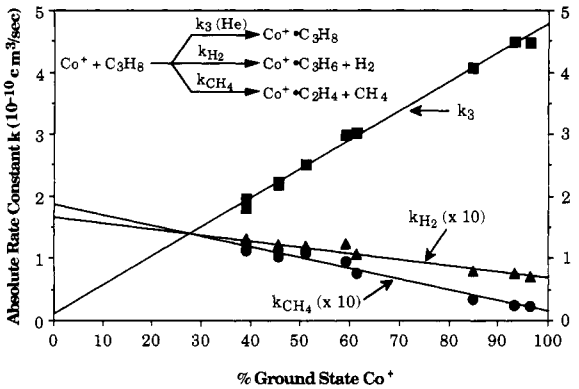

Figure 1. Absolute rate constants for $Co^+C_3H_8$ adduct formation and for H_2 and CH_4 elimination channels as a function of % ground-state Co^+. The linear least-square fit of the experimental data points is used to extrapolate to rates of reaction corresponding to 100% ground-state and 100% excited-state Co^+.[12]

Co^+, and k_{gs} and k_{ex} are the ground- and excited-state rate constants, respectively. We obtain k by plotting ln $Co^+/(Co^+)_0$ versus time.[12] We measure k as a function of % ground-state Co^+ and extrapolate to 100% ground-state ($f = 1$) and 100% excited-state Co^+ ($f = 0$) to determine the individual total rates of reaction. Product distributions are then also measured as a function of % ground-state Co^+ to obtain individual rate constants (Table I).

The rate of adduct formation as a function % ground-state Co^+ is shown in Figure 1. The experimental data points range from 38 to 96% ground-state Co^+. The linear least-squares fit of the data indicates that for 100% ground-state Co^+ (a^3F $3d^8$) the rate of adduct formation is 4.7×10^{-10} cm^3 s^{-1}, which is approximately 40 times greater than for the b^3F $4s3d^7$ state.[13] The repulsive 4s electron in the excited state is responsible for the greatly reduced clustering efficiency with propane.

The H_2 and CH_4 elimination channels are relatively minor for ground-state Co^+ in our high-pressure experiment, approximately two orders of magnitude smaller than the rate for adduct formation. These elimination channels are greatly enhanced for the electronically excited Co^+ as shown in Figure 1. The inefficiency of H_2 and CH_4 elimination for ground-state Co^+ reacting with propane has been shown to be due to the initial C–H bond activation transition state, which is rate-limiting.[16] This transition state was found to be located only 0.11 eV below the Co^+/C_3H_8 asymptotic energy. As a result, the vibrationally excited $CoC_3H_8^+$ complex can dissociate back to reactants or can be collisionally stabilized in competition with elimination channels.

The branching ratio for H_2 and CH_4 elimination, $k(H_2)/k(CH_4)$, is 4.7 for ground-state and 0.9 for excited-state Co^+ reacting with C_3H_8. The most plausible explanation for the dramatic increase in CH_4 elimination for the excited-state Co^+ is that both C–C and C–H bond activation are occurring on the excited-state surface, while only C–H bond activation occurs on the ground-state surface. The ratio of 4.7 for ground-state Co^+ is in good agreement with the results obtained by Armentrout et al.[11] and Tonkyn et al.[17] which are 3.3 and 3.0, respectively. This ratio is very sensitive to the presence of minor amounts of excited-state Co^+. Laser vaporization produces at least a few percent excited-state Co^+.[18] Correcting for an assumed 2% excited-state contribution in the laser vaporization results of Tonkyn et al. would increase the branching ratio from 3.0 to 4.0. This relatively large correction for a small percent excited-state population emphasizes the fact that the excited-state contribution to reactivity studies of transition-metal ions must be taken into consideration.

