The Journal of
Organic
Chemistry

VOLUME 56, NUMBER 11 MAY 24, 1991

Communications

Unsaturated Acylgermanes Isomerize by a Chain Mechanism Involving Radical Cyclization to the Carbonyl Group of an Acylgermane

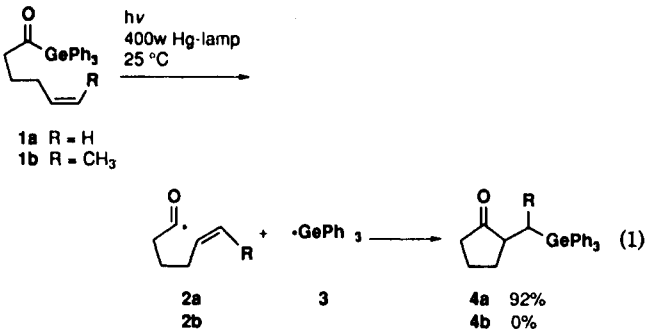
Dennis P. Curran*,[1] and Hongtao Liu

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received February 18, 1991

Summary: Experimental evidence indicates that unsaturated acylgermanes isomerize by a three-step chain mechanism that involves (1) addition of a germyl radical to the double bond, (2) radical cyclization to the acylgermane, and (3) fragmentation of the intermediate β-germyl alkoxy radical.

A recent paper from Kiyooka and co-workers[2] described the discovery of a photochemical intramolecular cyclization of unsaturated acylgermanes. Two examples from their study of this transformation are presented in eq 1. Photolysis of readily available[3] triphenylacylgermane **1a** with a 400-W mercury lamp at 25 °C provided isomerized 1-((triphenylgermyl)methyl)cyclopentanone (**4a**) in 92% yield. A variety of other acylgermanes containing terminal alkenes underwent related cyclizations. In sharp contrast, addition of a terminal methyl group to the alkene completely suppressed this isomerization; photolysis of **1b** did not produce detectable amounts of **4b**. The authors proposed a mechanism involving photolytic cleavage of the acylgermane to an acyl radical **2a** and a germyl radical **3** in a solvent cage, followed by transformation of this geminate radical pair into **4a**. There is a serious problem with this proposal:[4] normal radical cyclizations are much too slow to occur during the lifetimes of solvent cages. If this proposal is revised to invoke the cyclization of free acyl radicals, then two problems arise:[4] (1) there is no obvious pathway for the selective conversion of the cyclic radical to the product (selective radical/radical coupling is required), and (2) radicals **2a** and **2b** should cyclize with roughly comparable efficiency,[5] so the dramatic difference in yield between **1a** and **1b** cannot be explained. In this paper we propose a different mechanism for the isomerization of **1** to **4** and support this proposal with several experiments. Our observations presage the development of a new class of radical reactions based on acylgermanes and related acyl derivatives of tin and silicon.



We felt the results in eq 1 (and related observations in this paper[2]) could be explained by a radical chain mechanism that did not involve acyl radicals.[6] This mechanism

(1) Dreyfus Teacher–Scholar (1986–91); National Institutes of Health Research Career Development Awardee (1987–92).

(2) Kiyooka, S.; Kaneko, Y.; Matsue, H.; Hamada, M.; Fujiyama, R. *J. Org. Chem.* **1990**, *55*, 5562.

(3) Kiyooka, S.; Shibuya, T.; Shiota, F.; Fujiyama, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1361.

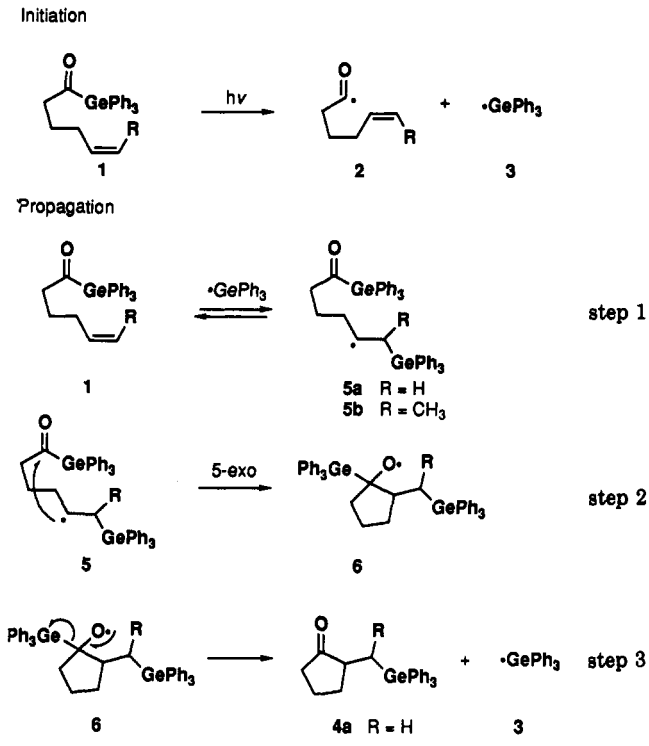
(4) For a discussion of the potential pitfalls involved in non chain radical mechanisms, see: Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206.

