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TMS TRIFLATE INDUCED SYNTHESIS OF 1, 1'-DISACCHARIDES FROM 1-HYDROXY SUGARS

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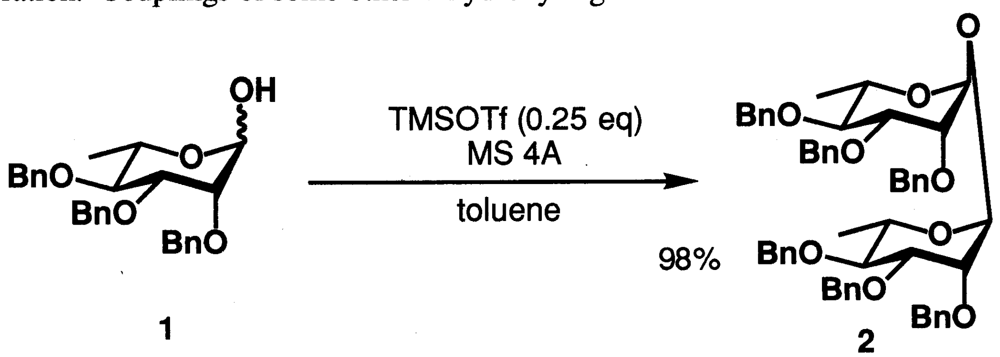
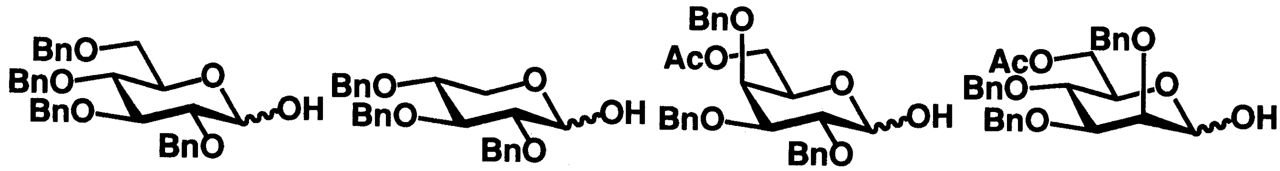
A variety of 1,1'-disaccharides have been prepared by TMS triflate induced coupling of 1-hydroxy sugars in reasonable yield.

KEYWORDS 1,1'-disaccharide; TMS triflate; 1-hydroxy sugar

We have been interested in the synthesis of cell wall glycolipids of mycobacteria, trehalose 6, 6'-dimycolate (TDM) and analogs,[2,3] and already reported the synthesis and characterization of four stereoisomers of trehalose 6, 6'-dicorynomycolates (TDCM).[4] Herein we wish to describe our recent observation that 1,1'-disaccharides are easily prepared from 1-hydroxy sugars by treatment with TMS triflate in the presence of molecular sieves. Trehalose and analogs have been prepared by Koenigs-Knorr reaction of an 1-hydroxy sugar with a glycosyl chloride,[5,6,7,8] perchloric acid catalyzed coupling of 2, 3, 4, 6-tetra-*O*-methyl-D-glucose,[9] or TMS triflate catalyzed coupling of 2, 3, 4, 6-tetra-*O*-benzyl-1-*O*-trimethylsilyl-α,β-D-glucopyranose.[10] Coupling of 2, 3, 4, 6-tetra-*O*-benzyl-D-glucose induced by perchloric acid,[11] diphenyldichlorosilane and silver sulfonate[12] or triflic anhydride[13] have also been recorded. Formations of trehalose as unexpected side products during glycosylations have also been expressed.[14,15] In this paper we describe the first stereoselective coupling of 1-hydroxy L-rhamnose as well as D-mannose derivatives to yield α, α-dimers by a very simple operation. Couplings of some other 1-hydroxy sugars are also examined.



To a solution of 2,3,4-tri-*O*-benzyl-L-rhamnose (**1**) (100 mg) in toluene (2 mL) containing MS 4A (100 mg) was added trimethylsilyl triflate (0.25 equiv) at room temperature over a period of 1 min, and the resulting mixture was stirred for an additional 10 min (entry 2). After quenching of the reaction with an aqueous solution of $NaHCO_3$, the concentrated ether extract was purified by column chromatography on silica gel to give αα dimer **2** in 98% yield. Although the coupling of **1** in dichloromethane afforded the dimer **2** in 88% yield, acetonitrile or THF was not suitable for this condensation. When the reaction was continued for a longer period (more than one hour), the dimer was slowly decomposed to give 1,2,3,4-tetra-*O*-benzyl-α-L-rhamnopyranose. This decomposition became serious without the use of molecular sieves. Thus molecular sieves act as scavengers of liberated triflic acid. Coupling reactions of 2, 3, 4, 6-tetra-*O*-benzyl-D-glucose (**3**), 2, 3, 4-tri-*O*-benzyl-D-xylose (**4**), 2, 3, 4-tri-*O*-benzyl-6-acetyl-D-galactose (**5**), and 2, 3, 4-tri-*O*-benzyl-6-acetyl-D-mannose (**6**) were examined analogously, and the results are summarized in Table I. Although the glucose derivative **3** afforded αβ dimer as the major product along with αα and ββ dimers (entries 5 and 6), xylose and galactose derivatives afforded a mixture of comparable amounts of αα and αβ dimers but not ββ dimers. D-Mannose derivative **6** afforded αα dimer selectively (entries 11 and 12). Condensations of glucose, xylose, galactose, and mannose derivatives were not quick enough with catalytic amounts of TMSOTf, thus excess reagent was employed. We are currently working to prepare a large number of galactose and mannose analogs of TDM and TDCM using coupling products of **5** and **6**.



3 **4** **5** **6**

Table I. TMSOTf Induced Coupling of 1-Hydroxy Sugars in the Presence of MS-4A

Entry	Sugar	TMSOTf (eq)	Solvent	Product (isolated yield, %)		
				αα	αβ	ββ
1	**1**	0.25	Dichloromethane	88	—	—
2	**1**	0.25	Toluene	98	—	—
3	**1**	0.25	Acetonitrile	15	2	—
4	**1**	0.25	THF	—	—	—
5	**3**	2	Dichloromethane	20	44	11
6	**3**	2	Toluene	17	48	8
7	**4**	1.5	Dichloromethane	27	11	—
8	**4**	1.5	Toluene	41	37	—
9	**5**	1.5	Dichloromethane	19	16	—
10	**5**	1.5	Toluene	28	36	—
11	**6**	3	Dichloromethane	76	—	—
12	**6**	3	Toluene	60	—	—

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