

CONVERSION OF GLYCOSYL FLUORIDES INTO C-GLYCOSIDES USING ORGANOALUMINUM

REAGENTS. STEREOSPECIFIC ALKYLATION AT C-6 OF A PYRANOSE SUGAR

Gary H. Posner* and Stephen R. Haines*

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Summary: Various furanosyl and pyranosyl fluorides react rapidly with alkyl, alkenyl, alkynyl, and aryl organoaluminum reagents at or below room temperature to form C-glycosides in 68-93% yields. Effective application of this procedure to a 6-fluoro 1,6-anhydroglucose derivative produced a chain-extended sugar stereospecifically.

The great and diverse medicinal value of many C-glycosides¹ has stimulated development of many new synthetic methods for their preparation.² Having previously utilized the very strong affinity of aluminum for fluoride ions,³ we were intrigued by the possibility that organoaluminum reagents might activate glycosyl fluorides toward carbon-carbon bond formation.⁴ With some new and effective procedures now available for preparation of glycosyl fluorides,^{4b,5} we report here the results in Table I for very mild C-glycoside formation via reaction of various glycosyl fluorides with organoaluminum reagents (eq. 1).

Several features of the results are especially noteworthy, as follows: (1) various unsaturated and therefore easily functionalized hydrocarbon groups can be introduced at the anomeric center; (2) the requisite unsaturated organoaluminum reagents are easily prepared via hydroalumination of terminal acetylenes or via organoaluminum chloride metathesis with organolithium species; (3) diisobutylaluminum hydride can convert a furanosyl fluoride into its parent tetrahydrofuran; (4) the reaction mechanism undoubtedly involves intermediate oxenium ions as indicated, for example, by the same product being formed from both of the mannofuranosyl fluorides; and (5) both furanosyl and pyranosyl fluorides undergo this type of C-glycoside formation.

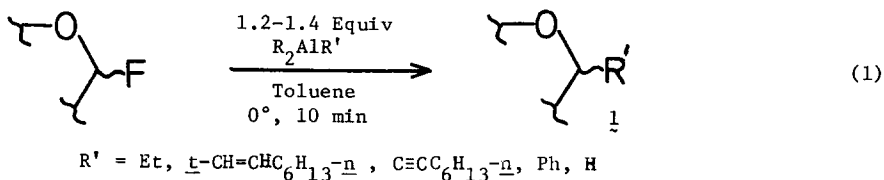
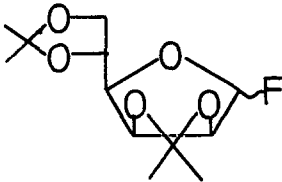
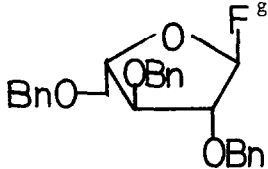
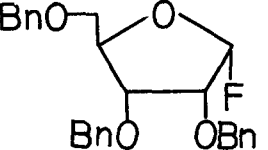
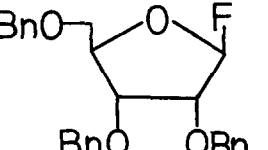
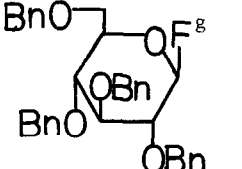


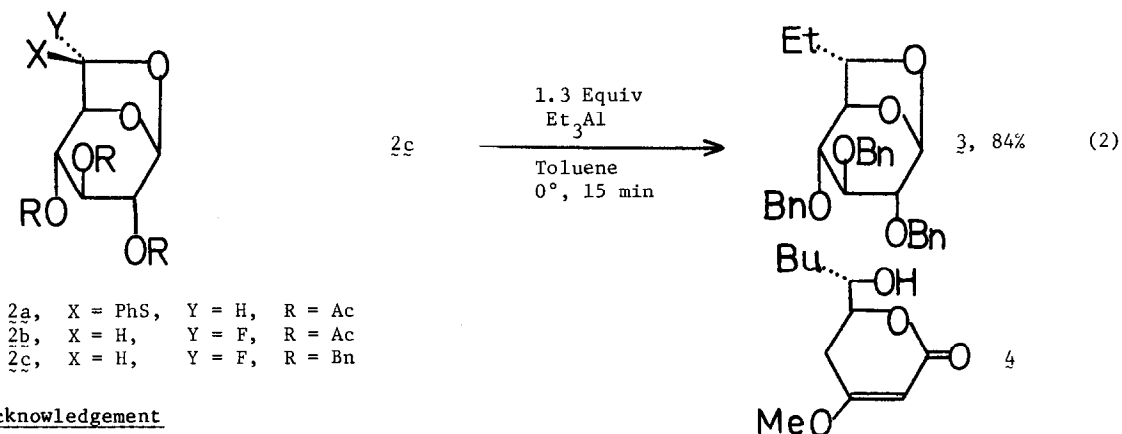
TABLE I.

