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An improved synthesis of 4-azido-4-deoxy- and 4-amino-4-deoxy-α,α-trehalose and their epimers

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ABSTRACT

The order of esterification of the eight hydroxyl groups of α,α-trehalose is HO-6,6′ > HO-2,2′ > HO-3,3′ > HO-4,4′. Under the appropriate conditions of benzoylation, the heptabenzoate with HO-4′ free was obtained in good yield (58%), along with the octabenzoate and the hexabenzoate having HO-4,4′ free. The readily isolated heptabenzoate was a convenient starting material for the synthesis of 4-azido-4-deoxy- (84%) and 4-amino-4-deoxy-α-D-galactopyranosyl α-D-glucopyranoside, and the heptabenzoate of α-D-galactopyranosyl α-D-glucopyranoside with HO-4′ free, which was used as a synthetic precursor of 4-azido-4-deoxy-α-D-glucopyranosyl α-D-glucopyranoside and its amino analogue.

INTRODUCTION

The disaccharide α,α-trehalose[1,2] is a sugar of great biological significance because of the varied roles it plays in Nature as a structural constituent. Furthermore, its 2-, 3-, and 4-amino deoxy derivatives[3] occur as metabolites of Actinomycetes, reported to show antibiotic activity[4].

Several groups of investigators have reported syntheses of aminated α-D-hexopyranosyl α-D-hexopyranosides[5,6]. Recently, Richardson and co-workers[6] prepared 4-amino-4-deoxytrehalose, together with its 4-epimer, by subjecting the 4-chloro or 4-mesylate compounds to displacement by azide in hexamethylphosphoric triamide as the solvent. The yield was poor from the 4-chloro derivative because of elimination to give the 4-ene byproduct. Also, Bundle and co-workers reported[7] the displacement of the methanesulfonate group by acetate in the presence of crown ether in *N,N*-dimethylformamide at high temperature. We now report a convenient synthesis of these 4-amino deoxy derivatives, in which we used

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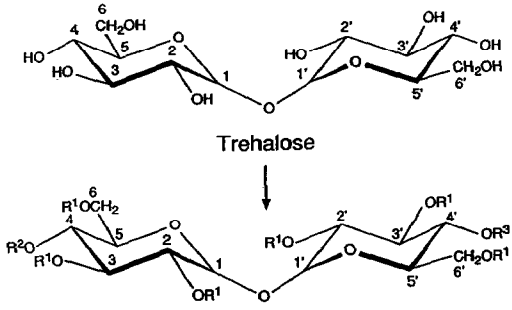


1 $R^1 = R^2 = R^3 = Bz$
2 $R^1 = R^2 = Bz$ $R^3 = H$
3 $R^1 = Bz$ $R^2 = R^3 = H$
4 $R^1 = R^2 = Bz$ $R^3 = Ac$
5 $R^1 = R^2 = Bz$ $R^3 = Tf$

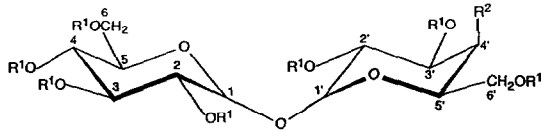
Ac = acetyl
Bz = benzoyl
Tf = trifluoromethylsulfonyl

a one-step reaction to prepare the key intermediate 4′-hydroxy heptabenzoate (**2**), first obtained by Lee[8], via a multistep procedure.

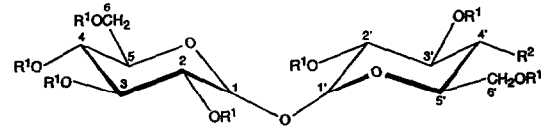
RESULTS AND DISCUSSION

A suspension of anhydrous α,α-trehalose in pyridine was reacted with 8.0 mol equiv of benzoyl chloride, initially at −40°C and then at room temperature. After 18 h one major and two minor products had been formed (TLC), and these were readily isolated by fractional crystallization. The most mobile component was the octabenzoate derivative (**1**), isolated crystalline in 27% yield and characterized by its ^1H and ^{13}C NMR spectra, which indicated symmetrical substitution. The heptabenzoate (**2**) was isolated crystalline in 58% yield. Its ^1H and ^{13}C NMR spectra indicated an unsymmetrical structure, and by comparison with the spectra of **1** it was clear that one of the H-4 resonances had moved upfield, and one of the C-4 resonances had moved downfield to δ 69.70. These changes indicated an unsubstituted OH group at the 4′ position *. On the basis of decoupling experiments, the signal for H-4′ was found at δ 3.75, whereas the spectrum of the acetyl derivative (**4**) of **2** showed an additional lowfield triplet at δ 5.42 due to H-4′, now downshifted by the conversion of OH-4′ into an acetoxy group. The hexabenzoate derivative[9] **3**, also isolated crystalline in 9.4% yield, was characterized by its ^1H

* Primed locants are assigned per normal practice to the partially benzoylated residue in **2**, and these assignments are retained for the subsequent products, in all of which the unique position is the one originally unsubstituted in **2**.



