Synthetic Study of C-1027 Chromophore. Highly Stereoselective Glycosylation

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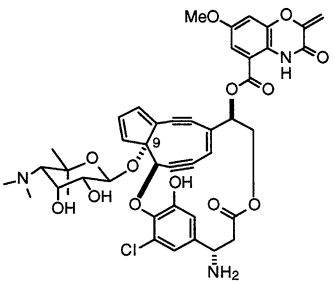
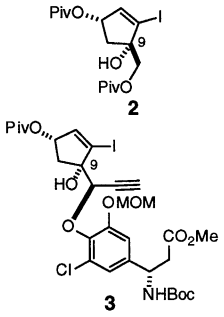
A highly stereoselective method for glycosylation of tertiary alcohols with the amino sugar moiety of C-1027 chromophore was developed.

C-1027 is a member of the chromoprotein antitumor antibiotics[1] which consist of a nine-membered enediyne chromophore[2] and a carrier apoprotein. In the total synthesis of the chromophore (**1**), the glycosylation reaction of the C9 tertiary alcohol represents one of the most significant synthetic problems.[3] We found that this glycosylation after constructing the bicyclo[7.3.0]dodecadiyne core system encountered with great difficulty. We describe here a stereoselective glycosylation of tertiary alcohols such as **2** and **3** with the C-1027 amino sugar moiety.



C-1027 chromophore (**1**)

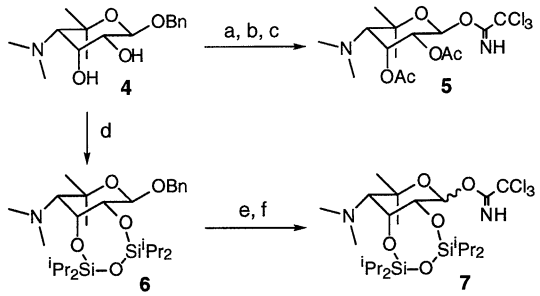


2

3

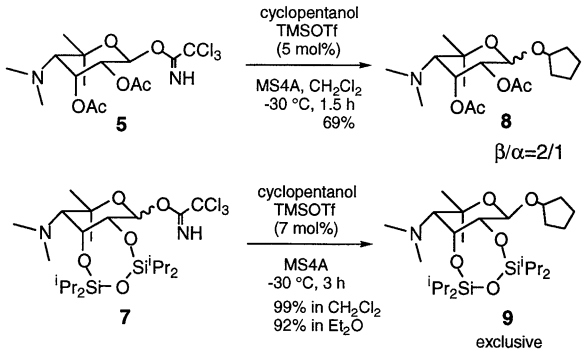
Numerous studies of glycosylation using the amino sugar of the neocarzinostatin chromophore[4,5] have indicated that trichloroacetimidate[6] is a promising glycosyl donor in a large scale synthesis, whereas it is well documented that Suzuki method using glycosyl fluoride and Cp_2HfCl_2-$AgClO_4$ activator is very useful for β-glycoside synthesis.[7] Benzyl β-glycoside (**4**) was synthesized in a fashion analogous to the methyl β-glycoside.[3a] Acetylation of **4**, followed by hydrogenolysis and treatment with trichloroacetonitrile in the presence of a catalytic amount of DBU gave the β-trichloroacetimidate (**5**) (Scheme 1). The diol (**4**) was readily silylated with TBDMSCl and debenzylated. However, the resultant bissilyl ether did not yield exclusively the trichloroacetimidiate. We then prepared the cyclic disiloxane derivative (**6**). The benzyl group of **6** was removed by Birch reduction, and the resultant protected sugar was converted to the trichloroacetimidate (**7**) as an anomeric mixture (β/α=10:1).

Glycosylation reaction using **5** and **7** was first examined using cyclopentanol to determine the stereoselectivity. The reaction in the presence of trimethylsilyl triflate and MS4A at -30 °C gave cyclopentyl glycoside (**8**) in low stereoselectivity (β/α=2/1) (Scheme 2), although high β-selectivity due to the neighboring acyl group participation was expected. The anomers



Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine, DMAP, 85%. (b) H_2, Pd/C, ethyl acetate 91%. (c) CCl_3CN, DBU, CH_2Cl_2, 99%. (d) $TIPDSCl_2$, imidazole, DMF 87%. (e) Na (10 eq), NH_3, THF, -60°C, 82%. (f) CCl_3CN, DBU, CH_2Cl_2, 97%. DBU: 1,8-diazabicyclo-[5.4.0]undec-7-ene, TIPDS: 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl.

