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STEREOSELECTIVITY OF D-PSICOFURANOSYLATION INFLUENCED BY PROTECTING GROUPS OF PSICOFURANOSYL DONORS†

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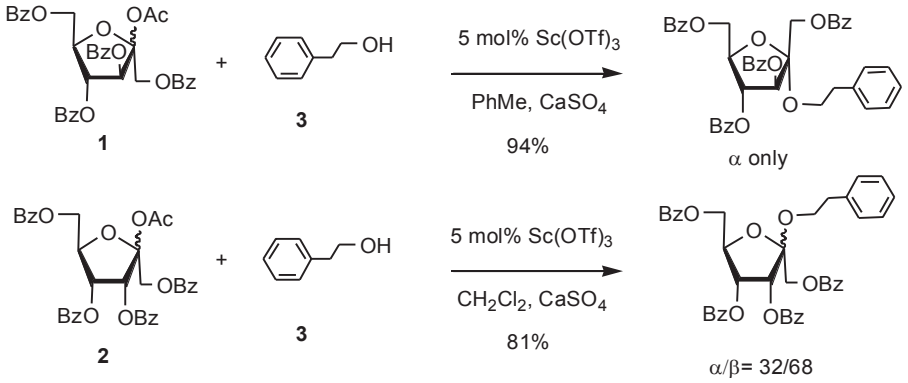
†Dedicated to Professor Dr. Lutz F. Tietze on his 75th birthday

Abstract – We synthesized several types of novel D-psicofuranosyl acetate derivatives, and investigated their use as glycosyl donors in scandium triflate-catalyzed D-psicofuranosylation reactions. Psicofuranosylation demonstrated unique stereoselectivities depending on the protecting groups of psicofuranosyl donors. The donor having a 3,4-isopropylidene group afforded β-psicofuranosides with high stereoselectivities. Donors having a C3 benzoyloxy group demonstrated low stereoselectivities with no neighboring group participation. This study also discusses the stereoselectivities of psicofuranosylation based on the conformers of the glycosyl oxocarbenium ion intermediates as influenced by the protecting groups of the psicofuranosyl donors. We also compared the neighboring group participation of the glycosyl donors bearing a C3 benzoyloxy group during D-psicofuranosylation and D-fructofuranosylation.

The glycosylation reaction is a very important technique for synthesizing biologically active sugar chains and glycosides.[1] In recent years, considerable recent attention has been focused on the development of efficient and stereoselective furanosylation reactions.[2] We are interested in studying the

ketofuranosylation reactions using protected D-fructose and D-psicose. We have previously reported highly reactive scandium triflate ($Sc(OTf)_3$)-catalyzed ketofuranosylation reactions using appropriately protected D-fructofuranosyl acetates and D-psicofuranosyl acetates as the glycosyl donors.[3]

