Regioselective Glycosylations of 4,6-*O*-Benzylidene Glucopyranosides with Glycosyl Trichloroacetimidates

Feng-Yan Zhou,[†,††] Jian-Ying Huang,[†] Qing Yuan,[†] and Yan-Guang Wang*[†]
[†]*Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China*
[††]*Department of Chemistry, Zaozhuang College, Zaozhuang 277160, P. R. China*

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An efficient method for synthesis of the (1 → 3)-linked disaccharides is reported. Glycosylations of 4,6-*O*-benzylidene glucopyranosides with glycosyl trichloroacetimidates regioselectively afforded (1 → 3)-linked disaccharides in good yields using trimethylsilyl triflate (TMSOTf)/4 Å MS as catalyst.

Oligosaccharides and glycoconjugates play a crucial role in a multitude of important biological process.[1] In recent years, an explosive growth in the field of glycobiology has stimulated interest in the synthesis of a large number of biologically and therapeutically important oligosaccharides and glycoconjugates.[2] The 1 → 3 or/and 1 → 2 branched oligosaccharides and glycoconjugates are abundant in nature.[3] Regioselective glycolysation of glycosyl 2,3-diol acceptor with glycosyl donor should be a perfect method for construction of this class of branched oligosaccharides. However, their synthesis is commonly performed using a regioselective protection/deprotection strategy,[4] since the similarity in relative reactivity of vicinal diequatorial diols raises the challenge of regioselective monoglycosylation.[5] As part of a program to construct phenylpropanoid glycosides library,[6] we report here our studies on the regioselective glycosylation of 4,6-*O*-benzylidene glucopyranosides **2**. The model reaction was performed using O-acetylated glycosyl trichloroacetimidates (TCA) **1** as donors and trimethylsilyl triflate (TMSOTf) as a promotor (Scheme 1).

Our initial investigations focused on determining the effect of the anomeric substituents and their configurations of acceptors on the reaction regioselectivity. For this purpose, we selected O-acetylated rhamnopyranosyl trichloroacetimidate (**1a**) as donor and different glucopyranosyl 2,3-diols **2a**–**2f** as acceptors for our experiments. To our delight, glycosylation of acceptors **2a**–**2f** with the activated donor **1a** in anhydrous CH_2Cl_2 at −35 °C using TMSOTf/4 Å MS catalyst regioselectively gave the (1 → 3)-linked disaccharides **3a**–**3f** in good yields (61–80%) (Table 1), while (1 → 2)-linked disaccharide could not be isolated.[7] As shown in Table 1, the α-glycoside acceptors (Table 1, Entries 4 and 6) gave the same regioselectivity as their β-isomers (Table 1, Entries 3 and 5). Curious about this regioselectivity, we then examined the glycosylations of accepter **2a** with O-acetylated glycosyl trichloroacetimidates **1b**–**1d**. It was found that the donors **1b**, **1c**, and **1d** also gave the (1 → 3)-linked disaccharides **3g**, **3h**, and **3i**, respectively (Table 1, Entries 7–9).

The establishment of the linkage position of disaccharides **3a**–**3i** is based on their ^{1}H NMR and H–H COSY spectra, which showed the H-3 at $\delta \approx 3.9$ ppm and the H-2 at $\delta \approx 3.5$ ppm (for 2,3-diol acceptors **2a**–**2f**: both H-3 and H-2 at $\delta \approx 3.5$ ppm). We also acetylated compounds **3a** and **3b** with acetic anhydride in pyridine to give **4a** and **4b**. The ^{1}H NMR and H–H COSY spectra of **4a** and **4b** showed the H-2 at $\delta \approx 5.0$ ppm and the H-3 at $\delta \approx 3.9$ ppm (for **3a** and **3b**: H-2 at $\delta \approx 3.5$ ppm, H-3 at $\delta \approx 3.9$ ppm).[8] These facts further confirm the presence of a (1 → 3) glycosidic bond in **3**.

In summary, we have demonstrated that the glycosylation of 4,6-*O*-benzylidene glucopyranoside accepters with O-acetylated glycosyl trichloroacetimidate donors could regioselectively afford (1 → 3)-linked disaccharides using TMSOTf/4 Å MS as catalyst. Further investigations in the utility of this method for preparation of phenylpropanoid glycosides library are currently underway.

