

**Figure 2.** HREELS of the  $c(2 \times 2)$ -N surface exposed to  $10^{-7}$  Torr of  $H_2$  at 400 K for 50 min (wide range spectrum) and growth of N-H stretching vibration peak at  $3190 \text{ cm}^{-1}$  in the presence  $10^{-7}$  Torr of  $H_2$  at 375 K: (1) starting  $c(2 \times 2)$ -N surface ( $N/Pd = 0.0216$ ,  $O/Pd = 0.0039$ ), (3) ambient  $H_2$  was replaced with  $1 \times 10^{-7}$  Torr  $D_2$  between (2) and (3) at 10 min, (6) ambient gas was replaced with  $5 \times 10^{-8}$  Torr of  $H_2 + 5 \times 10^{-8}$  Torr of  $D_2$  between (5) and (6) at 44 min, (7) ambient gas was evacuated between (6) and (7) at 55 min, (8) AES of the surface gave  $N/Pd = 0.016$ ,  $O/Pd = 0.004$ , (9) flashed surface at 450 K in vacuum ( $N/Pd = 0.016$ ,  $O/Pd = 0.005$ ).

and the formation of  $NH_3$  intermediates is reversible on Pd(100) surface. When a  $c(2 \times 2)$ -N Pd(100) surface was subjected to a temperature-programmed reaction in a flow of  $H_2$  at  $1 \times 10^{-6}$  Torr, a peak of  $NH_3$  appeared at 460 K which was coincident with the temperature for the decrease of N(a) in Figure 1. We conclude that the  $c(2 \times 2)$ -N is an intermediate in the  $NH_3$  formation reaction, and its hydrogenation reaction proceeds at the boundaries of islands of  $c(2 \times 2)$ -N on Pd(100).

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## Glycosylation of Unreactive Substrates

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In spite of the advances that have been made in carbohydrate chemistry in recent years, efficient glycosylation of unreactive substrates remains a significant problem. Hindered alcohols<sup>1a</sup> and derivatives of phenol<sup>1b</sup> present particular difficulties, and in many instances none of the available glycosylation methods work well.<sup>2</sup> We report a new method for rapid glycosylation of unreactive substrates in high yield under mild conditions (Scheme 1).<sup>3</sup> In a dramatic illustration of the efficacy of the method, we describe the first direct glycosylation of an amide nitrogen.

This investigation grew out of our interest in glycosylating deoxycholic acid derivative **1** (Table I). The C-7 hydroxyl in this compound is extremely hindered due to an unfavorable 1-3 diaxial interaction with the C-4 methylene in the A ring and available glycosylation procedures require extended reaction times and give poor yields (0-30%).<sup>2</sup> By contrast, our method glycosylates the C-7 hydroxyl rapidly and in good yield. In a typical reaction, 2 equiv of sulfoxide **6** (0.3 mmol) were added in toluene (1 mL) to triflic anhydride (0.3 mmol) in toluene (2 mL) at  $-78^\circ\text{C}$  followed by an acid scavenger (0.225 mmol, 2,6-di-*tert*-butyl-4-methylpyridine in toluene) and sterol **1** (0.15 mmol in 0.5 mL of toluene). After warming to  $-60^\circ\text{C}$  the reaction was poured into aqueous bicarbonate and a single steroid adduct was isolated in 86% yield after chromatography on silica gel.<sup>4</sup> The stereochemistry was assigned to be  $\alpha$ (axial) by NMR. An X-ray crystal structure of the debenzylated (Pd(OH)<sub>2</sub>-H<sub>2</sub>-MeOH, 50 psi, 12 h, 93%) glucosteroid (Figure 1) confirmed the stereochemical assignment<sup>5</sup> as well as the severe steric interaction between the

(1) For example, see: (a) Woodward, R. B., et al. *J. Am. Chem. Soc.* **1981**, *103*, 3215. (b) Koto, S.; Morishima, N.; Araki, M.; Tsuchiya, T.; Zen, S. *Bull. Chem. Soc. Jpn.* **1981**, *5*, 1895.

(2) Gargiulo, D.; Blizzard, T. A.; Nakanishi, K. *Tetrahedron*, in press.

