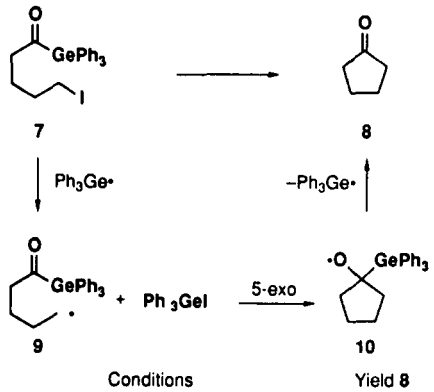
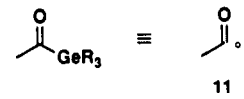


(3)

Conditions	Yield 8
10% AIBN/10 % Ph_3GeH	95%
hν,400w Hg-lamp (30 min)	92%
80°C, dark (12h)	not detected
10% AIBN/10% Ph_3GeH/10% galvinoxyl	not detected
hν, 400w Hg-lamp, 10% galvinoxyl	not detected

The discoveries of Kiyooka and co-workers and our new results provide strong support for a chain isomerization of unsaturated acylgermanes outlined in Scheme I. More importantly, our results indicate that radical cyclizations to acylgermanes are feasible. Related chain reactions of carbon–carbon double bonds (vinylstannanes[15]) are already useful, and our preliminary results hold forth the promise that a new class of radical chain reactions based on carbon–oxygen double bonds (acylgermanes as well as acylsilanes and -stannanes) can be developed. These compounds would be reagent equivalents of the imaginary synthon 11: a carbonyl radical acceptor.[16]



Acknowledgment. We thank the National Institutes of Health for funding this work.

(14) By considering known rate constants for hydrogen transfer from germanium hydrides (see: Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509), we can crudely estimate a lower limit for the rate of cyclization at 80 °C (9 → 10); $k_c \geq 1 \times 10^4$ s^{-1}).

(15) (a) Cyclizations to vinylstannanes: Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941. Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501. Curran, D. P.; Jasperse, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 5601. Bimolecular additions to vinylstannanes: Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622. Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133. Baldwin, J. E.; Kelly, D. R. *J. Chem. Soc., Chem. Commun.* **1985**, 682. Keck, G. E.; Byers, J. H.; Tafesh, A. M. *J. Org. Chem.* **1988**, *53*, 1127.

(16) (a) For an introduction to the notation of synthons like 11, see: Curran, D. P. *Synlett* **1991**, 63. (b) Existing reagent equivalents of 11 include nitriles and alkynes, see: Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313.

Syntheses and Transannular Cyclizations of Neocarzinostatin–Chromophore and Esperamicin–Calichemicin Analogues[1]

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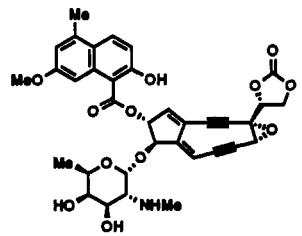
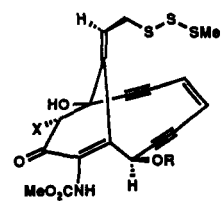
Summary: The syntheses of neocarzinostatin–chromophore (NCS–chr) analogues **3** and **4** and esperamicin–calichemicin analogue **5** using transannular [2,3]-Wittig rearrangement of 12-membered cyclic ether **6** and their transannular cyclizations are described.

The antitumor antibiotics neocarzinostatin (NCS),[2] esperamicin,[3] and calichemicin[4] undergo inter- or intramolecular addition of thiolate, followed by transannular cyclizations leading to biradical species which abstract hydrogen atoms from the sugar phosphate backbone of DNA.[5,6] We report here[7] (i) an efficient synthesis of the highly strained bicyclo[7.3.0]diyne **2**; (ii) syntheses of NCS–chr analogues **3** and **4** and Myers' type transannular cyclization[6] of **4**; and (iii) Bergman cyclization[8] of 9-membered ring enediyne **5**, an analogue of esperamicin–calichemicin.[9]



Neocarzinostatin-chromophore (1)

