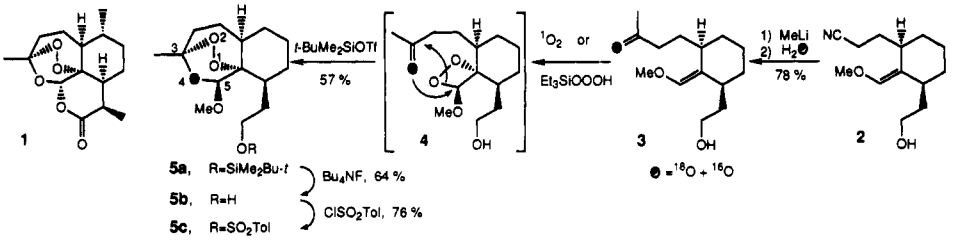
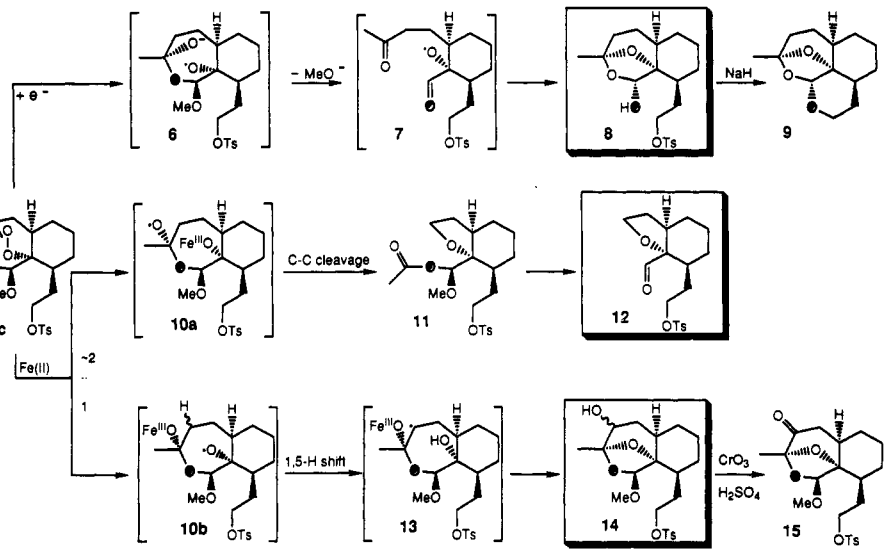
Scheme I



Scheme II



(190 °C) pyrolysis of artemisinin,[18] is offered to account for these room-temperature results. Iron(II)-induced cleavage of the peroxide bond in trioxane **5c** leads to radical intermediates **10a** and **10b** in about a 2:1 ratio: C–C bond cleavage of **10a** initially produces labile ring-contracted tetrahydrofuran acetal **11** (characterized by ^1H and ^{13}C NMR) with ^{18}O located in the acetoxy group as shown in Scheme II (mass spectrum, M – $CH_3CO^{18}O$) and then produces stable electrophilic tetrahydrofuran aldehyde **12** lacking ^{18}O. 1,5-Hydrogen atom abstraction in radical intermediate **10b** ultimately leads to stable dioxolane alcohol **14** as a mixture of two diastereomers with ^{18}O not located in the methoxyl group (mass spectrum M – CH_3O). Subsequent oxidation of this isomeric mixture of alcohols **14** gave the corresponding dioxolane ketone **15** as a single product.[13] The overall yields of isolated aldehyde **12** and hydroxy dioxolane **14** ranged from 60 to 70%.

In summary, these reactions of trioxane **5c** for the first time **(1) provide firm mechanistic evidence that deoxygenation of a 1,2,4-trioxane into the corresponding 1,3-dioxolane occurs via a tandem unzipping–zipping process and (2) show that trioxane cleavage by ferrous ions follows a different mechanistic course and leads to different products than trioxane cleavage by nonferrous reducing agents.** These results may help the development of better antimalarial trioxanes.[19,20]

Acknowledgment. We thank the Environmental Health Sciences Center, School of Hygiene and Public Health, The Johns Hopkins University, and Dr. Henry Sonneborn for financial support, Dr. Judith Stamberg (Union Memorial Hospital, Baltimore) for suggesting the use of a thiol to activate hemin reduction of trioxane **5c**, Professor Craig Townsend (Johns Hopkins) for a helpful discussion about ^{18}O labeling, and Professor Steven Meshnick (City University of New York Medical School) for some helpful preprints and discussions about porphyrin adducts with trioxanes like artemisinin.