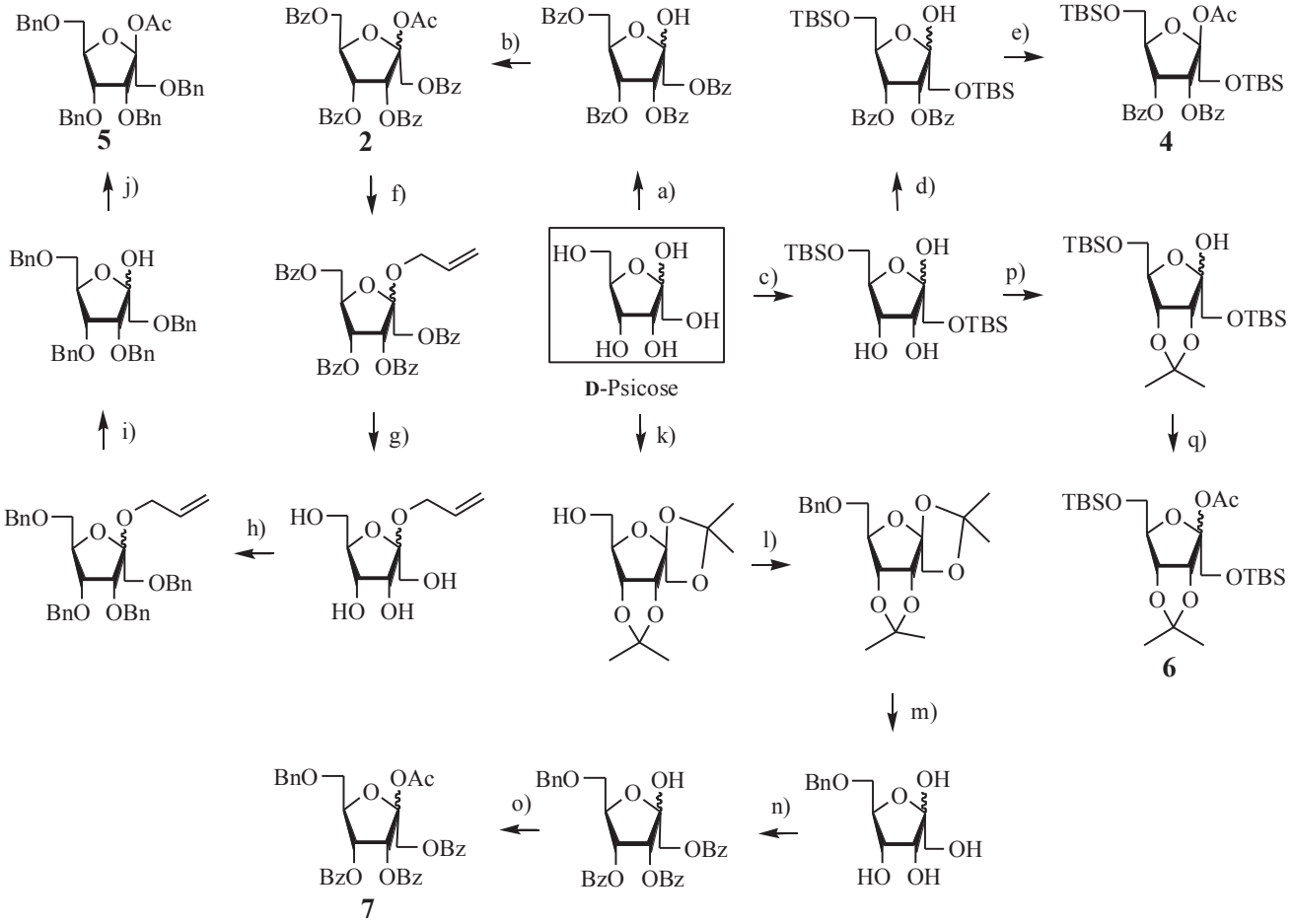


Scheme 1. D-Fructofuranosylation and D-psicofuranosylation reactions using phenethyl alcohol (**3**)

The fructofuranosylation of 1,3,4,6-tetra-*O*-benzoyl-D-fructofuranosyl acetate (**1**) afforded α-fructofuranosides with high stereoselectivity, whereas the psicofuranosylation of 1,3,4,6-tetra-*O*-benzoyl-D-psicofuranosyl acetate (**2**) produced psicofuranosides with α/β anomeric ratios of ca. 30/70. Scheme 1 shows the fructofuranosylation and psicofuranosylation reactions using phenethyl alcohol (**3**) as the glycosyl acceptor. These results suggest that α-fructofuranosides were successfully obtained through the neighboring group participation of the C3 benzoyloxy group of **1**; however, the C3 benzoyloxy group of **2** did not significantly contribute to increasing the β-stereoselectivity during the psicofuranosylation reaction. This prompted us to investigate the unique stereoselectivity of psicofuranosylation, and to explore stereoselective psicofuranosylation, through the use of several types of psicofuranosyl acetate derivatives as the glycosyl donors.

