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L-FRUCTO- AND D-PSICOFURANOSYLATION REACTIONS CATALYZED BY SCANDIUM TRIFLATE

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Abstract – This paper describes the formation of L-fructo- and D-psicofuranosidic bonds by the scandium triflate catalyzed glycosidation. The reaction of the benzoylated L-fructofuranosyl acetate with an alcohol in the presence of 5 mol% scandium triflate in toluene at room temperature for 3 h stereoselectively afforded the corresponding α-L-fructofuranoside in good yields. Several α-D-psicofuranosides were predominantly obtained in good yields by the reactions between the benzoylated D-psicofuranosyl acetate and alcohols under similar reaction conditions. This method successfully provided the sucrose mimics composed of D-glucopyranose and L-fructofuranose or D-psicofuranose.

INTRODUCTION

Rare sugars are monosaccharides that occur in nature in very small quantities. About 50 kinds of them are known. Although they have been only slightly available as research reagents, the discovery of a key enzymatic reaction converting abundantly occurring monosaccharides into the rare sugars has allowed the mass production of some of these rare sugars.[1] This led to the elucidation of the physiological functions of D-psicose and D-allose and has aroused much interest in rare sugar related compounds.[2] We expected that the glycosylation of the rare sugars would be an interesting approach to synthesizing new biologically active compounds. The study of the chemical glycosidation of rare sugars, however, has been reported only by Uenishi et al. regarding the synthesis of D-psicofuranosylceramide.[3,4]

D-fructose is known as one of the monosaccharides that abundantly exist in nature. Several glycosylation reactions using D-fructofuranose derivatives, i.e., the D-fructofuranosylations, have been already reported.[5] We also developed a highly efficient D-fructofuranosylation method which used the benzylated or benzoylated D-fructofuranosyl acetate derivative as the glycosyl donor and scandium triflate

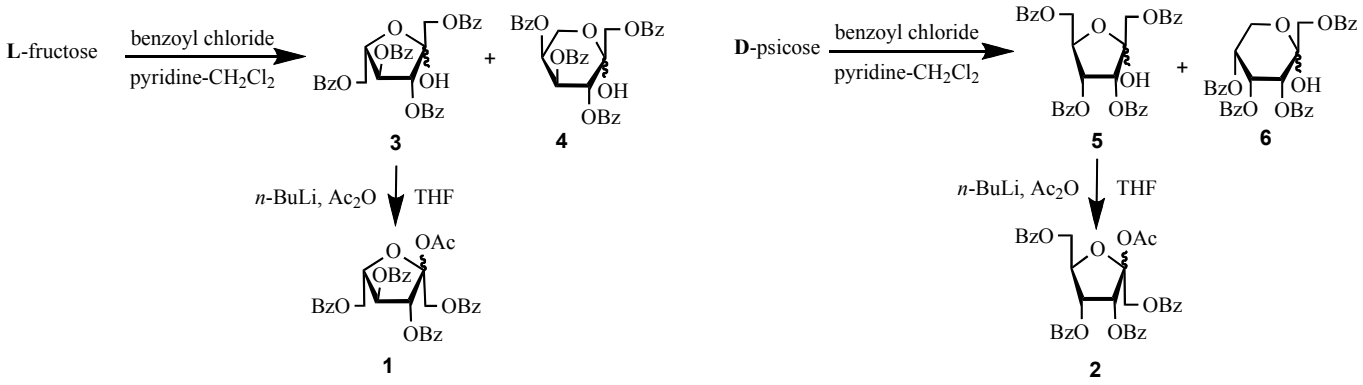
($Sc(OTf)_3$) as the activator.[6] Only 5 mol% $Sc(OTf)_3$ smoothly promoted the reactions of these D-fructofuranosyl acetates with alcohols to produce the corresponding D-fructofuranosides. A high α-stereoselectivity was found when the benzoylated D-fructofuranosyl acetate derivative was utilized as the glycosyl donor. This could be attributed to the effect of the neighboring group participation of the benzoyl group at C-3. In addition, we successfully synthesized several non-reducing disaccharides by D-fructosylation of 1-hydroxy aldopyranose derivatives. They are synthetic mimics of sucrose of which the glucopyranose moiety is replaced with a different kind of aldopyranose. They are expected to have biological functions useful as novel food ingredients.

