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SYNTHESIS AND GLYCOSYLATION SHIFT OF 1,1'-DISACCHARIDES

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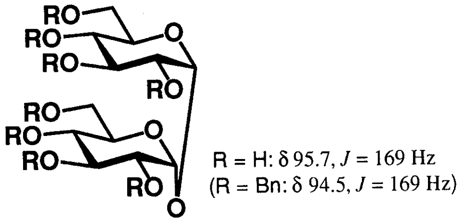
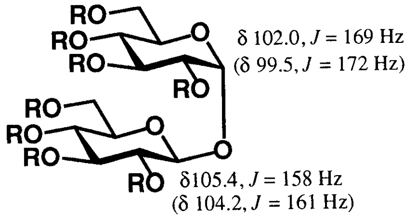
Nineteen kinds of nonreducing 1,1'-disaccharides have synthesized by modified Koenigs-Knorr method, and characterized by NMR. The glycosylation shift of each anomeric carbon has been estimated.

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

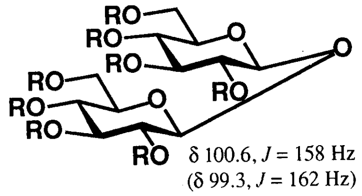
α,α-Trehalose (**1**) is a nonreducing naturally occurring 1,1'-disaccharide distributed in the plant, fungi, yeast, red alga, lichen, and insect kingdoms.[1] Although **1** and its stereoisomers were synthesized a long time ago,[2] only a few other 1,1'-disaccharides have been recorded so far. Recently enzymatic transfers of D-galactose to the anomeric positions of *N*-acetylgentosamine[3] and *N*-acetylkanos-amine[4] were reported. Conformation of β,β-trehalose in solutiohn 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 ^{13}C 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 Δδ) is equally applicable for the glycosylation shift of hemiacetals.[8, 9]



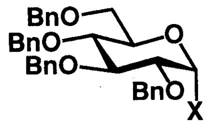
1b: R = Bn
1: R = H



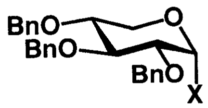
2b: R = Bn
2: R = H



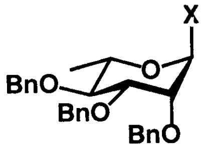
3b: R = Bn
3: R = H



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

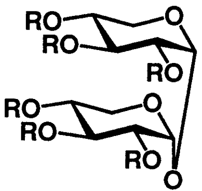


5a: X = OH
5b: X = Cl



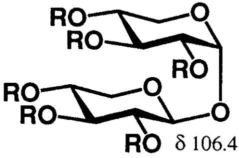
6a: X = OH
6b: X = Cl

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 αα isomer **1b**, $[\alpha]_D^{24}$ +82° (*c* 0.7, $CHCl_3$) in 24% yield, along with αβ isomer **2b**, $[\alpha]_D^{24}$ +46° (*c* 1.9, $CHCl_3$) in 59% yield, and ββ isomer **3b**, $[\alpha]_D^{22}$ +16° (*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 ^{13}C NMR, as shown in parentheses on each structure. Debenzylation of **1b**, **2b**, and **3b** under hydrogenolysis in the presence of $Pd(OH)_2$ in MeOH/EtOAc/H_2O 12:1:1 gave **1**, $[\alpha]_D^{21}$ +97° (*c* 0.4, CH_3OH), **2**, $[\alpha]_D^{21}$ +60° (*c* 0.5, CH_3OH), and **3**, $[\alpha]_D^{21}$



δ 96.4, J = 168 Hz
(δ 94.0, J = 169 Hz)

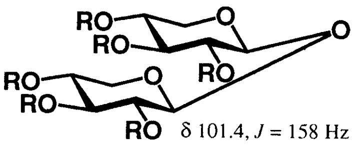
7: R = H
7b: R = Bn



δ 103.0, J = 169 Hz
(δ 98.5, J = 169 Hz)

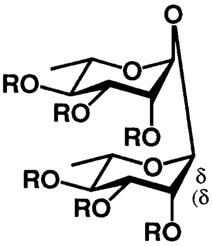
δ 106.4, J = 163 Hz
(δ 104.4, J = 161 Hz)

8: R = H
8b: R = Bn



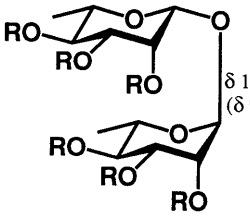
δ 101.4, J = 158 Hz
(δ 99.6, J = 160 Hz)

9: R = H
9b: R = Bn



δ 96.9, J = 168 Hz
(δ 93.3, J = 172 Hz)