Supplementary Material Available: Listing of full experimental details and spectral data for compounds **3**, **5a–c**, **8**, **9**, **11**, **12**, **14**, and **15** (36 pages). Ordering information is given on any current masthead page.

(18) Lin, A. J.; Klayman, D. L.; Hoch, J. M.; Silverton, J. V.; George, C. F. *J. Org. Chem.* **1985**, *50*, 4504–4508.

(19) For a recent review of the chemistry and biological activity of artemisinin and related antimalarials, see: Zaman, S. S.; Sharma, R. P. *Heterocycles* **1991**, *32*, 1593–1638.

(20) For recent use of ^{18}O labeling to study the mechanism of conversion of dihydroartemisinic acid into artemisinin, see: Acton, N.; Roth, R. J. *J. Org. Chem.* **1992**, *57*, 3610–3614. We thank Dr. Acton for a preprint of this article.

Remarkable Regioselectivity in the Chemical Glycosylation of Glycal Acceptors: A Concise Solution to the Synthesis of Sialyl-Lewis X Glycal

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The cell-surface-bound polysaccharide sialyl-Lewis X antigen (SLe^x, **1**)[2] has recently been identified as a ligand for binding to the cell-adhesion molecules ELAM-1 and CD-62.[3] These proteins are expressed on cell membranes in response to tissue injury, and

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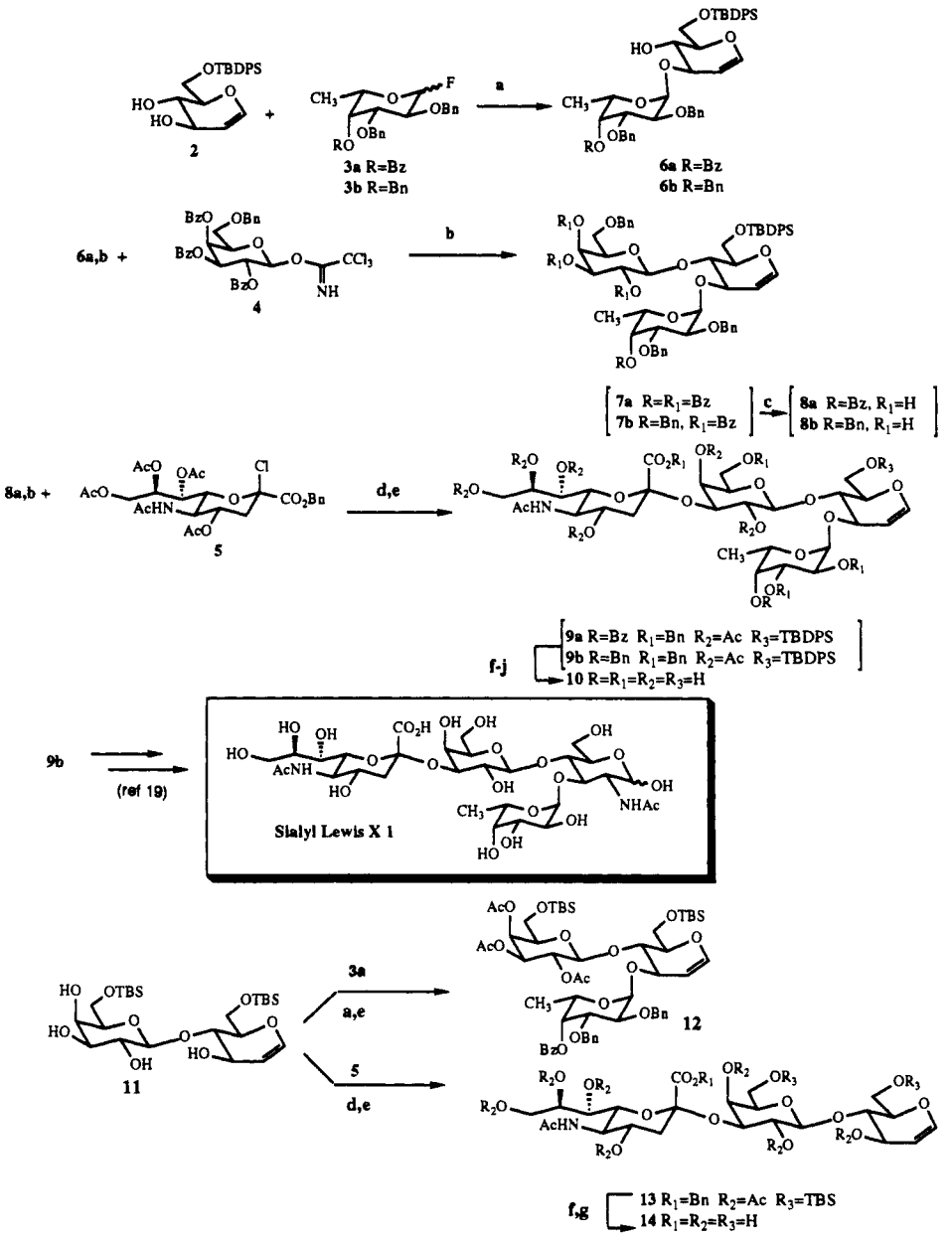
Scheme I