In summary, the new electronic-state chromatography technique allows the measurement of state-selected bimolecular rate constants of transition-metal ions at thermal translational energies. A much more complete account of the method and its application to the interesting Fe^+/propane system will be published shortly.[19]

Acknowledgment. The support of the National Science Foundation under grant CHE 88-17201 is gratefully acknowledged.

Note Added in Proof. Surface ionization experiments were done to determine the reactivity of the Co^+ a^5F first excited state. Surface ionization of $CoCl_2$ produced 15% a^5F $4s3d^7$ and 85% a^3F $3d^8$ ground state. The a^5F $4s3d^7$ state reacted with propane at about the same rate as the $4s3d^7$ electronic configuration(s) formed by electron impact. The b^3F $4s3d^7$ second excited state is known to be formed by electron impact on $Co(CO)_3NO$.[1,14] How much, if any, of the a^5F $4s3d^7$ first excited state is formed by electron impact has yet to be determined. However, the presence of any Co^+ a^5F should have a negligible effect on our reported Co^+ $b^3F + C_3H_8$ rate due to the similar reactivity of the two states.

Registry No. Co^+, 16610-75-6; C_3H_8, 74-98-6.

(12) The time used in the analysis corresponds to ground-state Co^+. The extrapolated rate constant for excited-state Co^+ (0% ground state in Figure 1) is corrected for the shorter reaction time for excited-state Co^+. These corrected values are listed in Table I.

(13) The b^3F $4s3d^7$ second excited state is known to be formed by electron impact on $Co(CO)_3NO$.[1,14] Fisher et al.[15] have observed the a^5F $4s3d^7$ first excited state using surface ionization. Electron impact may form the a^5F state as well. See Note Added in Proof.

(14) Hanratty, M. A.; Beauchamp, J. L.; Illies, A. J.; van Koppen, P. A. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 1.

(15) Fisher, E. R.; Sunderlin, L. S.; Armentrout, P. B. *J. Phys. Chem.* **1989**, *93*, 7375.

(16) van Koppen, P. A. M.; Brodbelt-Lustig, J.; Bowers, M. T.; Dearden, D. V.; Beauchamp, J. L.; Fisher, E. R.; Armentrout, P. B. *J. Am. Chem. Soc.* **1991**, *113*, 2359.

(17) Tonkyn, R.; Ronan, M.; Weisshaar, J. C. *J. Phys. Chem.* **1988**, *92*, 92.

(18) von Helden, G.; Kemper, P. R.; Bowers, M. T. Unpublished results.

(19) van Koppen, P. A. M.; Kemper, P. R.; von Helden, G.; Bowers, M. T. To be published.

Reagent-Based Stereocontrol in Formation of Substituted Tetrahydrofurans

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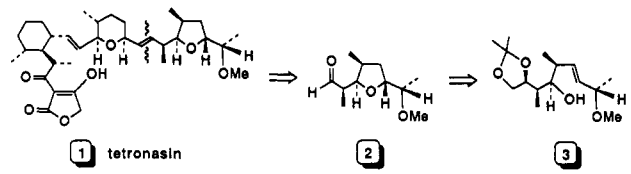
In planning an approach to the tetrahydrofuran (THF) portion (**2**)[1] of tetronasin (**1**)[2] utilizing our reiterative method for polypropionate constructions,[3] the key transformation was anticipated to be an electrophilic ring closure of a chiral, nonracemic homoallylic alcohol, **3**. Although cyclizations of related substrates with



the goal of controlling stereochemical relationships in particular between the 2- and 5-positions have begun to attract attention,[4]

(1) Lee, H. W.; Lee, I.-Y. C.; Kim, S. K. *Tetrahedron Lett.* **1990**, *31*, 7637. de Laszlo, S. E.; Ford, M. J.; Ley, S. V.; Maw, G. N., *Ibid.* **1990**, *31*, 5525.

(2) Ley, S. V.; Maw, G. N.; Trudell, M. L. *Tetrahedron Lett.* **1990**, *31*, 5521. Ley, S. V.; Wadsworth, D. J. *Ibid.* **1989**, *30*, 1001. Ager, D. J.; Mole, S. J. *Ibid.* **1988**, *29*, 4807.