We postulated that our D-fructofuranosylation system would be applicable for the glycosidation of the L-fructo- and D-psicofuranoses which are the available rare sugars and are the isomers of D-fructofuranose.[7,8] This paper describes the L-fructo- and D-psicofuranosylations catalyzed by $Sc(OTf)_3$, and the synthesis of novel sucrose mimics by glycosylating these rare sugars with a 1-hydroxy glucopyranose derivative.

RESULTS AND DISCUSSION

1. Preparation of glycosyl donors

We investigated the preparation of 1,3,4,6-tetra-*O*-benzoyl-L-fructofuranosyl acetate (**1**) and 1,3,4,6-tetra-*O*-benzoyl-D-psicofuranosyl acetate (**2**) as the glycosyl donors. These compounds were prepared from L-fructose and D-psicose as shown in Scheme 1. The reaction of L-fructose with benzoyl chloride (5 equiv.) in pyridine and dichloromethane at room temperature for 3 h[9] afforded the corresponding benzoylated L-fructofuranose **3** and L-fructopyranose **4** in 64% and 25% yields, respectively. Similar reaction conditions gave the benzoylated D-psicofuranose **5** and D-psicopyranose **6** from D-psicose in 54% and 12% yields, respectively. The subsequent acetylation of **3** using Ac_2O and *n*-BuLi (1.3 equiv.) in THF at -30 °C for 3 h afforded the desired **1** in 79 % yield with an α/β mixture having the isomer ratio of 85/15. The acetate **2** (isomer ratio= 13/87) was obtained from **5** in 75% yield using a similar acetylation procedure.

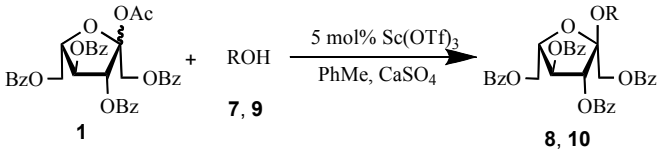


Scheme 1

2. L-Fructo- and D-psicofuranosylation reactions

We investigated the $Sc(OTf)_3$-catalyzed L-fructofuranosylation using **1** as shown in Scheme 2 according to our previously reported D-fructofuranosylation system.[6] The reaction of **1** with 1 equiv. of phenethyl alcohol (**7**) using 5 mol% $Sc(OTf)_3$ in the presence of the dry reagent, $CaSO_4$ in toluene at room temperature for 3 h stereoselectively afforded the corresponding phenethyl α-L-fructofuranoside **8** in 88% yield with no production of its β-isomer. The neighboring group effect of the benzoyl group at the C-3 of **1** seemed to promote the α-stereoselective L-fructofuranosylation reaction, which corresponded to our former observation of the D-fructofuranosylation reaction.

Compound **1** was smoothly glycosylated into 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**9**) under the same reaction conditions to produce the novel sucrose mimics **10a** and **10b** in a good total yield of 88%. The two isomers from the L-fructofuranosidic/D-glucopyranosidic linkages were α/α and α/β, and the isomer ratio from the D-glucopyranosidic linkage was 65/35. These observations almost corresponded to those from our former D-fructofuranosylation study. These results are shown in Table 1.[10]

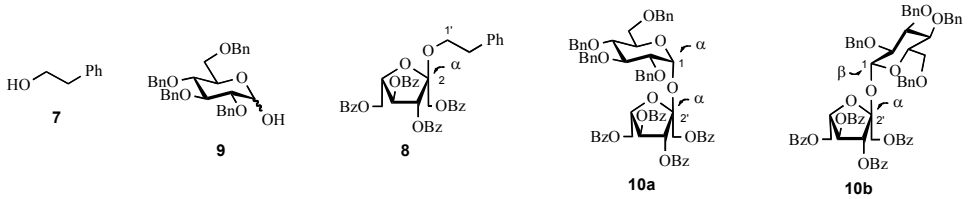


Scheme 2

Table 1. L-Frucotofuranosylation reaction using **1**

Entry	Acceptor	Product	Isomer ratio	Yield (%)
1	**7**	**8**	-	88
2	**9**	**10a** and **10b**	65/35[b)]	88[c)]

