A Direct Route from 1α,2α-Anhydroglucose Derivatives to α-Glucosides

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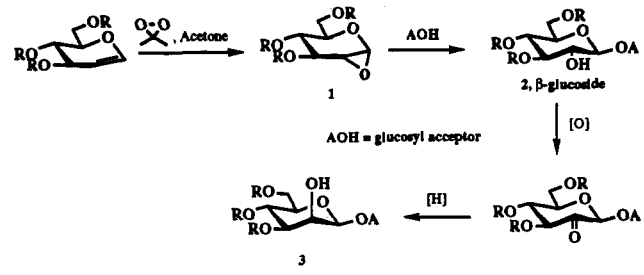
It is becoming increasingly clear that carbohydrate moieties, in contexts such as cell surface receptors, cell adhesion molecules, and tumor antigens, are carriers of sophisticated biomolecular information.[1] Not surprisingly, this recently growing perception has fostered renewed interest in the chemistry and stereospecific synthesis of various glyconjugates as well as oligosaccharides.[2] Our laboratory has been particularly active in exploiting glycals for this purpose, not only for their potential as glycosyl donors but also as glycosyl acceptors.[3] The direct epoxidation of various glucal and galactal derivatives by 2,2-dimethyldioxirane gives rise to the corresponding 1α,2α-oxiranes (cf. 1).[3a]

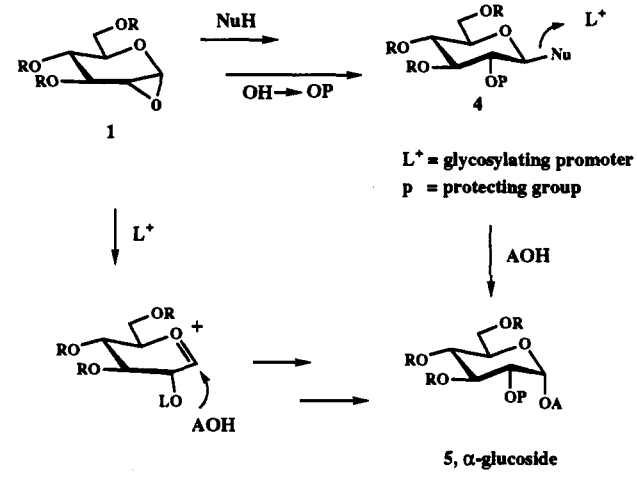
By appropriate selection of resident protecting groups, these oxiranes have functioned well as glycosyl donors leading to β-glucosides[3a] and β-galactosides.[3d,e] More recently, we have shown that the configuration of a unique $C_2(\alpha)$ hydroxyl group generated in the glycoside 2 can be inverted (by an oxidation–reduction sequence).[4] In this way, the 1α,2α-oxirane is also a valuable precursor for β-mannosides (cf. 3).

The value of such α-oxiranes would increase significantly if they could be incorporated as donor groups for the formation of α-glucosides (cf. 5). In a previously documented approach to the problem,[5] the epoxide is opened at the anomeric carbon with a heteronucleophile. The stereochemical sense of this opening is significantly dependent on the nature of the heteroatom. After protection of the C_2 hydroxyl group, the hetero group is suitably modified or promoted (cf. 4) to function as a glycosyl donor, leading to α-glycosides. This concept served us well in our synthesis of the cyanobacterial sulfolipid of possible interest as an anti HIV agent.[5a] Here, we focus on a chemicallly more ambitious goal, *i.e.*, that of using the α-epoxide to produce directly α-glycoside. Clearly, such a transformation requires retention of configuration in the displacement reaction. This displacement must occur even in the absence of an obvious directing group at C_2. Remarkably, considerable progress has been attained toward this goal, as is described below.

Scheme 1



Scheme 2



The strategy followed to meet this objective was to seek conditions which favor a considerable degree of "onium character" in the glycosylation mechanism.[2] Recently, we reported that β-glycosides can be synthesized from 1 (R = Bn) via the combination of stannylated acceptors[6] and zinc triflate as the promoter (Scheme 1).[7] *It has now been found that if silver tetrafluoroborate is used as the promoter, the reaction of oxirane 1 with various stannylated acceptors leads to 5 (Scheme 2).* In this fashion, the novel α glycosides 6–9 were obtained in the yields shown.