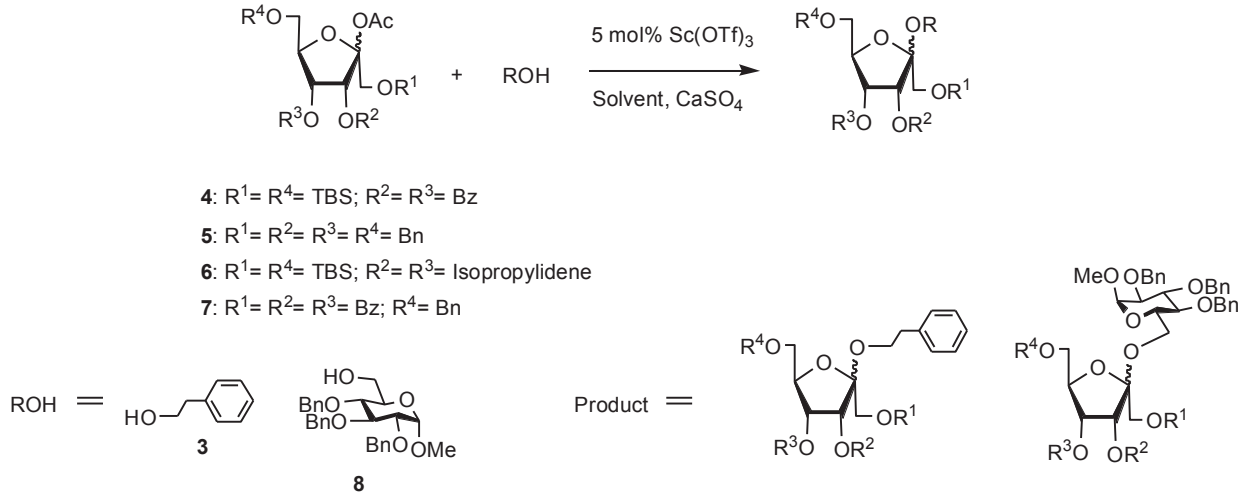
We designed and synthesized several D-psicofuranosyl acetate derivatives (**4**-**7**) as the novel glycosyl donors. The syntheses of **4**-**7** are shown in Scheme 2. 3,4-Di-*O*-benzoyl-1,6-di-*O*-tert-butyldimethylsilyl-D-psicofuranosyl acetate (**4**), 1,3,4,6-tetra-*O*-benzyl-D-psicofuranosyl acetate (**5**), 1,6-di-*O*-tert-butyldimethylsilyl-3,4-*O*-isopropylidene-D-psicofuranosyl acetate (**6**), and 1,3,4-tri-*O*-benzoyl-6-*O*-benzyl-D-psicofuranosyl acetate (**7**) were synthesized in good yields.

We then investigated D-psicofuranosylation reactions using **4**-**7** (Scheme 3). Phenethyl alcohol (**3**) and 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**8**) were used as the glycosyl acceptors, and $Sc(OTf)_3$ was used as the activator. The reactions of **4**-**7** with 1 equiv. of alcohol (**3** or **8**) using 5 mol% $Sc(OTf)_3$ in the presence of dry $CaSO_4$ in toluene or dichloromethane for 1-3 h afforded the corresponding D-psicofuranosides in good yields. These results are summarized in Table 1.



a) BzCl, Py/CH_2Cl_2, 67%, b) BuLi, Ac_2O/THF, -30 ºC, 75%, c) TBSCl, imidazole/DMF, 97%, d) BzCl, Py/CH_2Cl_2, 98%, e) BuLi, Ac_2O/THF, -30 ºC, 83%, f) prop-2-en-1-ol, $Sc(OTf)_3/CH_2Cl_2$, 87%, g) NaOMe/MeOH, quant., h) BnBr, NaH/DMF, 98%, i) $PdCl_2$/MeOH-H_2O, 51%, j) BuLi, Ac_2O/THF, -30 ºC, 82%, k) acetone, TsOH, l) BnBr, NaH/DMF, 84%, m) 3M HCl aq./THF, reflux, 50%, n) BzCl, Py/CH_2Cl_2, 98%, o) BuLi, Ac_2O/THF, -30 ºC, 73%, p) acetone, PPTS, 98%, q) BuLi, Ac_2O/THF, -30 ºC, 75%

Scheme 2. Synthetic routes toward D-psicofuranosyl acetate derivatives (**4-7**)



Scheme 3. D-Psicofuranosylation reaction of **4**, **5**, **6**, or **7** with alcohol **3** or **8**

Table 1. D-Psicofuranosylation reaction of **4**, **5**, **6**, or **7** with alcohol **3** or **8**

Entry[a)]	Donor	ROH	Solvent	Temp./ ºC	Yield /%	α/β ratio
1[b)]	**1**	**3**	PhMe	rt	94	α
2[b)]	**1**	**8**	PhMe	rt	94	α
3[c)]	**2**[d)]	**3**	CH_2Cl_2	rt	81	32/68
4[c)]	**2**[d)]	**8**	CH_2Cl_2	rt	72	25/75
5	**4**	**3**	PhMe	0	72	42/58
6	**7**	**3**	PhMe	0	82	40/60
7	**5**	**3**	CH_2Cl_2	rt	75	5/95
8	**5**	**3**	PhMe	rt	65	6/94
9	**5**	**3**	PhMe	0	81	4/96
10	**5**	**3**	PhMe	-10	78	8/92
11	**5**	**3**	PhMe	-20	78	53/47
12	**5**	**3**	PhMe	-78	56	53/47
13	**5**	**8**	PhMe	0	77	25/75
14[e)]	**6**	**3**	PhMe	0	76	β
15[e)]	**6**	**8**	PhMe	0	63	β

