Enyne[3]cumulene. Synthesis and Mode of Aromatization

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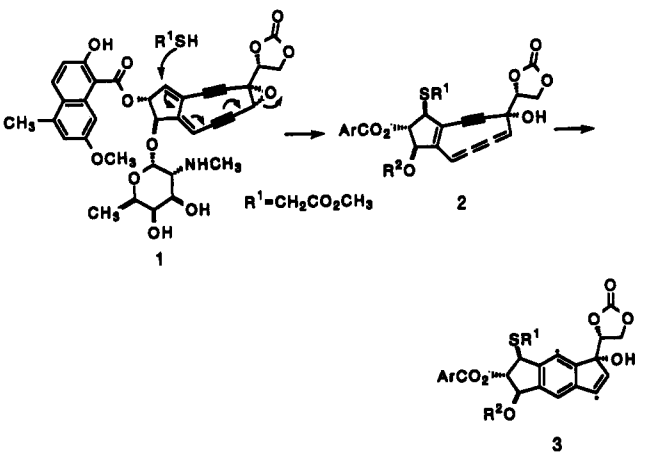
Received December 17, 1990

Summary: The noncyclic cross-conjugated diene-diyne system **4** undergoes the thiol-triggered vinylogous propargylic rearrangement (vinylogous S_N2' reaction) in the presence of amine leading to isolable enyne[3]cumulene **5**, which is capable of not only Bergman-type cyclization but also [2 + 2] cycloaddition reaction to produce benzocyclobutane derivative **14** when heated.

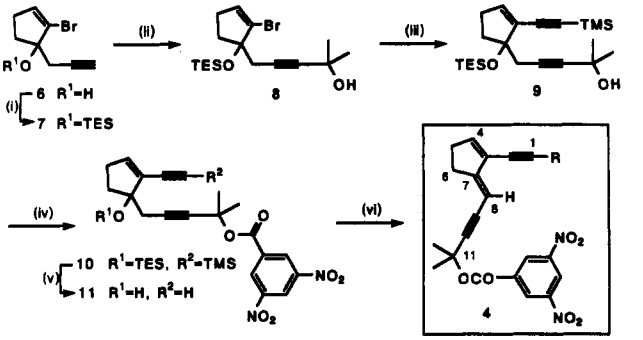
Enyne[3]cumulene derivative **2** is a proposed intermediate[1] leading to dehydroindene **3** through Bergman-type cyclization[2] in the aromatization of chromophore **1** of antitumor neocarzinostatin (NCS);[3] diradical **3** is believed to abstract hydrogen from deoxyribose backbone of DNA strand (Scheme I).[4] While the intermediacy of **2** was supported by low-temperature ^1H NMR measurements[1c] and the related enynallene system has been recently synthesized and characterized,[5,6] there is no precedent for a conjugated enynecumulene system. We report herein the first synthesis of such a compound, **5**, and its thermal behavior.

Cross-conjugated dienediyne **4**[7,8] was designed as a precursor to **5** that was expected to undergo a vinylogous propargylic rearrangement.[1a,9] Preliminary experiments indicated that the dimethyl substituents on C11 are necessary to prevent direct S_N2 reaction at C11.[10] Synthesis of **4** was carried out by employing standard methodology[7,8] as shown in Scheme II. Silylation of alcohol **6**[7b,8] (92%), metalation, and condensation with acetone gave alcohol **8** in 91% yield. Its palladium-mediated coupling[8,11] with

Scheme I

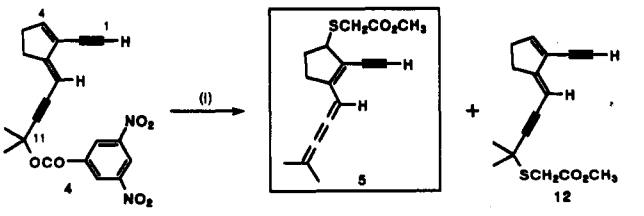


Scheme II[a]



