Pergamon

Tetrahedron Letters, Vol. 37, No. 14, pp. 2433-2436, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00311-5

Synthesis of 10-Membered Masked Oxaenediyne Analogue of Kedarcidin-chr. and C-1027-chr., and Its DNA Cleaving Activity

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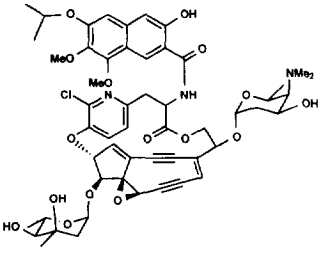
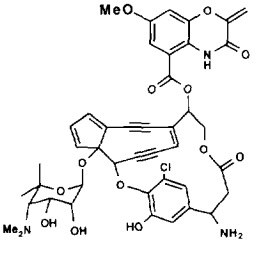
Abstract: Synthesis of the 10-membered masked oxaenediyne analogue and its DNA cleaving activity are described.

Kedarcidin (KD)[1] and C-1027[2] are a new class of highly potent antitumor chromoproteins whose biological activities stem from DNA cleaving ability of their labile chromophores (KD-chr. (**1**) and C-1027-chr. (**2**)) via biradical intermediates. Unlike other member of enediyne class of compounds, C-1027-chr. shows predominant DNA cleaving activity even in the absence of activator such as thiol, which indicates valuable implication for its application as potent cancer chemotherapeutic agents.[3] The biological activity and highly strained unique structures have stimulated a great deal of interest in the synthesis of the core structures as well as analogues of enediynes.[4,5] We have already reported a facile approach to 9-membered enediynes as the analogues of KD-chr.[6] and neocarzinostatin-chr.[7] via a transanular [2,3]-Wittig rearrangement. In this communication, we report the design and synthesis of 10-membered ether analogue[8] **8** which shows DNA cleaving activity without addition of the activator.



Kedarcidin-chr.(**1**)



C-1027-chr.(**2**)

Figure 1

The 10-membered oxadiyne analogue **7** and the 9-membered oxadiyne **4** were designed as masked enediynes for KD-chr. analogues **6** and **3**, respectively. The 1,5-diyne system in the masked enediynes **7** and **4** would be stable enough to allow their isolation and handling at ambient temperature. Elimination of the phthalic

acids at C(4) in **4** and **7** in weak basic buffer would lead to the reactive enediynes **3** and **6**, respectively which would take place spontaneous Bergman cyclization at room temperature to give benzonoid biradicals. This expectation was strongly supported by PM3 calculation[9] of **3** and **6** (Distances between a and b in **3** and **6** are calculated to be 2.86 and 3.20 Å, respectively).[10] Our synthetic plan for the 10-membered oxadiyne **7** involves intramolecular O-alkylation of the corresponding bromo alcohol **14**. The highly strained 9-membered diyne **4** would be constructed by using [2,3]- (path a) and/or [1,2]-Wittig (path b) rearrangements of the 10-membered ether **7**. In this ring contraction strategy,[6,7,11] both [1,2]- and [2,3]-Wittig rearrangements provide the same 9-membered diyne **4**. Hydroxyl groups at C(8), C(11), C(13) and C(14) could be used to introduce macrocycles in **1** and/or **2** at later stage of this program. In order to investigate the feasibility of the [1,2]- or [2,3]-Wittig approach and phthalic acid triggering system, the simplified diynes **5** and **8** were chosen as the initial targets.

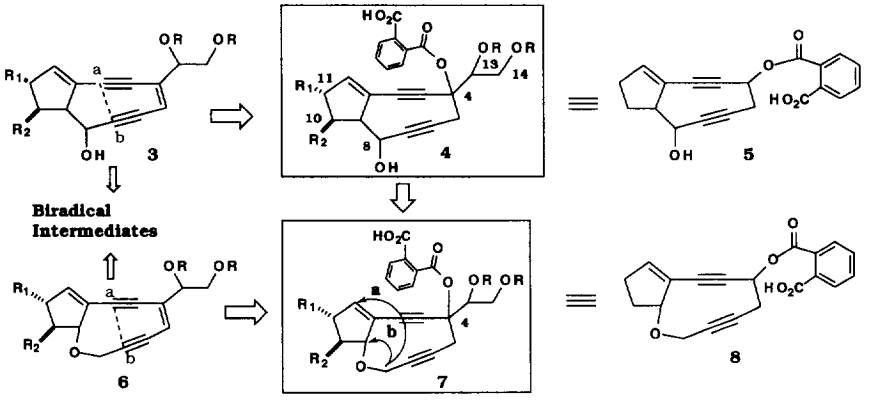


Figure 2

Synthesis of the 10-membered ether **15** was carried out as shown in Figure 3. Ether **15** served as a common precursor for the 10- and 9-membered diynes **5** and **8**. The reduction of enone **9** with $NaBH_4$ and $CeCl_3$ gave 60% yield of the alcohol, which was protected as silyl ether **10** (TBSCl, Imidazole, 95%). The palladium mediated coupling[12] of **10** with propargyl alcohol in benzene at room temperature afforded the alcohol in 54% yield. In the presence of Cu(I), substantial amount of the bisacetylene was obtained in this coupling reaction. Oxidation of the resulting alcohol with MnO_2 in hexane gave aldehyde **11** in 81% yield. Addition of propargylmagnesium bromide to **11**, followed by protection of the resulting alcohol with ethyl vinyl ether gave **12** in 92% yield. Treatment of **12** with ethyl magnesium bromide in THF, followed by addition of paraformaldehyde at 0 °C led to the formation of **13** in 84% yield. Removal of the silyl group with TBAF in THF (81%) and selective bromination of the primary alcohol with CBr_4, PPh_3 in CH_3CN gave bromo alcohol **14** in 95% yield. Then, the intramolecular O-akylation of **14** was examined.[13] Addition of **14** to a dilute solution (0.01 mmol/mL) of NaH in 10% HMPA/THF in the presence of a catalytic amount of water for 24 h at 40 °C gave the 10-membered ether **15** in 64% yield.

