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BIRADICAL FORMATION FROM ACYCLIC CONJUGATED ENEYNE-ALLENE SYSTEM RELATED TO NEOCARZINOSTATIN AND ESPERAMICIN-CALICHEMICIN

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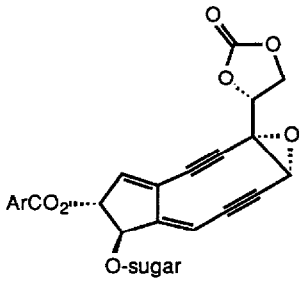
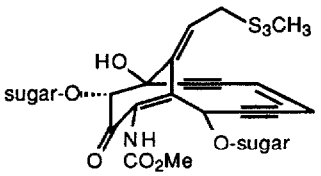
*Summary: Acyclic conjugated allenylphosphine oxide **4b** prepared by three step operations was stable at ambient temperature and underwent Bergman type cyclization to form biradical **5b** at 37 °C.*

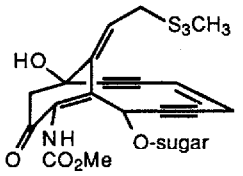
Recently reported antitumor antibiotics, neocarzinostatin,[1] esperamicin,[2] and calichemicin,[3] possessing cyclic enediyne systems in their molecules, have exhibited strong DNA cleaving activities. The mechanism of their action has been commonly proposed to involve hydrogen abstraction from DNA sugar backbone by reactive benzenoid biradical species generated by Bergman type cyclization[4] of the cyclic enediyne systems.[1b,2,3,5] This attractive proposal stimulated us to study on the design of a simplified DNA cleaving molecule which mimics the mechanism of the action of these antibiotics.[6] Here, we demonstrate that a simple, acyclic conjugated eneyne-allene system undergoes Bergman type cyclization at 37 °C to form a biradical.



Neocarzinostatin chromophore

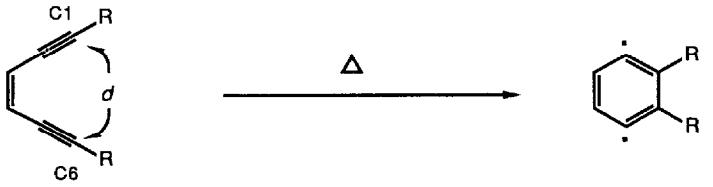


Esperamicin

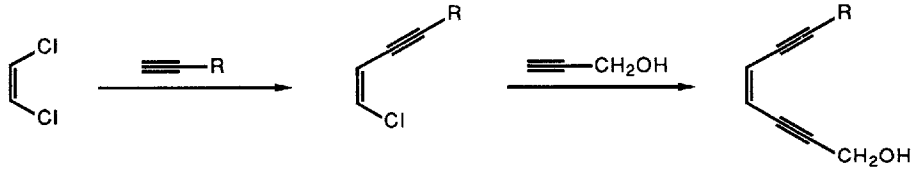


Calichemicin

According to the study on Bergman cyclization reported by Nicolaou,[6a] easiness of the cyclization of conjugated enediyne systems strongly depends on the distance between C1 and C6. For spontaneous cyclization at ambient temperature, the distance must be within ca. 3.3 Å.[6a] In the case of acyclic enediyne system where the distance (C1-C6) is estimated to be ca. 4 Å, thermal activation of more than 130 °C is required for Bergman cyclization.[4] On the basis of these data, it occurred to us that if one of the acetylenes in acyclic enediyne system is replaced by allene (acetylene equivalent), the distance (C1-C6) might fall down to a range close enough for spontaneous cyclization at ambient temperature and that the allenyl part would be easily introduced into the molecule by using [2,3]-sigmatropic rearrangement of propargylic phosphite or phosphinite to allenyl phosphonate or phosphine oxide.[7]



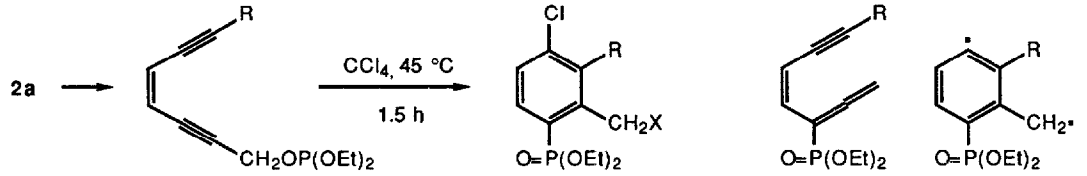
Propargyl alcohol derivative **2a** was prepared by the following sequence: 1) coupling of *cis*-dichloroethylene with TBDMS ether of 3-butyn-1-ol (1.0 equiv) by using $Pd(PPh_3)_4$ (0.1 equiv) and CuI (0.15 equiv) in benzene in the presence of *n*-propylamine (1.2 equiv) to form **1a** (91%); 2) second coupling of **1a** with propargyl alcohol by a similar procedure (50%). **2b** was also prepared via **1b** by a comparable sequence.