[a] Reagents and conditions: (i) TESOTf (1.3 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, 0 °C, 1 h; (ii) EtMgBr (1.8 equiv), THF, 50 °C, 50 min; then acetone (3.0 equiv), room temperature, 100 min; (iii) TMSC≡CH (1.5 equiv), *n*-$BuNH_2$ (2.0 equiv), CuI (0.3 equiv), $Pd(PPh_3)_4$ (0.05 equiv), 40 °C, 36 h; (iv) $(NO_2)_2C_6H_3COCl$ (1.3 equiv), DMAP (2.0 equiv), CH_2Cl_2, 0 °C, 25 min; (v) *n*-Bu_4NF (3.2 equiv), CH_3CO_2H (4.0 equiv), room temperature, 58 h; (vi) MsCl (10 equiv), DMAP (2 equiv), Et_3N (20 equiv), CH_2Cl_2, 0 °C, 5 min.

Scheme III[a]



[a] Reagents and conditions: (i) $HSCH_2CO_2CH_3$ (1.5 equiv), Et_3N (1 equiv), CH_3CN, 25 °C, 2 h.

(trimethylsilyl)acetylene afforded **9** (89%), which was esterified to 3,5-dinitrobenzoate **10** in 98% yield, and its silyl-bearing atoms were deprotected to **11** (96%). Deh-

(1) (a) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493. (b) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. (c) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146.

(2) (a) Darby, N.; Kim, C. U.; Salaün, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *J. Chem. Soc. D* **1971**, 1516. (b) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (c) Mayer, J.; Sondheimer, F. *J. Am. Chem. Soc.* **1966**, *88*, 602.

(3) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68.

(4) 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. Kappen, L. S.; Goldberg, I. H. *Nucleic Acids Res.* **1985**, *13*, 1637.

(5) (a) Myers, A. G.; Kuo, E. Y.; Finny, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (b) Myers, A. G.; Dragovich, P. S. *Ibid.* **1989**, *111*, 9130.

(6) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995. Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Ibid.* **1990**, *31*, 2907.

(7) (a) Nakatani, K.; Arai, K.; Hirayama, N.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 2323. Krebs, A.; Wehlage, T.; Kramer, C.-P. *Ibid.* **1990**, *31*, 3533. (b) For related studies on 10-membered ring derivatives, see: Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120. Fujiwara, K.; Kurisaki, A.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4329.

(8) For related 9-membered ring derivatives, see: Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909. Wender, P. A.; Mckinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369.

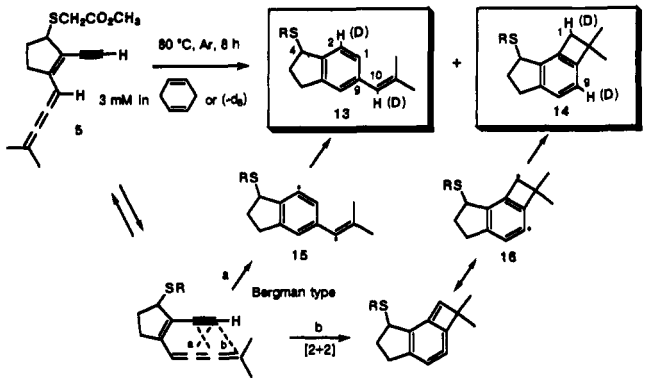
(9) (a) Zakaharova, A. I. *Zh. Obshch. Khim.* **1947**, *17*, 1277; *Chem. Abstr.* **1948**, *42*, 3722. (b) Jacobs, T. L.; Prempree, P. *J. Am. Chem. Soc.* **1967**, *89*, 6177. (c) Hopf, H. In *The chemistry of ketenes, allenes and related compounds*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1980; Part 2, Chapter 20, p 779 and references therein.

(10) Numbered temporarily as shown in Scheme II through the text fot the convenience.

(11) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Stephans, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. Cessar, L. *J. Organomet. Chem.* **1975**, *93*, 253. Dieck, H. A.; Heck, F. R. *Ibid.* **1975**, *93*, 259.

