Pergamon

Tetrahedron Letters 43 (2002) 6779–6781

TETRAHEDRON LETTERS

Synthesis of enediyne model compounds possessing a cyanohydrin moiety as a triggering device

Ichiro Suzuki,* Yuko Tsuchiya, Akira Shigenaga, Hisao Nemoto and Masayuki Shibuya

Faculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi 1-78, Tokushima 770-8505, Japan

Received 7 June 2002; revised 17 July 2002; accepted 19 July 2002

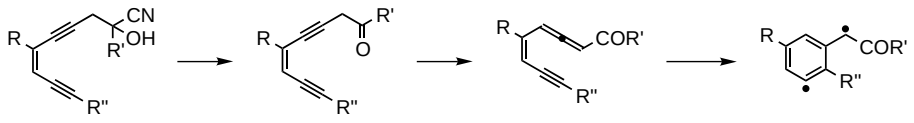
Abstract—Development of enediyne model compounds possessing a cyanohydrin moiety is described. These model compounds generate enyne–allenylketones efficiently under mild basic conditions and the resulting biradicals showed potent DNA cleaving abilities.

After the discovery of the potent antitumor antibiotics *neocarzinostatin* and related compounds which possess a cyclic enediyne structure and cycloaromatize to afford reactive biradicals, a great deal of effort has been made in the synthesis and design of analogs of these compounds that act in a similar mode.[1] In these studies, Myers–Saito type cycloaromatization seemed to receive much less attention than Masamune–Bergman type cyclization, probably because of the complicated reactivity of the resulting α,3-didehydrotoluene biradical. The α,3-didehydrotoluene biradical is considered to be a singlet biradical having a considerable ionic character due to the partial conjugation between two SOMOs.[2] This ionic character would be enhanced in protic media reducing DNA damaging abilities of the biradicals.[2c,3] To develop artificial anticancer drugs, a molecular design for controlling the reactivity of this biradical has to be exploited.

Previously, we demonstrated that enediyne models bearing an electron-withdrawing group on the allene terminus indicated enhanced DNA cleaving abilities.[4] According to this concept, we designed new enediyne models containing a cyanohydrin moiety which afford reactive allenylketones in basic conditions and finally generate DNA damaging biradicals (Scheme 1).

The targeting new models **5**, **6** and **4c** were synthesized in the manner shown in Scheme 2. The enediyne **4c** has a possibility to develop enediyne prodrugs possessing a biologically removable protecting group. The starting dibromide **1** was prepared according to the procedure reported by Myers et al.[5] Sonogashira type Pd-catalyzed cross coupling of **1** with methylpropargylether, and subsequent reduction gave enyne **2**. The methoxymethyl ether of **2** served as a common precursor for the enediyne models. Alkynes **7**, **8** and **9** were prepared by the propargylation of corresponding cyanohydrins and these alkynes were coupled with ether **3** in the presence of Pd-catalyst. The resulting enediynes **4a** and **4b** were treated with *p*-TsOH in MeOH and gave cyanohydrins **5** and **6**. These enediynes decomposed gradually at room temperature, and so were used without further purification. Since the enediyne **4c**, which was prepared from **3** and **9**, was stable enough to be purified with silica gel column chromatography, we used **4c** for DNA-cleaving studies.

The reactions of enediyne **5** and **6** with Et_3N (1.2 equiv.) in the presence of 50 equiv. of 1,4-cyclohexadiene (1,4-CHD) as a hydrogen donor in methanol at 37°C afforded the cycloaromatized products **10** and the adduct **11**, respectively, as shown in Table 1. The