6	$R^1 = Bz$	$R^2 = OH$
7	$R^1 = Bz$	$R^2 = OAc$
8	$R^1 = H$	$R^2 = OH$
9	$R^1 = Bz$	$R^2 = N_3$
10	$R^1 = H$	$R^2 = N_3$
11	$R^1 = H$	$R^2 = NH_2$
12	$R^1 = H$	$R^2 = NHAc$
13	$R^1 = Ac$	$R^2 = NHAc$
14	$R^1 = Bz$	$R^2 = OTf$



15	$R^1 = Bz$	$R^2 = N_3$
16	$R^1 = Bz$	$R^2 = NH_2$
17	$R^1 = Bz$	$R^2 = NHCOCF_3$
18	$R^1 = H$	$R^2 = NHCOCF_3$
19	$R^1 = H$	$R^2 = NH_2$
20	$R^1 = H$	$R^2 = NHCOCH_3$
21	$R^1 = Ac$	$R^2 = NHCOCH_3$

and ^{13}C NMR spectra indicating symmetrical substitution, showing a highfield position (δ 3.83) for H-4,4′ and a downfield shift (δ 69.67) for C-4,4′.

The ready availability of the heptabenzoate **2** permitted the synthesis of some unsymmetrically substituted trehaloses. Acylation of the HO-4′ group of **2** with trifluoromethanesulfonic anhydride (triflic anhydride)[9] gave the 4′-triflate derivative (**5**) in almost quantitative yield. Reaction of **5** with sodium nitrite in *N,N*-dimethylformamide[10,11] at room temperature, gave the heptabenzoate **6** (72%) with inversion of configuration at C-4′. Reaction of **5** with dry potassium acetate in the presence of dicyclohexano-18-crown-6[7] afforded the 4′-acetate derivative (**7**) (83%) with inversion of configuration. In a similar manner, treatment of **5** with sodium azide in *N,N*-dimethylformamide in the presence of dicyclopentano-15-crown-5 at ambient temperature gave the 4′-azido *galacto* derivative (**9**) (80%). The combination of triflate as the leaving group and azide as the nucleophile in the presence of crown ether provided an excellent yield of the displacement product **9**.

The characterization of compounds **6**, **7**, and **9** was based on their ^1H and ^{13}C NMR spectra, in which the signal for H-3′ showed a large ($J \sim 10.5$ Hz) and a

small ($J \sim 3.5$ Hz) spacing, typical of the H-4 of *galacto* derivatives. Catalytic *O*-debenzoylation of **6** or **7** gave the known α-D-galactopyranosyl α-D-glucopyranoside[8] (**8**) (94%) as a crystalline compound.

O-Debenzoylation of **9** gave the crystalline 4′-azido-*galacto* isomer (**10**), which on catalytic hydrogenation afforded the 4′-amino-4′-deoxy-*galacto* isomer as a syrup. This was further characterized as its *N*-acetate **12** and octaacetate **13**. Compound **13** has been reported by Richardson and co-workers[6] as a crystalline product having mp 134–136°C and $[\alpha]_D$ +131°; our values were mp 169–170°C and $[\alpha]_D$ +155°. The characterization of compounds **10**, **12**, and **13** was based on their ^1H and ^{13}C NMR spectra.

In an analogous manner, the 4′-hydroxy-*galacto* derivative **6** was also converted into a 4′-triflate (**14**), which on treatment with sodium azide afforded the 4′-azido-4′-deoxy-*gluco* isomer **15** (73%). Catalytic hydrogenation of **15** gave the 4′-amino-4′-deoxy-α,α-trehalose derivative **16** (90%), and the amino group was protected by trifluoroacetylation to give **17**. *O*-Debenzoylation of **17** gave **18**, and this latter compound on treatment with anion-exchange resin afforded 4-amino-4-deoxy-α,α-trehalose (**19**) as a syrup. Treatment of **19** with acetic anhydride in methanol furnished the 4-acetamido-4-deoxy-α,α-trehalose (**20**), which on further acetylation (acetic anhydride–pyridine) afforded the crystalline octaacetate derivative (**21**). The characterization of **15**, **16**, **17**, **18**, **19**, **20**, and **21** was based on their ^1H NMR spectra, in which the signal for H-3′, identified by decoupling experiments, showed two large spacings ($J_{2,3} = J_{3,4} = 10.0$ Hz) that are typical for *gluco* derivatives. The ^{13}C NMR spectra of these compounds showed an upfield shift of the signal (10–20 ppm) for C-4′ with respect to the key intermediate **6**.

EXPERIMENTAL

General methods—The instrumental and chromatographic procedures employed were given previously[2]. The following solvent combinations (v/v) were utilized for thin-layer and column chromatography: *A*, 29:1 $CHCl_3$–acetone; *B*, 19:1 toluene–EtOAc; *C*, 3:3:1 EtOAc–2-propanol–H_2O; *D*, 19:1 $CHCl_3$–MeOH. Melting points were measured with a Buchi 510 melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer model 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded at Glycomed, Inc. on a Varian Gemini 300 MHz spectrometer at ambient temperature, with decoupling as required for the identification of signals that could not be assigned unambiguously by inspection. All ^{13}C peak assignments were supported by carbon–proton shift correlation experiments. 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 (*m*-NBA, Aldrich) was employed as the sample matrix. Elemental analyses were performed at the University of Hamburg, Germany.