0022-3263/91/1956-1688$02.50/0

Scheme IV



ydration according to Wender's procedure[8] yielded *E* olefin **4** exclusively (61%)[12] as an air-sensitive pale yellow oil.[7]

Although the reaction of **4** with methyl thioglycolate in chloroform in the presence of triethylamine at room temperature under an argon atmosphere did not proceed, in DMSO it quickly gave **12**, a formal S_N2 product, surprisingly. In acetonitrile, however, the desired vinylogous S_N2' product **5** as a colorless liquid, was isolated in 46% yield together with a 15% yield of **12** after 2 h (Scheme III), while the yield of **12** increased when the reaction was prolonged.[13] The enyne[3]cumulene **5** exhibiting characteristic downfield resonances (^{13}C NMR) of the inner carbons (C9, δ 160.2; C10, δ 151.8)[14] is air-sensitive but seems to be rather stable at room temperature ($t_{1/2} \approx 2$ days in $CDCl_3$ with air) compared with tetramethyl[3]cumulene.[15,9c]

Thermolysis of **5** in deoxygenated 1,4-cyclohexadiene (0.003 M) at 80 °C showed its first-order decay ($k = 1.8 \times 10^{-4}$ s^{-1}, $t_{1/2} = 1.1$ h)[16] and yielded styrene derivative **13** (19%) and benzocyclobutane derivative **14** (21%), presumably through Bergman-type cyclization[2] leading to diradical intermediate **15** (path a) and through [2 + 2] cycloaddition[17] leading to diradical **16** (path b), respectively, in addition to polymeric materials (Scheme IV). These putative radical intermediates were supported by deuterium incorporation at the relevant positions. In 1,4-cyclohexadiene-d_8 (96.6% deuterium contents at allylic positions)[18] deuterium was incorporated at C2 and at C10 of **13** (16% yield) to the extent of 90% and 91%, respectively, and at C1 (>85%) and at C9 (92%) of **14** (16% yield).[16,19] When benzene was used as cosolvent with 1,4-cyclohexadiene (10:1, 80 °C),[16] **13** was poduced in much less yield (4%), while the yield of **14** did not change virtually (18%). This may reflect the longer lived σ,π-diradical intermediate **16** effected by both benzylic resonance[5a] and steric hindrance due to the *gem*-dimethyl group. Furthermore, **5** appears to be thermally less reactive than related acyclic enynallenes such as (*Z*)-3,5,6-octatrien-1-yne ($k = 3.2 \times 10^{-3}$ s^{-1}, at −78 °C).[5a,20]

In conclusion, we have demonstrated that the noncyclic cross-conjugated diene–diyne system **4** can undergo the thiol-triggered vinylogous propargylic rearrangement[9] (vinylogous S_N2' reaction) in the presence of amine leading to enyne[3]cumulene **5** that constitutes a simulation experiment on the proposed mechanism of thiol-triggered aromatization of neocarzinostatin chromophore **1**,[1] and disclosed that **5** is capable of not only Bergman-type cyclization[2] but also [2 + 2] cycloaddition reaction to produce a benzocyclobutane derivative.

Acknowledgment. This work was made possible through funds provided by the Ministry of Education, Science and Culture, Japanese Government [Grant-in-Aid for Scientific Research on Priority Areas No. 01649503 (Multiplex Organic Systems)] and by the Mitsubishi Foundation as well as the CIBA-GEIGY, the Shorai, and the TERUMO Life Science Foundations.

Supplementary Material Available: Spectral data (^1H NMR, ^{13}C NMR, IR, UV, and HRMS and/or MS) for new compounds **4**, **5**, **7–14** (7 pages). Ordering information is given on any current masthead page.

(12) Determined by NOE experiment between 1-H and 8-H; no NOE between 6-Hs and 8-H.

(13) Isolated **5** rearranged rapidly to **12** in DMSO at room temperature in the presence of methyl thioglycolate and triethylamine.