(3) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495. Lipshutz, B. H.; Kozlowski, J. B. *Ibid.* **1984**, *49*, 1147.

(4) (a) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995. (b) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1990**, *31*, 5917. (c) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Ibid.* **1991**, *32*, 4015. (d) Kocovsky, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580.

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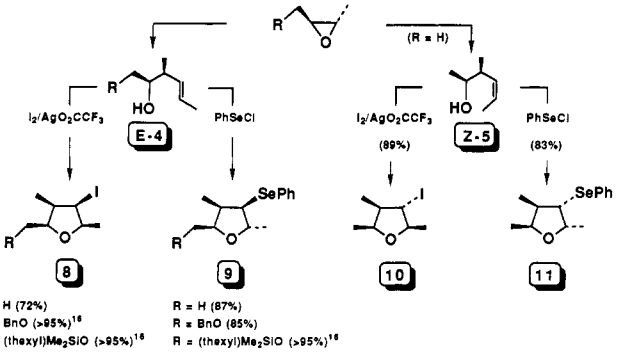
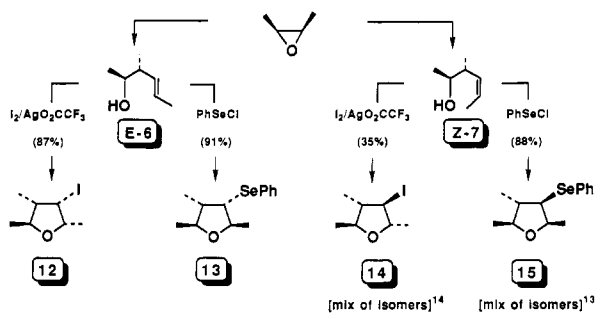
Scheme I. Cyclizations of *syn*-(*E*)-**4** and -(*Z*)-**5**[a]



there were relatively few experimental reports[5] or guiding principles[6] available at the outset of this work on which to base our synthesis. A study dealing with trisubstituted THF formation, as required in **2**, was therefore initiated. We now report the unexpected finding that the stereochemical outcome from these cyclizations can be controlled to afford either the 2,5-*cis* or 2,5-*trans* isomer from the *same* homoallylic alcohol precursor, simply by varying the nature of the electrophile.

Alcohols **4**–**7** were prepared from the corresponding epoxide openings using either an (*E*)- or (*Z*)-propenyl-based cyanocuprate[3,7a] or via an aluminum alkyne[7b] followed by reduction to the *Z* olefin (Lindlar). Isomerization ($h\nu$, cat. Ph_2S_2)[8] of the *Z* isomer readily produced the *E* form. Both were prepared since it was expected that the olefin geometry would exert a major influence on the stereochemistry of the cyclization.[5b] Treatment of (*E*)-**4** with PhSeCl afforded the 2,5-*trans* product (i.e., **9**);[9] the same stereochemical outcome resulted from the corresponding (*Z*)-**5** isomer, although the electrophile attacked in this case from the opposite face of the alkene to ultimately give **11**[9] (Scheme I). Remarkably, exposure of (*E*)-**4** to I_2[10a] (with or without AgO_2CCF_3)[10b] leads to the all-cis product **8**[9] while (*Z*)-**5** also affords the 2,5-*cis* relationship in **10**[9] but is epimeric at the carbon bearing iodine. Both products **8** and **10**, therefore, are formally the result of syn addition across the double bond. Thus, from either (*E*)-**4** or (*Z*)-**5**, the 2,5-*cis* or -*trans* substituted tetrahydrofurans can be realized simply by chosing the appropriate electrophile.[11,12]