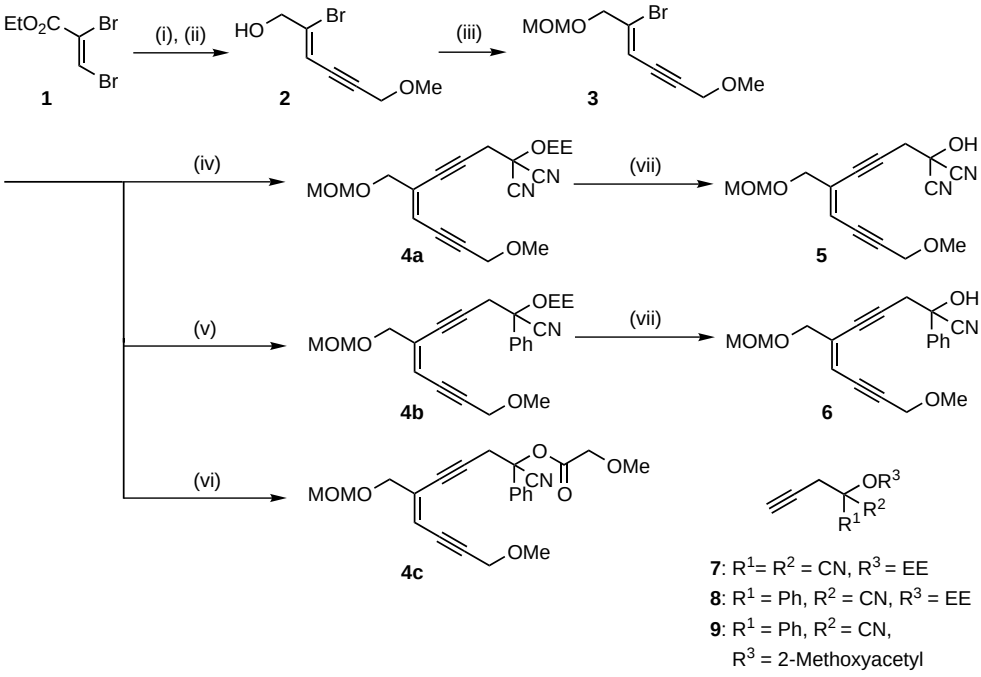


Scheme 1.

Keywords: diynes; enynes; radicals; ionization; cyanohydrins; DNA.

* Corresponding author. Tel.: +81 88 633 9534; fax: +81 88 633 9505; e-mail: isuzuki@ph2.tokushima-u.ac.jp

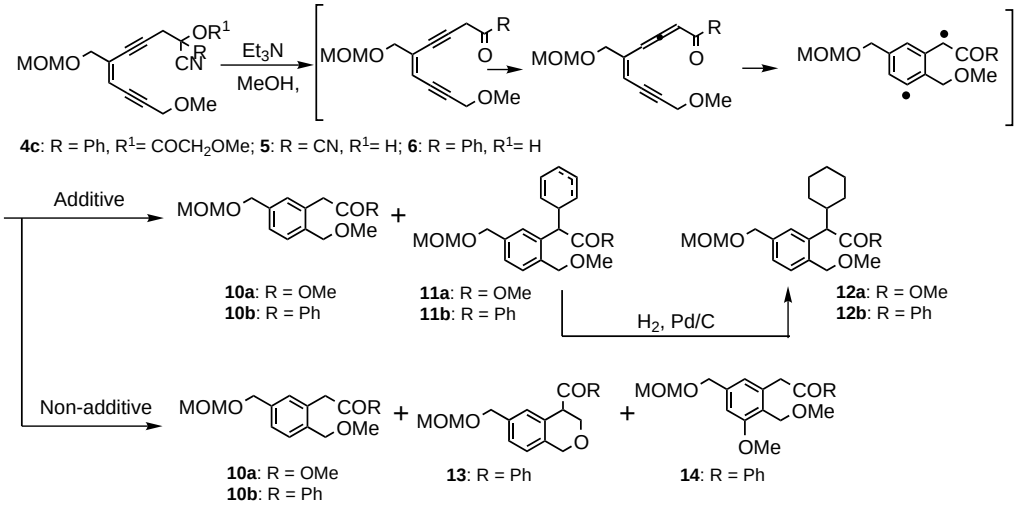
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01529-0



Scheme 2. *Reagents and conditions*: (i) $Pd(PPh_3)_4$, CuI, DIEA, $MeOCH_2C{\equiv}CH$/DMF, 0°C, 65%; (ii) DIBALH/THF, −78°C, 98%; (iii) MOMCl, DIEA/CH_2Cl_2, reflux, 93%; (iv) **7**, $Pd(PPh_3)_4$, CuI, *n*$PrNH_2$/toluene, 60°C, 33%; (v) **8**, $Pd(PPh_3)_4$, CuI, *n*$PrNH_2$/toluene, 60°C, 34%; (vi) **9**, $Pd(PPh_3)_4$, CuI, Et_2NH/toluene, 60°C, 74%; (vii) *p*-TsOH/MeOH, rt.

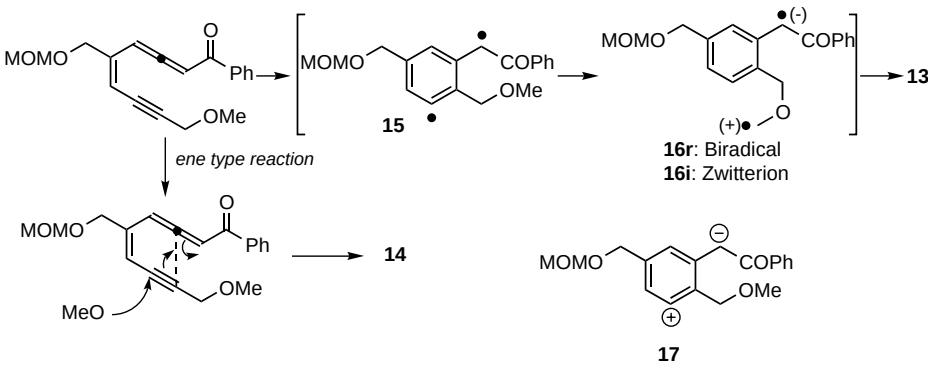
adduct **11** was converted to **12** by catalytic hydrogenation and the structure was confirmed. These results indicate that the base-promoted deprotonation of cyanohydrin gave the allenylketone and the facile cycloaromatization of enyne–allenylketone proceeded via a biradical cyclization pathway. An intermediate corresponding to ketoenediyne and allenylketones could not be detected with TLC or by ^1H NMR during each reaction. No products produced by the ionic reaction between the biradical and solvent MeOH were

