tert-butyldimethylsilyl triflate–lutidine.[5b,6] Selective deprotection of the trimethylsilyl ether with hydrogen fluoride–triethylamine in acetonitrile and elimination of the resultant alcohol[5a] with methanesulfonic acid anhydride–pyridine then afford the epoxy dienediyne **7**[5a] (22% yield from **6**, 4 steps). Spectroscopic data for **7** are in complete accord with the assigned structure, including ^{13}C NMR chemical shifts, which correlate well with corresponding signals for **1**.

Epoxy dienediyne **7** is considerably less stable in neat form than the parent chromophore (**1**), decomposing within seconds upon concentration in the absence of free radical inhibitors. The most dramatic distinction in reactivity observed for **1** and **7**, and the most elucidating in terms of mechanism, involves their disparate behavior toward methyl thioglycolate. Synthetic **7** is found to be completely inert to methyl thioglycolate in perdeuterioacetic acid–perdeuteriotetrahydrofuran (1:9, anaerobic incubation, monitored by ^1H NMR spectroscopy) to approximately 60 °C, whereas **1** reacts readily at −70 °C in the same medium. Addition of triethylamine (0.3 M, equimolar thiol) at 23 °C leads to formation of the indene derivative **8**[5a] ($t_{1/2} \simeq 15$ min, HPLC isolation, 38%) as, by far, the major reaction product. Deuterium is incorporated at C2 and C6 (ca. 50%) in **8**, in complete analogy to experiments with **1**. Both the rate and efficiency of thiol addition to **7** suffer by comparison with the corresponding transformation of **1** to **3**. It is also notable that the stereochemistry at C12 in **8** is inverted relative to the adduct **3**, suggesting that the stereochemistry of the epoxide is not a primary influence in directing these remote additions.

Spectroscopic studies of the stable "dihydro" product resulting from the addition of two hydrogen atoms to **3** reveal that the *N*-methylfucosamine residue occupies a conformation in which the methylamino group is located over the β-face of the cyclopentane ring, as predicted by the anomeric and exo-anomeric effects.[2f] Extension of this conformational analysis to **1** (Figure 1) shows that the methylamino group can reasonably function as an internal base in addition reactions to C12, providing an explanation for the observed reactivity difference of **1** and **7** toward methyl thioglycolate. A simple strategy to further test this hypothesis involves transformation of the amino group of **1** to a nonbasic functional group; however, the alkaline conditions of most acylation and alkylation reactions are incompatible with **1**, which decomposes rapidly at neutral pH and above.[7] In an unconventional solution to this problem, treatment of **1** with 1 equiv of sodium nitrite in acetic acid solution at 10 °C affords the nitrosamine **9**, a derivative of sufficient stability for purification and study.[8] Purified **9** provides spectroscopic data in full accord with the assigned structure. Treatment of **9** with thiol, under conditions described above, reveals that this derivative is inert as well to methyl thioglycolate below 0 °C; further warming leads to nonspecific decomposition.

The experiments outlined above provide strong evidence for participation of the carbohydrate amino group of **1** as an internal base in organic solvents. It is reasonable to propose that proton-assisted opening of the epoxide ring (e.g., with acetic acid in the experiments described) is also important in thiol addition. Ellestad et al. have reported similar observations concerning the role of the aminoglycoside in the reaction of calichemicin with thiols in acetonitrile,[9] while Townsend and Cramer find no evidence for amino participation in similar experiments conducted in water at pH 7.4.[10] Further experiments with neocarzinostatin and its derivatives may provide analogous results; the poor water solubility of synthetic materials prepared thus far has prevented these experiments. However, given the possibility that these drugs are activated while bound to DNA (K_d for DNA-bound **1** ca. 10^{-6} M),[11] it is reasonable to question which, if either, medium is relevant to processes occurring in vivo. The experiments described above clearly demonstrate that the potential exists for enormous variation in the rate of thiol addition to **1** and suggest a mechanism by which catalysis may occur. In one view, the data may be considered to support a proposal in which thiol addition to drug in water is slow relative to addition to drug bound or proximal to DNA. This speculative theory is appealing in that it suggests a rationale for selective activation of drug in the vicinity of DNA; once activated, the chromophore (**2**) is exceedingly short-lived ($t_{1/2} \simeq 0.5$ s at 37 °C).[1] Experiments designed to test these proposals are in progress.

