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Preliminary communication

Synthesis of 6,6′-di-*O*-acylated α,α-trehaloses via 2,3,4,2′,3′,4′-hexa-*O*-benzyl-α,α-trehalose

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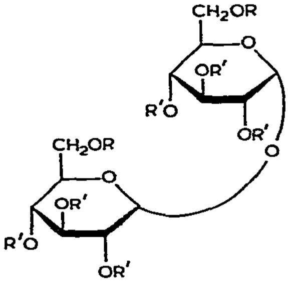
We report two related syntheses of 6,6′-di-*O*-acyl-α,α-trehaloses (analogs of cord factor)[1,2] that alleviate certain deficiencies inherent in some syntheses that have been described; namely, formation of multiesters or of isomeric diesters of trehalose during acylation of 2,3,4,2′,3′,4′-hexa-*O*-(trimethylsilyl)-α,α-trehalose[3] (our experience); poor yields in preparation, and contamination of 6,6′-di-*O*-tosyltrehalose with other isomers[4]; and formation of derivatives of 3,6-anhydrotrehalose in the condensation of 6,6′-di-*O*-tosyltrehalose with potassium mycolates[5]. Other synthetic schemes, also developed for similar reasons, relieved some of the deficiencies[3,6,7].

Our recent interest in preparing symmetrical diesters of (α-D-glucopyranosyluronic acid) (α-D-glucopyranosiduronic acid)[8,9] led us to examine 2,3,4,2′,3′,4′-hexa-*O*-benzyl-α,α-trehalose (**2**) as an intermediate for oxidation of the *O*-protected dicarboxylic acid. Following esterification with the selected alcohol, hydrogenolysis yields the desired diesters without disturbing the carbonyl-to-oxygen linkages. We have also employed the hexa-*O*-benzyltrehalose **2** as an intermediate in the preparation of homogeneous 6,6′-di-*O*-mesyltrehalose, and of homogeneous 6,6′-di-*O*-tosyltrehalose. The relevance of the latter two compounds for improving earlier-described syntheses of cord factor[5] is self-evident; successful exploitation of these approaches will be described later. The facility of these sequences prompted us to examine **2** as an intermediate in the synthesis of simple analogs of cord factor.

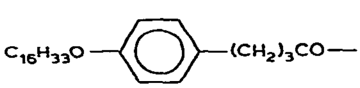
6,6′-Di-*O*-trityl-α,α-trehalose (**1**) was prepared according to Bredereck's method[10]. The dried, crude, gummy product was simply extracted with benzene and triturated extensively with ethanol until it became crystalline. Without further purification, **1** (homogeneous by t.l.c.) was benzylated in 2,4-dioxane solution to yield **2** (syrup). Generally, crude **2** was detritylated in 80% aqueous acetic acid to yield **3**, which was then purified to homogeneity by chromatography on silica gel; yield 69% (based on **1**); $[\alpha]_D^{24}$ +99° (*c* 1.0, chloroform). With mesyl chloride in pyridine, **3** was converted in quantitative yield into the 6,6′-disulfonate **4**; $[\alpha]_D^{24}$ +86° (*c* 1.47, chloroform). Condensation of **4** with the potassium salt of *p*-hexadecyloxyphenyl-4-butanoic acid in hexamethylphosphoric triamide (3 h, 90–95°) gave the symmetrical hexa-*O*-benzyl 6,6′-diester **5**, purified on silica gel (yield 85%).

As a variant, compound **5** was prepared by acylation of **3** with *p*-hexadecyloxyphenyl-4-butanoyl chloride (yield 56%). Hydrogenolysis of **5** for 3 h over palladium-on-carbon, and chromatography on silica gel gave the pure 6,6′-di-*O*-acyltrehalose **6** in 56% yield; m.p. 148–150°, $[\alpha]_D^{24}$ +53° (*c* 0.7, chloroform).

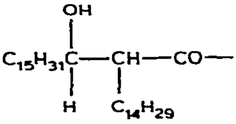


	R	R′
α,α-Trehalose	H	H
1	Tr	H
2	Tr	Bn
3	H	Bn
4	Ms	Bn
5	(a)	Bn
6	(a)	H
7	(b)	Bn
8	(b)	H

(a)



(b)



$C_{15}H_{31}CH(OH)-CH(C_{14}H_{29})-CO-$

DL-*threo*

The alternative scheme of acylation *via* the acid chloride is not applicable with (3-hydroxylated) mycolic acids for preparing "true" cord factors. Instead, compound **4** was treated at 100° in hexamethylphosphoric triamide with the potassium salt of racemic corynomycolic acid[11] to give the hexabenzyldicorynomycolate **7**; this was purified (50% yield) and hydrogenolyzed as before. Chromatography on silica gel gave trehalose 6,6′-DL-dicorynomycolate (**8**) in 65% yield as a wax; $[\alpha]_D^{24}$ +50.5° (*c* 0.87, chloroform); lit.[5] $[\alpha]_D^{20}$ +51.4°. The i.r. spectrum of **8** duplicates that of authentic material. The yields of several intermediate and final products (when purified in all instances by brief, simple, column chromatography) do not take into account the substantial amounts contained in even slightly nonhomogeneous column-effluents. Thus the actual yields are considerably higher than we report here. Proton-n.m.r. spectra of **3**, **4**, **6**, and **8** support the structural assignments.

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