Scheme II. Cyclizations of *anti*-(*E*)-**6** and -(*Z*)-**7**



The impact of variation on the stereochemistry of the educt, as in homoallylic alcohols (*E*)-**6**, and (*Z*)-**7**, was next examined. As shown in Scheme II, cyclizations based on PhSeCl now produce 2,5-*cis* disposed products **13**[9] and **15**,[13] respectively, while closures mediated by iodonium ion lead to 2,5-trans oriented tetrahydrofurans, **12**[9] and **14**.[14] In concert with the iodocyclizations above, iodides **12** and **14** reflect the unexpected syn mode of addition. In other words, changing from the syn ((*E*)-**4**/(*Z*)-**5**) to anti ((*E*)-**6**/(*Z*)-**7**) relationship completely reverses both the direction of attack by the electrophiles within the (*E*)-**4**/-**6** or (*Z*)-**5**/-**7** series as well as the stereochemical outcome at the newly formed ether center (compare **8** and **12**, **9** and **13**, **10** and **14**, and **11** and **15**).

Additional observations include the following: (1) all of the reactions shown are extremely rapid between room temperature and −40 °C;[15] (2) they allow for derivatization in R (cf. (*E*)-**4** → **8**, **9**), where R = OBn or dimethylhexylsiloxy;[9,16] (3) solvents play a major role, and of those examined, *only* CH_3CN is acceptable in terms of reaction rates and efficiency;[17] (4) the presence of Ag^+ together with I_2 is not essential,[10a] as the stereochemistry of the far more slowly produced product (over 3 days) is the same as when this additive is present; and (5) the reactions are completely inhibited by prior alkoxide formation (NaH) or the addition of soluble bases (e.g., Et_3N, pyr).[18]

In summary, from readily available homoallylic alcohol precursors and by the judicious choice of electrophile, kinetically generated,[19] substituted tetrahydrofurans bearing either 2,5-*cis* or -*trans* relationships can be obtained in excellent yields. A more detailed study on the scope of these closures (e.g., formation of (di)deoxyriboses, etc.) and experiments aimed at gaining a mechanistic picture[20,21] for these unusual results are being in-

(5) (a) Williams, D. R.; Grote, J.; Harigaya, Y. *Tetrahedron Lett.* **1984**, *25*, 5231. See also: (b) Murata, S.; Suzuki, T. *Ibid.* **1990**, *31*, 6535. (c) Tonn, C. E.; Palazon, J. M.; Ruiz-Perez, C.; Rodriguez, M. L.; Martin, V. S. *Ibid.* **1988**, *29*, 3149. (d) Tuladhar, S. M.; Fallis, A. G. *Ibid.* **1987**, *28*, 3523. (e) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533. (f) Ting, P. C.; Barlett, P. A. *Ibid.* **1984**, *106*, 2668. (g) Mulholland, R. L.; Chamberlin, A. R. *J. Org. Chem.* **1988**, *53*, 4062. (h) Semmelhack, M. F.; Zhang, N. *Ibid.* **1989**, *54*, 4483. (i) Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yoshida, Z. *Ibid.* **1987**, *52*, 4062. (j) Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097. For a recent review, see: Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(6) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846 and references therein.

(7) (a) Opening of *trans*-2-butene oxide with the (*E*)-propenyllithium-derived higher order cuprate ((*E*)-propenyl)(2-thienyl)Cu(CN)Li_2 afforded (*E*)-**4** in 83% yield, while treatment with the (*Z*)-propenyllithium-derived reagent ((*Z*)-propenyl)$_2$Cu(CN)Li_2 gave (*Z*)-**5** to the extent of 89%. Likewise, *cis*-2-butene gave (*E*)-**6** and (*Z*)-**7** in 85 and 98% yields, respectively. (b) Skrydstrup, T.; Benechie, M.; Khuong-Huu, F. *Tetrahedron Lett.* **1990**, *31*, 7145. Fried, J.; Lin, C-H.; Ford, S. H. *Ibid.* **1969**, 1379. Matthews, R. S.; Eickhoff, D. J. *J. Org. Chem.* **1985**, *50*, 3923.