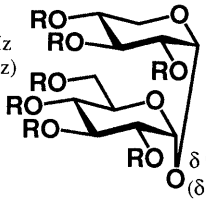
10: R = H
10b: R = Bn



δ 101.1, J = 154 Hz
(δ 100.2, J = 154 Hz)

δ 102.1, J = 170 Hz
(δ 98.7, J = 166 Hz)

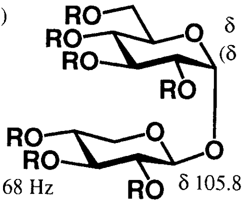
11: R = H
11b: R = Bn



δ 96.1, J = 168 Hz
(δ 94.2, J = 170 Hz)

δ 96.0, J = 168 Hz
(δ 94.1, J = 170 Hz)

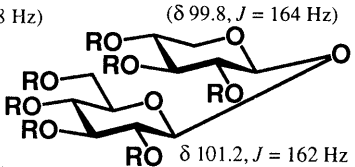
12: R = H
12b: R = Bn



δ 101.7, J = 168 Hz
(δ 99.1, J = 168 Hz)

δ 105.8, J = 156 Hz
(δ 104.8, J = 158 Hz)

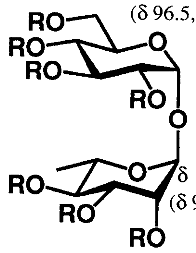
13: R = H
13b: R = Bn



δ 100.6, J = 160 Hz
(δ 99.8, J = 164 Hz)

δ 101.2, J = 162 Hz
(δ 99.2, J = 161 Hz)

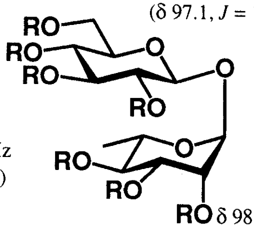
14: R = H
14b: R = Bn



δ 100.6, J = 164 Hz
(δ 96.5, J = 166 Hz)

δ 103.6, J = 167 Hz
(δ 99.1, J = 172 Hz)

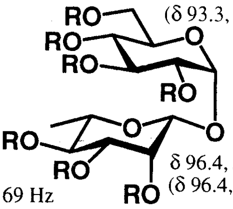
15: R = H
15b: R = Bn



δ 99.2, J = 159 Hz
(δ 97.1, J = 162 Hz)

δ 98.2, J = 169 Hz
(δ 93.8, J = 174 Hz)

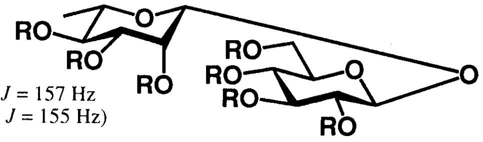
16: R = H
16b: R = Bn



δ 96.6, J = 171 Hz
(δ 93.3, J = 172 Hz)

δ 96.4, J = 157 Hz
(δ 96.4, J = 155 Hz)

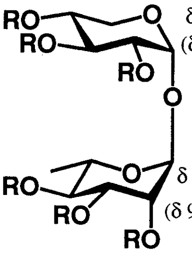
17: R = H
17b: R = Bn



δ 101.0, J = 156 Hz
(δ 101.0, J = 155 Hz)

δ 102.9, J = 162 Hz
(δ 102.7, J = 159 Hz)

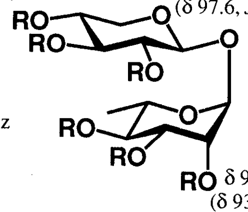
18: R = H
18b: R = Bn



δ 100.2, J = 166 Hz
(δ 96.3, J = 170 Hz)

δ 103.2, J = 168 Hz
(δ 98.9, J = 172 Hz)

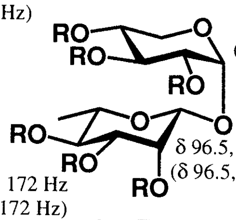
19: R = H
19b: R = Bn



δ 99.9, J = 157 Hz
(δ 97.6, J = 159 Hz)

δ 98.3, J = 172 Hz
(δ 93.8, J = 172 Hz)

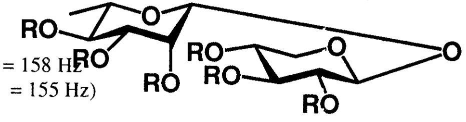
20: R = H
20b: R = Bn



δ 96.9, J = 167 Hz
(δ 93.5, J = 171 Hz)

δ 96.5, J = 158 Hz
(δ 96.5, J = 155 Hz)