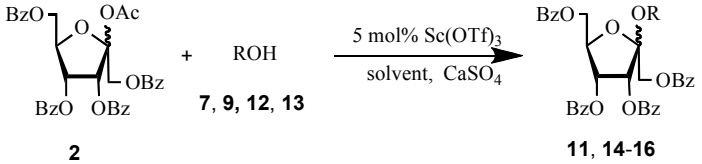
a) Molar ratio: **1**: **7** (or **9**): $Sc(OTf)_3$= 1: 1 (0.5): 0.05. Reaction time: 3h. b) Ratio of **10a**/**10b**. c) Total yield of **10a** and **10b**.



Our next investigation was the D-psicofuranosylation using **2** in the presence of $Sc(OTf)_3$ as shown in Scheme 3. As compound **2** had a poor solubility in toluene, dichloromethane was used as the solvent. The reaction of **2** with **7** using 5 mol% $Sc(OTf)_3$ in dichloromethane at room temperature for 3 h afforded the corresponding phenethyl α- and β-D-psicofuranoside **11a** and **11b** with an isomer ratio of 32/68 in a total yield of 81%. We found that the D-psicofuranosylation also smoothly proceeded under the above stated reaction conditions and predominantly produced the β-isomer. The preferential formation of the β-D-psicofuranosidic bond appeared to be attributed to the neighboring group participation of the C-3

benzoyl group of **2**. However, this effect was insufficient and could not prevent the formation of the α-D-psicofuranosidic bond.

Next, the effect of the solvents was examined using diisopropyl ether and acetonitrile. The reactions using these solvents afforded **11a** and **11b** with isomer ratios of 22/78 and 67/33 in total yields of 73% and 66%, respectively. Diisopropyl ether slightly increased the β-stereoselectivity, while acetonitrile considerably increased the α-stereoselectivity.[11]