In contemplating the use of this method in reiteratable oligosaccharide synthesis, it was important to ascertain its applicability if the intended acceptor were a stannylated glycal. In the event, reaction of 1 (R = Bn) with stannyl ether 10 (generated in situ) under promotion by silver tetrafluoroborate indeed afforded a 52% yield of 11. The glycal double bond present in 1 could be exploited for another iteration (see formation of the α,α-trisaccharide 12).

The reaction of 6-hydroxylglucal 13 [3a] with 1 (R = Bn) under mediation by zinc chloride underscores the tunability of glycosylation as a function of the nature of the promoter. Under these conditions the product, after acetylation, is the β-linked disaccharade 14. Epoxidation of 14 in the usual way followed by reaction with stannyl ether 10 under promotion with silver tetrafluorborate and acetylation gave a 43% overall yield of the β,α-trisaccharide 15.

(1) (a) Kornfeld, R.; Kornfeld, S. *Ann. Rev. Biochem.* **1976**, *45*, 217. (b) Wagh, P. V.; Bahl, O. P. *CRC Crit. Rev. Biochem.* **1981**, *10*, 307. (c) *Carbohydrate Recognition in Cellular Function*; Ciba Foundation Symposium; John Wiley & Sons: New York., 1989; p 277. (d) *Glycoconjugates—Composition, Structure and Function;* Allen, H. J., and Kisailus, E. C., Eds.; Marcel Dekker: New York, 1992.

(2) For recent reviews of O-glycosylation, see: (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (c) Garegg, P. J. *Acc. Chem. Res.* **1992**, *25*, 575. (d) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

(3) (a) Danishefsky, S. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Friesen, R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (c) Gordon, D. M.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *206*, 361. (d) Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science* **1993**, 260, 1307. (e) Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 8473.

(4) Liu, K. K.-C.; Danishefsky, S. J. *J. Org. Chem.*, previous paper in this issue and references cited therein.

(5) (a) Gordon, D. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 659. (b) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518.

(6) For review of stannyl alkoxide in organic synthesis: (a) Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363. (b) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.

(7) Liu, K. K.-C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 4933.

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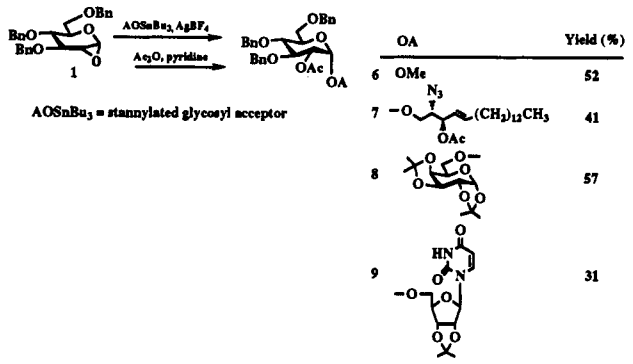
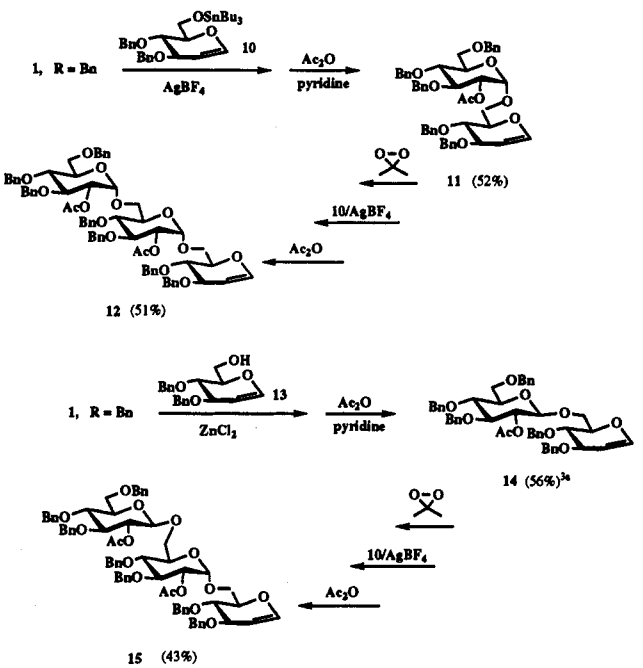
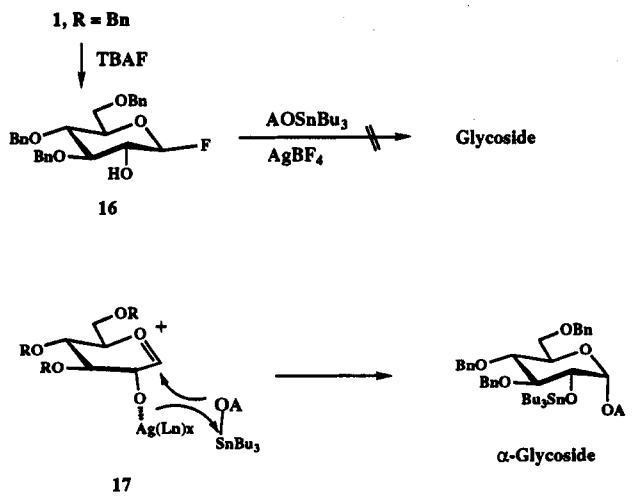
Scheme 3