1a R = $-CH_2CH_2OTBDMS$ (91%) **2a** (50%)

1b R = $-CH_2CH_2OAc$ (71%) **2b** (57%)

First attempt was made to obtain eneyne-allenyl phosphonate **4a**. Treatment of **2a** with diethyl chlorophosphite (1.2 equiv) and triethylamine (1.5 equiv.) in hexane at 0 °C afforded **3a**[8] in quantitative yield after extractive isolation. Although heating **3a** in CCl_4 (45 °C, 1.5 h) was expected to provide allenyl phosphonate **4a**, a number of products were formed under the conditions and **4a** could not be detected at all. Instead, aromatized compounds **6a**[9] (ca. 5%) and **7a**[10] (ca. 5%) were encouragingly isolated from the complex mixture. It appeared that both **6a** and **7a** are formed from biradical **5a** which might arise from a Bergman type cyclization of allenyl phosphonate **4a**.

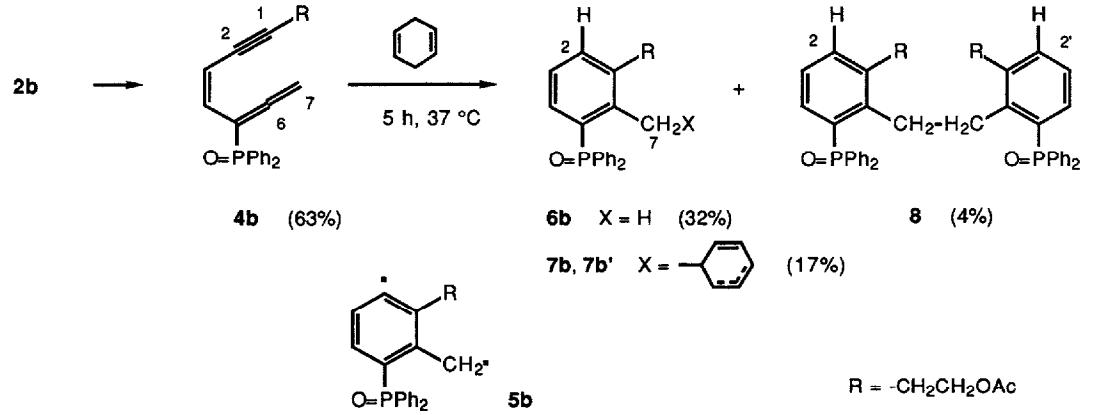


3a (quant.) **6a** X = Cl (ca. 5%) **4a** **5a**

7a X = CCl_3 (ca. 5%) R = $-CH_2CH_2OTBDMS$

When **2b** was treated with chlorodiphenylphosphine and triethylamine in hexane at -78 to 0 °C, allenylphosphine oxide **4b**[11] was directly formed and could be purified fortunately by silica gel column chromatography at ambient temperature (63%). In order to confirm whether the eneyne-allene system actually undergoes spontaneous cyclization to generate biradical, **4b** (35 mM) was heated at 37 °C in benzene in the presence of 1,4-cyclohexadiene (1.38 M). **4b** was nearly completely consumed after 5 h under the conditions and again aromatized compounds

6b,[12] a mixture of **7b** and **7b'**,[13] and dimer **8**[14] were isolated in 32, 17 and 4% yields, respectively. When thermal decomposition of **4b** (66 mM) was carried out in 5 : 1 THF-d_8 - H_2O at 60 °C, more than 90% of the deuterium was incorporated into C2 and C2' positions of **8** (28% isolated yield), as evidenced by the ^1H nmr and MS spectra. Furthermore, doubly deuterated **6b** was also detected in which two deuterium atoms were incorporated into both C2 and C7 positions.[15] In contrast, the thermal decomposition in THF - D_2O resulted in no deuterium incorporation into any positions of **8** or **6b**.[16] These results strongly suggest that thermal decomposition of **4b** actually involves a formation of biradical intermediate **5b**, in analogy with the cases of antibiotics, neocarzinostatin, esperamicin, and calichemicin.



Several advantages of the use of allenylphosphine oxide **4b** can be pointed out. First, the molecule can be readily constructed by simple three step operations. Secondly, the molecule is stable enough to be handled at ambient temperature but at body temperature generates reactive biradical species in an appreciable rate. Thirdly, the structural simplicity of **4b** might allow us to easily make suitable modifications of its substituents for the design of a DNA cleaving molecule. The results demonstrated here suggest that a strained energy is not necessarily important for spontaneous Bergman type cyclization at ambient temperature and open the question why eneyne-allene **4b** easily generates a reactive biradical species of high energy level. Further studies on the mechanism and application of this novel biradical forming reaction are underway.[17,18]

