CO_2 and CO byproducts, has a dramatic hindering effect on the tunneling; for theoretical arguments for the plausibility of the latter, see ref 9.

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Enantioselective Synthesis of the Epoxy Diyne Core of Neocarzinostatin Chromophore

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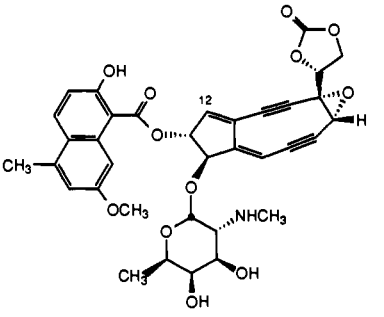
The chromophore component (**1**)[1] of the antitumor agent neocarzinostatin[2] exhibits potent cytotoxicity and DNA-cleaving activity.[3] DNA cleavage is believed to be initiated by an exceptionally facile nucleophilic addition of thiol to C12 of **1** followed by a rapid rearrangement reaction leading to the formation of a carbon-centered biradical.[4] The highly strained carbocyclic skeleton of **1** and unusual assembly of functional groups along its periphery, most notably the epoxy diyne subunit, are central to this reactivity. The epoxide ring plays a critical role in all known chemistry of **1**; epoxide opening has been clearly demonstrated to occur in thiol activation of **1**[4] and in the reaction of **1** with strong acids[5] and may underlie the extreme base sensitivity of **1** as well ($t_{1/2} \sim 30$ s, pH 8, 0 °C).[6] These same features of structure and chemical instability distinguish **1** as a challenging target for synthesis. This communication describes a convergent and enantioselective synthesis of a highly functionalized epoxy diyne analogue of **1**.[7]

(*Z*)-Ethyl 2,3-dibromopropenoate and (trimethylsilyl)acetylene (2.75 equiv) are coupled in the presence of $(Ph_3P)_2PdCl_2$, CuI, and triethylamine in tetrahydrofuran (THF) at 23 °C to afford the (*Z*)-enediyne **2** in 88% yield after flash column chromatography.[8] Reduction of **2** with diisobutylaluminum hydride in toluene then furnishes alcohol **3** (82%). The acetylenic groups of **3** are differentiated by selective desilylation with a reagent prepared by limited exposure (5 min at −20 °C) of sodium trimethoxyborohydride (1.25 equiv) to water (0.5 equiv) in THF (reaction at −20 °C for 2.5 h). Pure monodesilylated product **4** (60%) and recovered starting material **3** (20%) are obtained after flash column chromatography. Catalytic asymmetric epoxidation[9] of **4** ((−)-diethyl tartrate, CH_2Cl_2, −5 °C for 36 h) followed by in situ esterification with pivaloyl chloride produces *R,R* epoxy diyne **5** in 83% yield and 93% ee.[10]



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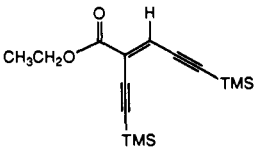

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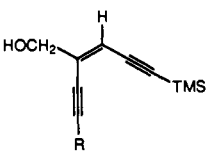

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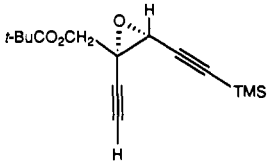
4 R = H



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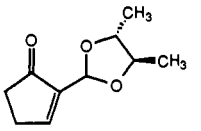

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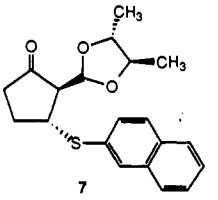

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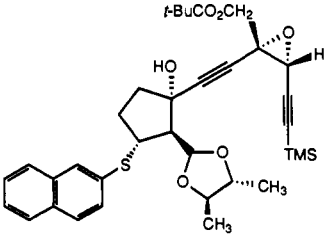

