

SYNTHESIS AND GLYCOSYLATION SHIFT OF 1,1'-DISACCHARIDES

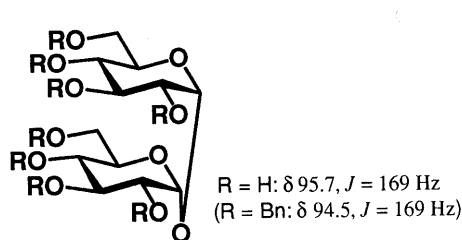
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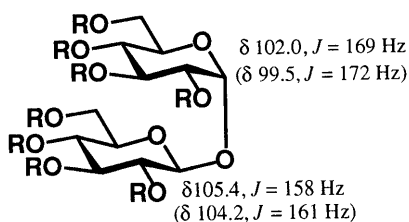
Nineteen kinds of nonreducing 1,1'-disaccharides have synthesized by modified Koenigs-Knorr method, and characterized by NMR. The glycosylation shift of each anomeric carbon has been estimated.

KEYWORDS 1,1'-disaccharide; Trehalose; Koenigs-Knorr glycosylation; glycosylation shift

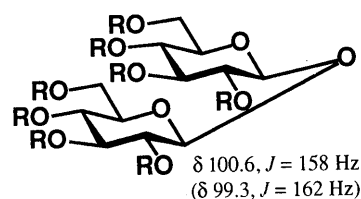
α,α -Trehalose (**1**) is a nonreducing naturally occurring 1,1'-disaccharide distributed in the plant, fungi, yeast, red alga, lichen, and insect kingdoms.¹⁾ Although **1** and its stereoisomers were synthesized a long time ago,²⁾ only a few other 1,1'-disaccharides have been recorded so far. Recently enzymatic transfers of D-galactose to the anomeric positions of *N*-acetylglucosamine³⁾ and *N*-acetylkanos-amine⁴⁾ were reported. Conformation of β,β -trehalose in solution was also discussed recently.⁵⁾ In the synthesis of sweet saponin, osladin,⁶⁾ we noted that most of the modern glycosylation procedures are not useful to prepare glycosides of hemiacetals, and classic Koenigs-Knorr glycosylation is the method of choice for this purpose.⁷⁾ Therefore we have prepared nineteen kinds of 1,1'-disaccharide by means of AgOTf catalyzed glycosylation of hemiacetals with glycosyl chlorides, and the stereochemistries were characterized by ¹³C NMR. By the comparison of the chemical shifts of anomeric carbons with those of mother hemiacetals, we found that the glycosylation shift discussed for alcohols (*RR* or *SS* combination results in a smaller shift, while *SR* combination induces larger $\Delta\delta$) is equally applicable for the glycosylation shift of hemiacetals.^{8,9)}