(8) A 0.2 M benzene solution of (*Z*)-**5** containing catalytic amounts of Ph_2S_2 was exposed to sunlight for 4–6 h, which virtually quantitatively converted this material to the *E* isomer. See: Lorenz, K.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1987**, *28*, 6437. Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557.

(9) This was the only tetrahydrofuran observed (TLC, GC) and isolated. All THFs were fully characterized by IR, NMR, MS, and HRMS data.

(10) (a) Use of ICl was also effective but somewhat slower, giving yields which were comparable to these obtained with I_2/AgO_2CCF_3. NIS, however, led to very complex mixtures, as did NCS and $Hg(O_2CCF_3)_2$. NBS, on the other hand, with (*E*)-**4**, R = TBDMSO, gave the 2,5-*cis* product akin to **8**, but with the halogen on the α-face! (b) Other salts of silver, e.g., $AgNO_3$, $AgBF_4$, $AgClO_4$, and Ag(acac), all consumed starting material; however, only the nitrate gave a reasonably clean closure.

(11) All stereochemical assignments were painstakingly made on the basis of extensive NOE measurements for each sample, **8**–**15**. The values obtained (see the supplementary material) are accurate to ±1%.

(12) Treatment of **8** and **9**, R = OBn, individually with Bu_3SnH afforded the corresponding products of reduction (>95% yield), which were shown by capillary GC to be unique.

(13) In this specific case, (*Z*)-**7** gave a 3.57:1 mix of **15** (major) and an isomer of as yet undetermined stereochemistry.

(14) As in the treatment of (*Z*)-**7** with PhSeCl, this reaction gave a mixture of isomers favoring **14** but in a low combined yield, as shown.

(15) (a) For typical procedures, see the supplementary material. (b) This temperature reflects the freezing point of CH_3CN, and it is likely that these reactions may proceed at colder temperatures using cosolvents.

(16) In three of the four cases studied where R ≠ H (see Scheme I, products **8** and **9**), the THF products were partly deprotected. Thus, the combined yields for each are shown. In each example, the alcoholic product was reconverted back to the fully protected material, and likewise the protected products isolated were deprotected to fully correlate the nature of the original mix. It was later discovered that the presence of propylene oxide (1 equiv) completely inhibits protecting group cleavage.

(17) This explains the failure of cyclizations attempted earlier with related substrates and $PhSe^+$, where THF and CH_2Cl_2 were used as solvents.[4a] Our closures are also sluggish and inefficient in these media, as well as in DMF, DMSO, H_2O, MeOH, Et_2O, EtOAc, acetone, $CHCl_3$, and benzene.

(18) Heterogeneous bases (e.g., K_2CO_3, $NaHCO_3$), however, had no effect on these cyclizations.

(19) Re-exposure of an iodotetrahydrofuran or selenotetrahydrofuran to the reaction conditions did not lead to the production of any new materials in either case. Moreover, treatment of the reaction mixture containing (*E*)-**4** (R = dimethylthexylsiloxy) generating iodide **8** with PhSeCl and that generating selenide **9** with I_2/AgO_2CCF_3 did not afford any of the crossover products.

tensively pursued and will be described in due course.

Acknowledgment. Financial support provided by the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We warmly thank Dr. Ata Shirazi and Mr. Tom O'Connell for their assistance with the acquisition of the NOE data.

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.

(20) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 673 and references therein.

(21) Intermediate diiodides were not observed in these reactions, whether run in the presence or absence of silver ion.