2,3,6-Tri-O-benzoyl-α-D-glucopyranosyl 2,3,4,6-tetra-O-benzoyl-α-D-glucopyrano-

side (**2**).—α,α-Trehalose dihydrate (10 g, 26.5 mmol) was dissolved in dry pyridine (400 mL), and the volume was then reduced to ~300 mL by evaporation under reduced pressure. The solution was stirred and cooled to −40°C, and benzoyl chloride (24.8 mL, 8 mol equiv) was added dropwise. The mixture was stirred at −40°C for a further 1 h and kept overnight at room temperature. After this period, TLC (solvent *A*) showed a single major product and two minor components, one moving faster than the major component and one slower. The mixture was poured into cooled 10% HCl, then extracted with CH_2Cl_2, and the extract was washed successively with $NaHCO_3$ solution and water, dried, and then evaporated. The resultant syrup after dissolution in hot abs EtOH afforded 8.5 g (27.3%) of 2′,3′,4′,6′-tetra-*O*-benzoyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (**1**) as needles; mp 173–176°; $[\alpha]_D$ +223°; $[\alpha]_{436}$ +476° (*c* 0.83, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 8.15–7.20 (m, 40 H, PhH), 6.32 (t, 2 H, *J* 10.0 Hz; → d, *J* 9.8 Hz on irradiation at 5.48, H-3,3′), 5.78 (d, 2 H, *J* 3.8 Hz; → s, on irradiation at 5.48, H-1,1′), 5.69 (t, 2 H, *J* 10.0 Hz; → d, *J* 9.7 Hz on irradiation at 6.27 or 4.27, H-4,4′), 5.53 (dd, 2 H, *J* 3.7, 10 Hz; → d, *J* 3.5 Hz on irradiation at 6.27, H-2,2′), 4.36–4.26 (m, 2 H, H-5,5′), and 4.03–3.82 (dq, 4 H; → q, *J* 12.5 Hz on irradiation at 4.27, H 6ab,6′ab); ^{13}C NMR ($CDCl_3$): δ 93.01 (C-1,1′), 71.82 (C-2,2′), 70.88 (C-3,3′), 69.33 (C-4,4′), 69.13 (C-5,5′), and 62.52 (C-6,6′); positive-ion LSIMS: *m/z* 1326.6 (M + *m*-NBA). Anal. Calcd for $C_{68}H_{54}O_{19}$ (1175.16): C, 69.50; H, 4.63. Found: C, 69.32; H, 4.61.

Chromatography on silica gel (solvent *B*) of the amorphous solid obtained from the mother liquor separated the residue into its components. Eluted first from the column was the major component (16.4 g after crystallization from EtOH, 58% yield from **1**), which was the title compound **2** (needles); mp 160–161°C; lit.[8] 154–159°C; $[\alpha]_D$ +225°, $[\alpha]_{436}$ +481° (*c* 1.97, CH_2Cl_2); lit.[8] $[\alpha]_D$ + 208°; ^1H NMR ($CDCl_3$): δ 8.20–7.10 (m, 35 H, PhH), 6.23 (t, 1 H, *J* 10.0 Hz; → d, *J* 9.3 Hz on irradiation at 5.67 or 5.42, H-3), 5.99 (t, 1 H, *J* 9.9 Hz; → d, *J* 9.5 Hz on irradiation at 5.42 or 3.78, H-3′), 5.75–5.60 (overlapping 2 d and t, 3 H, H-4,1,1′), 5.49–5.40 (two overlapping dd, 2 H, H-2,2′), 4.38–3.72 (m, 8 H, sugar C*H* and CH_2), and 3.36 (d, 1 H, *J* 4.7 Hz, D_2O-exchangeable, O*H*); ^{13}C NMR ($CDCl_3$): δ 93.62, 93.42 (C-1,1′), 74.08 (C-3′), 71.75 (C-2), 71.63 (C-5′), 71.17 (C-2′), 70.67 (C-3), 69.70 (C-4′), 69.34 (C-4), 69.01 (C-5), and 62.94, 62.47 (C-6,6′); negative-ion LSIMS: *m/z* 1223.5 $(M + m\text{-NBA})^-$. Anal Calcd for $C_{61}H_{50}O_{18}$ (1071.05): C, 68.40; H, 4.71. Found: C, 68.32; H, 4.85.

Eluted second was the minor component 2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (**3**) crystallized from EtOH as needles (2.4 g, 9.4% yield from **1**); mp 82–84°C; $[\alpha]_D$ + 197°, $[\alpha]_{436}$ +419° (*c* 1.25, CH_2Cl_2); lit.[9] $[\alpha]_D$ +173.6°; ^1H NMR ($CDCl_3$); δ 8.25–7.20 (m, 30 H, PhH), 5.96 (t, 2 H, *J* 10.0 Hz; → d, *J* 8.4 Hz on irradiation at 5.43, H-3,3′), 5.58 (d, 2 H, *J* 3.5 Hz; → s, on irradiation at 5.43, H-1,1′), 5.43 (dd, 2 H, *J* 3.5, 10.2 Hz; → d, *J* 10.1 Hz on irradiation at 5.58, → d, *J* 3.3 Hz on irradiation at 5.94, H-2,2′), and 4.28–3.70 (m, 10 H, sugar CH_2, and C*H*, and O*H*); ^{13}C NMR ($CDCl_3$); δ 93.88 (C-1,1′), 73.96

(C-3,3′), 71.61 (C-5,5′), 71.19 (C-2,2′), 69.67 (C-4,4′), and 62.99 (C-6,6′); positive-ion LSIMS: m/z 967.7 $(M + H^+)$; negative-ion LSIMS: m/z 965.0 $(M - H^+)$, 1119.0 $(M + m\text{-NBA})^-$. Anal. Calcd for $C_{54}H_{46}O_{17}$ (966.40): C, 67.05; H, 4.80. Found: C, 67.20; H, 4.94.