(5) Recent leading references on the generation and reactions of acyl radicals: (a) Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1275. (b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003, 4008. (c) Crich, D.; Eustace, K. A.; Fortt, S. M.; Ritchie, T. J. *Tetrahedron* **1990**, *46*, 2135.

(6) For isolated examples of related radical chain addition reactions with aldehydes and ketones, see: Kaszynski, P.; McMurdie, N. D.; Michl, J. *J. Org. Chem.* **1991**, *56*, 307. Wiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112*, 2194.

0022-3263/91/1956-3463$02.50/0

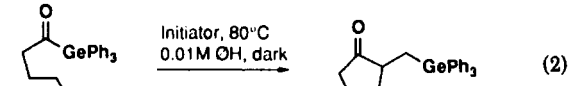
Scheme I



is shown in Scheme I. The photolytic cleavage of acylgermanes to give acyl radicals and germyl radicals is precedented,[7] and this is the initiation step in our mechanism. The key radical produced in this step is not the acyl radical **2** but the germyl radical **3**. The radical chain involves three steps: (1) addition of the germyl radical **3** to the alkene **1a** to give β-germyl radical **5a**, (2) 5-exo cyclization of **5a** to give β-germylalkoxyl radical **6a**, and (3) fragmentation of **6a** to form the product **4a** and regenerate the chain-carrying germyl radical **3**. The rapid addition of germyl radicals to both terminal and internal olefins (step 1) is well precedented;[8] however, the resulting adducts (**5a,b**) differ significantly in their resistance toward fragmentation (reverse of step 1). Adducts to terminal alkenes are relatively stable,[9] but adducts to internal alkenes rapidly revert to starting materials. Thus, we suspect that the reaction with **1b** fails because cyclization of **5b** cannot compete with its reverse reaction. The fragmentation reaction of the β-germylalkoxy radical **6a** (step 3) must be incredibly rapid.[10] The closest precedents for the key cyclization (step 2) are the radical cyclizations of aldehydes and ketones.[11] Ketones are relatively poor radical acceptors compared to aldehydes,[12] so it is not obvious that step 2 will be rapid enough to propagate a chain.

To determine whether the isomerization of **1a** to **4a** occurred by a chain mechanism, we prepared **1a** and irradiated it under the published conditions[2] in the presence and absence of the inhibitor galvinoxyl. In the absence of galvinoxyl, we observed smooth conversion of **1a** to **4a** in less than 30 min, as reported.[2] In the presence of galvinoxyl, the yield of **4a** after 30 min was less than 30%, and much of the starting germyl ester **1a** remained. That this reaction is subject to inhibition suggests a chain mechanism. Consideration of the mechanism proposed in Scheme I yields two predictions: (1) any method that generates small amounts of the triphenylgermyl radical could be substituted for the photochemical initiation step, and (2) the alkene is not needed; any precursor that reacts with **3** to form a radical should suffice. Experiments verified both of these predictions.

When **1a** was heated in the dark at 80 °C (0.01 M, C_6D_6), it remained unchanged for up to 8 h. Addition of 10% AIBN had no effect. However, when **1a** was heated at 80 °C in the presence of both AIBN (10%) and triphenylgermanium hydride (5%), smooth conversion to **4a** occurred.[13] After heating the mixture for 6 h and purification of the residue by flash chromatography, we isolated **4a** in 88% yield. These experiments support the contention that the chain carrier is the triphenylgermyl radical.



(2)

Initiator	yield **4a**
None	not detected
10% AIBN	not detected
10% AIBN/5% Ph_3GeH	88%

To test the prediction that the alkene could be replaced by another radical precursor, we prepared iodo germyl ester **7** (eq 3). When **7** was heated at 80 °C (0.05 M, C_6D_6) in the presence of AIBN and triphenylgermanium hydride, it suffered smooth conversion to cyclopentanone (**8**) and triphenylgermanium iodide. An NMR experiment in the presence of an internal standard indicated that the yield of cyclopentanone was 95%. Photolysis of **7** also produced cyclopentanone in high yield (92%). When these two experiments were repeated with 15% galvinoxyl present, cyclopentanone was not detected. Nor was cyclopentanone formed by simple heating. These experiments provide strong evidence that step 2 in Scheme I is viable—alkyl radicals can indeed undergo 5-exo cyclizations to acylgermanes. That the chain propagates indicates that the cyclization of **9** to **10** is more rapid than the reaction of **9** with low concentrations of triphenylgermanium hydride.[14]

(7) (a) Mochida, K.; Ichikawa, K.; Okui, S.; Sakaguchi, Y.; Hayashi, H. *Chem. Lett.* **1985**, 1433. (b) Taraban, M. B.; Maryasova, V. I.; Leshina, T. V.; Rybin, L. I.; Gendin, D. V.; Vyazankin, N. S. *J. Organomet. Chem.* **1987**, *326*, 347. (c) Kiyooka, S.; Hamada, M.; Matsue, H.; Fujiyama, R. *Chem. Lett.* **1989**, 1385.