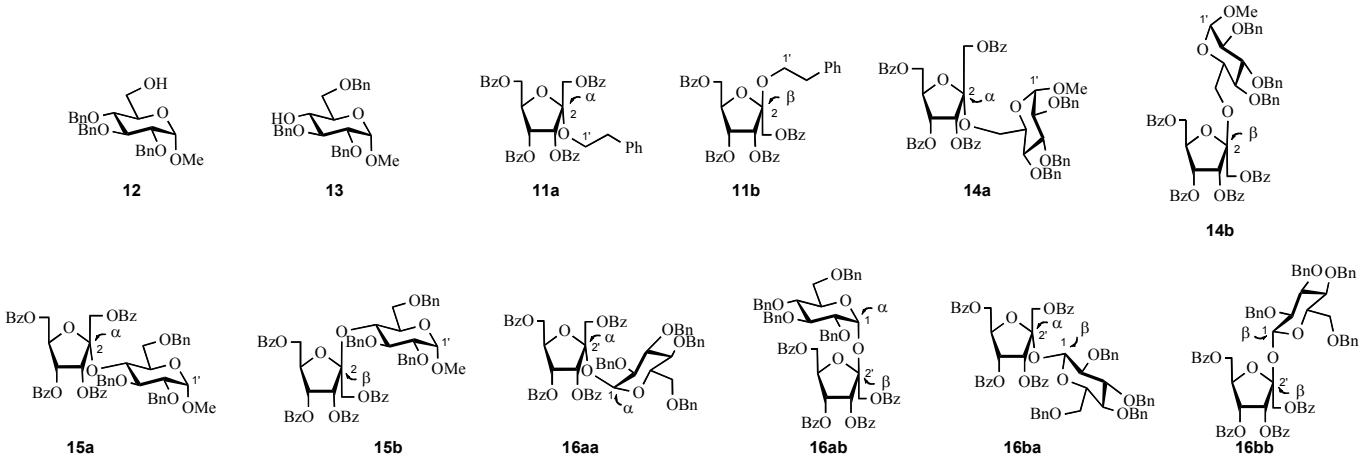


Scheme 3

Table 2. D-Psicofuranosylation reaction using **2**

Entry[a)]	Acceptor	Solvent	Product	Isomer ratio	Total yield (%)
1	**7**	CH_2Cl_2	**11a** and **11b**	32/68[b)]	81
2	**7**	*i*-Pr_2O	**11a** and **11b**	22/78[b)]	73
3	**7**	MeCN	**11a** and **11b**	67/33[b)]	66
4	**12**	CH_2Cl_2	**14a** and **14b**	25/75[c)]	72
5	**13**	CH_2Cl_2	**15a** and **15b**	31/69[d)]	50
6[e)]	**9**	CH_2Cl_2	**16aa**, **16ab**, **16ba** and **16bb**	20/8/28/44[f)]	80

a) Molar ratio: **2**: acceptor: $Sc(OTf)_3$= 1: 1: 0.05. Reaction time: 3h. b) Ratio of **11a**/ **11b**. c) Ratio of **14a**/ **14b**. d) Ratio of **15a**/ **15b**.
e) Molar ratio: **2**: acceptor: $Sc(OTf)_3$= 1: 0.5: 0.05. f) Ratio of **16aa**/ **16ab**/ **16ba**/ **16bb**.



Several sugar alcohols were used as glycosyl acceptors. The reactions of **2** with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**12**) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**13**) in dichloromethane in the presence of 5 mol% $Sc(OTf)_3$ afforded the corresponding α- and β-psicofuranosides **14a** and **14b**, and **15a** and **15b**. The isomer ratios and total yields of **14a** and **14b**, and **15a** and **15b** were 25/75 and 72%, and 31/69 and 50%, respectively. Compound **2** was also smoothly

glycosylated into **9** under similar reaction conditions to produce the novel sucrose mimics **16aa**, **16ab**, **16ba**, and **16bb** in a good total yield of 80%. The isomer ratio was 20/8/28/44. These results are summarized in Table 2.[10]

In summary, this paper reported the $Sc(OTf)_3$-catalyzed L-fructo- and D-psicofuranosylation reactions using **1** and **2**. We observed that the α-stereoselective L-fructofuranosylation using **1** smoothly proceeded with 5 mol% $Sc(OTf)_3$ in toluene at room temperature for 3 h and similar reaction conditions promoted the β-predominant D-psicofuranosylation using **2**. The L-fructo- and D-psicofuranosylations converting **1** and **2** into **9** successfully afforded the novel sucrose mimics.

ACKNOWLEDGEMENT

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10. A typical glycosidation procedure: To a stirred suspension of $Sc(OTf)_3$ (3.9 mg, 0.008 mmol) and **7** (19 μL, 0.16 mmol) in toluene (3 mL) was added **1** (100 mg, 0.16 mmol) in the presence of anhydrous $CaSO_4$ (ca. 100 mg) under an Ar atmosphere and stirred for 3 h. The reaction was then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a saturated aqueous NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified using a preparative silica gel TLC (PTLC; EtOAc/hexane = 1/2) to give the desired glycoside **8** (91 mg, 88%) as an amorphous solid. Compound (**8**): ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.86~2.93 (2H, m, H-2'), 3.87~3.89 (1H, m, H-5), 3.91~3.94 (1H, m, H-1'a), 3.97~4.00 (1H, m, H-1'b), 4.40 (1H, d, *J* = 11.7 Hz, H-1a), 4.55 (1H, dd,

