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THE HIGHLY STEREOSELECTIVE SYNTHESIS OF PERBENZYLATED α,α-TREHALOSE AND ITS D-*GALACTO* AND D-*MANNO* ANALOGS

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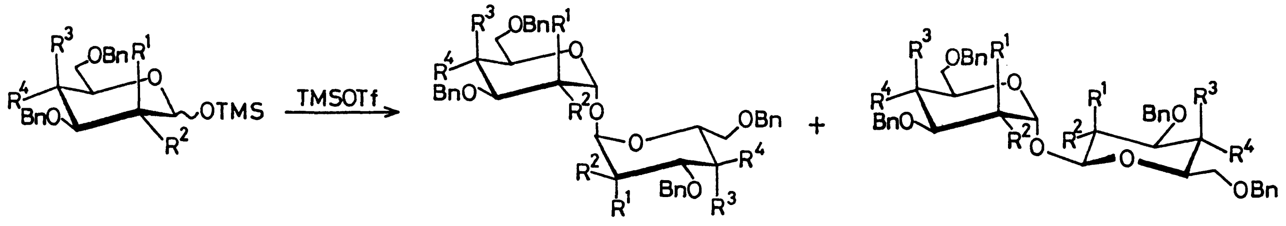
Treatment of 2,3,4,6-tetra-*O*-benzyl-1-*O*-trimethylsilyl-α,β-D-glucopyranose in dichloromethane with trimethylsilyl triflate catalyst gave the corresponding α,α- and α,β-trehaloses in quantitative yield. A similar treatment of D-*galacto* and D-*manno* analogs gave exclusively the corresponding α,α-anomers, respectively.

Many efforts have been made for the synthesis of α,α-trehalose from D-glucose derivatives.[1-6] However, the yields were moderate in almost all cases, excepting a recent report of Pavia *et al.*[7] They obtained perbenzylated α,α- (4a) and α,β-trehaloses (4b) in 97% yield in the ratio of 2.16:1 by treatment of 2,3,4,6-tetra-*O*-benzyl-D-glucose in dichloromethane with trifluoroacetic acid anhydride at -70°C. Similar results were obtained in cases of D-*galacto* and D-*manno* analogs. While the effectiveness of trimethylsilyl triflate (TMSOTf) as a powerful Friedel-Crafts catalyst has been generally known,[8] and it was also applied for *O*-glycosidation of 1-*O*-acetyl-,[9] 1-*O*-trichloroacetimino-,[10] and 1-*O*-trimethylsilyl-aldose[11] derivatives. In a preceding communication we reported an effective synthesis of spiro cyclic orthoesters by the reaction of perbenzylated D-gluconolactone and *O*-trimethylsilyl-1,2-diols with TMSOTf catalyst.[12] This condensation liberates hexamethyldisiloxane instead of water in a dehydration reaction,[13] and it was recently applied for synthesis of aryl glucosides from 1-*O*-trimethylsilyl-α,β-D-glucose derivatives and phenyl trimethylsilyl ethers.[14] This communication describes a facile synthesis of α,α-trehalose type disaccharides by the simple treatment of 1-*O*-trimethylsilyl-D-aldoses with TMSOTf catalyst.



1 $R^1=R^3=H$, $R^2=R^4=OBn$ 4a
2 $R^1=R^4=H$, $R^2=R^3=OBn$ 5
3 $R^2=R^3=H$, $R^1=R^4=OBn$ 6

4b

2,3,4,6-Tetra-*O*-benzyl-1-*O*-trimethylsilyl-α,β-D-glucopyranose (1) was treated

Table 1. Time-dependencea) of the Ratio of 4a to 4b.

Reaction time(h)	4a/4b
0.5	21/79
1	33/67
6	39/61
24	57/43
100	77/23

a) 5% Mol TMSOTf, estimated from ^{13}C-NMR.

Table 2. Solvent Effecta) on the Ratio of 4a to 4b.

Solvent	Dielectric constant	Yield(%)b)	4a/4b
Dioxane	2.2	98	25/75
Benzene	2.3	98	38/62
Ethyl ether	4.2	83	14/86
Dichloromethane	8.9	96	49/51
Acetonitrile	37.5	98	38/62

a) 10% Mol TMSOTf, 1h, estimated from ^{13}C-NMR.
b) Isolated yield.

with catalytic amount of TMSOTf (10% mol) in dichloromethane at room temperature to give the corresponding trehalose derivatives (4a and 4b) within 1 h. ^{13}C-NMR of 4a and 4b showed the anomeric carbon signals of α,α-anomer at 93.43 ppm (lit.7):94.26 ppm) and of α,β-anomer at 99.72 ppm (α-C-1) (lit.7):99.54 ppm) and at 103.62 ppm (β-C-1) (lit.7):104.27 ppm). The time dependence of the ratio of α,α- and α,β-anomers (Table 1) indicates that the kinetically controlled product (4b) isomerizes gradually to the thermodynamically stabler product (4a). Moreover, the solvent effect on the anomerization was examined under keeping the reaction time constant (Table 2). The results were not proportional to the dielectric constants of solvents as was observed in the anomeric effect.15) This may indicate that the trimethylsilyl cation is captured by the oxygen atom of ethers, but 4b can be selectively obtained by the use of ethyl ether or dioxane as solvent. In contrast, a similar treatment of 1-*O*-trimethylsilyl-α,β-D-galactopyranose (2) and -D-mannopyranose (3) derivatives gave exclusively the corresponding α,α-isomers (5 and 6) in quantitative yield, respectively [^{13}C-NMR: C-1 of 5 at 93.53 ppm (lit.7):93.54 ppm), C-1 of 6 at 93.28 ppm (lit.7): 93.25 ppm)].

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