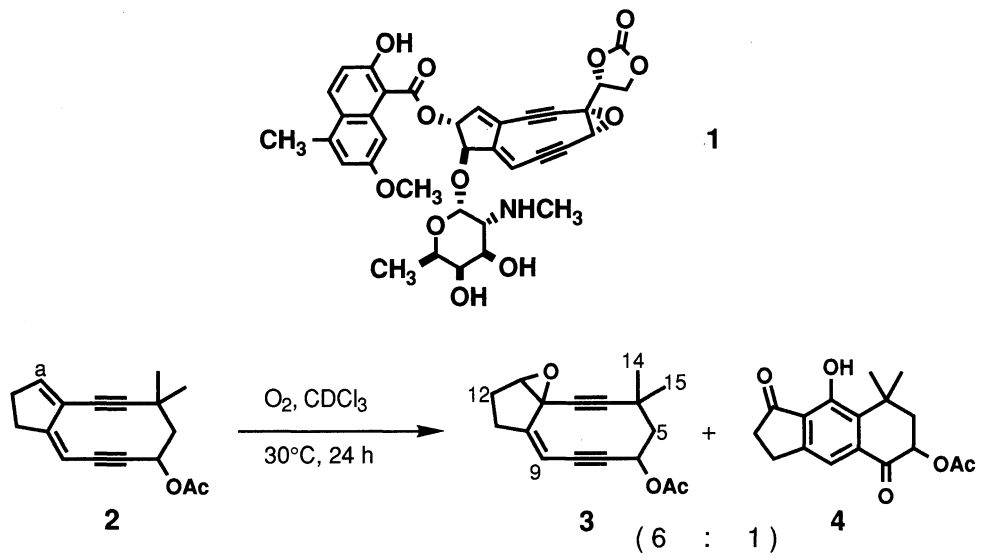
CHEMISTRY LETTERS, pp. 457-460, 1994. © 1994 The Chemical Society of Japan

Reactions of Neocarzinostatin Chromophore Analogues with Molecular Oxygen

Kenshu FUJIWARA, Hiromi SAKAI, Toshiyuki TANAKA, and Masahiro HIRAMA*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980

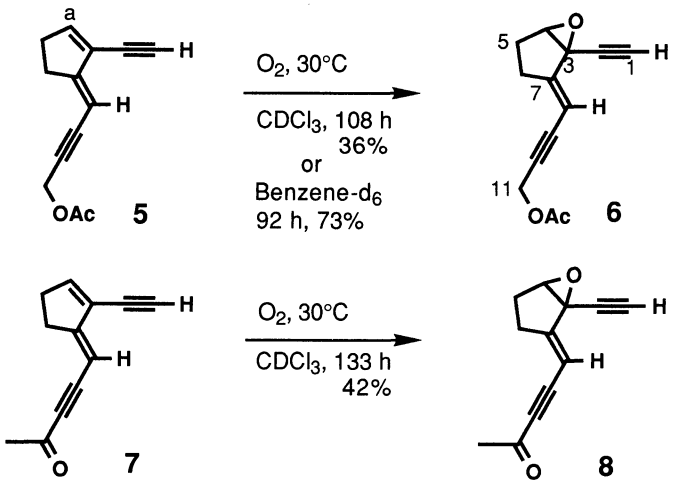
Cross-conjugated 5-methylene-3-heptene-1,6-diyne derivatives have been proved to be readily epoxidized by molecular oxygen.

Cross-conjugated dienediyne systems of neocarzinostatin (NCS) chromophore (**1**)[1] and its 10-membered ring analogues undergo addition of nucleophiles leading to the formation of carbon diradicals.[2,3] Recently we have reported that thiyl and hydroperoxy radicals also trigger their cycloaromatization.[3a,b,4] During these studies we found extreme lability of the 10-membered analogues toward molecular oxygen in a concentrated solution.[3] The related compounds including 9-membered analogues[5c] have also been reported to show a similar behavior.[5] We disclose herein the formation of the unstable epoxides in the reaction of 10-membered ring analogue **2**[3a] and acyclic analogues **5** and **7**[6,7] with molecular oxygen.



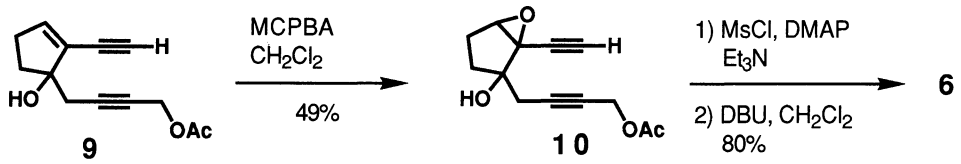
Scheme 1.