Scheme 4



Scheme 5



At the mechanistic level, we considered the notion that the fluorohydrin **16** derived in situ by fluoridolysis of **1** (R = Bn) is the active glycosyl donor. While we cannot rigorously exclude this possibility, it seems quite unlikely. Thus, when we started with **16**, and submitted it to the acceptor (stannyl ether **10**) under the promotion conditions used above, no α-disaccharides were obtained. We think it more likely that reaction of the promoter with the epoxide generates an entity with considerable onium ion character at the anomeric center and an O–metal bond at postion 2 (cf. 17). Attack of nucleophile occurs from the "preaxial" face of the onium equivalent, possibly directed by the α-O-metal array at C_1. Conceivably part of the stereoselecivity accrues from group transfer of the stannyl group to the C_2 oxygen.

We emphasize an important limitation in the method. At this writing, the protocol is not applicable to carbohydrate acceptors which are to be glycosylated at a secondary alcohol flanked by other functions. In these cases, the yields as well as the selectivity are significantly reduced. While this limitation remains to be overcome, the capacity to generate α-glycosides from 1α,2α-oxiranes is already valuable and interesing. Experiments expanding the range and applications of oxiranes as glycosyl donors continues.

Experimental Section

General Procedure for Epoxidation of Glycals and Conversion to α-Glycosides. The glycal (0.1 mmol) was dissolved in 1 mL of dry CH_2Cl_2, and cooled to 0 °C in a nitrogen atomsphere. A solution of dimethyldioxirane in acetone (2 equiv., ca. 0.07 M) was added.[8] The reaction mixture was stirred at 0 °C for 30 min. The α-1,2-anhydrosugar thus obtained was concentrated to dryness by passing a stream of nitrogen over the reaction mixture and placing it under vacuum for 1 h. A solution of the stannyl alkoxide[9] (2 equiv) in dry THF (2 mL) was added to the α-1,2-anhydro sugar (cf. 1 R = Bn)) and cooled at 0 °C. Silver tetrafluoroborate (2 equiv in 1 mL of dry THF) was added to the reaction mixture slowly.[10] The reaction mixture was allowed to warm to rt and stirred for 16–24 h. Upon dilution with aqueous KF and extraction with EtOAc, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was treated with acetic anhydride (0.5 mL) in anhydrous pyridine (1 mL). The mixture was stirred at rt for 12 h, after which it was added to 10 mL of $NaHCO_3$ (saturated) and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel gave the 2-*O*-acetyl-3,4-tri-*O*-benzyl-α-D-glucopyranoside in the yields shown.

Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (6): $[\alpha]^{23}_D$ +58.5 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3030, 2917, 1743, 1367, 1236, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.12 (m, 15 H), 4.91 (d, 1H, *J* = 0.9 Hz, H-1), 4.86 (dd, 1H, *J* = 3.9, 8.4 Hz), 4.80 (d, 1H, *J* = 4..5 Hz), 4.76 (d, 1H, *J* = 4.2 Hz), 4.75 (s, 1H), 4.60 (s, 1H), 4.52 (d, 1H, *J* = 5.1 Hz), 4.47 (d, 1H, *J* = 4.47 Hz), 3.98 (m, 1H), 3.81–3.65 (m, 4H), 3.37 (s, 3H, OCH_3), 2.02 (s, 3H, $OCOCH_3$); HRMS (FAB) calcd for $(M + Na)^+$ $C_{30}H_{34}O_7Na$ 529.2230, found 529.2228.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1 → 1)-(2*S*,3*R*,4*E*)-2-azido-3-*O*-acetyl-4-octadecene-1,3-diol (7):** $[\alpha]^{23}_D$ +45.2 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 2924, 2853, 2098, 1743, 1233, 1062, 697 cm^{-1}; ^1H NMR (300 MHz) δ 7.42–7.15 (m, 15 H) 5.78 (dt, 1H, *J* = 14.4, 7.1 Hz, $-CHOAcCH{=}CH(CH_2)_{12}CH_3$), 5.38 (dd, *J* = 14.4, 8.3 Hz, $-CHOAcCH{=}CH(CH_2)_{12}CH_3$), 5.26 (dd, 1H, *J* = 8.3, 5.2 Hz), 5.03 (d, 1H, *J* = 4.7 Hz, H-1), 4.82 (dd, 1H, *J* = 4.7, 11.8 Hz), 4.79(d, 1H, *J* = 13.6 Hz), 4.77 (d, 1H, *J* = 13.5 Hz), 4.72 (d, 1H, *J* = 13.6 Hz), 4.59 (d, 1H, *J* = 13.6 Hz), 4.5 (s, 1H), 4.47 (s, 1H), 4.02 (t, 1H, *J* = 11.8 Hz), 3.8–3.63 (m, 6H), 3.37 (dd, 1H, *J* = 8.3, 10.6 Hz), 2.02 (s, 3H, $OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 1.24 (brs, 24 H, 12 CH_2), 0.87 (t, 3H, *J* = 8.2 Hz, $-(CH_2)_{12}CH_3$); HRMS (FAB) calcd for $(M + Na)^+$ $C_{49}H_{67}O_9N_3Na$ 864.4802, found 864.4771.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1 → 6)-1,2;3,4-di-*O*-isopropylidene-α-D-galacto-**

(8) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
(9) Davies, A. G.; Kleinschmidt, D. C.; Palan, P. R.; Vasishta, S. C. *J.Chem. Soc., Chem., Commun.* **1971**, 3972.
(10) In the case of Bu_3SnOMe, silver tetrafluoroborate was added to the epoxide before adding Bu_3SnOMe.