(3) The sulfoxide is obtained by mCPBA oxidation of the corresponding sulfide (equiv, 0.1 mM,  $CH_2Cl_2$ ,  $-60^\circ\text{C}$  to room temperature, 85%). O-Glycosylation based on activation of 1-thioglycosides has been studied extensively. Inter alia: (a) Ferrier, R. J.; Hay, R. W.; Vethaviasar, N. *Carbohydr. Res.* **1973**, *27*, 55. (b) Mukaiyama, T.; Nakatsuka, T.; Shoda, S. *Chem. Lett.* **1979**, 487. (c) Van Cleve, J. W. *Carbohydr. Res.* **1979**, *70*, 161. (d) Hanessian, S.; Bacquet, C.; Lehong, N. *Ibid.* **1980**, *80*, C17. (e) Garegg, P. J.; Henrichson, C.; Norberg, T. *Ibid.* **1983**, *116*, 162. (f) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430. (g) Lonn, H. *Carbohydr. Res.* **1985**, *139*, 105, 115. (h) Sato, S.; Mori, M.; Ito, Y.; Ogawa, T. *Ibid.* **1986**, *155*, C6. (i) Pozsgay, V.; Jennings, H. J. *J. Org. Chem.* **1987**, *52*, 4635. (j) Murata, S.; Suzuki, T. *Chem. Lett.* **1987**, 849.

(4) Ratio determined by HPLC (resolve silica  $\mu\text{m}$ , 8 mm  $\times$  10 cm, flow rate 1.8 mL/min,  $CH_2Cl_2$ -ethyl acetate 98:2, UV 254 nm, retention time:  $\alpha = 10.7$  min,  $\beta = 15.3$  min). The stereochemical outcome of glycosylation is independent of the stereochemistry of the starting sulfide. All new compounds were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, and high-resolution mass spectral analysis.

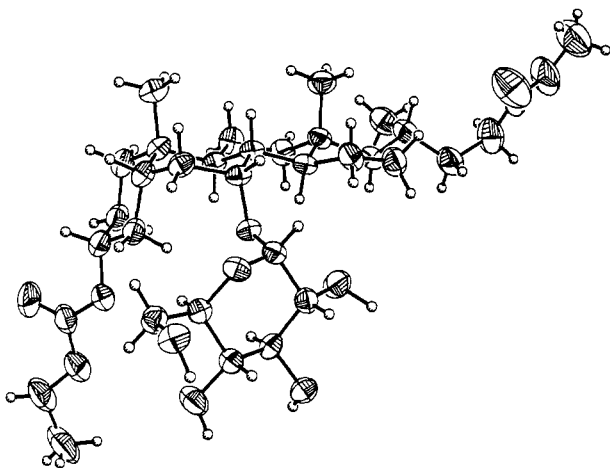
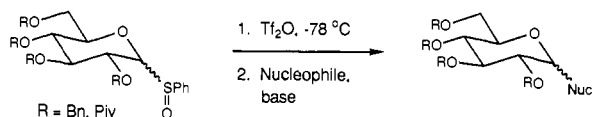


Figure 1.

## Scheme I



C-7 oxygen and the C-4 methylene. We were also able to bis- $\alpha$ -glycosylate cholic acid derivative **2** by the same procedure (toluene, 4 equiv of **6**, 4 equiv of  $\text{TiF}_2\text{O}$ , base, 1 equiv of **2**). This result is noteworthy because the C-12 hydroxyl does not react under any of the other conditions reported for glycosylation at C-7.<sup>2</sup>

In order to more clearly define the reactivity of the glycosyl donor, we undertook the glycosylation of a number of other substrates. As shown in Table I, both hindered and deactivated phenols can be glycosylated in good yield. These results are significant because a number of important natural products (e.g., calicheamicin  $\gamma^1$ ) contain glycosidic bonds to similar phenol derivatives. However, the most striking example of the effectiveness of the reaction undoubtedly involves glycosylation of acetamide **5** on nitrogen (with concomitant loss of TMS). As far as we know, direct glycosylation of amides on nitrogen has previously been accomplished only by means of enzymatic catalysis. Given the low nucleophilicity of **5**, it is not surprising that it reacts much more slowly than the other substrates (24 h at room temperature); however, it is certainly interesting that the intermediate glycosyl donor, which is reactive enough to glycosylate hindered secondary alcohols rapidly at  $-60^\circ\text{C}$ , is nevertheless stable at room temperature for prolonged periods.

The stereochemical outcome of the reaction in the absence of neighboring group participation is strongly influenced by solvent. In general, we find that the percentage of  $\beta$  glycoside produced increases with solvent polarity.<sup>6</sup> This holds true for **1** as well as for a number of other nucleophiles that we have examined,<sup>7</sup> including the C-6 hydroxyl of 1,2,3,4-tetra-*O*-acetylglucose (1:3  $\alpha$ : $\beta$

(5)  $\text{C}_{14}\text{H}_{18}\text{O}_{11}$ ,  $M = 640.9$ , monoclinic, space group  $P2_1$ ,  $a = 11.167$  (4) Å,  $b = 6.153$  (3) Å,  $c = 25.486$  (10) Å,  $\beta = 97.93$  (3) $^\circ$ ,  $V = 1734.4$  (9) Å<sup>3</sup>,  $D_c = 1.23$  g cm<sup>-3</sup>,  $Z = 2$ ,  $\lambda(\text{Cu K}\alpha) = 1.54178$  Å. Structure solved by direct methods (SHELXTL) and refined by blocked cascade least squares to  $R = 0.0441$ ,  $R_w = 0.045$  for 2374 observed reflections [ $F > 3\sigma(F)$ ].