GLYCOSYL FLUORIDE	R_2AlR'		C-GLYCOSIDE 1 ^a		
	R	R'	Yield ^b	(α : β) ^c	
	α -F	Et	Et	79%	(>20:1)
	α -F	i-Bu	$t\text{-CH=CHC}_6\text{H}_{13}\text{-n}^d$	76%	(>20:1)
	α -F	Et	$C\equiv CC_6H_{13}\text{-n}$ (5 Equiv) ^e	85%	(>20:1)
	α -F	Ph	Et (2 Equiv) ^f	68%	(>20:1)
	α -F	i-Bu	H	71%	
	β -F	Et	Et	76%	(>20:1)
		Et	Et	93%	(6:1)
		Et	Et	79%	(3:1)
		Et	Et	86%	(1:1)
		i-Bu	$t\text{-CH=CHC}_6\text{H}_{13}\text{-n}^d$	85%	(2.6:1)

Bn = PhCH₂. ^aAll new compounds were fully characterized spectroscopically and by microanalysis and/or by high resolution mass spectrometry. ^bYield of product after purification by short path chromatography or by preparative tlc. ^cAnomeric ratio determined by ¹H NMR.

^di-Bu₂AlH + HC≡CC₆H₁₃-n. ^eEt₂AlCl + LiC≡CC₆H₁₃-n. ^fEtAlCl₂ + 2 PhLi; highly selective transfer of phenyl group was observed after stirring overnight at room temperature. ^gContaining a small amount of the anomeric fluoride: see ref. 5a.

The ready availability and cheap price of natural carbohydrates in many enantiomerically pure forms has made these chiral, non-racemic compounds very popular starting materials for synthesis of various complex organic molecules.⁶ However, attempts to transfer chirality predictably from the ring-substituted carbon atoms of pyranose sugars to exocyclic (off-template⁷) positions (e.g. C-6) have been rare.⁸ Some success has been achieved recently by incorporating C-6 into a second ring and then allowing the rigidity of the bicyclic system to influence the stereochemistry of carbon-carbon bond formation at C-6.^{7a,9} Toward this significant and challenging goal, we converted 6-phenylthio 1,6-anhydro-D-glucose derivative 2a¹⁰ into the corresponding fluorides 2b and 2c.¹¹ Although fluoride 2b, with acetate ester protecting groups, was unreactive toward triethylaluminum, fluoride 2c, with benzyl ether protecting groups, reacted smoothly and stereospecifically to give exclusively the exo-substitution product 3 in 84% yield after purification by short path column chromatography (eq. 2).¹² The exo configuration of the ethyl group was established unambiguously by ¹H NMR ($J_{5,6}$ endo 0 Hz; H-1, H-1, H-3, H-4 and H-5, broad singlets)¹⁰ and by ¹³C NMR [$-\text{CH}_2\text{CH}_3$, δ (CDCl₃) 27.8]; equivalent carbon atoms in derivatives with syn-interactions with neighboring benzyloxy groups appeared in the range δ 21.6-22.6. This extremely successful, stereospecific alkylation at the off-template C-6 position of a 1,6-anhydroglucose system now can be applied to highly stereocontrolled syntheses of several biologically important chain-extended carbohydrates, including for example (-)-pestalotin (4), a synergist of the plant-growth regulator gibberellin.¹³



Acknowledgement

We thank the National Institutes of Health for financial support (GM 30052). We also thank Chris Switzer, Terrence Hamill, and Bill Nelson of this department for ¹³C NMR spectra and the National Institutes of Health (1 S10 RR 01934) and the National Science Foundation (PCM 83-03176) for assistance in purchasing the 400 MHz NMR spectrometer. GHP warmly acknowledges the hospitality of the Department of Organic Chemistry at the Weizmann Institute of Science, Rehovot, Israel as well as award of an Erna and Jakob Michael Visiting Professorship from January-June, 1983, which allowed time for reading and thinking about carbohydrate chemistry.

