Improved Synthesis of 6-Azido-6-deoxy- and 6,6′-Diazido-dideoxy-α,α-trehaloses

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Abstract: An efficient synthesis of 6-azido-6-deoxy and 6,6′-diazido-dideoxy-α,α-trehalose derivatives was achieved by reaction of trifluoromethanesulfonic anhydride with partially trimethylsilylated heptakis- and hexakis-*O*-(trimethylsilyl)-α,α-trehalose in the presence of pyridine and 4-(*N*,*N*-dimethylamino)pyridine. Displacement with azide and desilylation afforded the title compounds, which represent potential precursors for the corresponding 6-amino- and 6,6′-diamino-trehaloses.

Key words: carbohydrate chemistry, regioselectivity, azides, protecting groups

In a previous communication, we reported the synthesis of trehalose esters of corynomycolic acid, the simplest of the mycolic acids, for studies of trehalose-mycoloyl transferase.[1,2] We also reported the synthesis of a gluco-galacto analogue of trehalose for the same purpose.[3,4] Trehalosamines have been isolated from microorganisms and been synthesized and found to have antimicrobial activity,[5,6] and several groups of investigators have recently reported the syntheses of 6-amino- and 6,6′-diamino-α,α-trehalose.[7–9] In the present study, we describe a convenient synthesis of 6-azido- and 6,6′-diazido-α,α-trehalose compounds in which we have used the triflate derivatives of the partially trimethylsilylated-α,α-trehaloses, displacing the trifluoromethanesulfonate group by azide in the presence of a crown ether in *N*,*N*-dimethylformamide at room temperature.

As shown in Scheme 1, partially protected trehalose derivatives **2** and **3** were obtained from the known 2,3,4,6,2′,3′,4′,6′-octakis-*O*-(trimethylsilyl)-α,α-trehalose (**1**) by controlled alkaline hydrolysis.[1,10] The 2,3,4,2′,3′,4′-hexakis-*O*-(trimethylsilyl)-α,α-trehalose **2** was obtained from **1** as described by Toubiana et al. [methanolic K_2CO_3 solution for 2 h at 0 °C].[10] This hexakis ester **2** was isolated by direct crystallization in excellent yield (90%).[11] On the other hand, 2,3,4,2′,3′,4′,6′-heptakis-*O*-(trimethylsilyl)-α,α-trehalose **3** was prepared from **1** following the method developed by Anderson et al. [methanolic K_2CO_3 solution for ca. 20 min at 0–4 °C].[1] The yield of **3** was limited by the symmetry of its precursor, but a better than expected value of 65% was achieved. Isolation of **3** required chromatography; however, the unchanged starting material **1**, and any over-hydrolyzed product could be recovered for recycling.

The hexakis-*O*-(trimethylsilyl)-α,α-trehalose **2**, thus obtained, permitted the synthesis of symmetrically substituted trehaloses. Hence, acylation of the 6,6′-OH groups of **2** with trifluoromethanesulfonic anhydride (triflic anhydride) gave 6,6′-ditriflate derivative **4** in almost quantitative yield.[12] Reaction of the latter compound with sodium azide in *N*,*N*-dimethylformamide in the presence of dicyclopentano-15-crown-5 at ambient temperature gave 6-azido-6-deoxy-2,3,4-tri-*O*-(trimethylsilyl)-α-D-glucopyranosyl-(1→1)-6-azido-6-deoxy-2,3,4-tri-*O*-(trimethylsilyl)-α-D-glucopyranoside (**5**).[13] 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 **5**.

Desilylation of **5** afforded crystalline 6,6′-diazido-dideoxy-α,α-trehalose **6** in 65% overall yield from **2**.[14] The characterization of **6** was based on ^{1}H NMR spectroscopic analysis; irradiation of the 5,5′-H resonance at δ = 3.94–3.90 ppm simplified the triplet at δ = 3.40 ppm to a doublet (J = 9.5 Hz, H-4,4′) and simplified the double double doublet at δ = 3.56 ppm into a double doublet (H-$6_{a,b}$,$6'_{a,b}$), indicating a symmetrical structure for which the 1,1-H signal was observed as a doublet with a small coupling constant (J = 4.0 Hz).

Acetylation of **6** afforded hexa-acetyl derivative **7** in almost quantitative yield. The structure of **7** was again confirmed by ^{1}H NMR spectroscopy, indicating a symmetrical structure for which the signal of the 1,1′-H appeared as a doublet with a small coupling constant (J = 4.0 Hz) at δ = 5.34 ppm and the ring protons, except for ($6_{a,b}$,$6'_{a,b}$-H) were shifted downfield. Irradiation of the H-2,2′ resonance at δ = 5.09 ppm simplified the triplet at δ = 5.48 ppm to a doublet with a large coupling (H-3,3′), and collapsed the doublet at δ = 5.34 ppm to a singlet (H-1,1′). Irradiation of the H-4,4′ resonance at δ = 5.00 ppm collapsed the triplet at δ = 5.48 ppm to a doublet (H-3,3′) and simplified the multiplet at δ = 4.12–3.99 ppm (H-5,5′).