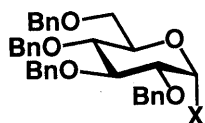
1b: R = Bn
1: R = H



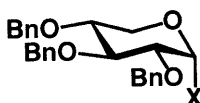
2b: R = Bn
2: R = H



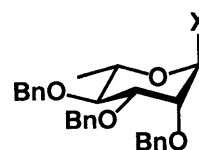
3b: R = Bn
3: R = H



4a: X = OH
4b: X = Cl

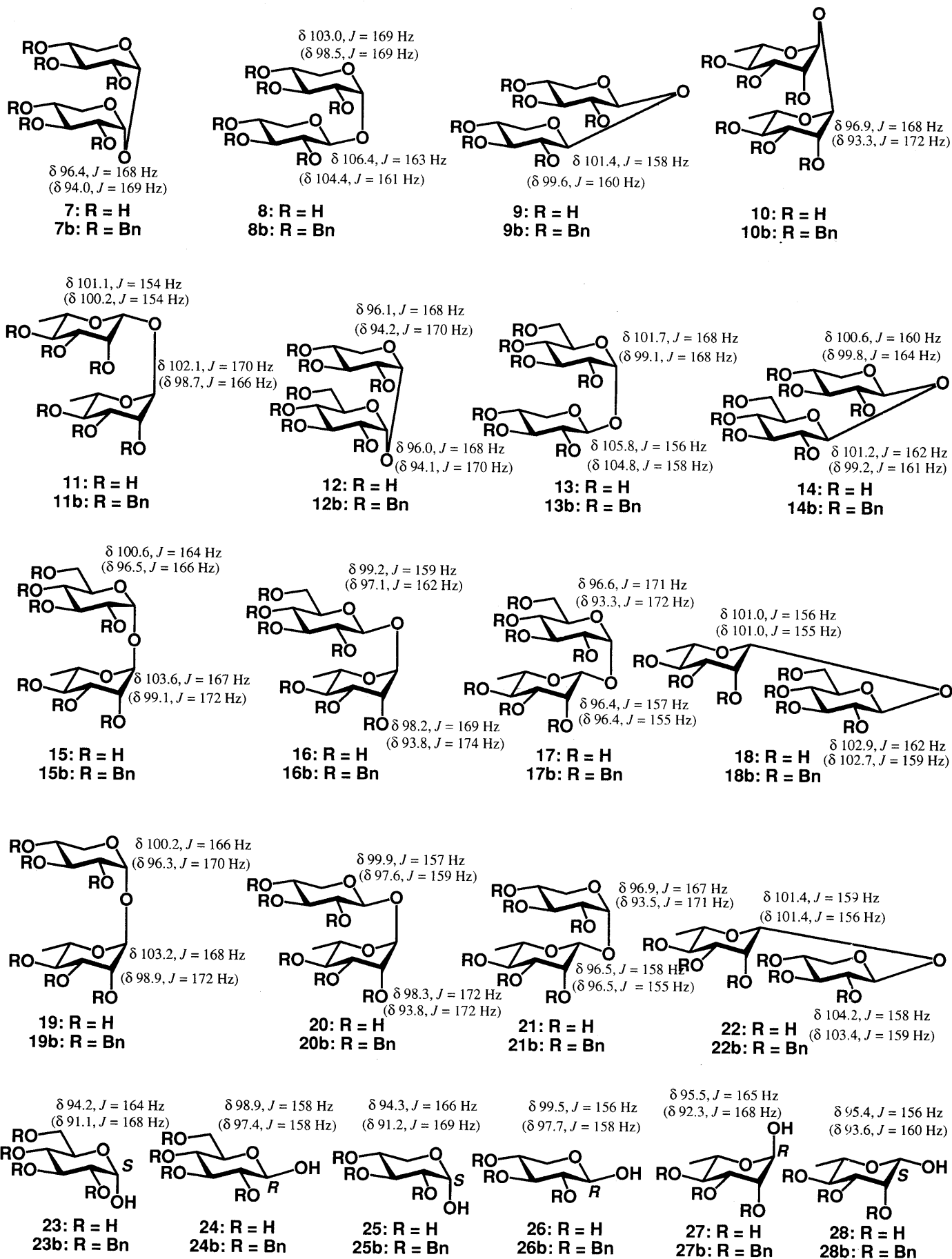


5a: X = OH
5b: X = Cl



6a: X = OH
6b: X = Cl

Condensation of two D-glucose units was achieved as follows. A mixture of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**4a**), 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranosyl chloride (**4b**) (1.5 eq), AgOTf (1.5 eq), tetramethylurea (hereafter TMU, 1.5 eq), and molecular sieves 4A in dichloromethane was stirred at room temperature for 3 h, providing disaccharides after silica gel column chromatography. Further purification by HPLC (Nomura D-Sil-5 column, 20 x 250 mm, hexane-ethyl acetate 8:1 as eluant) afforded $\alpha\alpha$ isomer **1b**, $[\alpha]_D^{24} +82^\circ$ (c 0.7, CHCl_3) in 24% yield, along with $\alpha\beta$ isomer **2b**, $[\alpha]_D^{24} +46^\circ$ (c 1.9, CHCl_3) in 59% yield, and $\beta\beta$ isomer **3b**, $[\alpha]_D^{22} +16^\circ$ (c 0.4, CHCl_3) in 9% yield. Stereochemistries of the products were assigned by the chemical shifts and coupling constants (J_{CH}) of their anomeric center of ¹³C NMR, as shown in parentheses on each structure. Debenzoylation of **1b**, **2b**, and **3b** under hydrogenolysis in the presence of Pd(OH)₂ in MeOH/EtOAc/H₂O 12:1:1 gave **1**, $[\alpha]_D^{21} +97^\circ$ (c 0.4, CH_3OH), **2**, $[\alpha]_D^{21} +60^\circ$ (c 0.5, CH_3OH), and **3**, $[\alpha]_D^{21}$