(6) In contrast, Nicolau et al. observe an increase in  $\alpha$  selectivity on going to more polar solvents using NBS activation of thioglycosides.<sup>3f</sup> For  $\beta$ -glycosylation in the absence of neighboring group participation see inter alia: (a) Garegg, P. J.; Iversen, T. *Carbohydr. Res.* **1979**, *70*, C13. (b) Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102. (c) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379. (d) Andersson, F.; Fugedi, P.; Garegg, P. J.; Nashed, M. *Ibid.* **1986**, *27*, 3919. (e) Ito, Y.; Ogawa, T. *Ibid.* **1987**, *28*, 4701. (f) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Ibid.* **1988**, *29*, 3567. (g) Crich, D.; Ritchie, T. J. *J. Chem. Soc. Chem. Commun.* **1988**, 1461. (h) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716.

(7) For example, methanol, the C-4 OH of a glcNAc derivative, and a serine derivative (unpublished results).

Table I.

Glycosyl acceptor	Glycosyl donor	Entry	Conditions	Product ratio (Yield)
 1	 6	1. <sup>a</sup>	toluene	$\alpha$ : $\beta$ = 27:1 (86%)
		2. <sup>a</sup>	$\text{CH}_2\text{Cl}_2$	$\alpha$ : $\beta$ = 1:3 (60%)
		3. <sup>a</sup>	$\text{CH}_3\text{CH}_2\text{CN}^b$	$\alpha$ : $\beta$ = 1:8 (50%)
 2	 7	4. <sup>b</sup>	$\text{CH}_2\text{Cl}_2$	all $\beta$ (83%)
		5. <sup>a</sup>	toluene	$\alpha$ : $\alpha$ (58%)
 3	 7	6. <sup>c</sup>	toluene	$\alpha$ : $\beta$ = 9:1 (78%)
		7. <sup>c</sup>	$\text{CH}_2\text{Cl}_2$	all $\beta$ (60%)
 4	 7	8. <sup>d</sup>	toluene	$\alpha$ : $\beta$ = 2:1 (70%)
		9. <sup>d</sup>	$\text{CH}_2\text{Cl}_2$	all $\beta$ (80%)
 5	 6	10. <sup>e</sup>	toluene	$\alpha$ : $\beta$ = 5:1 (66%)

All compounds were thoroughly dried by azeotropic ( $\times 3$ ) with toluene and the reaction was carried out under scrupulously anhydrous conditions. (a) Warmed to  $-60^\circ\text{C}$  and quenched. (b) Warmed to  $-24^\circ\text{C}$  and quenched. (c) Warmed to room temperature and quenched. (d) Warmed to room temperature and stirred for 12 hours before quenching. (e) No base was added with this solvent.

in toluene, 90%; 1:25  $\alpha$ : $\beta$  in propionitrile, 65%).<sup>8</sup> It is interesting that alcohols can be trapped in a sea of propionitrile, which is also known to react with activated glycosides.<sup>9</sup>

Finally, it is worth noting that the reaction works well regardless of the electron-releasing or electron-withdrawing properties of the sugar protecting groups. Thus, we were able to use neighboring group participation to obtain the  $\beta$  isomers of compounds **1–4** in good yield. In contrast to our method, other strategies involving neighboring group participation require long times and produce low yields with similarly unreactive substrates.<sup>1a,2</sup>

In conclusion, we have described a mild method to glycosylate even the most unreactive nucleophiles in good yield. In many cases either the  $\alpha$  or the  $\beta$  isomer can be obtained selectively by varying solvent conditions or protecting groups. We are currently exploring other aspects of the reaction and will report on them in due course.

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**Supplementary Material Available:** Crystal structure diagram, stereodrawing, and tables of coordinates, thermal parameters, and bond lengths and angles (11 pages). Ordering information is given on any current masthead page.

(8) Other factors, including the C-2 stereochemistry of the glycosyl donor, also influence the stereochemical outcome (unpublished results).

(9) Pavia, A. A.; Ung-Chhun, S. N.; Durand, J.-L. *J. Org. Chem.* **1981**, *46*, 3158.