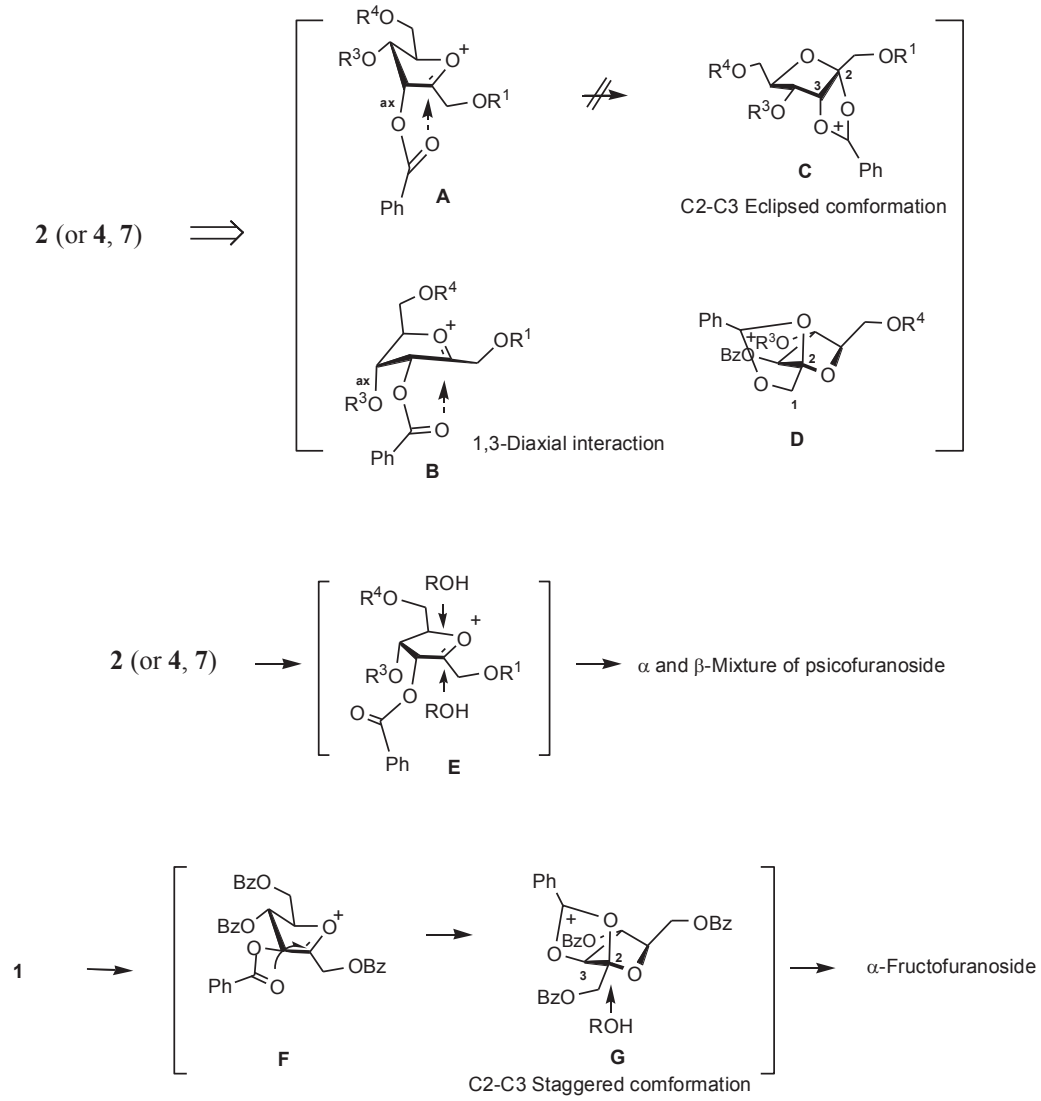
a) Molar ratio; Donor: ROH: $Sc(OTf)_3$= 1: 1: 0.05. Reaction time= 3 h. b) See Ref. 3a. c) See Ref. 3b. d) **2** is poorly soluble in PhMe.
e) Reaction time= 1 h.

