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Synthesis and Biological Evaluation of Novel Cyclic Enediyne Compounds Related to Dynemicin A as Antitumor Agents

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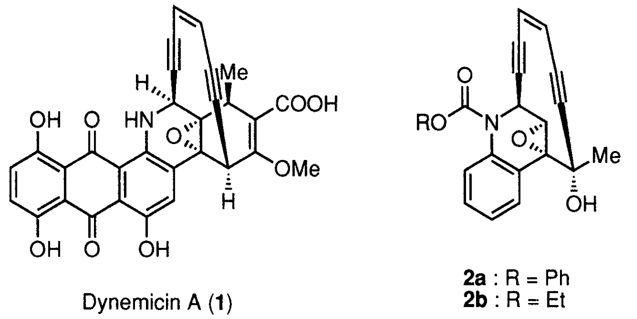
Novel cyclic enediyne compounds, which are simple functional analogs of dynemicin A (1) having the bicyclo-[7.3.1]tridec-4-ene-2,6-diyne system, were synthesized and evaluated for the DNA-cleaving ability, *in vitro* cytotoxicity and *in vivo* antitumor activity. All of the sulfones 19—24, which were equipped with a 2-(arylsulfonyl)-ethoxycarbonyl group or the 2-(methylsulfonyl)ethoxycarbonyl group as a triggering device, showed both potent DNA- cleaving activity and cytotoxicity against various tumor cell lines. However, these compounds were entirely inactive or only slightly active against murine P388 leukemia in mice. On the other hand, the enediyne 2a having a phenyl carbamate moiety as a stable N-protecting group showed effective antitumor activity both *in vitro* and *in vivo*. In particular, it exhibited significant antitumor activity against Lewis lung carcinoma in mice. These results show that the character of the carbamate moiety of the cyclic enediynes strikingly affects their biological activities, that is, the sulfonylethyl carbamate moiety is an effective triggering device for both DNA-cleaving activity and cytotoxicity, and the phenyl carbamate moiety is significant for antitumor activity *in vivo*. As part of a mechanistic study, the reactivities of 2a and 21 were examined under a weakly basic condition (pH 9.3); both compounds failed to give the Bergman cycloaromatization product.

Key words cyclic enediyne; DNA cleavage; cytotoxicity; antitumor activity; bicyclo[7.3.1]tridec-4-ene-2,6-diyne

In recent years, the molecular mode of action and syntheses of cyclic enediynes, a new class of potent antitumor antibiotics, have been reported.1) Members of this family include the neocarzinostatin chromophore,2) calicheamicins,3) esperamicins,4) dynemicin A (**1**, Fig. 1),5) kedarcidin chromophore,6) C-1027 chromophore7) and maduropeptin chromophore.8) Dynemicin A (**1**), having a novel 10-membered cyclic enediyne moiety, shows potent cytotoxicity, *in vivo* antitumor activity and DNA-cleaving ability. Dynemicin A (**1**) is unique in combining the enediyne unit with the anthraquinone chromophore of anthracycline antibiotics such as daunomycin.9) The mechanism of DNA cleavage by dynemicin A (**1**) was proposed to be as follows (Fig. 2)10): (i) intercalation of the anthraquinone moiety into double-stranded DNA, (ii) bioreduction of the quinone subunit in **1** to hydroquinone (**1a**), (iii) epoxide opening to form a conjugated imine (**1a**→**1b**), (iv) nucleophilic attack of water or protonation to form an sp^3 carbon which increases the strain in the system (**1b**→**1c**), (v) Bergman cycloaromatization11) to generate the phenylene diradical (**1c**→**1d**), (vi) abstraction of hydrogen atoms from the sugar phosphate backbone of DNA (**1d**→**1e**) and (vii) cleavage of the DNA chain. The anthraquinone moiety plays an important role during coordination with DNA, and the quinone reduction–epoxide ring opening is a device which triggers Bergman cycloaromatization. The enediyne ring is necessary for generation of the phenylene diradical by Bergman cycloaromatization, while existence of the epoxide ring prohibits Bergman cycloaromatization. These mechanistic studies led to total syntheses of di- and tri-*O*-methyl dynemicin A methyl esters by Schreiber *et al.*12) and dynemicin A (**1**) by the groups of Myers13) and Danishefsky.14,15) Partial molecules of dynemicin A, however, might have potential utility in the sense that the bicyclo[7.3.1]tridecene-diyne ring system could show antitumor activity. We herein describe our search for active compounds having a bicyclo[7.3.1]tridecene-diyne ring system.