References and Notes

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8. **3a**: ^{1}H nmr (200 MHz, chloroform-*d*) δ 5.78 (d, 1 H, *J* = 10 Hz), 5.75 (d, 1 H, *J* = 10 Hz), 4.62 (d, 2 H, *J* = 9 Hz), 3.90 (5et, 4 H, *J* = 7.5 Hz), 3.75 (t, 2 H, *J* = 7.5 Hz), 2.59 (bt, 2 H, *J* = 7.5 Hz), 1.26 (t, 6 H, *J* = 7.5 Hz), 0.86 (s, 9 H), 0.04 (s, 6 H).
9. **6a**: ^{1}H nmr (200 MHz, chloroform-*d*) δ 7.82 (dd, 1 H, *J* = 14, 8 Hz), 7.43 (dd, 1 H, *J* = 8, 4 Hz), 5.13 (s, 2 H), 3.95~4.25 (m, 4 H), 3.38 (t, 2 H, *J* = 7.5 Hz), 3.24 (t, 2 H, *J* = 7.5 Hz), 1.32 (t, 2 H, *J* = 7.5 Hz), 1.27 (s, 9 H), -0.16 (s, 6 H); MS, *m/e* 441, 439 (M^+-Me), 401 (14%), 399 (69%), 397 (M^+-*t*Bu, 100%).
10. **7a**: ^{1}H nmr (400 MHz, at 55 °C, chloroform-*d*) δ 7.65 (dd, 1 H, *J* = 14, 8 Hz), 7.37 (dd, 1 H, *J* = 8, 4 Hz), 5.14 (bs, 2H), 4.07~4.18 (m, 2 H), 3.97~4.07 (m, 2H), 3.77 (t, 2 H, *J* = 7.5 Hz), 3.48 (bt, 2 H, *J* = 7.5 Hz), 1.28 (t, 6 H, *J* = 7.5 Hz), 0.8 (s, 9 H), - 0.15 (s, 6 H); MS, *m/e* 525, 523, 521 (M^+ - Me), 485 (13%), 483 (51%), 481 (100%), 479 (M^+-*t*Bu, 76%).
11. **4b**: ^{1}H nmr (200 MHz, chloroform-*d*) δ 7.65~7.75 (m, 4 H), 7.36~7.55 (m, 6 H), 6.04 (bdd, 1 H, *J* = 7.5, 11 Hz), 5.71 (bd, 1 H, *J* = 11 Hz), 4.93 (bs, 1 H), 4.90 (bs, 1 H), 4.14 (t, 2 H, *J* = 7.5 Hz), 2.67 (td, 2 H, *J* = 7.5, 2.5 Hz), 2.01 (s, 3 H); MS *m/e* 376 (M^+).
12. **6b**: ^{1}H nmr (400 MHz, chloroform-*d*) δ 7.36~7.71 (m, 10 H), 7.32 (d, 1 H, *J* = 8 Hz), 7.08 (dt, 1 H, *J* = 4, 8 Hz), 6.90 (dd, 1 H, *J* = 14, 8 Hz), 4.21 (t, 2 H, *J* = 7.5 Hz), 2.95 (t, 2 H, *J* = 7.5 Hz), 2.44 (s, 3 H), 1.98 (s, 3 H); MS *m/e* 378 (M^+).
13. An inseparable mixture of **7b**, **7b'**: ^{1}H nmr (200 MHz, chloroform-*d*) δ 7.40~7.65 (m, 10 H), 7.37 (d, 1 H, *J* = 8 Hz), 7.10 (td, 1 H, *J* = 8, 4 Hz), 6.98 (bdd, 1 H, *J* = 14, 8 Hz), 4.17 (t, 2 H, *J* = 7.5 Hz), 1.96 (s, 3 H); peaks (total 11 H) also appeared at following regions: 5.65~5.90 (m), 5.60 (bd, *J* = 11 Hz), 5.48 (bd, *J* = 11 Hz), 2.90~3.30 (m), 3.06 (t, *J* = 7.5 Hz), 2.70~2.90 (m), and 2.53~2.65 (m); MS *m/e* 454 (M^+).
14. **8**: ^{1}H nmr (200 MHz, chloroform-*d*) δ 7.36~7.60 (m, 20 H), 7.16 (d, 2 H, *J* = 8 Hz), 7.03 (td, 1 H, *J* = 8, 4 Hz), 6.85 (dd, 2 H, *J* = 14, 8 Hz), 3.88 (t, 4 H, *J* = 7.5 Hz), 3.50 (s, 4 H), 2.38~2.51(m, 4 H), 1.97 (s, 6 H); MS *m/e* 754 (M^+).
15. In the MS spectra of the isolated product (15% yield), the presence of peaks at *m/e* 380 (M^++2, 37%), 379 (M^++1, 58%), and 378 (M^+, 39%) indicated that this product actually consists of a mixtur of doubly deuterated, monodeuterated, and non-deuterated **6b** in a ratio of 34 : 45 : 21.
16. The formation of THF adduct at C7 was also observed.
17. Recently, a similar biradical formation from thermolysis of 4-alkynylcyclobutenones via (2-alkenylethenyl)ketene intermediates has been suggested. See: L. D. Foland, J. O. Karlsson, S. T. Perri, R. Schwabe, S. L. Xu, S. Patil, and H. W. Moore, *J. Am. Chem. Soc.*, **111**, 975 (1989).

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