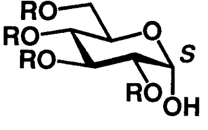
21: R = H
21b: R = Bn



δ 101.4, J = 159 Hz
(δ 101.4, J = 156 Hz)

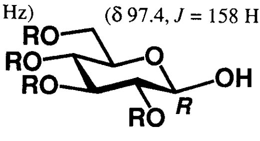
δ 104.2, J = 158 Hz
(δ 103.4, J = 159 Hz)

22: R = H
22b: R = Bn



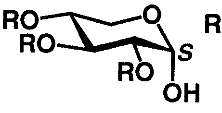
δ 94.2, J = 164 Hz
(δ 91.1, J = 168 Hz)

23: R = H
23b: R = Bn



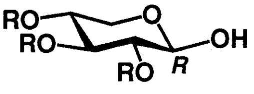
δ 98.9, J = 158 Hz
(δ 97.4, J = 158 Hz)

24: R = H
24b: R = Bn



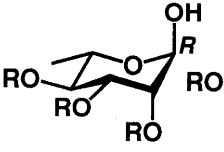
δ 94.3, J = 166 Hz
(δ 91.2, J = 169 Hz)

25: R = H
25b: R = Bn



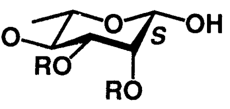
δ 99.5, J = 156 Hz
(δ 97.7, J = 158 Hz)

26: R = H
26b: R = Bn



δ 95.5, J = 165 Hz
(δ 92.3, J = 168 Hz)

27: R = H
27b: R = Bn



δ 95.4, J = 156 Hz
(δ 93.6, J = 160 Hz)

28: R = H
28b: R = Bn

-13° (*c* 0.2, CH_3OH), 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° (*c* 0.6, $CHCl_3$), **8b**, $[\alpha]_D^{20}$ +41° (*c* 1.3, $CHCl_3$), and **9b**, $[\alpha]_D^{22}$ -5° (*c* 0.7, $CHCl_3$), in 30%, 53%, and 18% yield, respectively. Rhamnose/rhamnose anologs **10b**, $[\alpha]_D^{20}$ -50° (*c* 1.4, $CHCl_3$), and **11b**, $[\alpha]_D^{24}$ -0.5° (*c* 1.1, $CHCl_3$), 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° (*c* 0.1, CH_3OH), **8**, $[\alpha]_D^{21}$ +20° (*c* 0.1, CH_3OH), **9**, $[\alpha]_D^{21}$ -17° (*c* 0.4, CH_3OH), **10**, $[\alpha]_D^{19}$ -64° (*c* 0.8, CH_3OH), and **11**, $[\alpha]_D^{18}$ -15° (*c* 1.0, CH_3OH) quantitatively. Upon analogous hydrogenolysis of **12b**-**22b**, mixed 1,1'-disaccharides **12**, $[\alpha]_D^{21}$ +74° (*c* 0.3. CH_3OH), **13**, $[\alpha]_D^{21}$ +84° (*c* 0.7, CH_3OH), **14**, $[\alpha]_D^{21}$ -5° (*c* 0.5, CH_3OH), **15**, $[\alpha]_D^{18}$ +9° (*c* 0.5, CH_3OH), and **16**, $[\alpha]_D^{20}$ +37° (*c* 0.2, CH_3OH), **17**, $[\alpha]_D^{20}$ +122° (*c* 1.0, CH_3OH), **18**, $[\alpha]_D^{21}$ +19° (*c* 0.2, CH_3OH), **19**, $[\alpha]_D^{21}$ +12° (*c* 0.7, CH_3OH), **20**, $[\alpha]_D^{21}$ -57°(*c* 0.4, CH_3OH), **21**, $[\alpha]_D^{20}$ +59° (*c* 0.2, CH_3OH), and **22**, $[\alpha]_D^{20}$ +15° (*c* 0.2, CH_3OH), 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 Δδ 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 (Δδ) of 1,1'-Disaccharide

R-R	*S-S*	*S-R*
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
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
rha(α)-rha(α) (**10b**) +1.0 +1.0		rha(β)-rha(α) (**11b**) +6.6 +6.4
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)-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
		rha(β)-glc(β) (**18b**) +7.4 +5.3
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
		rha(β)-xyl(β) (**22b**) +7.8 +5.7

R-R	*S-S*	*S-R*
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) (**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) (**10**) +1.4 +1.4		rha(β)-rha(α) (**11**) +5.7 +6.6
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) (**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) (**18**) +5.6 +4.0
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**) +6.0 +4.7

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