4-O-Acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranosyl 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranoside (**4**).—Acetylation of **2** (200 mg) with acetic anhydride–pyridine afforded the 4′-*O*-acetyl derivative **4** (92%) as needles; mp 155–157°C (from MeOH); $[\alpha]_D$ +230°, $[\alpha]_{436}$ +490° (*c* 1.31, CH_2Cl_2); ^1H NMR ($CDCl_3$): similar to that of **2** except: downfield shift of H-4′ to δ 5.42 (t, 1 H, J 10.0 Hz; → d *J* 9.9 Hz on irradiation at 6.13, H-4′), absence of O*H* signal, and an additional signal at δ 1.79 (s, 3 H, COCH_3); ^{13}C NMR ($CDCl_3$): δ 93.24 (C-1,1′), 71.73 (C-2,2′), 71.04 (C-3′), 70.70 (C-3), 69.23 (C-4), 69.16 (C-5), 68.92 (C-5′), 68.47 (C-4′), 62.20, 61.84 (C-6,6′), and 21.11 (CH_3); positive-ion LSIMS: m/z 1264.9 $(M + m\text{-NBA})^-$. *Anal.* Calcd for $C_{63}H_{52}O_{19}$ (1113.11): C, 67.92; H, 4.71. Found: C, 67.92; H, 4.65.

2,3,6-Tri-O-benzoyl-α-D-galactopyranosyl 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranoside (**6**).—A solution of **2** (3.2 g, 3.0 mmol) in dry CH_2Cl_2 (40 mL) and pyridine (0.4 mL, 7.5 mmol) was cooled to 0°C, triflic anhydride (0.8 mL, 6 mmol) was added dropwise with stirring, and the reaction was allowed to warm to room temperature and left for a further 30 min, when TLC (solvent *B*) showed the absence of starting material. 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 2,3,6-tri-*O*-benzoyl-4′-*O*-trifluoromethylsulfonyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (**5**) in almost quantitative yield; $[\alpha]_D$ +190°, $[\alpha]_{436}$ +401° (*c* 1.73, CH_2Cl_2); ^1H NMR ($CDCl_3$): similar to that of **2** except for the downfield shift of H-4′ to δ 5.71 (t, 1 H, *J* 9.7 Hz; → d, *J* 9.6 Hz on irradiation at 6.29 or 4.31) and the absence of O*H* signal at δ 3.36; ^{13}C NMR ($CDCl_3$): δ 93.52, 92.77 (C-1,1′), 71.82 (C-2), 71.38 (C-2′ or 3′), 70.83 (C-3), 69.47 (C-4), 69.14 (C-5′), 69.07 (C-5), 68.67 (C-2′ or 3′), 67.97 (C-4′), and 63.02, 62.67 (C-6,6′).

To a solution of **5** in dry *N*,*N*-dimethylformamide (10 mL) was added sodium nitrite (0.83 g, 12 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. Chromatography of the syrup on a column of silica gel (solvent *B*) furnished 2.3 g (72%) of pure compound **6** as a glass; $[\alpha]_D$ +151°, $[\alpha]_{436}$ +315° (*c* 1.85, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 8.15–7.20 (m, 35 H, PhH), 6.28 (t, 1 H, *J* 10.0 Hz; → d, *J* 9.6 Hz on irradiation at 5.52, H-3), 6.01 (dd, 1 H, *J* 3.6, 10.7 Hz; → d, *J* 10.4 Hz on irradiation at 5.76, H-2′), 5.90 (dd, 1 H, *J* 2.8, 10.6 Hz; → d, *J* 10.6 Hz on irradiation at 4.36, H-3′), 5.76 (t, 2 H, *J* 3.5 Hz, H-1,1′), 5.67 (t, 1 H, *J* 10.0 Hz; → d, *J* 10.0 Hz on irradiation at 6.29, H-4), 5.52 (dd, 1 H, *J* 3.7, 10.3 Hz; → d, *J* 3.6 Hz, on irradiation at 6.29, H-2), 4.40–3.94 (m, 7 H, sugar C*H* and CH_2), and 3.30 (d, 1 H, *J* 3.8 Hz; → s on irradiation at 4.36, D_2O-exchangeable, 4′-O*H*); ^{13}C NMR ($CDCl_3$): δ 93.32, 92.50 (C-1,1′), 71.53, 71.42,

70.67, 69.31, 69.18, 68.56, 68.02, 67.54, 62.99, and 62.47 (C-6,6′); positive-ion LSIMS: m/z 1053.5 ($M + H^+ - H_2O$), negative-ion LSIMS: m/z 1223.8 ($M + m$-NBA)$^-$. Anal. Calcd for $C_{61}H_{50}O_{18}$ (1071.05): C, 68.40; H, 4.71. Found: C, 68.55; H, 4.78.