J = 4.8 Hz, *J* = 12.4 Hz, H-6a), 4.70 (1H, dd, *J* = 2.8 Hz, *J* = 11.7 Hz, H-6b), 4.91 (1H, d, *J* = 12.4 Hz, H-1b), 5.45 (1H, d, *J* = 5.5 Hz, H-4), 5.86 (1H, d, *J* = 1.4 Hz, H-3): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 36.2 (C-2'), 59.6 (C-1), 62.5 (C-1'), 63.4 (C-6), 78.9 (C-4), 81.1 (C-5), 81.3 (C-3), 107.0 (C-2), 164.8~166.1 (C=O). Compounds (**10a** and **10b**): isomer mixture: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.99 (1H, d, *J* = 8.2 Hz, H-1**b**), 5.39 (1H, d, *J* = 3.4 Hz, H-1**a**): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 91.4 (C-1**a**), 95.3 (C-1**b**), 107.6 (C-2'**b**), 107.9 (C-2'**a**). Compound (**11a**): ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.90~2.98 (2H, m, H-2'), 3.92~3.96 (1H, m, H-1'a), 4.11~4.14 (1H, m, H-1'b), 4.31 (1H, dd, *J* = 2.9 Hz, *J* = 6.2 Hz, H-5), 4.54 (1H, d, *J* = 12.0 Hz, H-1a), 4.55 (1H, dd, *J* = 3.8 Hz, *J* = 12.0 Hz, H-6a), 4.63 (1H, d, *J* = 12.0 Hz, H-1b), 4.68 (1H, dd, *J* = 2.8 Hz, *J* = 12.0 Hz, H-6b), 5.70~5.72 (2H, m, H-3, H-4): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 36.5 (C-2'), 62.5 (C-1), 62.6 (C-1'), 63.9 (C-6), 71.0 (C-4), 73.2 (C-3), 80.5 (C-5), 103.5 (C-2), 165.2~166.2 (C=O). Compound (**11b**): ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.83 (2H, t, *J* = 6.2 Hz, H-2'), 3.82~3.86 (1H, m, H-1'a), 3.90 (1H, dt, *J* = 6.9 Hz, *J* = 8.9 Hz, H-1'b), 4.19 (1H, dd, *J* = 6.2 Hz, *J* = 11.7 Hz, H-6a), 4.34 (1H, dd, *J* = 4.1 Hz, *J* = 11.7 Hz, H-6b), 4.45 (1H, d, *J* = 12.4 Hz, H-1a), 4.71~4.74 (1H, m, H-5), 4.89 (1H, d, *J* = 12.4 Hz, H-1b), 5.90~5.93 (1H, m, H-4), 5.97 (1H, d, *J* = 4.8 Hz, H-3): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 36.1 (C-2'), 59.2 (C-1), 62.8 (C-1'), 64.8 (C-6), 72.8 (C-4), 75.1 (C-3), 79.2 (C-5), 107.3 (C-2), 164.7~166.0 (C=O). Compound (**14a**): ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.16 (3H, s, Me), 3.27 (1H, dd, *J* = 3.4 Hz, *J* = 9.6 Hz, H-2'), 3.54 (1H, t, *J* = 9.6 Hz, H-4'), 3.75~3.78 (1H, m, H-5'), 3.90~3.96 (3H, m, H-3', H-6'), 4.41 (1H, d, *J* = 3.4 Hz, H-1'), 4.50~4.53 (2H, m, H-1a, H-6a), 4.58~4.61 (3H, m, H-1b, H-6b, CH_2Ph), 4.66~4.69 (2H, m, H-5, CH_2Ph), 5.71~5.72 (1H, m, H-4), 5.77 (1H, d, *J* = 7.6 Hz, H-3): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 54.8 (Me), 61.4 (C-6'), 63.1 (C-1 or C-6), 63.7 (C-1 or C-6), 69.6 (C-5'), 70.9 (C-4), 73.2 (C-3), 77.9 (C-4'), 80.2 (C-5, C-2'), 81.8 (C-3'), 97.6 (C-1'), 103.7 (C-2), 165.1~166.1 (C=O). Compound (**14b**): ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.34 (3H, s, Me), 3.60 (1H, dd, *J* = 3.4 Hz, *J* = 9.6 Hz, H-2'), 3.65 (1H, t, *J* = 8.9 Hz, H-4'), 3.75~3.77 (1H, m, H-5'), 3.86 (1H, dd, *J* = 3.4 Hz, *J* = 10.3 Hz, H-6a), 3.95 (1H, t, *J* = 8.9 Hz, H-3'), 4.10 (1H, dd, *J* = 1.4 Hz, *J* = 10.3 Hz, H-6b), 4.44 (1H, d, *J* = 12.4 Hz, H-1a), 4.64~4.81 (7H, m, H-1', H-6', CH_2Ph), 4.83~4.86 (1H, m, H-5), 4.89 (1H, d, *J* = 12.4 Hz, H-1b), 5.96~5.98 (1H, m, H-4), 6.03 (1H, d, *J* = 4.1 Hz, H-3): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 55.1 (Me), 60.0 (C-6), 60.2 (C-1), 65.7 (C-6'), 69.4 (C-5'), 73.3 (C-4), 75.1 (C-3), 77.4 (C-4'), 79.6 (C-5), 80.3 (C-2'), 81.8 (C-3'), 97.7 (C-1'), 107.3 (C-2), 164.7~166.1 (C=O). Compound (**15a**): ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.44 (Me), 3.59~3.63 (2H, m, H-4', H-6'a), 3.84~3.89 (3H, m, H-3', H-5', H-6'b), 4.03 (1H, t, *J* = 9.6 Hz, H-2'), 4.10~4.19 (2H, m, H-1a, H-5), 4.25~4.27 (2H, m, H-1b, H-6a), 4.63 (1H, d, *J* = 4.1 Hz, H-1'), 5.05 (1H, d, *J* = 12.4 Hz, H-6b), 5.71 (1H, dd, *J* = 2.7 Hz, *J* = 5.5 Hz, H-4), 5.93