[a] a. 2eq. $AgClO_4$, 2eq $SnCl_2$, 2eq di-*t*-butylpyridine 4Å mol sieves, ether: **3a** reflux (59%); **3b** rt (52%); **11** rt (30%). b. 0.1 eq $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C (75%). c. NaOMe/MeOH (88%). d. 2eq. AgOTf, 2eq di-*t*-butylpyridine, $CaSO_4$, THF, −78° to −10°C. e. Ac_2O, pyridine, DMAP, CH_2Cl_2; **d** and **e** combined yields **9a** (40%, isolated; 78% based on recovered starting material (BORSM)); **9b** (38%, isolated; 75% BORSM); **13** (28%, isolated; 88% BORSM). f. TBAF, THF. g. NaOMe/MeOH. h. Na/NH_3. i. Ac_2O, pyridine, DMAP, CH_2Cl_2. j. NaOMe/MeOH/H_2O: **9a** → **10** (77%), **9b** → **10** (61%), **13** → **14** (73%).

their expression results in binding to neutrophils and monocytes which bear the SLe^x antigen at the nonreducing terminus of membrane-bound polysaccharides. SLe^x was previously identified in a number of human tumor cell lines, and it is also found in the serum of cancer patients.[4] The biosynthesis of SLe^x results from the action of sialyl- and fucosyltransferases on terminal lactosamines of cell-surface polysaccharides.[5] Thus, our interest in the sialyl-Lewis X antigen was fueled by the possibility that a small-molecule analog bearing the pertinent structural features of SLe^x might serve as an antagonist of ELAM-1 or as a sialyl- or fucosyltransferase inhibitor.[6]

(1) (a) National Institutes of Health Postdoctoral Fellow, 1990–1992. (b) Kent Graduate Fellow, Yale University. (c) American Cancer Society Postdoctoral Fellow, 1990–1992. (d) Visiting fellow on leave from Japan Tobacco, Inc., 1991–1992. (e) Visiting fellow on leave from Ibaraki University, 1991–1992. (f) Dox Graduate Fellow, Yale University.

(2) (a) Palcic, M. M.; Venot, A. P.; Ratcliffe, R. M.; Hindsgaul, O. *Carbohydr. Res.* **1989**, *190*, 1. (b) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1991**, *209*, C1. (c) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1991**, *10*, 549. (d) Nicolaou, K. C.; Hummel, C. W.; Bockovich, N. J.; Wong, C. H. *J. Chem. Soc., Chem. Commun.* **1991**, *10*, 870. (e) Dumas, D. P.; Ichikawa, Y.; Wong, C. H. *Biomed. Chem. Lett.* **1991**, *1*, 425. (f) Nicolaou, K. C.; Hummel, C. W.; Iwabuchi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3126.