8

Cyclopentanone is formylated in high yield in a new procedure involving sequential treatment of a mechanically stirred solution of potassium *tert*-butoxide in THF (1.1 equiv, 1.3 M) at 0 °C with ethyl formate (3.9 equiv; **CAUTION**: gas evolution!) and a solution of cyclopentanone (1 equiv) in ethyl formate (9.5 equiv).[11] After stirring at 0 °C for 3 h and at 23 °C for 12 h, acidification (pH 1), and extractive isolation, 2-formylcyclopentanone is obtained as a solid in 87% yield (mp 78 °C, lit. mp[11a] 76–77 °C). Selenenylation of 2-formylcyclopentanone with

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(9) Experiments with **4** and (*Z*)-enediynes lacking a free hydroxyl group have shown that the allylic alcohol is required for successful epoxidation, having only been achieved via the catalytic version of the Sharpless asymmetric epoxidation: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765 and references therein.

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(11) Self-condensation of cyclopentanone is a serious problem in other procedures. 2-Formylcyclopentanone: (a) Johnson, W. S.; Shelberg, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 1745 (10% yield). (b) Gustafsson, H.; Ericsson, H.; Lindqvist, S. *Acta Chem. Scand.* **1974**, *B28*, 1069 (yield not reported). 2-Formylcyclohexanone: (c) Ainsworth, C. In *Organic Syntheses*; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 536.

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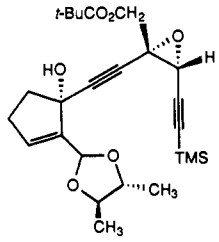
C_6H_5SeCl (1.05 equiv) and pyridine (1.1 equiv) in CH_2Cl_2 affords the α-(phenyl selenide) in 69% yield. Acetal formation with (2*R*,3*R*)-2,3-butanediol (1.2 equiv, 98%, Aldrich Chemical Co.) and camphorsulfonic acid (CSA, azeotropic removal of water) followed by selenide oxidation and elimination (*m*-chloroperbenzoic acid (MCPBA); *i*-Pr_2NH, CH_2Cl_2, 0–23 °C)[12] provides enone **6** in 85% overall yield. 1,4-Addition of 2-naphthalenethiol (1.2 equiv) to **6** (Et_3N (4 equiv), THF, 23 °C) proceeds in high yield to form a 1:1 mixture of the two trans diastereomers. Pure (2*R*,3*R*)-**7** is obtained by crystallization from hexanes (50% of theory after recrystallization, mp 100 °C, stereochemistry determined by X-ray analysis of the corresponding anti oxime).[13] Concentration of the mother liquors and treatment of the residue with triethylamine (5 equiv) and 2-naphthalenethiol (0.2 equiv, 0.1 M) in THF at 23 °C reestablishes a 1:1 mixture of trans diastereomers and allows for the recycling of (2*S*,3*S*)-**7**.



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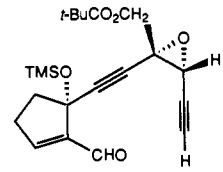

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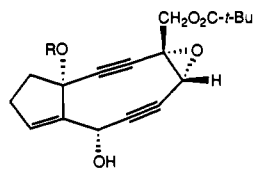

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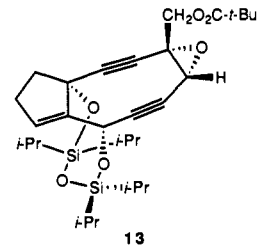

