tensively pursued and will be described in due course.

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Supplementary Material Available: Representative procedures for both seleno- and iodocyclizations, NMR spectra, and all NOE data for products **8-15** (16 pages). Ordering information is given on any current masthead page.

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Evidence for Aminoglycoside Participation in Thiol Activation of Neocarzinostatin Chromophore. Synthesis and Reactivity of the Epoxy Dienediyne Core

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The reaction of the chromophore subunit (**1**) of the natural antitumor antibiotic neocarzinostatin with methyl thioglycolate produces an NMR-observable intermediate, assigned as **2**, which decays with a half-life of ~2 h at −38 °C to form the putative biradical **3**.[1,2] While the latter rearrangement is striking, perhaps no less so is the thiol addition step (**1** → **2**), which occurs readily at −70 °C in acetic acid–tetrahydrofuran (1:9, $t_{1/2} \simeq 1.5$ h, 0.2 M thiol).[1] Reported herein are (1) the assembly of the full core functionality of neocarzinostatin chromophore in a synthetic system and (2) the preparation of a nonbasic derivative of the chromophore itself. Experiments with these synthetic materials provide strong evidence that thiol activation of **1** is facilitated dramatically through participation of the carbohydrate amino group as an internal base.

The highly reactive epoxy dienediyne **7** is synthesized in 6 steps, employing **4** (≥95% ee) as the starting material.[3,4] Attempts to bring about allylic transposition, or indeed any chemical transformation, in **4** or derivatives are complicated by the instability of the strained epoxy cyclononadiyne functional group.[5] After considerable experimentation, a simple transposition scheme was developed involving brief exposure of the bis-trimethylsilyl ether **5**,[5b] prepared from **4** and trimethylsilyl chloride–triethylamine, to trifluoroacetic acid (0.2 M in CH_2Cl_2, 5 equiv) at 0 °C, forming the trifluoroacetate **6** in 49% yield.[5a] Suprafacial transposition in the formation of **6** is demonstrated by the conversion of **6** to a cyclic phenylphosphonite diester[5a] (stereochemistry at phosphorus unknown) by sequential treatment of **6** with (1) methanol–triethylamine,[5b] (2) hydrogen fluoride–triethylamine,[5b] and (3) dichlorophenylphosphine–pyridine. Hydrolysis of trifluoroacetate **6** with methanol and triethylamine in toluene at 0 °C furnishes the corresponding alcohol,[5b] which is silylated at −78 °C with

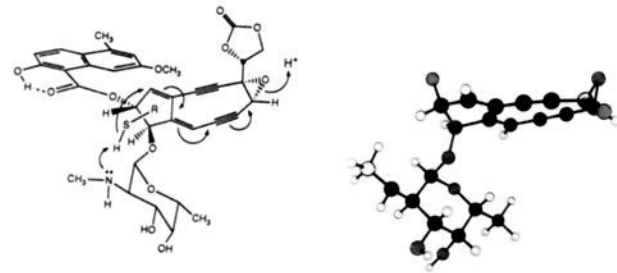
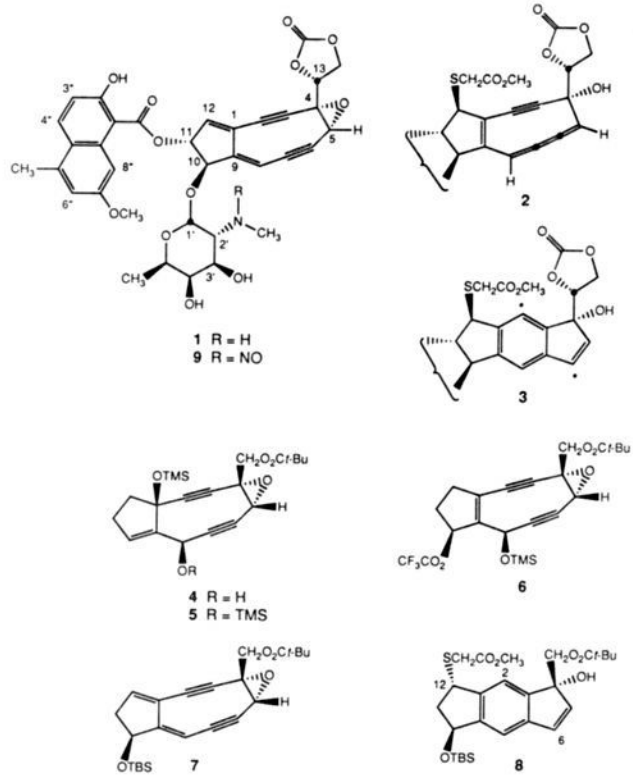


Figure 1. Proposed mode of thiol addition to **1** through base and acid catalysis and a representation of a conformation favorable for amino participation (naphthoate and carbonate groups abbreviated as diagonally striped spheres for clarity).

Chart I



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(5) This instability arises primarily from facile free radical induced decomposition and, in certain intermediates, by an apparent sensitivity toward silica gel and strong acids as well. Yields are determined by use of an internal standard and reflect more the instability of the compounds produced than the efficiency of a given chemical transformation. (a) This intermediate was concentrated for brief periods in the presence of a free radical inhibitor, was purified by flash chromatography (at 0 °C in the case of **6** and **7**), and afforded satisfactory ^{1}H NMR, IR, and high-resolution mass spectroscopic data. (b) This intermediate was not subjected to purification or concentration.

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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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