4-O-Acetyl-2,3,6-tri-O-benzoyl-α-D-galactopyranosyl 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranoside (**7**).—The 4-*O*-triflate (**5**) from (2.2 g, 2 mmol) of **2** was dissolved in *N,N*-dimethylformamide (8 mL) and to the solution were added dicyclohexano-18-crown-6 (200 mg, 0.4 mol equiv) together with dry potassium acetate (700 mg, 3.5 mol equiv). The suspension was stirred at room temperature, and it was shown to be complete after 6 h (TLC, solvent *A*). The mixture was then diluted with CH_2Cl_2, washed with water, and concentrated. The residue was purified on a column of silica gel (solvent *B*) that furnished an amorphous solid that crystallized from EtOAc–hexane to give pure **7** as needles (1.9 g, 83%); mp 102–104°C; $[\alpha]_D$ +214, $[\alpha]_{436}$ +453° (*c* 1.51, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.15–7.16 (m, 35 H, Ph*H*), 6.24 (t, 1 H, *J* 9.9 Hz; → d, *J* 9.5 Hz on irradiation at 5.46, H-3), 6.02 (dd, 1 H, *J* 3.6, 10.5 Hz, H-3′), 5.82–5.60 (m, 4 H, H-1,1′,2′,4′), 5.49 (dd, 1 H, *J* 3.7, 10.2 Hz; → d, *J* 3.3 on irradiation at 6.24, H-2), 4.41–3.82 (2m, 6 H, sugar C*H* and CH_2); ^{13}C NMR ($CDCl_3$): δ 93.56, 93.03 (C-1,1′), 71.78 (C-2), 70.82 (C-3), 69.46 (C-4), 69.28 (C-5), 68.90 (C-2′ and 3′), 68.45 (C-4′), 68.00 (C-5′), 62.64 and 61.99 (C-6,6′), and 20.64 (CH_3); negative-ion LSIMS: m/z 1265.1 ($M + m$-NBA)$^-$. Anal. Calcd for $C_{63}H_{52}O_{19}$ (1113.11): C, 67.92; H, 4.71. Found: C, 67.83; H, 4.76.

α-D-Galactopyranosyl α-D-glucopyranoside (**8**).—A solution of **6** or **7** (0.5 g) in MeOH (10 mL) was treated with methanolic M NaOMe (2 mL) at room temperature for 1 h (TLC solvent *C*) and then neutralized with Amberlite IR-120 (H^+) resin, and concentrated to give **8** in almost quantitative yield; hexane was added and then decanted (to remove methyl benzoate). The syrup obtained was crystallized by adding ether; mp 165–170°C; $[\alpha]_D$ +202°, $[\alpha]_{436}$ +397° (*c* 0.51, H_2O), lit.[8] $[\alpha]_D$ +183°; ^{1}H NMR (D_2O): δ 5.15 (t, 2 H, $J_{1,2}$ 3.7 Hz, H-1,1′), 4.04—3.29 (m, 12 H, sugar C*H* and CH_2); ^{13}C NMR (D_2O): 93.86, 93.66 (C-1,1′), 73.02, 72.59, 71.79, 71.58, 70.18, 69.75, 69.45, 69.42, and 61.65, 61.00 (C-6,6′); positive-ion LSIMS: m/z 343.1 ($M + H^+$), 365.1 ($M + Na^+$), 435.1 ($M + H^+ + 92$), negative-ion LSIMS: m/z 341.1 ($M - H^+$),433.1 ($M - H^+ + 92$). Anal. Calcd for $C_{12}H_{22}O_{11} \cdot H_2O$ (360.31): C, 40.00; H, 6.71. Found: C, 39.82; H, 6.94.

4-Azido-2,3,6-tri-O-benzoyl-4-deoxy-α-D-galactopyranosyl 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranoside (**9**).—The 4-*O*-triflate (**5**) from 1 g (1 mmol) of **2** was dissolved in *N,N*-dimethylformamide (3 mL) and to this solution were added dicyclopentano-15-crown-5 (53 μL, 0.2 mol equiv) together with dry sodium azide (200 mg, 3.5 mol equiv). The suspension was stirred at room temperature, and it was shown to be complete after 4 h by TLC (solvent *A*). The mixture was then diluted with CH_2Cl_2, washed with water, and concentrated. The residue was crystallized from EtOAc–hexane to give **9** (0.86 g, 83.5%) upon recrystallization from EtOH; mp 96–99°C; $[\alpha]_D$ +162°, $[\alpha]_{436}$ +342° (*c* 0.92, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 8.45–7.20 (m, 35 H, PhH), 6.34 (t, 1 H, *J* 9.9 Hz; → d, *J* 9.7 Hz on irradiation at 5.54, H-3),

6.20 (dd, 1 H, *J* 3.4, 10.5 Hz on irradiation at 4.35, H-3′), 5.92 (dd, 1 H, 3.8, 10.7 Hz; → d, *J* 3.6 Hz on irradiation at 6.20, H-2′), 2.90 (d, 2 H, *J* 3.8 Hz, H-1,1′), 5.73 (*t*, 1 H, *J* 9.9 Hz; → d, *J* 9.7 Hz on irradiation at 6.33, H-4), 5.55 (dd, 1 H, *J* 3.7, 10.2 Hz; → d, *J* 3.6 Hz on irradiation at 6.33, H-2), 4.46-3.98 (2 m, 7 H, sugar C*H* and CH_2); ^{13}C NMR ($CDCl_3$): δ 93.17, 92.74 (C-1,1′), 71.66, 70.69, 69.34, 69.13, 68.75, 67.70, and 63.02, 62.54 (C-6,68j7), and 61.45 (C-4′); positive-ion LSIMS: *m/z* 1096.0 ($M + H^+$), negative-ion LSIMS: *m/z* 1248.4 ($M + m$-NBA)$^-$. Anal. Calcd for $C_{61}H_{49}N_3O_{17}$ (1096.06): C, 66.84; H, 4.51; N, 3.83. Found: C, 66.71, H, 4.55; N, 3.76.