-13° (*c* 0.2, CH₃OH), respectively. Anomeric carbons chemical shifts with J_{CH} of free 1,1'-disaccharides are also shown on each structure. Coupling reaction between **5a** and **5b** under the same conditions afforded xylose/xylose analogues **7b**, $[\alpha]_D^{23} +86^\circ$ (*c* 0.6, CHCl₃), **8b**, $[\alpha]_D^{20} +41^\circ$ (*c* 1.3, CHCl₃), and **9b**, $[\alpha]_D^{22} -5^\circ$ (*c* 0.7, CHCl₃), in 30%, 53%, and 18% yield, respectively. Rhamnose/rhamnose analogs **10b**, $[\alpha]_D^{20} -50^\circ$ (*c* 1.4, CHCl₃), and **11b**, $[\alpha]_D^{24} -0.5^\circ$ (*c* 1.1, CHCl₃), were also prepared from **6a** and **6b** by the same operations in 65% and 33% yields, respectively. Upon reaction of **4b** with **5a**, mixed 1,1'-disaccharides **12b**, **13b**, and **14b** were obtained. Glucose/rhamnose series **15b-18b**, as well as xylose/rhamnose disaccharides **19b-22b** were also prepared. Catalytic hydrogenolysis of **7b-11b** afforded disaccharides **7**, $[\alpha]_D^{21} +298^\circ$ (*c* 0.1, CH₃OH), **8**, $[\alpha]_D^{21} +20^\circ$ (*c* 0.1, CH₃OH), **9**, $[\alpha]_D^{21} -17^\circ$ (*c* 0.4, CH₃OH), **10**, $[\alpha]_D^{19} -64^\circ$ (*c* 0.8, CH₃OH), and **11**, $[\alpha]_D^{18} -15^\circ$ (*c* 1.0, CH₃OH) quantitatively. Upon analogous hydrogenolysis of **12b-22b**, mixed 1,1'-disaccharides **12**, $[\alpha]_D^{21} +74^\circ$ (*c* 0.3, CH₃OH), **13**, $[\alpha]_D^{21} +84^\circ$ (*c* 0.7, CH₃OH), **14**, $[\alpha]_D^{21} -5^\circ$ (*c* 0.5, CH₃OH), **15**, $[\alpha]_D^{18} +9^\circ$ (*c* 0.5, CH₃OH), and **16**, $[\alpha]_D^{20} +37^\circ$ (*c* 0.2, CH₃OH), **17**, $[\alpha]_D^{20} +122^\circ$ (*c* 1.0, CH₃OH), **18**, $[\alpha]_D^{21} +19^\circ$ (*c* 0.2, CH₃OH), **19**, $[\alpha]_D^{21} +12^\circ$ (*c* 0.7, CH₃OH), **20**, $[\alpha]_D^{21} -57^\circ$ (*c* 0.4, CH₃OH), **21**, $[\alpha]_D^{20} +59^\circ$ (*c* 0.2, CH₃OH), and **22**, $[\alpha]_D^{20} +15^\circ$ (*c* 0.2, CH₃OH), were prepared, respectively. Each chemical shift value of anomeric carbon shown on the structure is compared with those of mother free hemiacetals **23-28** as well as benzyl protected hemiacetals **23b-28b**. The results are summarized in Table I, in which the *R* or *S* represents each stereochemistry of corresponding mother hemiacetals. *RR* or *SS* disaccharides showed smaller shift (less than 3.5 ppm), while *SR* disaccharides induced larger $\Delta\delta$ value (more than 4 ppm). This tendency is the same as that observed for a variety of optically active alcohols.^{8,9)}

Table I. Glycosylation Shift ($\Delta\delta$) of 1,1'-Disaccharide

<i>R-R</i>	<i>S-S</i>	<i>S-R</i>	<i>R-R</i>	<i>S-S</i>	<i>S-R</i>
glc(β)-glc(β) (3b) +1.9 +1.9	glc(α)-glc(α) (1b) +3.4 +3.4	glc(α)-glc(β) (2b) +8.4 +6.8	glc(β)-glc(β) (3) +1.7 +1.7	glc(α)-glc(α) (1) +1.5 +1.5	glc(α)-glc(β) (2) +7.8 +6.5
xyl(β)-xyl(β) (9b) +1.9 +1.9	xyl(α)-xyl(α) (7b) +2.8 +2.8	xyl(α)-xyl(β) (8b) +7.3 +6.7	xyl(β)-xyl(β) (9) +1.9 +1.9	xyl(α)-xyl(α) (7) +2.1 +2.1	xyl(α)-xyl(β) (8) +8.7 +6.9
rha(α)-rha(α) (10b) +1.0 +1.0		rha(β)-rha(α) (11b) +6.6 +6.4	rha(α)-rha(α) (10) +1.4 +1.4		rha(β)-rha(α) (11) +5.7 +6.6
glc(β)-xyl(β) (14b) +1.8 +2.1	glc(α)-xyl(α) (12b) +3.0 +3.0	glc(α)-xyl(β) (13b) +8.0 +7.1	glc(β)-xyl(β) (14) +2.3 +1.1	glc(α)-xyl(α) (12) +1.8 +1.8	glc(α)-xyl(β) (13) +7.5 +6.3
glc(β)-rha(α) (16b) -0.3 +1.5	glc(α)-rha(β) (17b) +2.2 +2.8	glc(α)-rha(α) (15b) +5.4 +6.8	glc(β)-rha(α) (16) +0.3 +2.7	glc(α)-rha(β) (17) +2.4 +1.0	glc(α)-rha(α) (15) +6.4 +8.1
		rha(β)-glc(β) (18b) +7.4 +5.3			rha(β)-glc(β) (18) +5.6 +4.0
xyl(β)-rha(α) (20b) -0.1 +1.5	xyl(α)-rha(β) (21b) +2.3 +2.9	xyl(α)-rha(α) (19b) +5.1 +6.6	xyl(β)-rha(α) (20) +0.4 +2.8	xyl(α)-rha(β) (21) +2.6 +1.1	xyl(α)-rha(α) (19) +5.9 +7.7
		rha(β)-xyl(β) (22b) +7.8 +5.7			rha(β)-xyl(β) (22b) +6.0 +4.7

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