Recently, other groups have reported syntheses of simple functional analogs of **1**.16—19) Nicolaou *et al.* reported that dynemicin A analogs equipped with a 2-(phenylsulfonyl)ethoxycarbonyl group as a triggering device showed DNA-cleaving activity and potent cytotoxicity against various cell lines.17e) However, *in vivo* data for their compounds have not yet been reported. Previously, we reported the design of novel cyclic enediynes **2**, simple functional analogs of dynemicin A (**1**) having the bicyclo-[7.3.1]tridec-4-ene-2,6-diyne system, and their synthesis from lepidine in 10 steps.20) These compounds **2**, which could be cycloaromatized to the Bergman product *via* pinacol rearrangement under acidic conditions, also exhibited DNA-cleaving activity.20e) In view of the importance of a triggering device for antitumor activity, we planned to introduce various carbamate moieties, which could be removed under physiological conditions, onto the bicyclo[7.3.1]tridec-4-ene-2,6-diyne system.

In this report, we describe the synthesis of novel



Dynemicin A (**1**)

2a : R = Ph
2b : R = Et

Fig. 1. Structures of Dynemicin A (**1**) and Simple Cyclic Enediynes (**2**)

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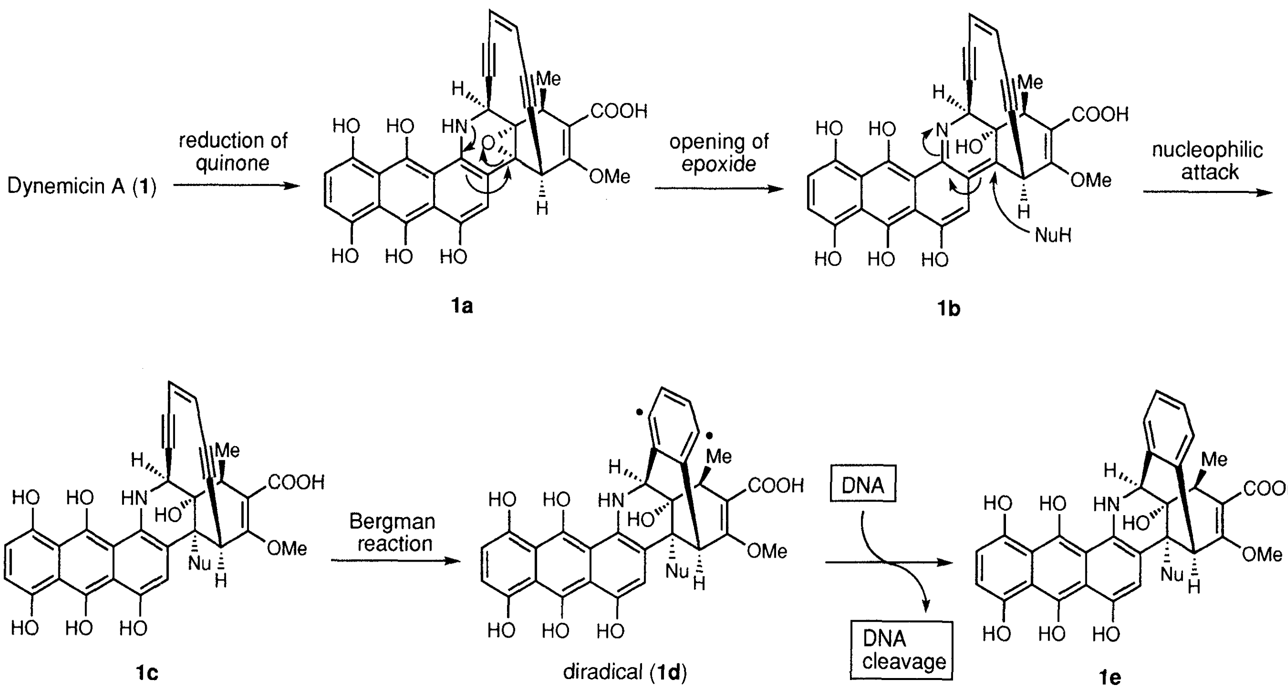
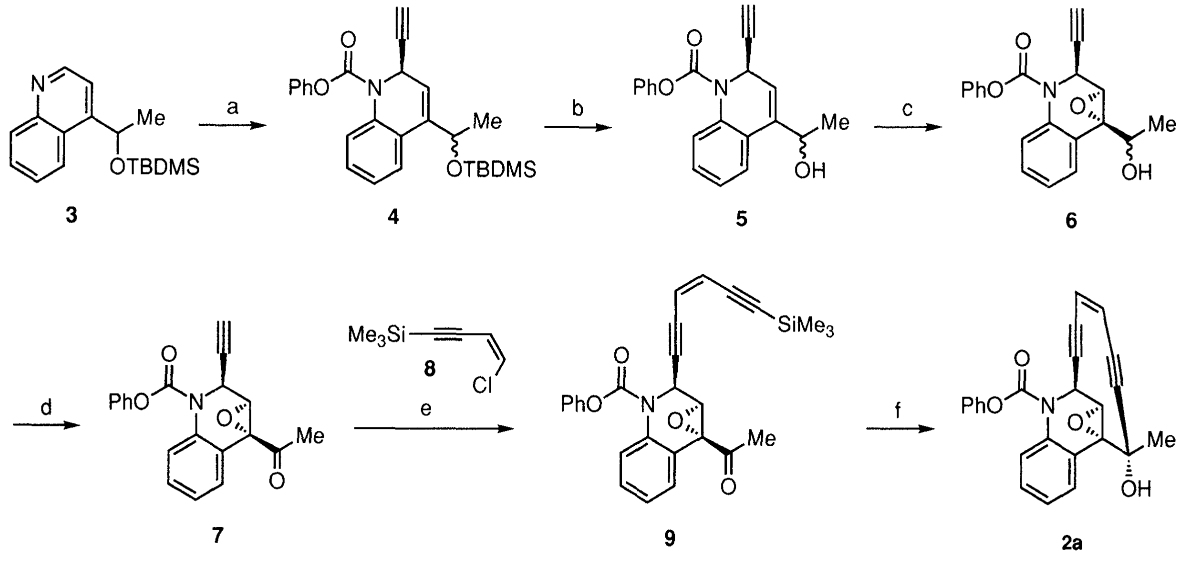