*4-Azido-4-deoxy-α-*D*-galactopyranosyl α-*D*-glucopyranoside* (**10**).—The azide **9** (0.54 g) was *O*-debenzoylated as described for **8**, to give **10** (0.16 g, 89%) upon crystallization from EtOH; mp 108–111°C; lit.[6] 109–111°C; $[\alpha]_D$ +150°, $[\alpha]_{436}$ + 298° (*c* 0.72, MeOH); lit.[6] $[\alpha]_D$ +154°; ^1H NMR (D_2O): δ 5.13, 5.10 (2 d, *J* 3.5, 3.3 Hz, H-1,1′), 4.28–2.78 (m, 12 H, sugar C*H* and CH_2); ^{13}C NMR (D_2O): δ 93.97 (C-1,1′), 72.99, 72.63, 71.50, 70.23, 70.17, 69.91, 68.48, 63.88 (C-4′), and 61.58, 60.99 (C-6,6′); positive-ion LSIMS: *m/z* 460.6 ($M + H^+ + 92$), negative-ion LSIMS: *m/z* 365.9 ($M - H^+$)$^-$, 458.1 ($M - H^+ + 92$)′.

*4-Acetamido-4-deoxy-α-*D*-galactopyranosyl α-*D*-glucopyranoside* (**12**).—A solution of **10** (0.3 g) in MeOH (30 mL) was hydrogenated over 10% Pd–C (60 mg) at 40 psi for 18 h at room temperature, then filtered through Celite, and concentrated to give 4′-amino-4′-deoxy-α-D-galactopyranosyl α-D-glucopyranoside (**11**) as a syrup[6]. To a solution of **11** in MeOH (10 mL) was added acetic anhydride (1 mL), and the solution was evaporated to dryness to afford **12** as a glass (0.27 g, 86%); $[\alpha]_D$ +184°, $[\alpha]_{436}$ +364° (*c* 3.0, MeOH); ^1H NMR (D_2O): δ 5.21, 5.16 (2 d, 2 H, *J* 3.7, 3.5 Hz, H-1,1′), 4.42–3.35 (m, 12 H, sugar C*H* and CH_2), and 1.82 (s, 3 H, $COCH_3$); ^{13}C NMR (D_2O): δ 94.03, 93.97 (C-1,1′), 73.19, 72.84, 71.74, 70.72, 70.18, 69.01, 68.68, 61.62, 61.19 (C-6,6′), 51.56 (C-4′), 22.35 (CH_3); positive-ion LSIMS: *m/z* 384.3 ($M + H^+$), 476.4 ($M + H^+ + 92$), negative-ion LSIMS: *m/z* 382.2 ($M - H^+$)$^-$, 474.0 ($M - H^+ + 92$)$^-$. Anal. Calcd for $C_{14}H_{25}NO_{11}$ (383.35): C, 43.86; H, 6.57; N, 3.65. Found: C, 43.60; H, 6.68; N, 3.42.

*4-Acetamido-2,3,6-tri-*O*-acetyl-4-deoxy-α-*D*-galactopyranosyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranoside* (**13**).—Acetylation of **12** with acetic anhydride in pyridine afforded the octaacetyl derivative (TLC, solvent *D*) **13** (90%). Recrystallization from ether gave needles of pure **13**; mp 169–170°C; lit.[6] 134–136°C; $[\alpha]_D$ +155°, $[\alpha]_{436}$ +303° (*c* 0.63, CH_2Cl_2); lit.[6] $[\alpha]_D$ +131°; ^1H NMR ($CDCl_3$); δ 6.07 (d, 1 H, *J* 9.9 Hz; → s, on irradiation at 4.82, D_2O-exchangeable, N*H*), 5.50 (t, 1 H, *J* 9.6 Hz; → br s on irradiation at 4.99, H-3), 5.36–5.21 (m, 3 H; → br d on irradiation at 4.99, H-1,1′,3′), 5.14–4.96 (m, 3 H; → simplified m on irradiation at 5.23, H-2,2′,4), 4.82 (dd, 1 H, *J* 2.9, 9.6 Hz; → d *J* 9.9 Hz, and → d *J* 2.8 Hz on irradiation at 5.23 and 6.06, respectively, H-4′), 4.10–3.88 (m, 6 H, sugar C*H* and CH_2), and 1.90–2.20 (m, 24 H, 8 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 92.48, 92.19 (C-1,1′), 70.09, 69.92, 68.93, 68.57, 68.40, 67.79, 67.72, 62.70, 62.08 (C-6,6′), and 48.34 (C-4′); positive-ion LSIMS: *m/z* 678.2 ($M + H^+$), negative-ion LSIMS: *m/z*

676.1 $(M - H^+)^-$, 830.3 $(M + m\text{-NBA})^-$. Anal. Calcd for $C_{28}H_{39}NO_{18}$ (677.61): C, 49.63; H, 5.80; N, 2.07. Found: C, 49.58; H, 5.82; N, 2.09.