(1H, d, *J* = 6.2 Hz, H-3): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 55.1 (Me), 62.5 (C-6), 64.3 (C-1), 69.4 (C-6'), 70.2 (C-5'), 71.4 (C-4), 71.7 (C-3), 72.3 (C-2'), 79.7 (C-5), 80.1 (C-4'), 80.8 (C-3'), 97.4 (C-1'), 105.2 (C-2), 165.2~165.9 (C=O). Compound (**15b**): ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.99 (1H, dd, *J* = 4.1 Hz, *J* = 9.7 Hz, H-2'), 3.31 (3H, s, Me), 3.40 (1H, dd, *J* = 7.6 Hz, *J* = 10.3 Hz, H-6'a), 3.76 (1H, t, *J* = 9.6 Hz, H-4'), 3.83~3.88 (3H, m, H-3', H-5', H-6'b), 4.37 (1H, d, *J* = 3.4 Hz, H-1'), 4.59~4.64 (3H, m, H-1a, H-5, H-6a), 4.80~4.90 (2H, m, H-1b, CH_2Ph), 5.34 (1H, d, *J* = 11.7 Hz, H-6b), 5.90 (1H, d, *J* = 6.9 Hz, H-3), 5.94 (1H, dd, *J* = 4.1 Hz, *J* = 6.2 Hz, H-4): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 55.0 (Me), 63.7 (C-6), 64.8 (C-1), 69.9 (C-5'), 70.2 (C-6'), 70.8 (C-4), 71.1 (C-4'), 75.0 (C-3), 79.8 (C-3'), 80.3 (C-5), 80.9 (C-2'), 97.1 (C-1'), 107.5 (C-2), 164.6~166.1 (C=O). Compounds (**16aa**, **16ab**, **16ba**, and **16bb**): isomer mixture: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.02 (1H, d, *J* = 7.6 Hz, H-1**ba**), 5.06 (1H, d, *J* = 8.3 Hz, H-1**bb**), 5.55 (1H, d, *J* = 3.4 Hz, H-1**ab**), 5.65 (1H, d, *J* = 2.8 Hz, H-1**aa**): ^{13}C NMR ($CDCl_3$, 150 MHz): δ 90.6 (C-1**aa**), 90.9 (C-1**ba**), 95.2 (C-1**bb**), 96.9 (C-1**ab**), 104.0 (C-2'**aa**), 104.4 (C-2'**ab**), 107.2 (C-2'**ba**), 107.8 (C-2'**bb**).

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