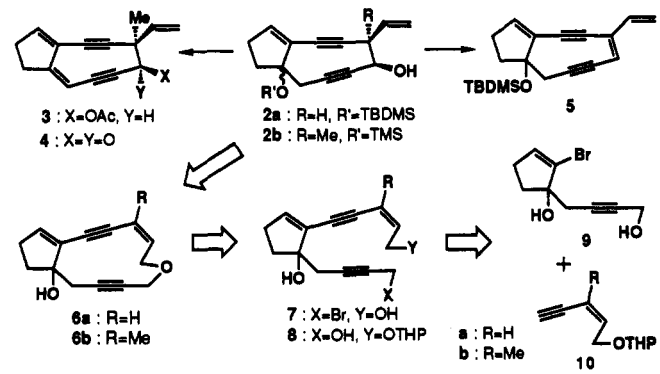


Esperamicin A_1 aglycone : X=OH

Calichemicin aglycone : X=H

[†] Fellowships of the Japan Society for the Promotion of Science for Japanese Junior Scientists.

Scheme I



We have recently demonstrated that macroring contraction methodology[10] is very useful for natural product

(1) Macroring Contraction Methodology 5. Previous papers are described in ref 10.

(2) Structure of NCS–chr: (a) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, Ser. *A18*, 68. (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. (d) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. (e) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212.

(3) Esperamicin: (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *Ibid.* **1987**, *109*, 3462.

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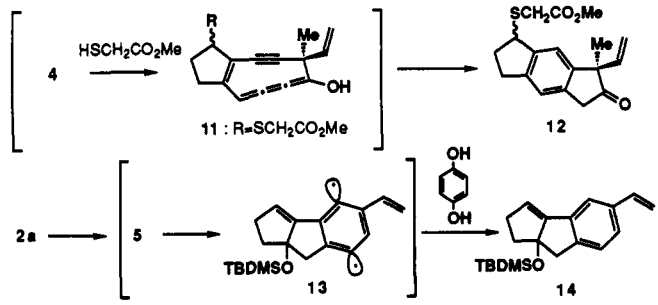
syntheses and molecular modeling[11] based on MM2 calculations has the predictable value in designing synthetic key intermediates. In our synthetic plan[12,13] (Scheme I), transannular [2,3]-Wittig rearrangement[10a-c,14] of **6** provides the highly strained 9-membered diyne **2** in which tertiary and secondary alcohols can be used as a leaving group to generate three enediynes **3**, **4**, and **5**, respectively, and the vinyl group in **2** can be converted to the cyclic carbonate in NCS-chr. The 12-membered cyclic ether **6** is constructed by intramolecular O-alkylation of the bromo alcohol **7**. MM2 calculations[15] using the ring making program[16] indicate that all conformers of **6a** have a short distance (~3.5 Å) between the two reactive sites with good overlap of the π orbitals of the olefin oriented in the plane of the ring.[17] Assuming an early reactant-like transition state[18] for this rearrangement, it is clear that the reaction

Scheme II



of **6a** should proceed smoothly leading to a "cis" relative stereochemistry[19] between the vinyl and hydroxy groups in **2a**.

The coupling of **9**[13a] with **10a** under palladium-copper catalysis[20] provided **8a** in 91% yield (Scheme I). Formation of the bromide from the primary alcohol **8a** (CBr_4/PPh_3/py, at −40 °C) and removal of the THP group (PPTS/MeOH) afforded **7a** in 50% yield. Cyclization of **7a** using 10^{-2} molecular solution (NaH/HMPA/THF, at rt) gave **6a** in 80% yield. Similarly the methyl derivative **6b** was prepared from **10b** and **9**. Silylation of **6a** (*t*-$BuMe_2SiOTf$/ET_3N) and its [2,3]-Wittig rearrangement (*t*-BuLi in THF at −100 °C for 10 min) gave **2a** in 66% yield with high "cis" stereoselectivity (>99%).[17,21] Rearrangement of the trimethylsilyl derivative of **6b** under the same conditions similarly gave **2b** in 67% yield.[17,21] Protection of the hydroxy group in **6a** (and **6b**) was essential for the success of this rearrangement. Without protection, rearrangement resulted in much lower yield. The cis relative stereochemistry between vinyl and hydroxy groups in **2a** was confirmed by NOE observation.[17]