4-Azido-2,3,6-tri-O-benzoyl-4-deoxy-α-D-glucopyranosyl 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranoside (**15**).—The heptabenzoate derivative **6** was reacted with triflic anhydride as described for **5**, to give 2′,3′,6′-tri-*O*-benzoyl-4′-*O*-trifluoromethylsulfonyl-α-D-galactopyranosyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (**14**) as a syrup. The 4-*O*-triflate (**14**) from 0.5 g (0.5 mmol) of **6** was dissolved in *N*,*N*-dimethylformamide (2 mL) and to this solution were added dry sodium azide (150 mg) and dicyclopentano 15-crown-5 (40 μL). The suspension was stirred at 60°C for 6 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 *B*) furnished pure **15** (0.37 g, 73%) as an amorphous solid; $[\alpha]_D$ +259°, $[\alpha]_{436}$ +325° (*c* 1.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.17–7.21 (m, 35 H, PhH), 6.28 (t, 1 H, *J* 10.1 Hz; → d, *J* 9.9 Hz on irradiation at 5.76 or 5.50, H-3), 6.18 (t, 1 H, *J* 9.9 Hz; → d *J* 9.8 Hz on irradiation at 5.41, H-3′), 5.76–5.64 (m, 3 H, H-1,1′,4), 5.50 (dd, 1 H, *J* 3.7, 10.3 Hz; → d *J* 3.7 Hz on irradiation at 6.28, H-2), 5.41 (dd, 1 H, *J* 3.8, 10.3 Hz; → d *J* 3.6 Hz on irradiation at 6.17, H-2′), 4.38–4.28 (m, 1 H; → br s on irradiation at 5.76, (H-5), and 4.08–3.78 (m, 6 H, sugar C*H* and CH_2); ^{13}C NMR ($CDCl_3$): δ 93.50 (C-1,1′), 71.50, 71.29, 70.44, 69.28, 69.01, 62.63, 62.15 (C-6,6′), and 60.85 (C-4′); positive-ion LSIMS: *m/z* 1096.3 $(M + H^+)$. Anal. Calcd. for $C_{61}H_{49}N_3O_{17}$ (1096.06): C, 66.84; H, 4.51; N, 3.83. Found: C, 66.93; H, 4.44; N, 3.70.

2,3,6-Tri-O-benzoyl-4-deoxy-4-trifluoroacetamido-α-D-glucopyranosyl 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranoside (**17**).—Hydrogenation of the 4-azide **15** (0.2 g) was achieved as described for **11**, to give 4′-amino-4′-deoxy-2′,3′,6′-tri-*O*-benzoyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (**16**) as a syrup. To a solution of dry **16** in CH_2Cl_2 (3 mL) was added trifluoroacetic anhydride (0.15 mL), and the mixture was stirred at room temperature for 15 min. The mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$, water, and concentrated to dryness. Column chromatography of the residue gave syrupy **17** (0.15 g, 69% from **14**); $[\alpha]_D$ +204°, $[\alpha]_{436}$ +436° (*c* 1.79, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.14–7.16 (m, 35 H, PhH), 6.28 (t, 1 H, *J* 10.2 Hz; → d, 10.2 Hz on irradiation at 5.47, H-3), 6.19 (t, 1 H, 10.2 Hz; → d, *J* 10.0 Hz on irradiation at 4.55, H-3′), 7.76–7.68 (m, 3 H, H-4, H-1,1′), 5.51 (dd, 1 H, *J* 3.6, 10.2 Hz; → d, *J* 3.3 Hz on irradiation at 6.18, H-2), 5.47 (dd, 1 H, *J* 3.5, 10.2 Hz; → d, *J* 3.4 Hz on irradiation at 6.27, H-2), 4.55 (two overlapping t, 1 H, *J* 10.3 Hz; → t, *J*, 10.2 Hz on irradiation at 6.18, H-4′), 4.39–4.28 (m, 1 H; → br s on irradiation at 7.72, H-5), 4.16–4.07 (m, 1 H; → br s on irradiation at 4.55, H-5), and 4.05–3.73 (m, 4 H, sugar CH_2); ^{13}C NMR ($CDCl_3$): δ 93.13, 92.94 (C-1,1′), 71.78, 71.11, 70.65, 70.09, 69.61, 69.20, 68.80, 62.17, 62.04 (C-6,6′), and 50.99 (C-4′); negative-ion LSIMS: *m/z* 1164.3 $(M - H^+)^-$. Anal. Calcd for $C_{63}H_{50}F_3NO_{18}$ (1166.08): C, 64.89; H, 4.32; N, 1.20. Found: C, 64.78; H, 4.54; N, 1.09.