References

- Buchanan, J. G. in "Progress in the Chemistry of Organic Natural Products", W. Herz, H. Grisebach, and G. W. Kirby, Eds., Springer-Verlag, New York, NY, Vol. IX, 1983.
- For some 1984 reports, see (a) Tulshian, D. B. and Fraser-Reid, B., J. Org. Chem., 1984, 49, 518; (b) Dawe, R. D. and Fraser-Reid, B., ibid., 1984, 49, 522; (c) Keck, G. E., Enholm, E. J., and Kachensky, D. F., Tetrahedron Lett., 1984, 25, 1867; (d) Hosomi, A., Sakata, Y., and Sakurai, H., ibid., 1984, 25, 2383; (e) Kunz, H., Weissmuller, J., and Muller, B., ibid., 1984, 25, 3571; (f) Kozikowski, A. P. and Sorgi, K. L., ibid., 1984, 25, 2085; (g) Wilcox, C. S., Long, G. W., and Suh, H., ibid., 1984, 25, 395; (h) Hanessian, S., Sato, K., Liak, T. J., Danh, N., Dixit, D., and Cheney, B. V., J. Amer. Chem. Soc., 1984, 106, 6114; (i) Myers, R. W. and Lee, Y. C., Carbohydrate Res., 1984, 132, 61; For reviews, see (j) Hanessian, S., Pernet, A. G., Adv. Carbohydr. Chem., 1976, 33, 111; (k) James, S. R., J. Carbohydr. Nucleosid. Nucleotid., 1979, 6, 417.
- Posner, G. H., Ellis, J. W., and Ponton, J., J. Fluorine Chem., 1981, 19, 191.
- For recent use of glycosyl fluorides to form C-glycosides, see (a) Nicolaou, K. C., Dolle, R. E., Chucholowski, A., and Randall, J. L., J. Chem. Soc., Chem. Commun., 1984, 1153; (b) Araki, Y., Watanabe, K., Kuan, F-H., Itoh, K., Kobayashi, N., and Ishido, Y., Carbohydr. Res., 1984, 127, C5.
- (a) Posner, G. H. and Haines, S. R., Tetrahedron Lett., 1985, 26, 5; (b) Nicolaou, K. C., Dolle, R. E., Paphatjis, D. P., and Randall, J. L., J. Amer. Chem. Soc., 1984, 106, 4189; (c) Mukaiyama, T., Murai, Y., and Shoda, S., Chem. Lett., 1981, 431 and Mukaiyama, T., Hashimoto, Y., and Shoda, S., ibid., 1983, 935; (d) Hashimoto, S., Hayashi, M., and Noyori, R., Tetrahedron Lett., 1984, 25, 1379; (e) Hayashi, M., Hashimoto, S., and Noyori, R., Chem. Lett., 1984, 000.
- (a) Hanessian, S., "Total Synthesis of Natural Products: The 'Chiron' Approach", Pergamon Press, New York, N.Y. 1983; (b) Fraser-Reid, B., Sun, K. M., and Tam, T. F., Bull. Soc. Chim. Fr. II, 1981, 238; (c) Fraser-Reid, B., and Anderson, R. C., Progress Chem. Org. Natural Products, 1980, 39, 1.
- (a) Fraser-Reid, B., Magdzinski, L., and Molino, B., J. Amer. Chem. Soc., 1984, 106, 731; (b) Georges, M., Tam, T. F., and Fraser-Reid, B., J. Chem. Soc., Chem. Commun., 1984, 1122.
- (a) Ireland, R. E., and Daub, J. P., J. Org. Chem., 1981, 46, 479; (b) Jarosz, S., and Fraser-Reid, B., Tetrahedron Lett., 1981, 22, 2533; (c) Paulsen, H., and Stubbe, M., Liebigs Ann. Chem., 1983, 535; (d) Isobe, M., Kitamura, M., and Goto, T., J. Amer. Chem. Soc., 1982, 104, 4997; (e) Danishefsky, S. J., Maring, C. J., Barbachyn, M. R., and Segmuller, B. E., J. Org. Chem., 1984, 49, 4564.
- (a) Nicoll-Griffith, D., and Weiler, L., J. Chem. Soc. Chem. Commun., 1984, 659; cf. Pougny, J-R., Tetrahedron Lett., 1984, 25, 2363; cf. (b) Ohrui, H., Nishida, Y., and Meguro, H., Agric. Biol. Chem., 1984, 48, 1049.
- Ferrier, R. J., and Furneaux, R. H., Aust. J. Chem., 1980, 33, 1025; we warmly thank Prof. Ferrier and Dr. Furneaux for a generous gift of 6-phenylthio 1,6-anhydroglucose derivative 2a.
- 2b ← NBS, DAST^{5b} 2a 1) K₂CO₃, MeOH 2) BnBr, NaH, DMF 3) NBS, DAST → 2c
- [α]_D²⁸ - 26.5° (C 0.9, CHCl₃); ¹³C (CDCl₃); δ 138.0, 138.0, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8 (Ph), 101.1 (C-1), 78.0, 77.8, 77.2 (C-2,3,4), 76.6, 76.5 (C-5,6), 72.1, 71.7, 71.2 (PhCH₂), 27.8 (CH₂CH₂⁻), 9.7 (-CH₃); mass spectrum: m/e 369.169 (calcd for M-PhCH₂ 369.170).
- (a) Carlson, R. M., and Oyler, A. R., Tetrahedron Lett., 1974, 2615; (b) Seebach, D., and Meyer, H., Angew. Chem. Int. Ed. Engl., 1974, 13, 77; (c) Izawa, T., and Mukaiyama, T., Chem. Lett., 1975, 161; (d) Mori, K., Oda, M., and Matsui, M., Tetrahedron Lett., 1976, 3173; (e) Takeda, A., Amano, E., and Tsuboi, S., Bull. Chem. Soc. Japan, 1977, 50, 2191; (f) Midland, M. M., and Graham, R. S., J. Amer. Chem. Soc., 1984, 106, 4294; (g) Masaki, Y., Nagata, K., Serizawa, Y., and Kaji, K., Tetrahedron Lett., 1984, 25, 95.

(Received in USA 21 December 1984)