Fig. 2. Proposed Action Mechanism of Dynemicin A (1)



(a) ethynylmagnesium bromide, PhOCOCl/THF, quant. ; (b) *p*TsOH•H_2O /MeOH, 90%;
(c) *m*CPBA, Na_2HPO_4/ CH_2Cl_2, 99%; (d) SO_3•Py , Et_3N/DMSO-CH_2Cl_2, 87%;
(e) $Pd_2(dba)_3$•$CHCl_3$, Ph_3P, CuI , *n*-$BuNH_2$/benzene, 64%; (f) CsF, 18-crown-6/THF, 18%.

Chart 1

enediynes equipped with various triggering devices and the evaluation for their DNA-cleaving activity, *in vitro* cytotoxicity and *in vivo* antitumor activity. Furthermore, we report on the reactivities of these compounds under weakly basic conditions.

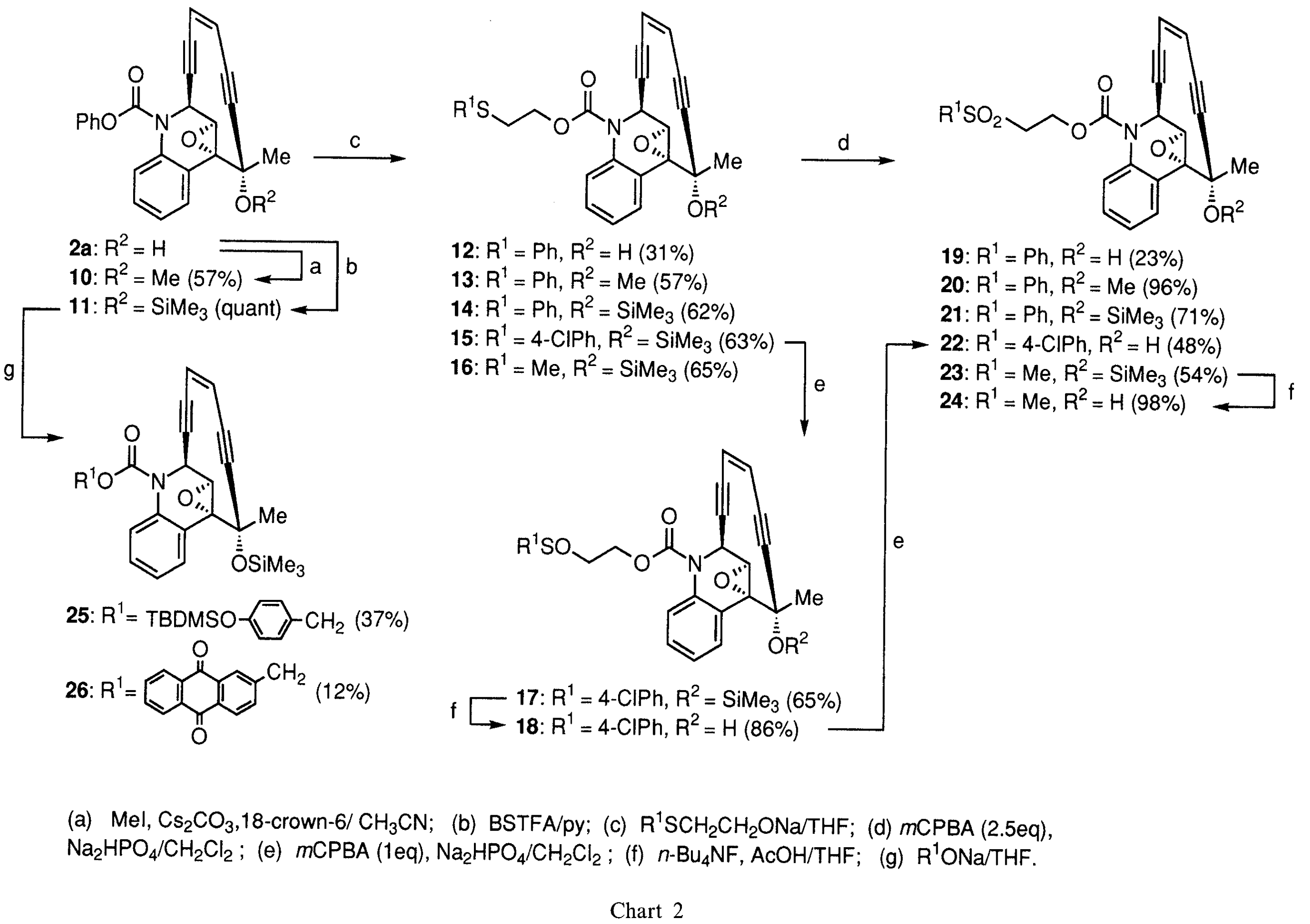
Chemistry

The enediyne **2a**$^{20e)}$ was selected as a key compound for the syntheses of analogs having different triggering devices, and it was synthesized as shown in Chart 1. The key step in the synthesis of **2a** is formation of the highly strained 10-membered ring. Various methods have been reported for the construction of the cyclic enediyne ring system.$^{21)}$ We have previously established a useful cyclization method by coupling between trimethylsilylacetylene and a carbonyl group in the presence of CsF and 18-crown-6.$^{20d)}$ This CsF-promoted cyclization avoids the desilylation step and the use of strong base required in the acetylide coupling method developed by Kende and Smith$^{22)}$ and Danishefsky *et al.*,$^{23)}$ independently. The synthesis commenced from the reaction among three components, the silyl ether **3**, ethynylmagnesium bromide and phenyl chloroformate, to provide **4** in a quantitative yield as a 2 : 1 mixture of isomers. Desilylation of the *tert*-butyldimethylsilyl (TBDMS) group in **4** under acidic conditions (*p*TsOH/MeOH) afforded the allyl alcohol **5** in 90% yield. Face-selective epoxidation of **5** with *m*-chloroperoxybenzoic acid (*m*CPBA) gave the epoxy alcohol **6** in 99% yield, and **6** was converted to the epoxy ketone **7** by oxidation with $SO_3 \cdot$Py–DMSO in 87% yield as a single isomer. Coupling of **7** with the vinyl chloride **8**[22)] under Pd(0)–Cu(I) catalysis[24)] gave the acyclic enediyne ketone **9** in 64% yield. Finally, the cyclic enediyne **2a** could be obtained from **9** with CsF in the presence of 18-crown-6 in 18% yield.[20d)]