The NCS-chr analogue **3** was synthesized as follows (Scheme I). Acetylation of **2b** (AcCl/py, 0 °C), desilylation of the tertiary alcohol (AcOH/THF/H_2O, at 25 °C), and its mesylation[13a] (MsCl/DMAP/CH_2Cl_2, at 0 °C) afforded **3** in 82% overall yield. The Myers' type transannular cyclization of **3** in the presence of methyl thioglycolate was attempted,[5,6] but only decomposition of **3** was observed. Then alcohol **2b** was converted to ketone **4** in order to activate the chromophore to nucleophilic addition.[13b] Desilylation of **2b** (AcOH/THF/H_2O, 20 °C, 93%), Swern oxidation of the resulting alcohol (DMSO/$(COCl)_2$/Et_3N, −30 °C), and spontaneous elimination of the tertiary alcohol gave **4** (Scheme I).[22] Without isolation of the labile ketone **4**, addition of methyl thioglycolate at −30 °C gave a 1:1 mixture of diastereomers of the benzenoid product **12** in 54% overall yield. It seems reasonable to suppose that the conjugated ketone **4** undergoes in situ an addition of thiol to produce the cumulene **11**, which undergoes Myers' type transannular cyclization leading to the compound **12**. Moreover dehydration of the secondary alcohol of **2a** via its mesylation (MsCl/DMAP at −10 to 0 °C) should generate **5**, which was easily decomposed under concentration even at −20 °C. The labile **5** upon standing

(4) Calichemicin: (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *Ibid.* **1987**, *109*, 3466.

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(6) (a) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493. (b) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146. (c) Tanaka, T.; Fujiwara, K.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 5947.

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(9) Many examinations in Bergman cyclizations of larger than 10-membered ring models have been reported: (a) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626. (b) Magnus, P.; Lewis, R. T.; Huffman, J. C. *Ibid.* **1988**, *110*, 6921. (c) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *Ibid.* **1988**, *110*, 4866. (d) Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781. (e) Haseltine, J. N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 7638. (f) Haseltine, J. N.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2576. (g) Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851. (h) Singh, R.; Just, G. *Ibid.* **1990**, *31*, 185.

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(11) (a) Shirahama, H.; Ōsawa, E.; Matsumoto, T. *J. Am. Chem. Soc.* **1980**, *102*, 3208. (b) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (c) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Ibid.* **1984**, *40*, 2275.

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(13) Synthetic studies of NCS-chr: (a) Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909. (b) 10-membered analogue of NCS-chr: Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120. (c) Nakatani, K.; Arai, K.; Hirayama, N.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 2323.

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(15) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127; QCPE 395. (b) Jamie, C.; Osawa, E. *Tetrahedron* **1983**, *39*, 2769.

(16) The program MacroModel (Version 2.0) was employed for these calculations. We are grateful to Professor W. Clark Still for providing a copy of this program; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440.

(17) Further information is available in the supplementary material.

(18) (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. (b) Mikami, K.; Kimura, Y.; Kishi, N.; Nakai, T. *J. Org. Chem.* **1983**, *48*, 279.

(19) Experimental and calculated results in our previous studies indicated that the [2,3]-Wittig rearrangements of the 13-membered compounds gave the "trans" stereochemistry between the vinyl and hydroxy groups (see ref 10a-c).

(20) (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (c) Ratovelomanana, V.; Linstrumelle, G. *Ibid.* **1981**, *22*, 315.

(21) The [1,2]-rearrangement product was also obtained in about 15% yield.

(22) Methyl group in **2b** is essential to prevent the β-elimination of secondary alcohol.

in the presence of hydroquinone at 25 °C for 24 h cyclized to 14 via the biradical 13 in 50% yield.[23]

Thus these results demonstrate that our synthetic analogues 4 and 5 undergo transannular ring closure to produce 12 and 14, respectively, in the same manner as naturally occurring NCS-chr and esperamicin-calichemicin. Moreover MM2 calculations are useful in designing the synthetic intermediate 6 to construct the highly strained bicyclo[7.3.0] enediyne 2.