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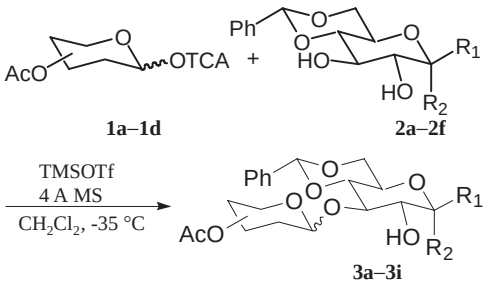
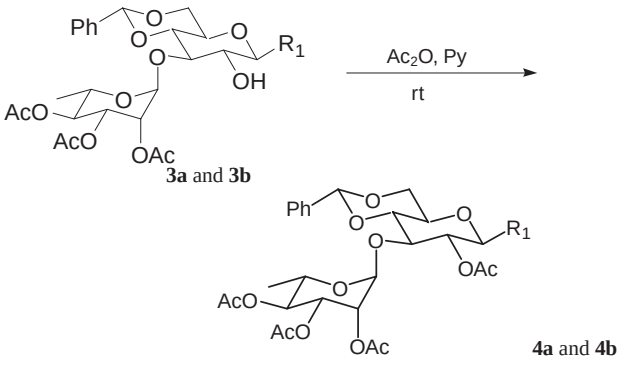


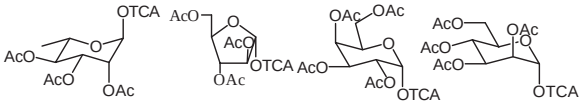
2a R_1 = SPh, R_2 = H
2b R_1 = SPhMe-*p*, R_2 = H
2c R_1 = $OCH_2CH{=}CH_2$, R_2 = H
2d R_1 = H, R_2 = $OCH_2CH{=}CH_2$
2e R_1 = OMe, R_2 = H
2f R_1 = H, R_2 = OMe

Scheme 1. Regioselective glycosylation of 4,6-*O*-benzylidene glucopyranosides **2**.

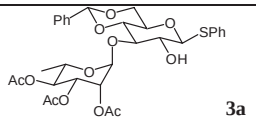
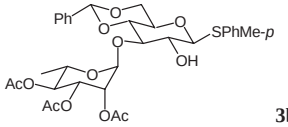
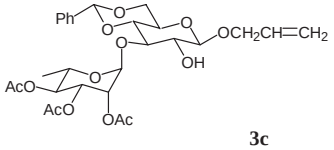
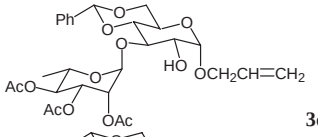
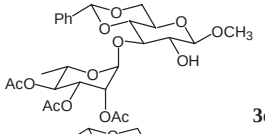
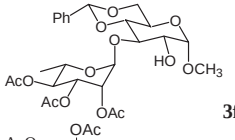
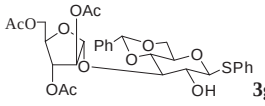
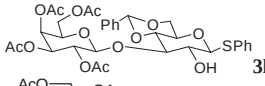
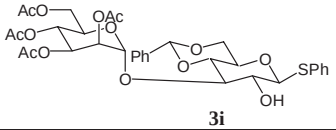


Scheme 2. Acetylation of compounds **3a** and **3b**.

Table 1. Reaction of glucopyranoside donors **1a**–**1d** with acceptors **2a**–**2f**



1a **1b** **1c** **1d**

Entry	Donor/ acceptor	Product	Yield /%
1	**1a/2a**	 **3a**	79
2	**1a/2b**	 **3b**	80
3	**1a/2c**	 **3c**	65
4	**1a/2d**	 **3d**	61
5	**1a/2e**	 **3e**	67
6	**1a/2f**	 **3f**	64
7	**1b/2a**	 **3g**	74
8	**1c/2a**	 **3h**	77[a]
9	**1d/2a**	 **3i**	81

[a]A mixture of (1 → 3)- and (1 → 2)-linkeded products in a ratio of 85:15 based on ^{1}H NMR analysis.

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References and Notes

1 "Carbohydrates in Chemistry and Biology," ed. by B. Ernst, G. W. Hart, and P. Sinaÿ, Wiley-VCH, Weinheim (2000), Vol. 1–4.

2 a) K. H. Jung, M. Müller, and R. R. Schmidt, *Chem. Rev.*, **100**, 4423 (2000). b) P. H. Seeberger and W. C. Haase, *Chem. Rev.*, **100**, 4349 (2000). c) P. Sears and C. H. Wong, *Science*, **291**, 2344 (2001). d) P. Pornsuriyasak, U. B. Gangadharmeth, N. P. Rath, and A. V. Demchenko, *Org. Lett.*, **6**, 4515 (2004). e) L. Petersen, J. B. Laursen, K. Larsen, M. S. Motawia, and K. J. Jensen, *Org. Lett.*, **5**, 1309 (2003).

3 a) A. Varki, *Glycobiology*, **3**, 97 (1993). b) J. J. Gao, K. Igarashi, and M. Nukina, *Chem. Pharm. Bull.*, **48**, 1075 (2000). c) V. Seidel, F. Bailleul, F. Libot, and F. Tillequin, *Phytochemistry*, **44**, 691 (1997).