The 2-(phenylsulfonyl)ethyl group can be smoothly removed under nearly neutral conditions, and has been used as a protecting group in the syntheses of natural products[25)] as well as for the same deprotection of the enediyne by Nicolaou *et al.*[17c)] 2-(Arylsulfonyl)ethyl or 2-(methylsulfonyl)ethyl carbamate moieties[26)] were then introduced as triggering devices onto the bicyclo[7.3.1]-tridec-4-ene-2,6-diyne system (Chart 2). First, the *tert*-alcohol group of **2a** was protected with a methyl group or trimethylsilyl (TMS) group, because it was unstable under basic conditions. Methylation of **2a** using Cs_2CO_3/18-crown-6 and excess MeI in acetonitrile[17c)] afforded **10** in 57% yield. Silylation of compound **2a** using excess bis(trimethylsilyl)trifluoroacetamide (BSTFA) in pyridine afforded **11** in a quantitative yield. Compounds **2a**, **10** and **11** were reacted with $R^1SCH_2CH_2ONa$ in tetrahydrofuran (THF)[17c)] to furnish the sulfides **12**—**16**, respectively. Each of these sulfides **12**—**14** and **16** was then converted to the corresponding sulfones **19**—**21** and **23** by treatment with excess *m*CPBA. The sulfide **15** was converted in a stepwise fashion to the sulfone **22** *via* the sulfoxide **17** by treatment with a stoichiometric amount of *m*CPBA.[17c)] Desilylation of the TMS group in **17** and **23** under neutral conditions (*n*-Bu_4NF, AcOH/THF) afforded the alcohols **18** and **24** in good yield.

Two types of enediyne compounds **25** and **26**, which were equipped with the 4-(*tert*-butyldimethylsilyloxy)-benzyl group or the anthraquinone-2-methyl group[27)] as a triggering device, were designed and synthesized (Chart 2). Compound **25** was designed to include the 4-(*tert*-butyldimethylsilyloxy)benzyl carbamate moiety that could be removed under mild chemical or physiological conditions. Compound **26** involved the anthraquinone-2-methyl carbamate[28)] moiety that, in principle, could be intercalated with DNA and be removed by bioreduction in the same manner as in the case of dynemicin A (**1**). These compounds **25** and **26** were synthesized from **11** by treatment with sodium alkoxide.

In our recent report on DNA cleavage, the enediyne **2a** showed cycloaromatization to give the Bergman product *via* pinacol rearrangement under acidic conditions.[20d)] We became interested in whether the enediynes **2a** and **21** could be cycloaromatized to a Bergman product under weakly basic or physiological conditions. The reactivity of these compounds was monitored by ^{1}H-NMR in DMSO-d_6 and 100 mM phosphate buffer in D_2O (7 : 3 v/v, final pH = 9.3) at 37 °C. As shown in Chart 3 and Fig. 3, the enediyne **2a** remained intact after 33 h, whereas the sulfone **21** with a half-life of about 4 h generated the labile free amine **27**; however, this amine failed to give the Bergman cycloaromatization product. An authentic sample of **27** was



(a) MeI, Cs_2CO_3,18-crown-6/ CH_3CN; (b) BSTFA/py; (c) $R^1SCH_2CH_2ONa$/THF; (d) *m*CPBA (2.5eq), Na_2HPO_4/CH_2Cl_2 ; (e) *m*CPBA (1eq), Na_2HPO_4/CH_2Cl_2 ; (f) *n*-Bu_4NF, AcOH/THF; (g) R^1ONa/THF.

