.35 (t, 2 H, J 9.5 Hz) and the absence of the OH signal at δ 3.35; ^{13}C NMR ($CDCl_3$): δ 93.55 (C-1,1′), 78.64 (C-4,4′), 71.61, 69.32, 68.28, and 60.76 (C-6,6′).

2,3,6-Tri-O-benzoyl-α-D-galactopyranosyl-(1 → 1)-2,3,6-tri-O-benzoyl-α-D-galactopyranoside (**3**).—To a solution of 4,4′-ditriflate **2** (2.0 g 1.62 mmol) in dry *N,N*-dimethylformamide (15 mL) was added sodium nitrite (1.0 g, 14.5 mmol). The suspension was stirred for 1 h at ambient temperature until the reaction was complete as indicated by TLC (solvent A). The mixture was then diluted with CH_2Cl_2, washed with water, and concentrated to give a crude syrupy product that was chromatographed on a column of silica gel (solvent B) to give 1.13 g (72%) of pure compound **3** as a glass: $[\alpha]_D$ +204°, $[\alpha]_{436}$ +424° (*c* 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.07–7.13 (m, 30 H, Ph*H*), 5.92 (dd, 2 H, *J* 3.6, 10.6 Hz; → d, *J* 10.5 Hz on irradiation at 5.69, H-2,2′), 5.84 (dd, 2 H, *J* 2.8, 10.6 Hz; → d, *J* 10.6 Hz on irradiation at 4.29, → d, *J* 2.8 Hz on irradiation at 5.92, H-3,3′), 5.70 (d, 2 H, *J* 3.7 Hz; → s, on irradiation at 5.92, H-1,1′), 4.30–4.05 (m, 8 H, sugar C*H* and CH_2), and 3.10 (d, 2 H, *J* 4.3 Hz; → s, on irradiation at 4.29, D_2O–exchangeable, OH-4,4′); ^{13}C NMR ($CDCl_3$): δ 93.31 (C-1,1′), 71.25 (C-2,2′), 68.97 (C-4,4′ or C-5,5′), 68.61 (C-3,3′), 68.08 (C-4,4′ or C-5,5′), and 62.89 (C-6,6′); positive-ion LSIMS: *m/z* 967.2 $[M + H^+]$, negative-ion LSIMS: *m/z* 965.0 $[M - H^+]^-$, 1118.9 $[M + m\text{-NBA}]^-$. Anal. Calcd for $C_{54}H_{46}O_{17}$ (966.91): C, 67.07; H, 4.80. Found: C, 67.32; H, 5.04.

Preparation of α-D-galactopyranosyl-(1 → 1)-α-D-galactopyranoside (**4**).—A solution of **3** (2.0 g) in MeOH (20 mL) was treated with methanolic M NaOMe (5 mL). The reaction mixture was stirred at room temperature until TLC (solvent D) showed complete reaction. Following deionization with Amberlite IR-120 (H^+) resin, the solution was concentrated to give **4** in almost quantitative yield. Then hexane was added and decanted (to remove methyl benzoate). The syrup thus obtained was crystallized from methanol to give pure **4**: mp 258–261°C; $[\alpha]_D$ +245°, $[\alpha]_{436}$ +478° (*c* 0.86, H_2O) (lit. [7] mp 267–272°, $[\alpha]_D$ +244°; lit. [9] mp 264–267°, $[\alpha]_D$ 235°).

4-Azido-2,3,6-tri-O-benzoyl-4-deoxy-α-D-galactopyranosyl-(1 → 1)-4-azido-2,3,6-tri-O-benzoyl-4-deoxy-α-D-galactopyranoside (**5**).—To a solution of **2** (2.0 g, 1.62 mmol) in anhydrous *N,N*-dimethylformamide (15 mL) were added dicyclopentano-15-crown-5 (86 μL, 0.2 mol equiv) and dry sodium azide (0.74 g, 7.0 mol equiv). The suspension was stirred at 60°C for 5 h, at which time TLC (solvent A) revealed a single product. The mixture was cooled and diluted with CH_2Cl_2, washed with water, dried, and the solvents were evaporated to give a crude syrup, which when applied on a column of silica gel (solvent C) furnished pure **5** (1.24 g, 75%) as an amorphous solid: $[\alpha]_D$ +129°, $[\alpha]_{436}$ +270° (*c* 2.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.10–7.20 (m, 30 H, Ph*H*), 6.08 (dd, 2 H, *J* 3.5, 10.6 Hz, H-3,3′), 5.80 (dd, 2 H, *J* 3.8, 10.6 Hz, H-2,2′), 5.66 (d, 2 H, *J* 3.8 Hz, H-1,1′), 4.32–4.02 (m, 8 H, sugar C*H* and CH_2); ^{13}C NMR ($CDCl_3$): δ 93.08 (C-1,1′), 70.48, 68.57, 67.59, 62.92 (C-6,6′), and 61.36 (C-4,4′); positive-ion LSIMS: *m/z* 1017.3 $[M + H^+]$, negative-ion LSIMS: *m/z* 1169.7 $[M + m\text{-NBA}]^-$. Anal. Calcd for $C_{54}H_{44}N_6O_{15}$ (1016.94): C, 63.77; H, 4.36. Found: C, 63.62; H, 4.52.

4-Azido-4-deoxy-α-D-galactopyranosyl-(1 → 1)-4-azido-4-deoxy-α-D-galactopyranoside (**6**).—The diazide **5** (2.0 g, 2 mmol) was *O*-debenzoylated as described for **4**, to give **6** as a syrup in almost quantitative yield; $[\alpha]_D$ +142°, $[\alpha]_{436}$ +284° (*c* 1.3, CH_3OH); ^{1}H NMR (D_2O): δ 5.14 (d, 2 H, *J* 3.9 Hz, H-1,1′), 4.30–3.58 (m, 12 H, sugar C*H* and CH_2); ^{13}C NMR (D_2O): δ 93.70 (C-1,1′), 70.03, 69.68, 68.22, 63.67

(C-4,4′), and 61.36 (C-6,6′). Anal. Calcd for $C_{12}H_{20}N_6O_9 \cdot H_2O$ (410.35): C, 35.12; H, 5.41. Found: C, 34.89; H, 5.69.

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