Dry oxygen gas was bubbled through a 0.1 M $CDCl_3$ solution of **2**[3a] at 30 °C and the reaction was monitored by ^1H NMR spectroscopy. The compound **2** disappeared completely within a day and formation of a 6:1 mixture of epoxide **3** (a 1:1 diastereomeric mixture)[8] and diketone **4** was detected (Scheme 1), whereas **2** was stable under an argon atmosphere. The structure of **3** was determined by H-C COSY and COLOC experiments of the mixture without isolation, since **3** deteriorated rapidly during the concentration of the reaction mixture and the purification of the products.



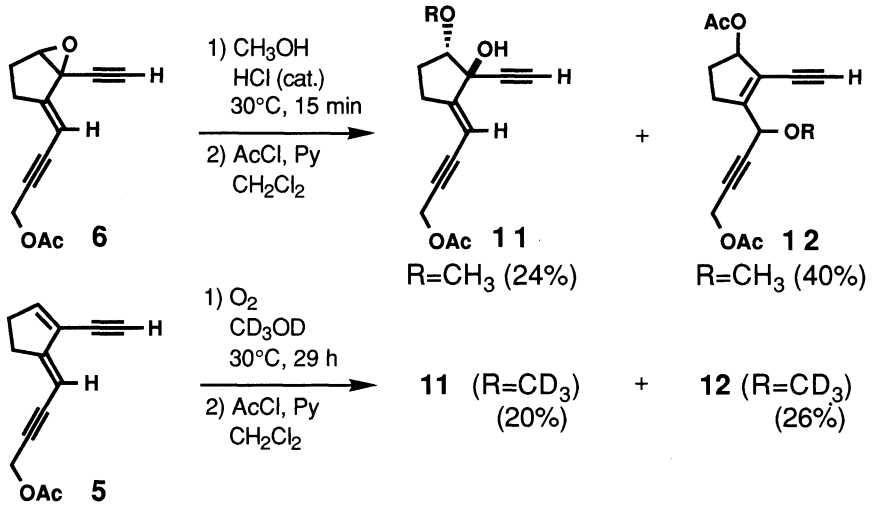
Scheme 2.

On the other hand, the acyclic analogues **5**[9] and **7**[6,7,9] in aerated $CDCl_3$ gave relatively stable epoxides **6**[8] and **8**[8] in 36% and 42% yield, respectively (Scheme 2). The structure of **6** was unambiguously established by the alternative synthesis of **6** from **9** (Scheme 3): Epoxidation of **9** with MCPBA gave **10** (49% yield), which was mesylated and treated with DBU to afford **6** in 80% yield. Lability of the epoxide **6** under acidic conditions was confirmed by the formation of **11** (24%) and **12** (a 1:1 diastereomeric mixture, 40% yield) by treatment with methanolic HCl and subsequent acetylation (Scheme 4).[10] Thus, treatment of **5** with O_2 in CD_3OD in the presence of trace amounts of HCl provided **11** (R=CD_3) and **12** (R=CD_3, a 1:1 diastereomeric mixture) in 20% and 26% yield, respectively, after acetylation.[10]

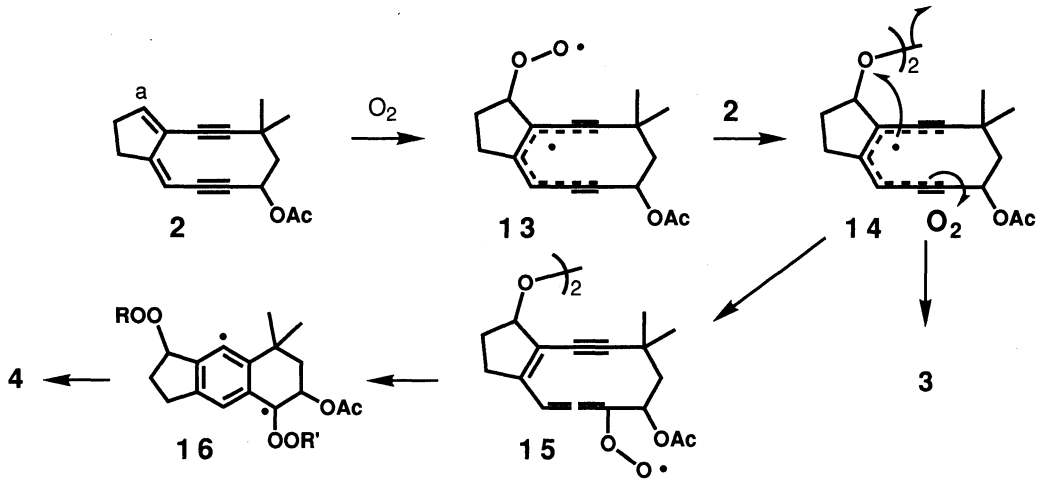


Scheme 3.