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Supplementary Material Available: Reproductions of high-field ^1H NMR spectra for all synthetic intermediates including **9**, tabulated spectroscopic assignments, and a ^{13}C NMR spectrum of **7** and its tabulation and comparison with corresponding data for **1** (18 pages). Ordering information is given on any current masthead page.

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Stereocontrolled Synthesis of Disaccharides via the Temporary Silicon Connection

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One of the important problems in carbohydrate chemistry is that of devising a method of some generality to achieve the stereocontrolled attachment of one carbohydrate to the anomeric center of another. Considerable progress has been made on this problem over the years, but although much fascinating chemistry has been uncovered, a general solution has proved elusive.[1]

The significance of the work reported here is that it achieves, for the first time, the formation of a glycosidic linkage predictably and stereospecifically, even in the difficult case of a β-mannoside connection.

We illustrate our general approach to this problem. Carbohydrate A is attached via a temporary connector Y to a properly chosen hydroxyl of B (the "controlling" hydroxyl) as shown in Figure 1, using the 2-β hydroxyl of a mannose derivative as an illustration. The intramolecularity of the process indicated in **2** → **3** → **4** now dictates whether an α or a β anomer will be formed.

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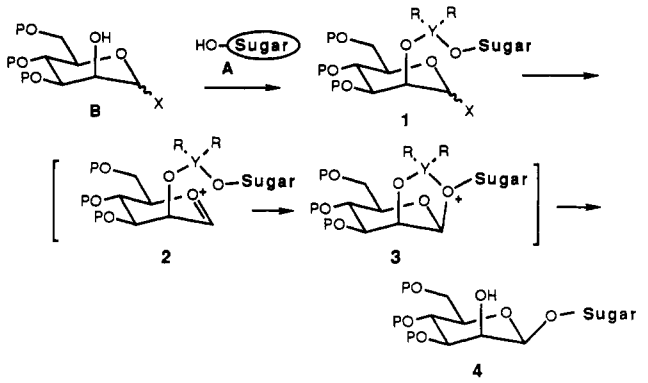
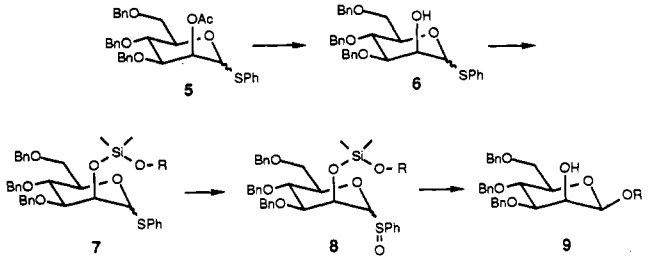


Figure 1.

Scheme I

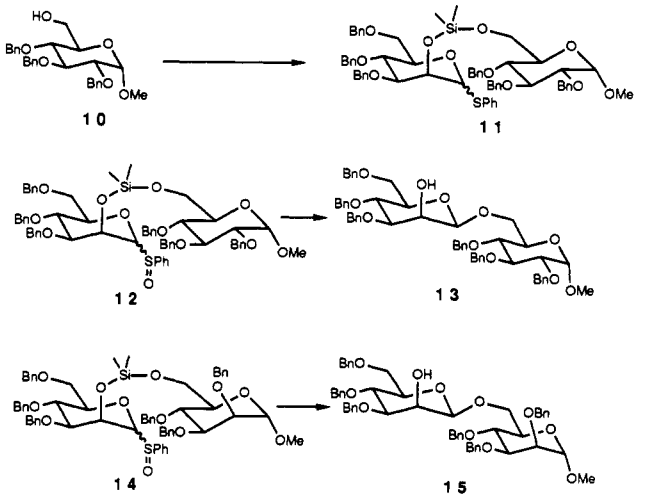


We now report the implementation of this scheme, in which Y is a silicon atom[2] and the departing group X is derived from a phenylthio group, in the construction of β-mannosides. They were selected as targets because they are known to be difficult to make by conventional methods.[3] Indeed, most intermolecular glycosidation procedures lead mainly to the anomeric α isomers.