(14) Representative spectral data of **5**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (dddd, 1 H, J = 3.9, 4.0, 8.8, 13.8 Hz, H^{5a}), 2.00 (s, 3 H, H^{12}), 2.00 (s, 3 H, H^{12}), 2.43 (dddd, 1 H, J = 7.2, 8.1, 9.0, 13.8 Hz, H^{5b}), 2.54 (br ddd, 1 H, J = 4.0, 7.2, 17.5 Hz, H^{6a}), 2.69 (br ddd, 1 H, J = 8.1, 8.8, 17.5 Hz, H^{6b}), 3.31 (d, 1 H, J = 15.1 Hz, SCH_2), 3.42 (br s, 1 H, H^1), 3.49 (d, 1 H, J = 15.1 Hz, SCH_2), 3.74 (s, 3 H, OCH_3), 4.15 (br d, 1 H, J = 9.0 Hz, H^4), 6.34 (br s, 1 H, H^8); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.46 (CH_3, C^{12}), 25.32 (CH_3, C^{12}), 31.00 (CH_2, C^5), 31.67 (CH_2, C^6), 32.49 (CH_2, SCH_2), 52.31 (CH_3, OCH_3), 53.86 (CH, C^4), 79.22 (C, C^2), 85.28 (CH, C^1), 98.30 (CH, C^8), 119.78 (C, C^3), 121.01 (C, C^{11}), 151.11 (C, C^7), 151.82 (C, C^{10}), 160.20 (C, C^9), 170.98 (C, CO_2); IR (film) ν 3292, 2954, 2932, 2852, 2100, 2050, 1738, 1620, 1549, 1437, 1350, 1282, 1207, 1129, 1011, 756 cm^{-1}; UV (cyclohexane) λ_{max} (log ϵ) 334 (4.51), 303 (sh 4.22), 231 nm (3.61); EIMS (70 eV) m/z 274 [33.4%, M$^+$], 201 [8.53%, M$^+$ − ($CH_2CO_2CH_3$)], 167 [bp, M$^+$ − ($SCH_2CO_2CH_3$)]; HRMS (EI, 70 eV) calcd for $C_{16}H_{18}O_2S$ 274.1027, found 274.1029.

(15) Skattebøl, L. *Tetrahedron* **1965**, *21*, 1357.

(16) Monitored by HPLC, the first-order disappearence was also observed in other degassed solvents at 80 °C: 1,4-cyclohexadiene-d_8, $k = 1.7 \times 10^{-4}$ s^{-1}; benzene–1,4-cyclohexadiene (10:1), $k = 1.9 \times 10^{-4}$ s^{-1}; and tetrahydrofuran, $k = 5.4 \times 10^{-5}$ s^{-1} (at 65 °C).

(17) (a) Intermolecular [2 + 2] cycloaddition of [5]cumulene with hexafluoro-2-butyne was reported, see: Hartzler, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 4527. (b) For [2 + 2] cycloadditions of allenes and alkynes, see: Pasto, D. J.; Kong, W. *J. Org. Chem.* **1988**, *53*, 4807; **1989**, *54*, 3215 and references therein.

(18) Prepared by the reduction of benzene-d_6 (99.6%) with Na (2.5 equiv) in HMPA in the presence of CH_3CH_2OD (2.0 equiv) and CH_3CO_2D (3.0 equiv) at room temperature in 36% yield (99.9% isomeric purity by GC) after fractional distillation (cf. Whitesides, G. M.; Ehmann, W. J. *J. Am. Chem. Soc.* **1969**, *91*, 3800; *J. Org. Chem.* **1970**, *35*, 3565).

(19) Extent of deuterium incorporation was determined by 400-MHz ^1H NMR.

(20) At this moment, however, it has not been concluded that enyne-[3]cumulenes are generally more stable than the corresponding enyne-allenes, because the substitution patterns and the bond angles of central double bond are not identical between **5** and (*Z*)-3,5,6-octatrien-1-yne.[5a]

Oxidative Fragmentation of Catharanthine by Dichlorodicyanoquinone

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Received July 31, 1990

Summary: Oxidation of catharanthine by DDQ leads to formation of products resulting from fragmentation of the C16–C21 bond as well as C3 and C5 dehydrogenation. Among the products are compounds containing a cyclopropane ring formed by bonding between C14 and C16. Cyclopropane ring formation can be also be observed from the intermediate generated by Potier–Polonovski fragmentation of catharanthine *N*-oxide.

0022-3263/91/1956-1689$02.50/0