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(5) Review: Hakomori, S. *Cancer Res.* **1985**, *45*, 2405.

(6) Wong, C. H.; Dumas, D. P.; Ichikawa, Y.; Koseki, K.; Danishefsky, S. J.; Weston, B. W.; Lowe, J. B. *J. Am. Chem. Soc.*, in press. A recombinant human α1,3 fucosyltransferase and LacNAc acceptor were used in the inhibition analysis.

In this paper we report a highly concise chemical route to differentially functionalized congeners of the Lewis X antigen, including the critical sialyl-Lewis X series. The major finding herein is that both D-glucal and D-lactal derivatives, where only the primary alcohol functions are protected, undergo regiospecific fucosylation at the allylic alcohol. Furthermore, in the D-lactal series, sialylation occurs specifically at the C3′ hydroxyl in the galactosyl domain. The sum of these findings illustrates the enormous potential to be gained from the use of glycals as glycosyl acceptors.[7]

We first found that 6-*O*-(TBDPS)-D-glucal (**2**)[8] was regio- and stereoselectively glycosylated with fluoride **3a**[9,10] to provide **6a**. Under similar reaction conditions the corresponding tribenzyl donor **3b**[11] gave a 5:3 mixture of α and β anomers favoring **6b**. The stereochemistry observed[12] in **6a,b** was independent of the anomeric stereochemistry of fluorides **3a,b**. The ratio of O3- to O4-fucosylated products was typically 8:1 independent of the fucosyl donor (Scheme I).[12]

Galactosyl trichloroacetimidate **4**[13,14] provided a single β-linked trisaccharide glycal **7a**, which upon debenzoylation gave the required triol **8a**. Coupling with sialyl donor **5**[15] and acetylation of the crude product mixture provided a single stereoisomer of the tetrasaccharide glycal **9a**.[13,16] The above protocol was also successfully demonstrated for the synthesis of **9b** starting from **3b**. By this concise route we synthesized multigram quantities of **9b**. Global deprotection of both **9a** and **9b** provided ready access to sialyl-Lewis X glycal (**10**).

With a view to instituting additional synthetic economies, we explored regioselective glycosylations of D-lactal derivatives. Reaction of 6,6′-bis(*O*-TBS)lactal (**11**)[17] with fucosyl donor **3a** occurred at the allylic alcohol to afford trisaccharide glycal **12**, with no other regio- or stereoisomers detected. In contrast, sialylation of **11** with sialyl donor **5** stereoselectively provided the O3′-sialylated lactal **13**,[18] which was completely deprotected to give sialyllactal **14**.

Both sialyllactal (**14**) and sialyl-Lewis X glycal (**10**) were tested for fucosyltransferase inhibition. **14** was not an inhibitor, but **10** was a moderate inhibitor of α-1,3-fucosyltransferase (IC_{50} = 41 mM). In conclusion, our synthetic approach to **10** provides ready access to a host of small-molecule analogs of sialyl-Lewis X antigen. Specifically, the glycal at the reducing terminus of **9a,b** has been successfully utilized as a handle for introducing the SLe^x unit to other haptens as well as for completing the total synthesis of sialyl-Lewis X antigen (**1**).[19]

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Registry No. 1, 98603-84-0; **2**, 87316-22-1; **3a**, 142800-26-8; **3b**, 127061-08-9; **4**, 142800-27-9; **5**, 113757-77-0; **6a**, 142800-28-0; α-**6b**, 142800-29-1; β-**6b**, 142865-32-5; **7a**, 142800-30-4; **7b**, 142800-31-5; **8a**, 142800-32-6; **8b**, 142800-33-7; **9a**, 142800-34-8; **9b**, 142800-35-9; **10**, 142800-36-0; **11**, 142800-37-1; **12**, 142800-38-2; **13**, 142800-39-3; **14**, 142810-05-7.

Supplementary Material Available: Listings of complete experimental details and analytical and spectral data for all new compounds (**3–10, 13, 14**) (14 pages). Ordering information is given on any current masthead page.

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(8) Guthrie first demonstrated the reactivity order O6 > O3 > O4 for silylation of D-glucal hydroxyl groups: (a) Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381. (b) Shakhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.