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

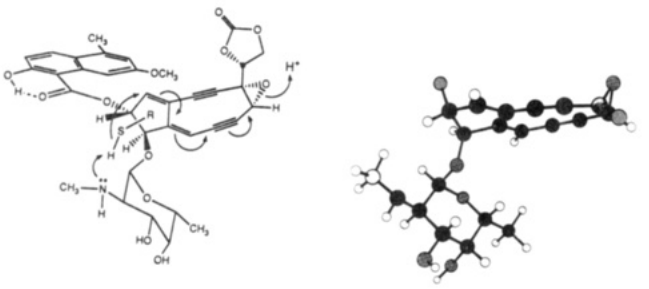
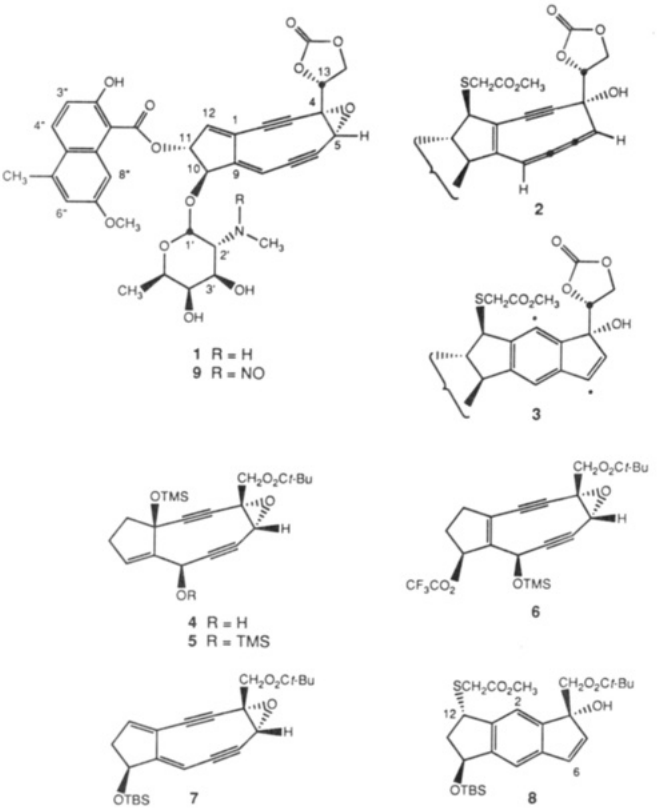


Figure 1. Proposed mode of thiol addition to **1** through base and acid catalysis and a representation of a conformation favorable for amino participation (naphthoate and carbonate groups abbreviated as diagonally striped spheres for clarity).

Chart I



(1) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146.

(2) Isolation of neocarzinostatin: (a) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68. Identification of the chromophore subunit: (b) Napier, M. A.; Holmquist, B.; Strydom, D. J.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 635. (c) Koide, Y.; Ishii, F.; Hasuda, K.; Koyama, Y.; Edo, K.; Katamine, S.; Kitame, F.; Ishida, N. *J. Antibiot.* **1980**, *33*, 342. Chromophore structure: (d) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Carbohydrate stereochemistry: (e) Edo, K.; Akiyama, Y.; Saito, K.; Mizugaki, M.; Koide, Y.; Ishida, N. *J. Antibiot.* **1986**, *39*, 1615. Chromophore stereochemistry: (f) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. Reaction of **1** and methyl thioglycolate: (g) Hensens, O. D.; Dewey, R. S.; Liesch, J. M.; Napier, M. A.; Reamer, R. A.; Smith, J. L.; Albers-Schönberg, G.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 538. Proposed mechanism of thiol activation of **1**: (h) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493. Reaction of **1** and methyl thioglycolate product identification: ref 2f,h.

(3) Compound **4** is prepared by a simple modification of a route previously described for the synthesis of a diastereomer of **4**: Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694.

(4) For the synthesis of various neocarzinostatin chromophore model systems and analogues, see: (a) Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909. (b) Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120. (c) Wender, P. A.; McKinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369. (d) Fujiwara, K.; Kurisaki, A.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4329. (e) Magnus, P.; Pitterna, T. *J. Chem. Soc., Chem. Commun.* **1991**, 541. (f) Doi, T.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 3465. (g) Magnus, P.; Davies, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1522.

(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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