Chart 2

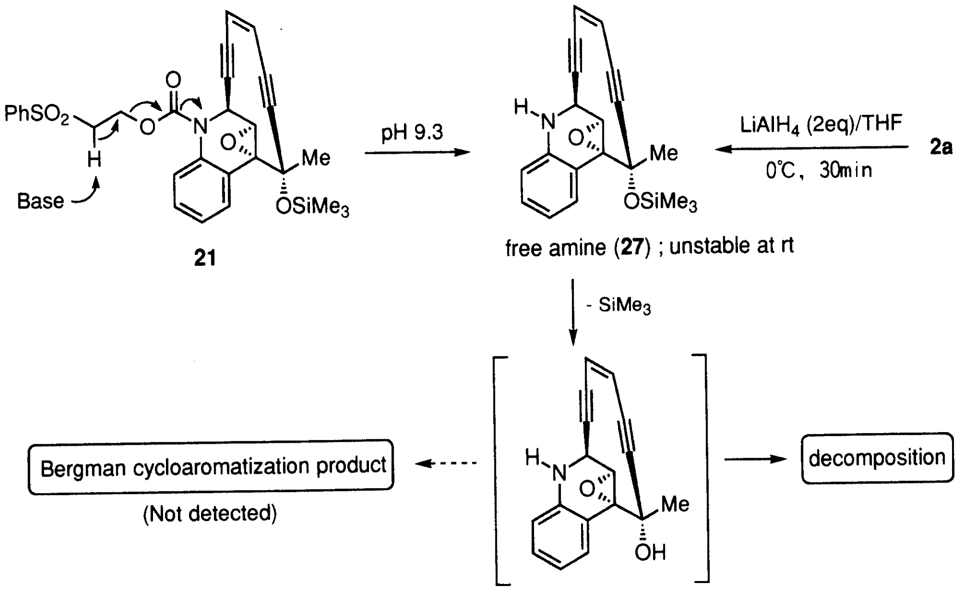


Chart 3

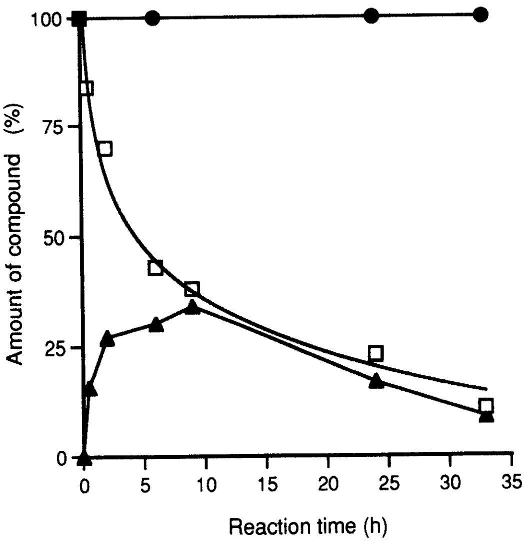


Fig. 3. Reaction of Each of Compounds **2a** and **21** in DMSO-d_6 and 100 mM Phosphate Buffer in D_2O (7 : 3 v/v, Final pH 9.3, Concentration 2 mM) at 37 °C as Monitored by ^{1}H-NMR

●, compound **2a**; □, compound **21**; ▲, free amine **27**.

prepared from **2a** by reduction with $LiAlH_4$,[17a)] and the product could not be isolated due to its instability. The structure of **27** was characterized by ^{1}H-NMR spectroscopy and mass spectroscopy in the reaction mixture.

Biological Results and Discussion

DNA Cleavage The DNA-cleaving activity of enediyne compounds was tested with supercoiled DNA as shown in Fig. 4.[29)] The ΦX174 supercoiled DNA (two different lots were used in **a** and **b**, respectively) was employed as the substrate and incubated with each enediyne compound in pH 7.4 buffer solution. Cleavage of DNA was monitored using agarose gel electrophoresis. As expected,[17e)] the sulfones **19**—**24**, which were equipped with a 2-(arylsulfonyl)ethoxycarbonyl group or the 2-(methylsulfonyl)ethoxycarbonyl group as a triggering device, exhibited noticeable DNA-cleaving activities. This efficacy may be due to the labile free amine **27**, which was slowly generated by decomposition of the sulfones as shown in Chart 3.[17e)] On the other hand, none of compounds **13**, **14**, **16**—**18** having the stable N-protecting groups showed any DNA-cleaving activity. The methoxy compound **10** also showed no activity. The 4-(*tert*-butyldimethylsilyloxy)benzyl carbamate **25** showed slight DNA-cleaving activity, whereas anthraquinone-2-methyl carbamate **26** did not show any activity. These results indicate that the difference in activities of the sulfones **19**—**21** and other enediynes was probably due to the chemical stability of their carbamate moieties. This suggests that the free amine **27** plays an important role in the DNA-cleaving activity of the enediynes.

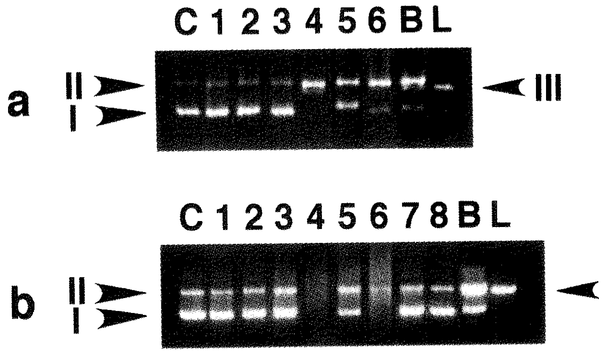
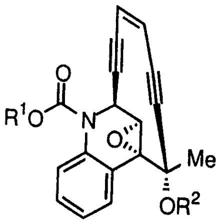