In an analogous manner, heptakis-*O*-(trimethylsilyl)-α,α-trehalose **3** was also converted into 6′-triflate **8**, which, on treatment with sodium azide, afforded 6′-azido-6′-deoxy-α,α-trehalose derivative **9**.[12,13] Desilylation of **9** afforded

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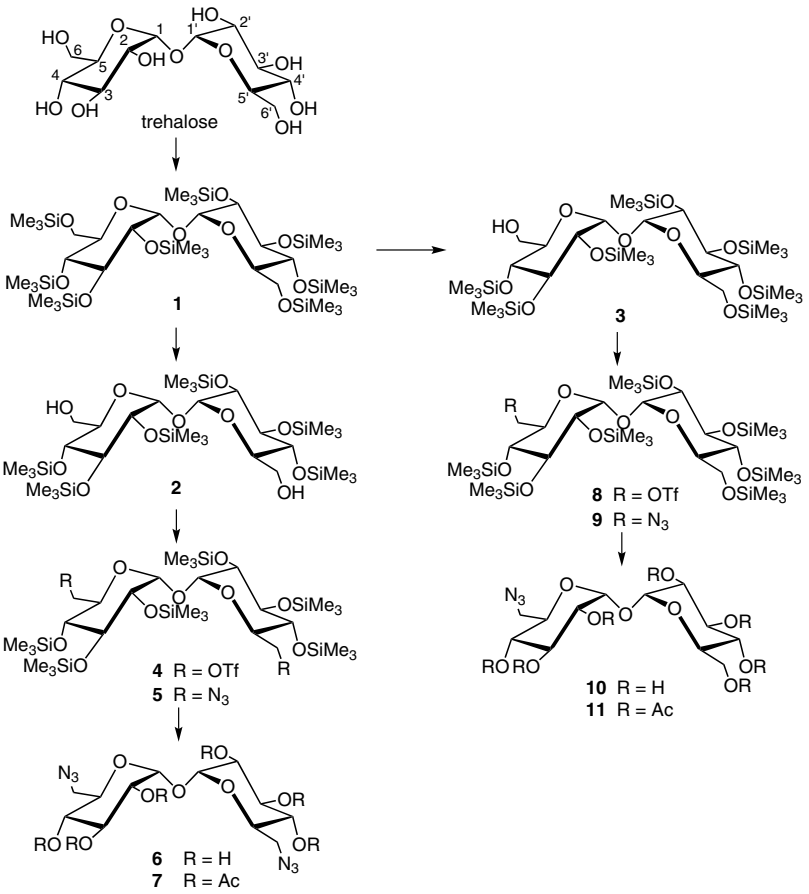

Scheme 1 Synthesis of 6-azido-6-deoxy- and 6,6′-diazido-dideoxy derivatives of α,α-trehalose, and related compounds

crystalline 6′-azido-6′-deoxy-α,α-trehalose (**10**; 56% overall yield from **3**).[14] The characterization of **10** was based on ^{1}H NMR spectroscopy, indicating an unsymmetrical structure for which the signals for H-1 and H-1′ appeared as two doublets at δ = 5.15 ppm (J = 4.5 Hz) and δ = 5.14 ppm (J = 4.0 Hz), respectively. In the ^{1}H NMR spectrum of hepta-acetyl derivative **11**, all the ring proton signals were shifted downfield except the signal of H-6′$_{a,b}$ carrying the azido group.

The ^{1}H NMR spectrum of unsymmetrical trehalose disaccharide **10** possesses a combination of the features of both the 6,6′-diazido derivative **6** and the unsubstituted α,α-trehalose. A noteworthy feature of the ^{1}H NMR spectrum of **11** is that it is similar to that of **7**, with additional signals at δ = 5.51 (t, 3′-H), 5.32 (d, 1′-H), 5.07 (t, 4′-H-), 5.05 (dd, 2′-H), 4.27 (dd, 6′$_a$-H), 4.11–4.07 (m, 5′-H), 4.01 (dd, 6′$_b$-H), and an additional methyl signal at δ = 2.04 ppm (s, 3H, $COCH_3$).

In summary, we have investigated the azido-triflate displacement of readily prepared heptakis- and hexakis-*O*-(trimethylsilyl) derivatives of α,α-trehalose as a practical route to obtain the corresponding mono- or diazido analogues.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General procedure for sulfonylation:** To a dry round-bottom flask, equipped with a magnetic stirring bar, was added trimethylsilylated trehalose **2** or **3** (1 equiv), and a catalytic amount of 4-dimethylaminopyridine (DMAP) and the vessel was sealed with a rubber septum and subjected to high vacuum for 2–3 h to ensure anhydrous conditions. Anhydrous CH_2Cl_2 (10 mL/g) and pyridine (5 equiv for each

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OH) were added and the reaction mixture was stirred for 15 min at room temperature, and then cooled to –5 °C. Triflic anhydride (2.5 equiv for each OH) was injected dropwise with stirring while the reaction mixture was continually maintained at –5 °C. The reaction mixture was then allowed to warm gradually to room temperature and stirred for a further 30 min, when TLC (toluene–EtOAc, 19:1) showed the absence of starting material. The mixture was diluted with CH_2Cl_2, filtered, washed successively with cold aq HCl (1%), aq $NaHCO_3$ (5%), and water, dried (Na_2SO_4), filtered and evaporated to give an amorphous solid that was used for the next step without further purification.

(13) **General procedure for displacement reaction:** To a solution of trehalose derivative **4** or **8** (1 equiv) in anhydrous *N*,*N*-dimethylformamide (3 mL/g) were added dicyclopentano-15-crown-5 (0.15 equiv for each OH) and anhydrous sodium azide (3 equiv for each OH). The suspension was stirred at room temperature, and reaction was shown to be complete after 2 h by TLC (toluene–EtOAc, 19:1). The mixture was then diluted with CH_2Cl_2 and then processed by conventional work-up.

(14) **General procedure for deprotection:** Compound **5** or **9** was dissolved in a mixture of trifluoroacetic acid–tetrahydrofuran–water (8:17:33) and kept at room temperature until TLC analysis showed the hydrolysis to be complete (ca. 1 h). The product was purified by chromatography on silica, eluting successively with hexane–diethyl ether (19:1) and EtOAc–1-propanol (9:3).

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