4 T. Kawada, R. Asano, S. Hayashida, and T. Sakuno, *J. Org. Chem.*, **64**, 9268 (1999).

5 a) H. I. Duynstee, M. C. de Koning, H. Ovaa, G. A. van der Marel, and J. H. van Boom, *Eur. J. Org. Chem.*, **1999**, 2623. b) G. F. Gu, Y. G. Du, and R. J. Linhardt, *J. Org. Chem.*, **69**, 5497 (2004).

6 J. B. Li and Y. G. Wang, *Synth. Commun.*, **34**, 515 (2004).

7 General Procedure for the glycosylation. To a mixture of partially protected monosaccharide 2,3-diol acceptor (0.5 mmol), O-acetylated monosaccharide trichloroacetimidate donor (0.5 mmol) and molecular sieves (4 Å MS, 1.5 g) in anhydrous dichloromethane (20 mL) was added a catalytic amount of trimethylsilyl triflate (0.05 mmol) at −35 °C under N_2 protection. The reaction mixture was stirred under this condition for 40 min, and then was neutralized with triethylamine. The mixture was filtered over a short pad of silica gel and concentrated. The residue was subjected to chromatography on a silica gel column with hexane/EtOAc as the eluent to give pure disaccharide. All products give satisfactory ^{1}H NMR, ^{13}C NMR, H–H COSY and HRMS data. For compound **3f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.52 (4H), 5.48 (1H, s), 5.30 (1H, dd, $J_{1,2} = 1.5$ Hz, $J_{2,3} = 3.5$ Hz, H-2 Rha), 5.22 (1H, dd, $J_{2,3} = 3.5$ Hz, $J_{3,4} = 10$ Hz, H-3 Rha), 5.14 (1H, s, H-1 Rha), 4.90 (1H, t, $J_{3,4} = J_{4,5} = 10$ Hz, H-4 Rha), 4.68 (1H, d, $J_{1,2} = 3.5$ Hz, H-1 Glu), 4.24 (1H, dd, $J_{5,6b} = 4.5$ Hz, $J_{6a,6b} = 10$ Hz, H-6b Glu), 4.14 (1H, m, H-5 Rha), 3.90 (1H, t, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3 Glu), 3.74 (1H, m, H-6a Glu), 3.70–3.66 (2H, m, H-2 Glu, H-5 Glu), 3.48 (1H, t, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4 Glu), 3.39 (3H, s, –OCH_3), 2.50–1.88 (9H, 3 × s, Ac), 0.79 (3H, d, $J_{5,6} = 6.0$ Hz, H-6 Rha); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.1, and 170.0 (3 × –$COCH_3$), 137.3 (aromatic C), 129.0, 128.0, and 126.3 (aromatic CH), 101.7 (PhCH, benzylidene), 100.0 (C-1 Rha), 97.7 (C-1, Glu), 55.0 (–OCH_3), 29.7, 21.0, and 20.8 (3 × –$COCH_3$), 16.8 (C-6 Rha), other signals at δ 79.0, 75.5, 73.7, 71.1, 69.7, 69.4, 69.0, 66.0, and 62.8; HRMS m/z calcd for $C_{26}H_{34}O_{13}Na$ ($[M + Na]^+$) 577.1892, found 577.1898.

8 **4a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.27 (m, 10H), 5.47 (s, 1H), 4.90 (m, 3H, H-2 Glu, H-4 Rha, H-3 Rha), 4.71 (d, $J_{1,2} = 10.0$ Hz, 1H, H-1 Glu), 4.62 (d, $J_{1,2} = 2.0$ Hz, 1H, H-1 Rha), 4.53 (dd, $J_{1,2} = 2.0$ Hz, $J_{2,3} = 4.0$ Hz, 1H, H-2 Rha), 4.39 (dd, $J_{5,6b} = 4.5$ Hz, $J_{6a,6b} = 10.5$ Hz, 1H, H-6b Glu), 4.08 (t, $J_{2,3} = J_{3,4} = 9.0$ Hz, 1H, H-3 Glu), 3.76 (t, $J_{4,5} = J_{5,6b} = 10.0$ Hz, 1H, H-5 Glu), 3.54 (m, 2H, H-4 Glu, H-6 Glu), 3.08 (m, 1H, H-5 Rha), 2.14, 2.03, 1.64 (3 × s, 12H, Ac), 1.11 (d, $J_{5,6} = 6.0$ Hz, 3H, H-6 Rha). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.0, 169.4, 137.3, 133.0, 132.4, 129.6, 129.2, 128.7, 128.4, 126.5, 123.2, 102.1, 97.6, 87.2, 80.0, 76.1, 74.1, 71.3, 70.8, 70.6, 69.8, 69.3, 68.8, 24.79, 21.3, 21.04, 21.01, 17.7. HRMS (ESI) m/z calcd for $C_{33}H_{38}O_{13}SNa$ ($[M + Na]^+$) 697.1931, found 697.1925.

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