Fig. 4. Supercoiled DNA Cleavage by Enediyne Compounds

The ΦX174 supercoiled DNA (250 μM/base pair; two different lots were used in **a** and **b**, respectively) was incubated with 1 mM (final concentration) of each enediyne compound in a buffer solution (50 mM phosphate buffer, pH 7.4) at 37 °C for 18 h and analyzed by agarose gel electrophoresis to separate the various forms of DNA. The DNA bands were visualized with ethidium bromide binding and UV illumination. C, DNA control; B, bleomycin (5 μM) and $FeCl_3$ (25 μM); L, Φ174 supercoiled DNA/Pst I endonuclease. (**a**) lane 1, **10**; lane 2, **13**; lane 3, **14**; lane 4, **19**; lane 5, **20**; lane 6, **21**. (**b**) lane 1, **16**; lane 2, **17**; lane 3, **18**; lane 4, **22**; lane 5, **23**; lane 6, **24**; lane 7, **25**; lane 8, **26**. Key: I, supercoiled DNA; II, nicked DNA; III, linear DNA.

***In Vitro* Cytotoxicity** The *in vitro* cytotoxicity of these compounds against the human carcinoma KB cell line is shown in Table 1. All of the sulfones **19**—**24** showed

Table 1. Cytotoxicity and *in Vivo* Antitumor Activity of Cyclic Enediyne Compounds



Compd. No.	R^1	R^2	IC_{50} (μM)	*T*/*C* (%)
			KB[a]	P388 (i.p.–i.p.)[b]
2a	Ph	H	5.0	165
2b	Et	H	>10	NT
10	Ph	Me	>10	135
13	$PhSCH_2CH_2$	Me	>10	101
14	$PhSCH_2CH_2$	$SiMe_3$	9.7	96
16	$MeSCH_2CH_2$	$SiMe_3$	>10	106
17	4-$ClPhSOCH_2CH_2$	$SiMe_3$	8.8	111
18	4-$ClPhSOCH_2CH_2$	H	2.8	115
19	$PhSO_2CH_2CH_2$	H	0.44	108[c]
20	$PhSO_2CH_2CH_2$	Me	0.79	94[c]
21	$PhSO_2CH_2CH_2$	$SiMe_3$	0.17	97
22	4-$ClPhSO_2CH_2CH_2$	H	0.52	139
23	$MeSO_2CH_2CH_2$	$SiMe_3$	0.24	101
24	$MeSO_2CH_2CH_2$	H	0.10	120
25	4-TBDMSOPhCH_2	$SiMe_3$	4.3	120
26	Anthraquinone-2-methyl	$SiMe_3$	>10	111

a) Human epidermoid carcinoma KB cell line. *b*) CDF_1 mice were inoculated intraperitoneally (i.p.) with 1×10^6 cells/mouse of P388 on day 0, and 2 mg/kg of test compound was administered i.p. once daily for 4 d from day 1 to 4. *c*) A 10 mg/kg dose of test compound was administered i.p. once on day 1. NT: not tested.

significantly higher *in vitro* cytotoxicity than compound **2a**. The sulfone **24** having the 2-(methylsulfonyl)ethyl carbamate moiety showed the most potent activity (IC_{50} = 0.10 μM). The sulfoxide **18** was less active than the corresponding sulfone **22**. Compounds **2b**, **13**, **14** and **16**, with stable N-protecting groups, were all almost inactive. The 4-(*tert*-butyldimethylsilyloxy)benzyl carbamate **25** was slightly effective, whereas anthraquinone-2-methyl carbamate **26** was ineffective. The methoxy compounds **10** and **20** showed lower *in vitro* potency than the corresponding hydroxy compounds **2a** and **19**. This result suggests that the propargylic substituents significantly affect the biological activity of the cyclic enediynes. Moreover, the cytotoxic activities of compounds **2a** and **19**—**21** were examined against other tumor cell lines and the results are shown in Table 2. The sulfone **21** was the most potent compound and its IC_{50} values were 30, 52, 66, and 57 nM against MOLT-4, L1210, P388 and the doxorubicin-resistant P388 subline, respectively. The hydroxy compound **19** showed about the same activity as **21**, whereas the methoxy compound **20** was 3—6 times less active than the corresponding alcohol **19**, and **2a** was 160—260 times less active than **21**. These results indicate that the *in vitro* cytotoxicities of our enediyne compounds, as well as Nicolaou's analogs,[17e] can be significantly increased by utilizing a 2-(arylsulfonyl)ethoxycarbonyl group or the 2-(methylsulfonyl)ethoxycarbonyl group as a triggering device.