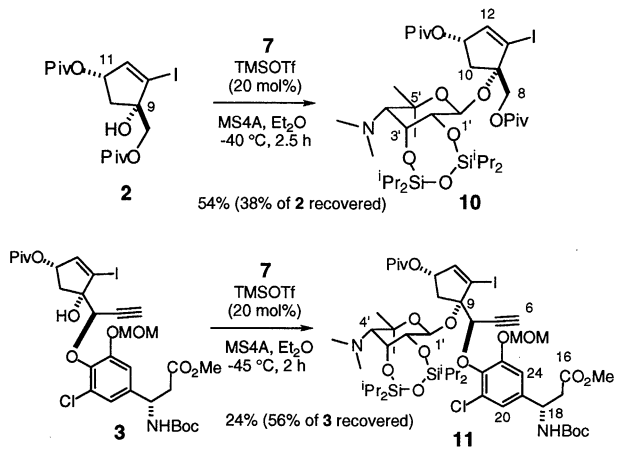
of **8** were assigned according to the coupling constants: $J_{1,2}$=8.2 Hz for β-anomer; $J_{1,2}$=4.4 Hz for α-anomer. Both stereoselectivity and yield improved remarkably when disiloxane derivative (**7**) was used. Under similar glycosylation conditions, **7** gave β-glycoside (**9**) exclusively in good yield. Changing the solvent did not affect the stereoselectivity.[4a] Thus, the bulky disiloxane group appears to block the α-face of the oxocarbenium ion intermediate.



Scheme 2. Glycosylation of cyclopentanol.

Finally, glycosylation reactions of the functionalized tertiary alcohols, **2**[3e] and **3**,[8] were investigated. The reaction of **2** was first examined in dichloromethane at -30 °C. The desired glycoside (**10**) was obtained only in 27% yield. The major product (37%) was a glycoside of the C11 secondary alcohol with pivalates at C8 and C9, which apparently arose via the pivaloyl group migration from the C11 to C9 alcohol. In contrast, the reaction in diethyl ether at -40 °C suppressed this migration, giving the desired β-glycoside (**10**)[9] exclusively in

54% yield (87% based on recovery of **2**) (Scheme 3). Glycosylation of the highly functionalized **3** also gave β-glycoside (**11**)[10] stereoselectively in 24% yield (55% based on recovery of **3**).



Scheme 3. Stereoselective glycosylation of **2** and **3**.

In conclusion, stereoselective glycosylation reaction of tertiary alcohols using trichloroacetimidate donor (**7**) was achieved under mild conditions. Further synthetic studies directed toward C1027 chromophore (**1**) from **10** and **11** are currently underway in our laboratory.

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References and Notes

1 a) J. Hu, Y.-C. Xue, M.-Y. Xie, R. Zhang, T. Otani, Y. Minami, Y. Yamada, and T. Marunaka, *J. Antibiot.*, **41**, 1575 (1988). b) T. Otani, Y. Minami, T. Marunaka, R. Zhang, and M.-Y. Xie, *J. Antibiot.*, **41**, 1580 (1988).

2 a) Y. Minami, K. Yoshida, R. Azuma, M. Saeki, and T. Otani, *Tetrahedron Lett.*, **34**, 2633 (1993). b) K. Yoshida, Y. Minami, R. Azuma, M. Saeki, and T. Otani, *Tetrahedron Lett.*, **34**, 2637 (1993). c) K. Yoshida, Y. Minami, T. Otani, Y. Tada, and M. Hirama, *Tetrahedron Lett.*, **35**, 5253 (1994). d) K. Iida, S. Fukuda, T. Tanaka, M. Hirama, S. Imajo, M. Ishiguro, K. Yoshida, and T. Otani, *Tetrahedron Lett.*, **37**, 4997 (1996).

3 a) K. Iida, T. Ishii, M. Hirama, T. Otani, Y. Minami, and K. Yoshida, *Tetrahedron Lett.*, **34**, 4079 (1993). b) K. Iida and M. Hirama, *J. Am. Chem. Soc.*, **116**, 10310 (1994). c) K. Iida and M. Hirama, *J. Am. Chem. Soc.*, **117**, 8875 (1995). d) I. Sato, Y. Akahori, K. Iida, and M. Hirama, *Tetrahedron Lett.*, **37**, 5135 (1996). e) I. Sato, K. Toyama, T. Kikuchi, and M. Hirama, *Synlett*, **1998**, 1308.

4 a) T. Kaneko, K. Takahashi, and M. Hirama, *Heterocycles*, **47**, 91 (1998). b) A. G. Myers, J. Liang, M. Hammond, P. M. Harrington, Y. Wu, and E. Y. Kuo, *J. Am. Chem. Soc.*, **120**, 5319 (1998).