13

Metalation of epoxy acetylene **5** with $NaN(TMS)_2$ (1.05 equiv, 1.0 M in THF) in toluene at −78 °C followed by addition of ketone **7** (1.15 equiv), also at −78 °C, produces an 18:1 mixture of coupling product **8** and the β-hydroxy epimer, respectively, which are separated by flash column chromatography to provide **8** in 40% yield.[14] Sulfoxide formation (MCPBA, CH_2Cl_2, −78 °C; 1:1 mixture of diastereomers) and elimination (*i*-Pr_2NEt, toluene reflux, 4 h) proceed smoothly with exclusive formation of the trisubstituted cyclopentene **9** (84% overall). Deprotection of the silylacetylene is accomplished in quantitative yield upon exposure of **9** to $KF{\cdot}2H_2O$ in methanol at 23 °C for 3 h. Acetal hydrolysis (1:1 CH_3CN/water, 0.05 M CSA, 0 °C, 20 h) and silylation of the tertiary hydroxyl group (2,6-lutidine (20 equiv), $(CH_3)_3SiO$-SO_2CF_3 (8 equiv), CH_2Cl_2, −78 °C) then afford aldehyde **10** in 80% combined yield. Cyclization of **10** is achieved by treating a slurry of **10** and anhydrous $CeCl_3$ (3 equiv) in THF at −78 °C with excess $LiN(TMS)_2$ (25 equiv) for 1 h. After quenching with pH 7 phosphate buffer solution, aqueous workup, and flash column chromatography, the cyclic epoxy diyne **11** is obtained as a single diastereomer in 87% yield. Cyclizations conducted in the absence of $CeCl_3$ are less clean and do not proceed to completion. Spectroscopic data for **11** are in full accord with the assigned structure; in particular, ^{13}C NMR data are consistent with strained acetylenic bonds.[15] Though neat samples of **11** readily decompose, solutions of **11** can be stored at −20 °C without serious deterioration. The cyclization reaction which converts **10** to **11** involves an intramolecular acetylide addition similar to that employed in syntheses of molecules related to the calichemicin–esperamicin antibiotics.[16] It is noteworthy that this type of reaction is effective in forming the more strained cyclononadiyne ring of **11** and proves to be compatible with the epoxy diyne functional group. Desilylation of **11** ($Et_3N{\cdot}3HF$, CH_3CN, 23 °C, 2 h) affords diol **12** in high yield which, upon treatment with 1,3-dichlorotetraisopropyldisiloxane and imidazole in *N*,*N*-dimethylformamide at 23 °C for 4 h, efficiently produces disiloxane **13**, thereby establishing the cis-stereochemical relationship of the hydroxyl groups of **12**. This stereochemistry results from acetylide attack on the s-trans aldehyde rotamer of **10**, a stereochemical outcome observed in the earlier studies of Danishefsky and co-workers.[16a]

The synthetic route to **11** outlined above is convergent and enantioselective and demonstrates a viable strategy for construction of the strained and reactive core functionality of **1**, potentially applicable to a synthesis of **1** itself. It is further anticipated that **11** will be of value as a direct precursor to molecules of importance in elucidation of the mechanism of DNA cleavage by **1**.

Acknowledgment. We are indebted to Dr. Richard Kondrat and Mr. Ron New of the University of California Riverside for mass spectroscopic measurements. Financial support was generously provided by the National Institutes of Health, the National Science Foundation, the David and Lucile Packard Foundation, and the following industrial sponsors: Merck & Co., Inc.; Proctor and Gamble Co.; and Eli Lilly and Company. A Kodak graduate fellowship to E.Y.K. is also gratefully acknowledged.

Supplementary Material Available: High-resolution ^1H NMR spectra of compounds **2**–**11**, a ^{13}C NMR spectrum of **1**, and an ORTEP representation of the anti oxime of (2*R*,3*R*)-**7** (14 pages). Ordering information is given on any current masthead page.

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(14) Approximately 50% of epoxide **5** can be recovered from the coupling reaction. Stereochemical assignments are based on NOE studies of the diimide reduction products (saturation of the silylacetylene, cis reduction of the internal acetylene) of **8** and the β-hydroxy diastereomer. Acetylide addition to form **8** is apparently directed by the acetal appendage.

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Effect of the Solvent on Enzyme Regioselectivity

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The realization that enzymes can act as catalysts in neat organic solvents[1] has led to the introduction of a new fundamental variable, the reaction medium, into studies of enzyme–substrate (and also antibody–antigen[2]) interactions. It has been found that the nature of the solvent has a profound effect on substrate specificity[3] and enantioselectivity[4] of enzymes. In the present investigation, we have addressed the question of whether it is possible to regulate

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