Before attempting the synthesis of a β-mannosyl *disaccharide*, we examined the feasibility of the scheme for the synthesis of the simpler β-methyl and β-isopropyl mannosides. Deacetylation of the 2-acetate of the 3,4,6-tribenzyl ether of phenylthio mannoside **5**[4] (1:1 mixture of anomers) freed the 2-hydroxyl to produce **6**, which was then converted (~83–100% from **5**) to methoxysilane **7**, R = methyl, by reaction with chloromethoxydimethylsilane[5] (Scheme I). Conversion of the phenylthio group to a departing group was achieved by the method of Kahne[6] (1 equiv of MCPBA in CH_2Cl_2, −25 → 0 °C, to sulfoxide **8**; then, 3 equiv of triflic anhydride, 2 equiv of 2,6-di-*tert*-butylpyridine, 0.05 M in CH_2Cl_2, 4A sieves, −78 °C → room temperature). The process shown in **1** → **3** in Figure 1 apparently took place because workup gave the β-methyl mannoside derivative **9**, identified by comparison of its ^1H NMR spectrum and its optical rotation ($[\alpha]^{27}_D$ − 13.2°, c = 1.0, $CHCl_3$; reported −13.1°) with those of an authentic sample.[7,8]

In a similar manner, the mixed dialkoxysilane **7**, R = isopropyl, gave the β-isopropyl mannoside analogue of **9** ($[\alpha]^{27}_D$ −23.6°, c = 0.55, $CHCl_3$; anomeric center, ^{13}C δ 97.6, ^1H δ 4.5; the α-isopropyl anomer of **9** showed $[\alpha]^{27}_D$ +52.0°, c = 0.53, $CHCl_3$; anomeric center, ^{13}C δ 97.1, ^1H δ 5.0). In that case, we established that, as might be anticipated if an oxonium salt is an intermediate, the yield of β-mannoside was quite similar whether the sequence

Scheme II



was carried out starting with one or the other of the pure phenylthio anomers.

We were now ready to attempt the construction of a β-mannoside in which the anomeric connection is to the primary 6-hydroxyl of glucose, as shown in Scheme II. This was successful, as shown in Scheme I. α-Methyl tri-*O*-benzyl-D-glucopyranoside **10**[9] was first converted to its chlorodimethylsilyl ether.[10] The crude chlorosilane was then converted to the silicon-tethered disaccharide **11** by reaction with **6**.[11] The sequence described above for the conversion **7** → **9** then gave the desired 6-*O*-glucosyl-β-D-mannopyranoside **13** (73% from the α sulfoxide; 61% from the β anomer). The rotation ($[\alpha]^{25}_D$ +24.0°, c = 1.0 in $CHCl_3$), HRMS, ^{13}C NMR, ^1H NMR, and IR data were all consistent with the assigned structure.

Further confirmation was provided by comparison with the α-mannosyl anomer of **13**, which we made by *intermolecular* coupling, using Kahne's method,[6] of the phenyl sulfoxide of the acetate of mannose 3,4,6-tri-*O*-benzyl ether with the methyl glucoside **10**. The α anomer of **13** differed in the expected manner from **13** (the α anomer of **13** exhibited higher rotation ($[\alpha]^{27}_D$ +59°, c = 1.0, $CHCl_3$) and a lower field ^{13}C resonance of the mannose anomeric center (δ 100.8 vs δ 101.2 in **13**).[12]

We have also applied the method to the synthesis of the 6-*O*-mannosyl-β-D-mannopyranoside **15**. This was carried out exactly as above, except that the phenylthio anomer intermediates were not separated before oxidation to sulfoxides **14**. The β-mannoside structure **15** (68% yield from the sulfoxide mixture; $[\alpha]^{27}_D$ +16.5°, c = 1.0, $CHCl_3$; reported[12] for the α anomer, $[\alpha]^{24}_D$ +40.1°, c = 1.35, $CHCl_3$) was confirmed by comparison of the ^{13}C NMR spectrum and the rotation of the derived mesylate with those of the known compound ($[\alpha]^{31}_D$ +7.0°, reported[13] $[\alpha]^{23}_D$ +7.3°).

We have demonstrated the suitability of the method of temporary silicon connection for the stereospecific synthesis of disaccharides in which the connection is between the *primary* hydroxyl group of one sugar and the anomeric center of another. We are now investigating the extension of this route to stereocontrolled disaccharide constructions which involve connection to a *secondary* hydroxyl.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their support of this work.

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(11) By addition of 1 equiv of **6** and 1.5 equiv of imidazole to 2.5 equiv of the crude chlorodimethylsiloxane in THF (room temperature, 10 min) to give the required **11** in nearly quantitative yield after flash chromatography.

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