The efficient formation of **6** (73%) from **5** in benzene-d_6 (Scheme 2) might support the direct addition mechanism of O_2 toward **5** rather than the oxidation via peroxides generated by an autoxidation of solvent. As reported previously,[3,6] the terminus position "a" of these cross-conjugated dienediyne systems in the compounds such as **2** and **5** is very susceptible to attack of radical species, which would form a radical intermediate stabilized by conjugation with the enediyne system. Therefore, molecular oxygen as a biradical is likely to react with **2** and highly delocalized radical intermediate **13** would be formed (Scheme 5). Then the peroxy radical **13** might react with another **2** and would form dimeric peroxide **14**. Intramolecular reaction of the radical with the peroxide moiety may result in the formation of the epoxide **3**. The formation of **4** could be explained by the oxidative triggering aromatization:[3b,4] Thus, the delocalized radical **14** is trapped by O_2 at the terminal of the conjugated system, enynallene intermediate **15** would be formed and could undergo the cycloaromatization.[3] The resulting phenyl radical of **16** will be trapped by another O_2, and subsequent decomposition of the peroxides would yield **4**.



Scheme 4.



Scheme 5.

In connection with the above extreme lability of the synthetic analogues to molecular oxygen,[5] we then examined the reaction of NCS chromophore (**1**) with O_2: Interestingly, there was no distinct difference in the rates of decomposition of **1** between the degassed and aerated 0.1 M AcOH/MeOH solutions, in the dark. This unexpected insensitivity of **1** toward O_2 should not arise from the highly strained 9-membered ring structure, because the synthetic 9-membered analogues are liable.[5] Substituents such as the naphthoate possessing a phenolic hydroxy group and/or the dense substitution on the core might be responsible for the stability of **1**. The study on the O_2-susceptibity difference is a current subject in our laboratory.

Acknowledgement: This work was supported by the Ministry of Education, Science, and Culture, Japan, Takeda and Fujisawa Science Foundations.

References

1) N. Ishida, K. Miyazaki, K. Kumagai, and M. Rikimaru, *J. Antibiot.*, **18**, 68 (1965); K. Edo, M. Mizugaki, Y. Koide, H. Seto, K. Furihata, N. Otake, and N. Ishida, *Tetrahedron Lett.*, **26**, 331 (1985); A. G. Myers, P. J. Proteau, and T. M. Handel, *J. Am. Chem. Soc.*, **110**, 7212 (1988).

2) A. G. Myers and P. J. Proteau, *J. Am. Chem. Soc.*, **111**, 1146 (1989); I. H. Goldberg, *Acc. Chem. Res.*, **24**, 191 (1991).

3) a) M. Hirama, K. Fujiwara, K. Shigematu, and Y. Fukazawa, *J. Am. Chem. Soc.*, **111**, 4120 (1989); b) K. Fujiwara, A. Kurisaki, and M. Hirama, *Tetrahedron Lett.*, **31**, 4329 (1990); c) K. Fujiwara, H. Sakai, and M. Hirama, *J. Org. Chem.*, **56**, 1688 (1991); d) M. Hirama, M. Tokuda, and K. Fujiwara, *SYNLETT*, **1991**, 651; e) M. Hirama, T. Gomibuchi, K. Fujiwara, Y. Sugiura, and M. Uesugi, *J. Am. Chem. Soc.*, **113**, 9851 (1991); f) M. Tokuda, K. Fujiwara, T. Gomibuchi, M. Hirama, M. Uesugi, and Y. Sugiura, *Tetrahedron Lett.*, **34**, 669 (1993); g) M. Hirama, "Antibiotics and Antiviral Compounds-Chemical Synthesis and Modification," ed by K. Krohn, H. A. Kirst, and H. Maag, VCH, Weinheim, **1993**, p. 289.

4) T. Tanaka, K. Fujiwara, and M. Hirama, *Tetrahedron Lett.*, **31**, 5947 (1990).