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(10) **3a** was synthesized in five steps from methyl L-fucopyranoside (34% overall yield): (1) $(Bu_3Sn)_2O$, toluene, 110 °C; (2) 4 equiv of benzyl bromide, 2 equiv of Bu_4NBr, toluene, 110 °C; (3) benzoyl chloride cat. DMAP, pyridine; (4) 1 N HCl, acetic acid, 100 °C; (5) DAST, THF, −30 °C.

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(12) The presence of the glycal as an inert reaction partner required avoiding strongly acidic or electrophilic conditions; fucosylation and sialylation were successful only when conducted in the presence of 2,6-di-*tert*-butylpyridine.

(13) **4** was synthesized in four steps from 6-benzyl-1,2:3,4-diisopropylidene-D-galactopyranose (23% overall yield): (1) 1 N HCl, dioxane, 100 °C; (2) benzoyl chloride, pyridine, $CHCl_3$, −10 °C; (3) saturated ammonia in THF/MeOH (7:3); (4) potassium carbonate, trichloroacetonitrile, CH_2Cl_2.

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(15) Ratcliffe, M. R.; Venot, A. P.; Abbas, Z. S. Eur. Pat. Appl. EP 319,253 (*Chem. Abstr.* **1990**, *112*, 175281a).

(16) The stereochemistry of the NeuAcα(2→3)Gal linkage was assigned based on the chemical shift of the NeuAc H4.

(17) **11** was prepared from D-lactal in one step: 2 equiv of TBDMSCl, cat. DMAP, pyridine (67% yield).

(18) We have also observed that allylation and silylation of **11** occur selectively at O3′. The factors responsible for this inversion of regioselectivity are under investigation. See also: (a) Murase, T.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1988**, *184*, C1. (b) Lönn, H.; Stenvall, K. *Tetrahedron Lett.* **1992**, *33*, 115.

(19) These studies are the subject of a manuscript in preparation.

Azaglycosylation of Complex Stannyl Alkoxides with Glycal-Derived Iodo Sulfonamides: A Straightforward Synthesis of Sialyl-Lewis X Antigen and Other Oligosaccharide Domains

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Our previous communication documented the synthesis of sialyl-Lewis X glycal (**2**).[2] In our initial attempts to synthesize sialyl-Lewis X antigen (**1**) from the fully protected tetrasaccharide glycal **2**, we encountered difficulty in extending our sulfonamidoglycosylation methodology[3] to the synthesis of SLe^x-containing glycoconjugates. More specifically, the glycosylation conditions (lithium or potassium alkoxides of a glycosyl acceptor) were not compatible with acetyl or benzoyl esters. In this communication we disclose the successful application of stannyl alkoxide addition to glycal-derived iodo sulfonamides, resulting in the total synthesis of sialyl-Lewis X antigen (**1**) and a synthesis of hexasaccharide **7** (Scheme I).

Reaction of **2** with iodonium di-*sym*-collidine perchlorate and either benzenesulfonamide[2] or 2-(trimethylsilyl)ethanesulfonamide[4] provided iodo sulfonamides **3a** and **3b** in 91% and 82% yields, respectively. The formation of a simple β-benzyl glycoside **4** containing all of the necessary heteroatoms found in sialyl-Lewis X antigen was achieved under very mild conditions, by reaction of **3b** with tributylstannyl *O*-benzyl alkoxide[5] in the presence of silver triflate. Fluoride-mediated desilylation removed both the silyl ether and the 2-silylethanesulfonamido group; acetylation

(1) (a) Visiting Fellow on leave from Japan Tobacco, Inc., 1991–1992. (b) Dox Graduate Fellow, Yale University. (c) National Institutes of Health Postdoctoral Fellow, 1990–1992. (d) Kent Graduate Fellow, Yale University. (e) American Cancer Society Postdoctoral Fellow, 1990–1992. (f) Visiting Fellow on leave from Ibaraki University, 1991–1992.

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(4) (a) 2-(Trimethylsilyl)ethanesulfonamide was synthesized in two steps from sodium 2-(trimethylsilyl)ethanesulfonate (ref 4b) (62% overall): (1) PCl_5, CCl_4; (2) NH_3, CH_2Cl_2, 0 °C. (b) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.

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