Table 1. Results of cycloaromatization reactions of enediyne models **4c**, **5** and **6**



Entry	Enediyne	Time	Additive	Products
1	**5**	1 h	CHD[a]	**10a**, 7%; **11a**, 31%
2	**5**	1 h	–	Complex mixture
3	**6**	<5 min	CHD[a]	**10b**, 36%; **11b**, 31%
4	**6**	<5 min	–	**10b**, 14%; **13**, 12%; 14: 6%
5	**4c**	35 min	CHD[a]	**10b**, 20%; **11b**, 19%

[a] 50 equiv. of 1,4-cyclohexadiene was used.



Scheme 3.

detected. When the enediyne **4c** bearing a protected cyanohydrin moiety was treated with Et_3N in MeOH, removal of the methoxyacetyl group and subsequent cycloaromatization gave a similar result to the reaction of **6**. While the cycloaromatization of **5** gave a complex mixture, **6** afforded **10**, **13** and **14** in the absence of a hydrogen donor.

The formation of **13** and **14** should be explained as shown in Scheme 3. The biradical **16r** formed via 1,5-hydrogen shift of **15** is assumed to have the stable zwitterionic mesomer **16i**.[6] Both biradical **16r** and zwitterion **16i** can give **13** by recombination or ionic cyclization. Mechanistically, the formation of **14** can be rationalized by considering the participation of solvent MeOH in the course of the reaction, but it is also possible that zwitterionic mesomer **17** participates in the reaction, and this should not be ignored.

DNA strand cleavage by the synthetic enediyne **4c** was estimated on agarose gels by conversion of covalently closed circular DNA (Form I) to open circular DNA (Form II) and the results were summarized in Table 2. In a basic buffer solution, **4c** showed potent DNA-cleaving abilities, as was expected. This result is consistent with the base-promoted deprotection–cycloaromatization reaction mechanisms mentioned above.

In summary, we developed enediyne model compounds which cycloaromatize by a base-promoted triggering mechanism via a biradical pathway. Studies for development of compounds having a biologically removable protecting group on a cyanohydrin moiety is now on going.

Table 2. pH dependence of DNA cleavage by enediyne **4c**

Entry	pH	DNA cleavage (%)[a]
1	5	11±3
2	6	15±4
3	7	32±1
4	8	49±3
5	9	46±4

[a] Col E1 DNA (12.5 μg/ml) was incubated for 12 h at 37°C with enediyne **4c** (1 mM) in pH 5, 6, 7, 8 and 9 phosphate buffers, and analyzed by electropholysis (1% agarose gel, ethidium bromide staining). Results presented are mean value+SD of three runs. A Control reaction mixture without the addition of any drug was incubated and the mean value of three runs was used as the background to be subtracted from the obtained values.

Acknowledgements

This work was supported by a research grant from Faculty of Pharmaceutical Sciences, The University of Tokushima and Grant-in-Aid for Scientific Research (No. 13771334) from the Ministry of Education, Sports and Culture, Japan.

References

1. (a) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett*. **1989**, *30*, 4995–4998; (b) Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5881–5888; (c) Maeda, H.; Edo, K.; Ishida, N. *Neocarzinostatin, The Past, Present, and Future of an Anticancer Drug*; Springer: Tokyo, 1997.
2. (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc*. **1989**, *111*, 8057–8059; (b) Saito, I.; Nagata, R.; Yamanaka, H.; Murahashi, E. *Tetrahedron Lett*. **1990**, *31*, 2907–2910; (c) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc*. **1992**, *114*, 9369–9386; (d) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc*. **1993**, *115*, 12611–12612; (e) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc*. **1994**, *116*, 7378–7392.
3. (a) Sugiyama, H.; Yamashita, K.; Fujiwara, T.; Saito, I. *Tetrahedron* **1994**, *50*, 1311–1325; (b) Myers, A. G.; Stephen, P. A.; Robert, W. L. *J. Am. Chem. Soc*. **1996**, *118*, 4725–4726; (c) Suzuki, I.; Shigenaga, A.; Nemoto, H.; Shibuya, M. *Heterocycles* **2001**, *54*, 571–576.
4. (a) Suzuki, I.; Wakayama, M.; Shigenaga, A.; Nemoto, H.; Shibuya, M. *Tetrahedron Lett*. **2000**, *41*, 10019–10023; (b) Brückner, R.; Suffert, J. *Synlett* **1999**, 657–679.
5. Myers, A. G.; Alauddin, M. M.; Fuhry, A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett*. **1989**, *30*, 6997–7000.
6. (a) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl*. **1972**, *11*, 92–111; (b) Smart, R. P.; Peelen, T. J.; Blankespoor, R. L.; Ward, D. L. *J. Am. Chem. Soc*. **1995**, *119*, 461–465.