(23) 1,4-Hydroquinone was added as the radical quencher. We could not detect the benzenoid adduct 15 in the absence of hydroquinone.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research in Priority Areas No. 02231210 and No. 02250213 from the Ministry of Education, Science and Culture, Japan. We are grateful to Prof. Yoshimasa Fukazawa (Hiroshima University), Prof. Masahiro Hirama (Tohoku University), Prof. Haruo Seto (The University of Tokyo), and Prof. Gilbert Stork (Columbia University) for their stimulating discussions.

Supplementary Material Available: Compound characterization data, experimental procedures, discussion of conformational analysis, and copies of spectra (20 pages). Ordering information is given on any current masthead page.

Conformation of DNA-Bound Spermidine by Double ^{13}C Labeling

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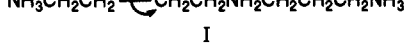
Received February 20, 1991

Summary: Double-^{13}C-labeling experiments show conclusively that the central bond of the C_4 unit in spermidine adopts an anti configuration when bound to various types of DNA. Double-^{13}C-labeling is a powerful though laborious method of securing conformational information on biomolecules in aqueous media.

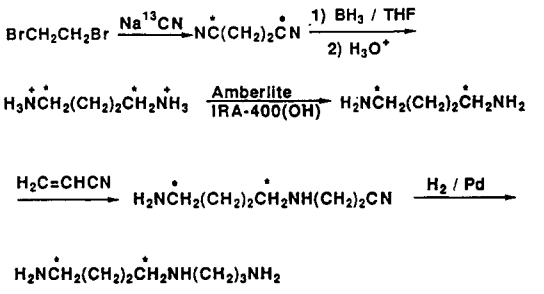
Several years ago we began studying the conformations of flexible molecules by double-^{13}C-labeling.[1] The method is based on the long-range NMR coupling ($^3J_{cc}$) in acyclic compounds that possess two ^{13}C atoms spaced four atoms apart (*C-C-C-C*). These couplings respond to the dihedral relationship between the labeled carbons in a typical Karplus fashion.[2] Although compounds with two ^{13}C atoms can be tedious to synthesize, they provide anti-gauche ratios at explicit sites, information that is difficult to obtain by other means. The method has already been applied to hydrocarbon chains dissolved in diverse solvents, to succinic acid derivatives at varying pH, to an enzyme-inhibitor complex, and to surfactant tails embedded in micellar aggregates.[1] We describe herein the rotamer population of double-^{13}C-labeled spermidine (I) bound to DNA. The results foreshadow applications to macromolecular chemistry in general.



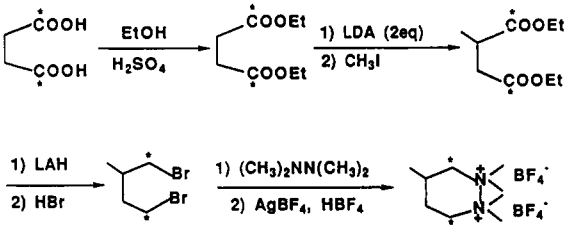
I

Spermidine belongs to a group of naturally occurring polyamines known to complex with DNA.[3] Interest in such compounds stems from their surge in concentration just prior to the synthesis phase of cellular proliferation.[4]

Scheme I



Scheme II



It has been suggested that potential regulatory functions of the polyamines may involve electrostatic association to the DNA phosphates as well as specific binding to certain DNA sequences.[5] At present, however, only limited information is available on the role of spermidine in modulating gene expression related to cell growth.

A crystal structure of spermine, $NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$, complexed with B-DNA shows that the tetramine is stretched across the major groove while interacting with phosphates and a guanine base.[6] The central bond of the spermine C_4 unit is gauche. On the other hand, an X-ray structure of a spermine complex with A-DNA reveals an anti central bond.[5] X-ray pictures of spermidine/DNA complexes are unavailable. Previously reported NMR chemical shift data suggested tentatively that spermidine, associated with 5'-AMP, adopts a gauche conformation within its C_4 unit.[7,8] We establish below that

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(4) Tabor, C. W.; Tabor, H. *Ann. Rev. Biochem.* **1984**, *53*, 749.

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