5 For other examples, see; a) S. A. Hitchcock, M. Y. Chu-Moyer, S. H. Boyer, S. H. Olson, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **117**, 5750 (1995). b) K. C. Nicolaou, C. W. Hummel, M. Nakada, K. Shibayama, E. N. Pitsinos, H. Saimoto, Y. Mizuno, K.-U. Baldenius, and A. L. Smith, *J. Am. Chem. Soc.*, **115**, 7625 (1993). c) K. Toshima and K. Tatsuta, *Chem. Rev.*, **93**, 1503 (1993).

6 R. R. Schmidt, *Angew. Chem., Int. Ed.*, **25**, 212 (1986); R. R. Schmidt and K.-H. Jung, in "Preparative Carbohydrate Chemistry," ed by S. Hanessian, Marcel Dekker, New York (1997), Chap. 12, p. 283.

7 For synthesis of β-glycosides of tertiary-alcohols, see; a) K. Suzuki, H. Maeta, T. Matsumoto, and G. Tsuchihashi, *Tetrahedron Lett.*, **29**, 3571 (1998). b) K. Suzuki, H. Maeta, and T. Matsumoto, *Tetrahedron Lett.*, **30**, 4853 (1989). c) Y. Konda, T. Toida, E. Kaji, K. Takeda, and Y. Harigaya, *Tetrahedron Lett.*, **37** 4015 (1996).

8 I. Sato, T. Kikuchi, and M. Hirama, *Chemistry Lett.*, in press.

9 **10**: colorless oil; $[\alpha]_D^{28}$ -85 (c 0.49, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.0-1.2 (28H, m, TIPDS), 1.18 (9H, s, Piv), 1.21 (9H, s, Piv), 1.28 (3H, s, 5'-dimethyl), 1.62 (3H, s, 5'-dimethyl), 2.48 (1H, d, *J*=2.6 Hz, 4'-H), 2.54 (6H, s, 4'-*N*-dimethyl,), 2.61 (1H, dd, *J*=13.6, 7.8 Hz, 10-H), 2.76 (1H, dd, *J*=13.6, 5.4 Hz, 10-H), 3.64 (1H, dd, *J*=7.4, 3.6 Hz, 2'-H), 4.05 (1H, d, *J*=11.0 Hz, 8-H), 4.08 (1H, d, *J*=11.0 Hz, 8-H), 4.69 (1H, dd, *J*=3.6, 2.6 Hz, 3'-H), 4.98 (1H, d, *J*=7.4 Hz, 1'-H), 5.44 (1H, ddd, J=7.8, 5.4, 2.0 Hz, 11-H), 6.50 (1H, d, *J*=2.0 Hz, 12-H); FT-IR (neat) ν 2944, 2868, 2775, 1731, 1480, 1463, 1397, 1386, 1366, 1281, 1146, 1045, 1004 cm^{-1}; MALDI-TOF MS $(M+Na)^+$ 876.

10 **11**: colorless oil; $[\alpha]_D^{28}$ -215 (c 0.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.1-1.2 (21H, m, TIPDS), 1.23 (9H, s, Piv), 1.28 (3H, s, C5'-dimethyl), 1.45 (9H, s, Boc), 1.60 (3H, s, C5'-dimethyl), 2.22 (1H, s, H6), 2.50 (1H, d, *J*=2.5 Hz, H4'), 2.53 (3H, s, C4'-*N*-dimethyl), 2.55 (3H, s, C4'-*N*-dimethyl), 2.7-2.9 (2H, m, H17), 3.12 (1H, dd, *J*=14.5, 5.0 Hz, H10), 3.43 (1H, dd, *J*=14.5, 8.0 Hz, H10), 3.48 (3H, s, MOM), 3.62 (3H, s, CO_2Me), 3.74 (1H, dd, *J*=7.5, 3.5 Hz, H2'), 4.67 (1H, dd, *J*=3.5, 2.5 Hz, H3'), 4.95 (1H, m, H18), 5.06 (1H, d, *J*=7.5 Hz, H1'), 5.23 (1H, d, *J*=11.0 Hz, MOM), 5.25 (1H, d, *J*=11.0 Hz, MOM), 5.41 (1H, s, H8), 5.48 (1H, ddd, *J*=8.0, 5.0, 2.0 Hz, H11), 5.50 (1H, m, C18-NH), 6.68 (1H, d, *J*=2.0 Hz, H12), 6.99 (1H, d, *J*=2.0 Hz, H20 or 24), 7.00 (1H, d, *J*=2.0 Hz, H20 or 24); FT-IR (film) ν 3311, 2946, 2868, 2147, 1727, 1579, 1481, 1367, 1282, 1159, 1044, 1023 cm^{-1}; MALDI-TOF MS $(M+H)^+$ 1165.