With the cyclic ether **15** in hand, **15** was subjected to Wittig rearrangement with various bases. However, no rearranged product **16** was obtained. Next we focused on the synthesis of the 10-membered diyne **8**. Hydrolysis of **15** and treatment of the resulting alcohol with phthalic anhydride in the presence of DMAP gave the desired diyne **8**[14] in 70% yield.

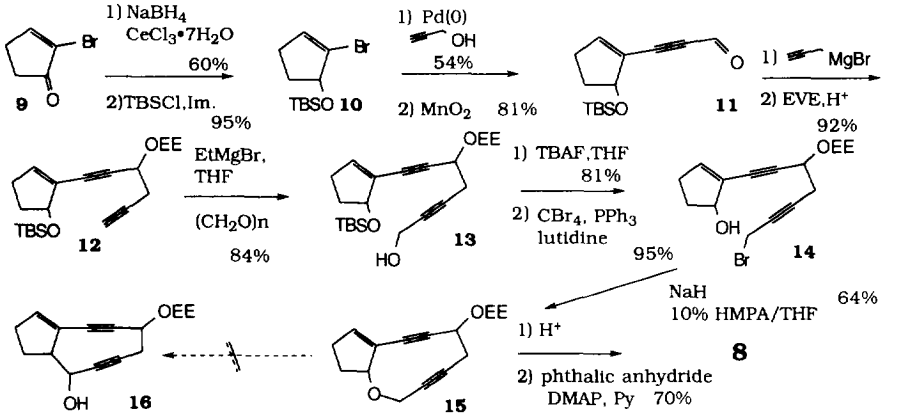


Figure 3

Then, cycloaromatization of the 10-membered diyne **17** and the DNA cleaving activity of **8** were examined. Hydrolysis of **15** (PPTS / MeOH), mesylation of the resulting alcohol (MsCl / Py.) and a base treatment (DBU / THF) of the 10-membered diyne at room temperature for 24 h gave the aromatized product **18**[15] possibly through Bergman cycloaromatization of the 10-membered oxaenediyne (Figure 4). When supercoiled pBR322 plasmid DNA was incubated with **8** at 1 mM concentration in 10% MeOH/20 mM Tris-HCl buffer (pH 7.5) at 37 °C for 15 h in the absence of the activator, the single strand DNA cleavage with the formation of Form II DNA was observed[16] (Table 1).

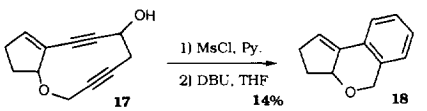


Figure 4

	Amount of DNA (%)		
	Form I	**Form II**	**Form III**
Intact	**93.3**	**6.7**	**0**
1 mM	**29.7**	**68.7**	**1.6**

Table 1. DNA cleaving activity of **8** :
The electrophoresis was performed by using a 1% agarose gel containing ethidium bromide (0.5 m%/mL) in TBE buffer. The change of DNA form was quantitatively estimated by densitometer.

In summary, we have succeeded in design and synthesis of the 10-membered masked oxaenediyne analogue possessing DNA cleaving activity. While Wittig rearrangement approach to a 9-membered enediyne failed, a concise synthesis of the 10-membered analogue should allow access to a wide variety of analogues for biological evaluation. At this stage, detail of the mechanism of DNA cleavage of **8** is not clear, further study to elucidate the precise mechanism of the DNA cleavage is currently under investigation in our laboratory.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research on Priority Area No. 06240104 from the Ministry of Education, Science and Culture, Japan.

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13. Intramolecular O-alkylation of the bromoalcohol having sp2 carbons at C(4) and C(5) gave only dimer in 40% yield.
14. Spectral data **8**: IR (KBr) 3474, 2918, 2848, 1642, 1631, 1401, 1259, 1071 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.81-7.54 (m, 4H), 6.17-6.16 (m, 1H), 5.92-5.85 (m, 1H), 4.64-4.61 (m, 1H), 4.34-4.27 (m, 1H), 4.20-4.11 (m, 1H), 3.07-2.27 (m, 5H), 1.85-1.77 (m, 1H).
15. Spectral data **18**: IR (neat) 2930, 2842, 1341, 1252, 1091, 1033, 832, 794, 756, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54-7.23 (m, 1H), 7.23-7.18 (m, 2H), 7.04-7.27 (m, 1H), 6.15 (dd, 1H, *J*= 3.2, 1.8 Hz), 4.99 (d, 1H, *J*= 15.1 Hz), 4.85 (d, 1H, *J*= 15.1 Hz), 4.74 (ddd, 1H, *J*= 8.3, 4.6, 1.8 Hz), 2.60-2.43 (m, 3H), 1.89-1.81 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 134.1, 129.4, 127.5, 126.9, 124.5, 124.2, 122.7, 83.0, 69.1, 31.3, 30.2.
16. When methyl hydrogen phthalate was incubated with supercoiled pBR322 plasmid DNA, no DNA cleavage was observed.

(*Received in Japan* 18 *December* 1995; *revised* 2 *February* 1996; *accepted* 15 *February* 1996)