(8) The tributylgermyl radicals adds to cyclohexene with a $k = 5.7 \times 10^6$ M^{-1} s^{-1} at 25 °C. Addition to 1-nonene is less than 2 times faster. See: Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 1151.

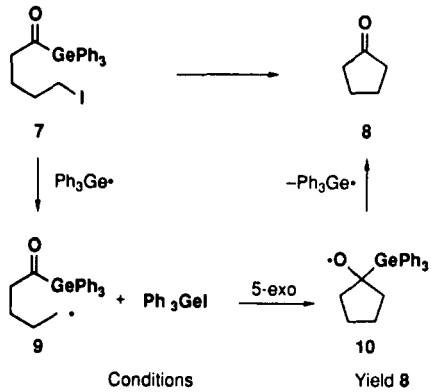
(9) For example, chain reactions with allylgermane will not propagate because the adduct radical will not eliminate $Bu_3Ge^•$ rapidly enough (see: Light, J. P., II; Ridenour, M.; Beard, L.; Hershberger, J. W. *J. Organomet. Chem.* **1987**, *326*, 17), and Bu_3GeH readily hydrogermylates terminal alkenes but it only causes cis/trans equilibration of internal alkenes (see: Nozaki, K.; Ichinose, Y.; Wakamatsu, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2268).

(10) β-Fragmentation reactions of alkoxy radicals are very rapid when carbon-centered radicals are expelled. Therefore, expulsion of more stable silicon-, germanium-, or tin-centered radicals must be very fast. Even though ring-opening reactions of cyclopentyloxy radicals are very rapid, we suspect that step 3 is probably so rapid that the reverse of step 2 cannot compete. See: Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230, 2674.

(11) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. Dowd, P.; Choi, S.-C. *Tetrahedron* **1989**, *45*, 77. Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565. Baldwin, J.; Adlington, R. M.; Robertson, J. *Tetrahedron* **1989**, *45*, 909.

(12) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102.

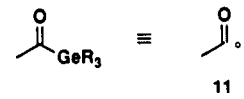
(13) A solution of 1-(triphenylgermyl)hex-5-en-1-one (**1a**) (40.4 mg, 0.1 mmol), triphenylgermanium hydride (1.5 mg, 0.005 mmol), and AIBN (2 mg, 0.01 mmol) in degassed benzene (10 mL) was heated in the dark at 80 °C for 6 h. The solvent was evaporated under reduced pressure, and the crude mixture was purified by chromatography (hexane/EtOAc, 20/1) to provide 35.5 mg of pure 1-((triphenylgermyl)methyl)cyclopentanone (**4a**).



(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]

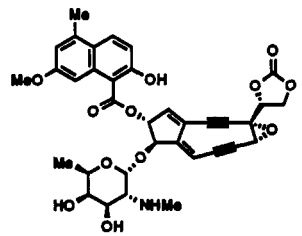
Takayuki Doi[†] and Takashi Takahashi*

Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

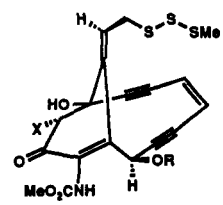
Received January 16, 1991 (Revised Manuscript Received March 28, 1991)

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)

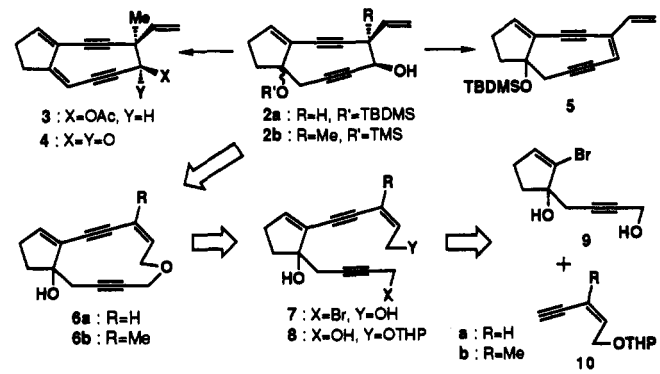


Esperamicin A_1 aglycone : X=OH

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.

0022-3263/91/1956-3465$02.50/0