As for the anomeric ratios of the produced psicofuranosides, the reactions with **4** and **7** gave anomeric mixtures with α/β ratios of 42/58 and 40/60 (entries 5 and 6), respectively. Judging from these anomeric ratios, it seems as though the neighboring group participation of the C3 benzoyloxy group of **4** and **7** did not occur in the same manner as **2**. In contrast, the reactions with **5** or **6**, bearing a benzyl or isopropylidene group[4] at the C3 position proceeded without the neighboring group participation in high β-stereoselectivities (entries 7-9, 14, and 15). However, the β-stereoselectivity of the reaction with **5** was low at low temperatures (entries 11 and 12). In particular, the reaction with **6** stereoselectively afforded only β-psicofuranosides (entries 14 and 15).

Next, we discuss the stereoselectivities of psicofuranosylation with a focus on the conformers of the glycosyl oxocarbenium ion intermediates influenced by the protecting groups of the psicofuranosyl donors.[5] The glycosyl oxocarbenium ion from **2**, **4**, or **7** could exist as two conformers (**A** and **B**), as shown in Scheme 4. The formation of 2,3-cyclic oxocarbenium conformer **C** from conformer **A** through the neighboring group participation of the C3 benzoyloxy group is disfavored as conformer **C** has a C2-C3 eclipsed conformation with severe strain between the pseudoaxially oriented C3 group and the C2

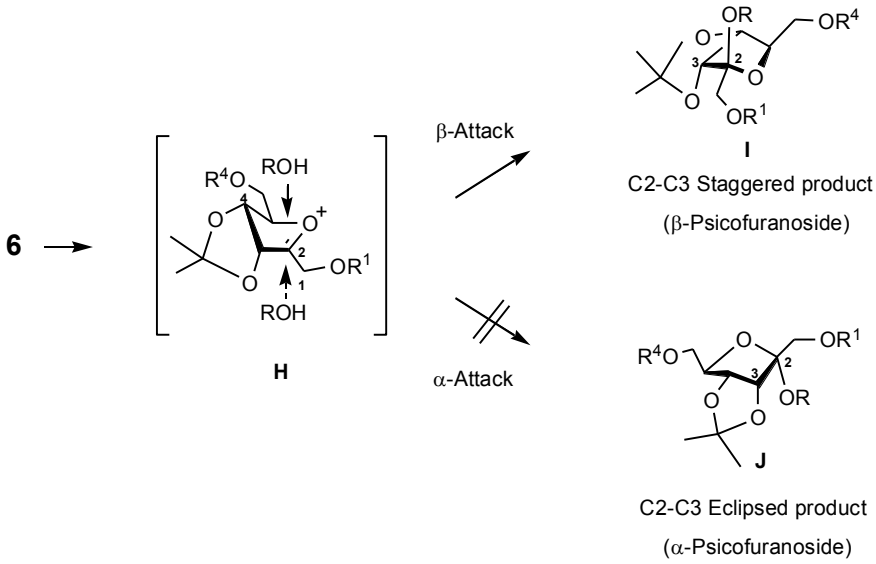
group. Formation of a 2,3-cyclic oxocarbenium ion intermediate from conformer **B** is also disfavored due to the 1,3-diaxial interaction. Based on the anomeric ratios of the produced psicofuranosides, it seems as though stereospecific 1,2-cyclic oxocarbenium conformer **D** from **2** or **7** was not formed as a result of the C1 benzoyloxy group. Therefore, it was concluded that the stereoselectivity of psicofuranosylation with **2**, **4**, or **7** is poor as the stereospecific glycosyl oxocarbenium ion intermediates were not formed, as shown in **E**.

In contrast, conversion of **1** to 2,3-cyclic oxocarbenium ion intermediate **G** via an oxocarbenium conformer **F** is favorable because conformer **G** has a stable C2–C3 staggered conformation. Consequently, the S_N2 attack of alcohols toward **G** occurs to stereoselectively produce α-fructofuranosides.



Scheme 4. Speculated glycosyl intermediates influenced by the C3 benzoyloxyoxy group

For compound **6**, we speculated that cyclic acetal, isopropylidene would transform the oxocarbenium conformer into C4-endo envelope conformer **H**. Nucleophilic α-attack of the alcohol forms disfavored C2–C3 eclipsed product **I**, and its β-attack forms a favored C2–C3 staggered product **J**. Therefore, formation of the staggered product, i.e., β-psicofuranoside, would be expected, as shown in Scheme 5.