5) a) P. Wender, M. Harmata, D. Jeffrey, C. Mukai, and J. Suffert, *Tetrahedron Lett.*, **29**, 909 (1988); P. A. Wender, J. A. Micknney, and C. Mukai, *J. Am. Chem. Soc.*, **112**, 5359 (1990); b) T. Doi and T. Takahashi, *J. Org. Chem.*, **56**, 3465 (1991); c) A. G. Myers, P. M. Harrington, and B.-M. Kwon, *J. Am. Chem. Soc.*, **114**, 1086 (1992); d) M. Hirama,"Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products," Vol. 2, ed by G. Lukacs, Springer-Verlag, Berlin, **1993**, p. 293.

6) M. Hirama, *J. Syn. Org. Chem. Jpn.*, **49**, 1032 (1991).

7) P. A. Wender and M. J. Tabbe, *Tetrahedron Lett.*, **32**, 4863 (1991).

8) Representative spectral data. **3** (a 1:1 diastereomeric mixture): ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.26(3H/2, s, H15), 1.27(3H/2, s, H15), 1.30(3H/2, s, H14), 1.34(3H/2, s, H14), 1.78(1H/2, dd, J=3.5, 11.0Hz, H5a), 1.86(1H/2, dd, J=3.5, 11.0Hz, H5a), 1.75-1.90(1H, m, H12a), 2.00-2.10(1H, m, H12b), 2.07(1H, dd, J=11.0, 11.6Hz, H5b), 2.08(3H/2, s, Ac), 2.09(3H/2, s, Ac), 2.20-2.30(2H, m, H11), 3.94(1H/2, d, J=1.3Hz, H13), 3.96(1H/2, d, J=1.3Hz, H13), 5.63(1H, t, J=1.0Hz, H9), 5.68(1H/2, ddd, J=1.0, 3.5, 11.0Hz, H6), 5.72(1H/2, ddd, J=1.0, 3.5, 11.0Hz, H6); ^{13}C-NMR (150 MHz, $CDCl_3$) δ21.00($\underline{C}H_3CO$), 21.01($\underline{C}H_3CO$), 25.57(C11), 25.62(C12), 26.55(C14), 27.73(C14), 27.84(C11), 29.73(C4), 30.14(C15), 30.67(C15), 44.21(C5), 46.72(C5), 55.73(C1), 55.80(C1), 62.62(C6), 62.90(C6), 68.04(C13), 68.11(C13), 75.98(C2), 76.36(C2), 84.37(C8), 84.46(C8), 91.46(C7), 92.34(C7), 97.43(C3), 97.48(C3), 106.64(C9), 106.79(C9), 151.76(C10), 152.80(C10), 169.63($CH_3\underline{C}O$), 169.82($CH_3\underline{C}O$). **6** (colorless oil): ^{1}H-NMR (600 MHz, $CDCl_3$) δ1.88(1H, dtd, J=1.6, 8.4, 13.1Hz, H5), 2.09-2.15(1H, m, H5), 2.11(3H, s, OAc), 2.18(1H, dtd, J=3.0, 8.4, 17.3Hz, H6), 2.60(1H, s, H1), 2.61-2.67(1H, m, H6), 4.05(1H, d, J=1.6Hz, H4), 4.83(2H, d, J=2.1Hz, H11), 5.99(1H, br quint., J=2Hz, H8); ^{13}C-NMR (150 MHz, $CDCl_3$) δ20.70($\underline{C}H_3CO$), 25.20(C6), 25.67(C5), 52.73(C11), 56.75(C3), 68.17(C4), 75.81(C1), 75.95(C2), 82.92(C10), 88.74(C9), 106.29(C8), 153.25(C7), 170.18($CH_3\underline{C}O$). **8** (pale yellow oil): ^{1}H-NMR(400 MHz,$CDCl_3$) δ1.93(1H, dtd, J=1.5, 8.5, 14.0Hz, H5), 2.14-2.21(1H, m, H5), 2.25(1H, dtd, J=3.0, 8.5, 17.0Hz, H6), 2.38(3H, 5, H12), 2.64(1H, S, H1), 2.71(1H, m, H6), 4.11(1H, d, J=1.5Hz, H4), 6.10(1H, dd, J=1.5, 3.0Hz, H8): HRMS(EI) *m/z* 186.0679 (M^+, Calcd for $C_{12}H_{10}O_2$: 186.0680).

9) The *E*-geometry of the tri-substituted exo double bond of **5** and **7** was assigned by NOE experiment.

10) Since partial cleavage of the acetate group occurred simultaneously during the epoxide opening, the reaction products were acetylated for the convenience of the product analysis.

(Received November 15, 1993)