4-Deoxy-4-trifluoroacetamido-α-D-glucopyranosyl α-D-glucopyranoside (**18**).—*O*-Debenzoylation of **17** in the usual way afforded the title compound **18** as an amorphous solid in almost quantitative yield; ^{1}H NMR (D_2O): δ 5.22, 5.15 (2 d, 2 H, *J* 3.4, 3.5 Hz, H-1,1′), and 3.95–3.35 (m, 12 H, sugar C*H* and CH_2); ^{13}C NMR (D_2O): δ 93.80 (C-1,1′), 72.94, 72.63, 71.63, 71.41, 70.72, 70.23, 70.07, 60.89, and 60.77 (C-6,6′), and 52.34 (C-4′); positive-ion LSIMS: *m/z* 438.2 ($M + H^+$), negative-ion LSIMS *m/z* 436.1 $(M - H + 1)^-$. Anal. Calcd for $C_{14}H_{22}F_3NO_{11} \cdot H_2O$ (455.34): C, 36.93; H, 5.31; N, 3.08. Found: C, 36.72; H, 5.46; N, 2.89.

4-Amino-4-deoxy-α-D-glycopyranosyl α-D-glucopyranoside (**19**).—To remove *N*-trifluoroacetyl groups, compound **18** (100 mg) was dissolved in 50% EtOH (5 mL) and the solution was treated with Dowex-1 × 8 (OH^-) resin (20–50 mesh, 0.5 mL). The mixture was stirred at room temperature for 4 h, at which time TLC (solvent *C*) showed complete reaction. The mixture was then filtered and evaporated to give a hygroscopic syrup in 80% yield; $[\alpha]_D$ +169° (*c* 0.7, H_2O); lit.[6] $[\alpha]_D$ +175°; ^{13}C NMR (D_2O): δ 94.23, 93.97 (C-1,1′), 73.57, 73.20, 72.81, 72.03, 71.83, 71.75, 70.39, and 61.52, 61.18 (C-6,6′), and 53.20 (C-4′).

Acetylation of **19** with acetic anhydride in MeOH afforded 4′-acetamido-4-deoxy-α-D-glucopyranosyl α-D-glucopyranoside (**20**) as a glass; ^{1}H NMR (D_2O): δ 5.20–5.15 (2 d, 2 H, *J* 3.0, 3.7 Hz, H-1,1′), 3.95–3.35 (m, 12 H, sugar C*H* and CH_2), and 2.05 (s, 3 H, OCH_3); ^{13}C NMR (D_2O): δ 93.96 (C-1,1′), 73.17, 72.84, 72.03, 71.96, 71.89, 71.65, 70.84, 70.33, and 61.41, 61.11 (C-6,6′), and 52.19 (C-4′).

4-Acetamido-2,3,6-tri-O-acetyl-4-deoxy-α-D-glucopyranosyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (**21**).—Acetylation of **20** with acetic anhydride in pyridine, afforded the title compound **21** in almost quantitative yield. After crystallization from ether–EtOH, the compound melted at 134–137°C [lit.[6] mp 134–135°C]; $[\alpha]_D$ +132°, $[\alpha]_{436}$ +257° (*c* 0.56, CH_2Cl_2), lit.[6] $[\alpha]_D$ +129°; ^{1}H NMR ($CDCl_3$): 5.95 (d, 1 H, $J_{NH,H-4}$ 9.1 Hz, D_2O-exchangeable, N*H*), 5.47 (t, 1 H, $J_{2,3}$ 10.1 Hz, H-3), 5.34 (t, 1 H, $J_{2',3'}$ 10.2 Hz, H-3′), 5.27 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.22 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.08–4.97 (m, 3 H, H-4, H-2,2′), 4.27—3.82 (m, 7 H, sugar C*H* and CH_2), 2.10–2.00 (m, 21 H, 7 COCH_3) and 1.92 (s, 3 H, NCOCH_3); ^{13}C NMR ($CDCl_3$): 92.90, 92.81 (C-1,1′), 70.64, 70.37, 70.30, 70.23, 70.08, 68.74, 68.65, and 63.18, 62.04 (C-6,6′), 50.80 (C-4′).

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REFERENCES

1 H.H. Baer and B. Radatus, *Carbohydr. Res.,* 128 (1984) 165–174.
2 A.K. Datta, K. Takayama, M.A. Nashed, and L. Anderson, *Carbohydr. Res.,* 218 (1992) 95–109.
3 H.H. Baer and B. Radatus, *Carbohydr. Res.,* 146 (1986) 73–88.
4 L.A. Dolak, T.M. Castle, and A.L. Laborde, *J. Antibiot.,* 33 (1980) 690.
5 H. Paulsen and B. Sumfleth, *Chem. Ber.,* 112 (1979) 3203–3213.
6 R.C. Garcia, L. Hough and A.C. Richardson, *Carbohydr. Res.,* 200 (1990) 307–317.
7 H.P. Wessel, T. Iversen, and D.R. Bundle, *Carbohydr. Res.,* 130 (1984) 5–21.
8 C.K. Lee, *Carbohydr. Res.,* 50 (1976) 152–157.
9 T. Ogawa and M. Matsui, *Tetrahedron,* 37 (1981) 2363–2369.
10 P.J. Burger, M.A. Nashed, and L. Anderson, *Carbohydr. Res.,* 119 (1983) 221–230.
11 R. Albert, K. Dax, R.W. Link, and A.E. Stütz, *Carbohydr. Res.,* 118 (1983) c5–c6.
12 R.I. El-Sokkary, B.A. Silwanis, M.A. Nashed, and H. Paulsen, *Carbohydr. Res.,* 203 (1990) 319–323.