Scheme 5. Speculated glycosyl intermediate from **6**

In summary, we investigated $Sc(OTf)_3$-catalyzed D-psicofuranosylation reactions using several types of novel D-psicofuranosyl acetate derivatives as the glycosyl donors.[6] Psicofuranosylation demonstrated unique stereoselectivities influenced by the protecting groups of psicofuranosyl donors. We discussed the stereoselectivities of psicofuranosylation with a focus on the glycosyl oxocarbenium ion intermediates from the psicofuranosyl donors.

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REFERENCES AND NOTES

1. H. Pellissier, *Tetrahedron*, 2005, **61**, 2947.
2. a) N. Oka, R. Kajino, K. Takeuchi, H. Nagakawa, and K. Ando, *J. Org. Chem*., 2014, **79**, 7656; b) A. Ishiwata and Y. Ito, *J. Am. Chem. Soc*., 2011, **133**, 2275.
3. a) T. Yamanoi, N. Misawa, and M. Watanabe, *Tetrahedron Lett*., 2007, **48**, 6458; b) T. Yamanoi, T. Ishiyama, Y. Oda, S. Matsuda, and M. Watanabe, *Heterocycles*, 2010, **81**, 1141; c) T. Yamanoi, N. Misawa, S. Matsuda, M. Watanabe, and Y. Oda, *Heterocycles*, 2012, **86**, 919.

4. Uenishi et al. also reported the stereoselective β-psicofuranosylation using the donor haiving a 3,4-isopropylidene group. See. J. Uenishi and A. Ueda, *Heterocycles*, 2009, **77**, 1297.
5. See. For example: a) C. H. Larsen, B. H. Ridgway, J. T. Shaw, and K. A. Woerpel, *J. Am. Chem. Soc*., 1999, **121**, 12208; b) D. M. Smith, M. B. Tran, and K. A. Woerpel, *J. Am. Chem. Soc*., 2003, **125**, 14149; c) A. Ishiwata, H. Akao, and Y. Ito, *Org. Lett*., 2006, **8**, 5525.
6. A typical psicofuranosylation procedure: To a stirred suspension of $Sc(OTf)_3$ (2.5 mg, 0.005 mmol) and **3** (12 μL, 0.1 mmol) in toluene (3 mL) was added **6** (50 mg, 0.1 mmol) in the presence of anhydrous $CaSO_4$ (ca. 50 mg) under an Ar atmosphere and stirred for 1 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 = 1/20) to give the desired psicofuranoside (43 mg, 76%) as amorphous. $[\alpha]_D^{26}$ -10.7 (*c* 2, $CHCl_3$). ^{1}H NMR: δ 0.06 (6H, s, $Si(CH_3)_2$), 0.07 (6H, s, $Si(CH_3)_2$), 0.88 (18H, s, $SiC(CH_3)_3$), 1.31 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.79 ~ 2.89 (2H, m, CH_2CH_2Ph), 3.55 ~ 3.60 (2H, m, H-6), 3.64 ~ 3.68 (1H, m, $CH_aH_bCH_2Ph$), 3.76 ~ 3.86 (1H, m, $CH_aH_bCH_2Ph$), 3.79 (1H, d, *J* = 11.0 Hz, H-1a), 3.85 (1H, d, *J* = 11 Hz, H-1b), 4.07 (1H, t, *J* = 7.6 Hz, H-5), 4.49 (1H, d, *J* = 5.5 Hz, H-3), 4.66 (1H, d, *J* = 5.5 Hz, H-4), 7.12 ~ 7.29 (Ph), ^{13}C NMR: δ −5.5 ($Si(CH_3)_2$), −5.3 ($Si(CH_3)_2$), −5.2 ($Si(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), 25.1 (CH_3), 25.8 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 26.6 (CH_3), 36.4 (CH_2CH_2Ph), 59.3 (C-1), 61.7 (CH_2CH_2Ph), 64.2 (C-6), 82.5 (C-4), 84.7 (C-3), 86.6 (C-5), 110 (C-2), 112.1 ($C(CH_3)_2$), 126.2 ~ 138.9 (Ph). Anal. calcd for $C_{29}H_{52}O_6Si_2 \cdot 0.25\ H_2O$: C, 62.49; H, 9.49. found: C, 62.67; H, 9.69.