pyranose (8): $[\alpha]^{23}_D$ +27.8 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$) 2986, 2933, 1743, 1370, 1278, 1068, 1002, 739 cm^{-1}; ^1H NMR (400 MHz) δ 7.19–7.04 (m, 15H), 5.53 (d, 1H, J = 5 Hz, H-1), 5.09 (d, 1H, J = 3.7 Hz, H-1′), 4.91 (dd, 1H, J = 3.7, 10.6 Hz), 4.82 (d, 1H, J = 6.7 Hz), 4.80 (d, 1H, J = 6.7 Hz), 4.77 (d, 1H, J = 11.6 Hz), 4.68 (s, 1H), 4.65 (s, 1H), 4.62 (dd, 1H, J = 2.4, 7.9 Hz), 4.52 (d, 1H, J = 2.1 Hz), 4.49 (d, 1H, J = 3.6 Hz), 4.32 (dd, 1H, J = 2.4, 5.0 Hz), 4.21 (dd, 1H, J = 2.4, 5.0 Hz), 4.05 (t, 1H, J = 9.3 Hz), 3.96 (dt, 1H, J = 1.5, 7.1 Hz), 3.87–3.66 (m, 5H), 2.04 (s, 3H, $OCOCH_3$), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); HRMS (FAB) calcd for $(M + Na)^+$ $C_{41}H_{50}O_{12}Na$ 757.9244, found 757.3212.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1 → 5)-2,3-isopropylideneuridine (9):** $[\alpha]^{23}_D$ +60.7 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 2924, 1693, 1454, 1377, 1235, 1063, 746. cm^{-1}; ^1H NMR (300 MHz) δ 8.21 (brs, 1H, N*H*), 7.44 (d, 1H, J = 8.1 Hz, –NC*H*=CH–), 7.41–7.12 (m, 15 H), 5.77 (d, 1H, J = 1.9 Hz, H-1), 5.65 (dd, J = 2.1, 8.0 Hz, –COC*H*=CHN–), 5.06 (d, 1H, J = 3.7 Hz, H-1′), 4.88 (dd, J = 3.7, 10.1 Hz), 4.79–4.49 (m, 6H), 4.29 (m, 1H), 3.82–3.95 (m, 2H), 3.71–3.60 (m, 4H), 3.48 (m, 1H), 2.02 (s, 3H, $OCOCH_3$), 1.59 (s, 3H, CH_3), 1.52 (s, 3H, CH_3); HRMS (FAB) calcd for $(M + Na)^+$ $C_{41}H_{46}O_{12}N_2Na$ 781.3051, found 781.2977.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1 → 6)-1, 5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (11):** $[\alpha]^{23}_D$ +59.6 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 2923, 1742, 1603, 1237, 1060, 737 cm^{-1}; ^1H NMR (300 MHz) δ 7.13–7.35 (m, 15H), 6.32 (dd, 1H, J = 1.2, 6.2 Hz, H-1), 5.14 (d, 1H, J = 3.7, H-1′), 4.86–4.78 (m, 4H), 4.74 (d, 1H, J = 11.3 Hz), 4.68 (d, 1H, J = 11.3 Hz), 4.63 (d, 1H, J = 11.5 Hz), 4.61 (d, 1H, J = 10.7Hz), 4.54 (d, 1H, J = 11.7 Hz), 4.52 (d, 1H, J = 11.7 Hz), 4.48 (d, 1H, J = 12.1 Hz), 4.20 (d, 1H, J = 5.4 Hz, H-2), 4.03–3.93 (m, 4H), 3.85 (t, 1H, J = 8.1 Hz), 3.79–3.69 (m, 4H), 3.61 (dd, 1H, J = 1.8, 10.9 Hz), 1.99 (s, 3H, $OCOCH_3$); HRMS (FAB): calcd for $(M + Na)^+$ $C_{49}H_{52}O_{10}Na$ 823.3458, found 823.3464.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyroanosyl)-(1 → 6)-*O*-(2-*O*-acetyl,3,4-di-*O*-benzyl-α-D-glucopyranosyl)-(1 → 6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (12):** $[\alpha]^{D}_{23}$ +91.5 (*c* 0.47, $CHCl_3$); IR ($CHCl_3$) 2923, 1742, 1453, 1365, 1235, 1042, 738, 668 cm^{-1}; ^1H NMR (400 MHz) δ 7.32–7.12 (m, 35H), 6.32 (d, 1H, J = 6.1 Hz, H-1), 5.13 (d, 1H, J = 3.5 Hz, H-1′ or H-1″), 5.02 (d, 1H, J = 2.7 Hz, H-1″ or H-1′), 4.88–4.47 (m, 17 H), 4.20 (d, 1H, J = 6.2 Hz, H-2), 4.00–3.59 (m, 14H), 2.03 (s, 3H,. $OCOCH_3$), 2.01 (s, 3H, $OCOCH_3$); HRMS (FAB) calcd for $(M + Na)^+$ $C_{71}H_{76}O_{16}Na$ 1207.5055, found 1207.5050.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1 → 6)-*O*-(2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranosyl)-(1 → 6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (15):** $[\alpha]^{D}_{23}$ +34.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3030, 2922, 1746, 1454, 1366, 1234, 1063, 737 cm^{-1}; ^1H NMR (300 MHz) δ 7.49–7.15 (m, 35 H), 6.30 (d, 1H, J = 6.1 Hz, H-1), 5.11 (d, 1H, J = 3.6 Hz, H-1′), 5.05 (t, 1H, J = 8.4 Hz), 4.85–4.50 (m, 16H), 4.40(d, 1H, J = 8.1 Hz), 4.2 (1H, m, H-2), 4.08–3.48 (m, 14H), 1.98 (s, 3H, $OCOCH_3$), 1.87 (s, 3H, $OCOCH_3$); HRMS (FAB) calcd for $(M + Na)^+$ $C_{71}H_{76}O_{16}Na$ 1207.5055, found 1207.5074.

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Supplementary Material Available: ^1H NMR spectra of 6–9, 11, 12, and 15 (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.