Table 2. Cytotoxicity of Enediynes **2a** and **19**—**21** against Several Tumor Cell Lines[a]

Compd. No.	IC_{50} (μM)			
	MOLT-4	L1210	P388	P388/ADM
2a	6.8	8.4	12	15
19	0.041	0.063	0.088	—
20	0.26	0.18	0.58	—
21	0.030	0.052	0.066	0.057

a) Human T cell leukemia MOLT-4, murine leukemia L1210, murine leukemia P388 and doxorubicin-resistant P388 subline (P388/ADM).

Table 3. Antitumor Activity of the Enediyne **2a** against Lewis Lung Carcinoma (s.c.–i.p.)

Compd. No.	Dose (mg/kg/d)	Schedule	Inhibition (%)
2a	1.0	day 1—4	51
	1.5	day 1—4	69
	2.0	day 1—4	70

***In Vivo* Antitumor Activity** These compounds were evaluated for antitumor activity in mice inoculated intraperitoneally (i.p.) with murine P388 leukemia, and the results are shown in Table 1. A $T/C \geqq 125\%$ was taken as the criterion of activity. Although high *in vitro* potency was observed, all the sulfones **19**—**24** exhibited little or no activity *in vivo*. This might indicate that the sulfones were unstable under physiological conditions and did not reach the tumor. Only compound **2a** showed effective antitumor activity ($T/C = 165\%$). Compounds **25** and **26** were also inactive. Although the cytotoxicities of the sulfide **14** and the sulfoxides **17** and **18** were almost the same as that of the enediyne **2a**, these compounds did not show any activity *in vivo*. These results indicate that the phenyl carbamate moiety of **2a** plays an important role in the antitumor activity. This in turn suggests that the diradical formation in **2a** might not be a prerequisite for the antitumor activity, and other mechanisms[17g,19,30] could possibly contribute to the observed *in vitro* and *in vivo* activities. Furthermore, as shown in Table 3, compound **2a** also showed significant activity against Lewis lung carcinoma in mice, causing 51, 69 and 70% inhibition of the tumor growth at dosages of 1.0, 1.5 and 2.0 mg/kg, respectively.

In conclusion, it has been demonstrated that the novel cyclic enediyne compounds, simple functional analogs of dynemicin A (**1**) having the bicyclo[7.3.1]tridec-4-ene-2,6-diyne system, can be effective antitumor agents both *in vitro* and *in vivo*. It is particularly noteworthy that only the enediyne **2a** having a phenyl carbamate moiety, which is a stable N-protecting group, exhibited effective antitumor activity *in vivo*. In contrast, the sulfones **19**—**24** were entirely inactive or slightly active *in vivo*, although these compounds had more potent DNA-cleaving activity and cytotoxicity than the enediyne **2a**. These results show that the character of the carbamate moiety of the cyclic enediynes strikingly affects their biological activities, that is, the sulfonylethyl carbamate moiety is an effective triggering device for both the DNA-cleaving activity and cytotoxicity, and the phenyl carbamate moiety is significant for antitumor activity *in vivo*.

Experimental

Melting points were measured on a Yanaco MP-1 apparatus without correction. Infrared (IR) spectra were recorded on a Jasco FT/IR-8000 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM GSX-270 (270 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are given in ppm, and the following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, m = multiplet, br = broad. Low-resolution mass spectra (MS) and high-resolution mass spectra (HR-MS) were recorded on JEOL JMS-DX300 and JMS-SX1020 spectrometers. Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, Merck). Preparative thin-layer chromatography was carried out by precoated silica gel plates (Art 5774, Merck).

4-(1-*tert*-Butyldimethylsilyloxyethyl)-2-ethynyl-1,2-dihydro-1-phenoxycarbonylquinoline (4) A solution of silyl ether **3** (10.4 g, 36.2 mmol) in dry THF (150 ml) was cooled to −70 °C and treated with ethynylmagnesium bromide (87.0 ml of a 0.5 M solution in THF, 43.5 mmol). The solution was briefly warmed to 0 °C and cooled to −70 °C again. Phenyl chloroformate (6.80 g, 43.5 mmol) was added, and then the reaction mixture was allowed to warm slowly to 22 °C. The mixture was stirred for 1 h, then the reaction was quenched with saturated NH_4Cl solution (20 ml), and the whole was extracted with ethyl acetate (150 ml × 2). The combined organic layers were washed with saturated $NaHCO_3$ solution (40 ml) and brine (100 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica, $Et_2O : CHCl_3 = 2 : 1$) to give **4** (16.5 g, quantitative, *ca.* 2 : 1 mixture of isomers). IR (KBr) cm^{-1}: 2120 (C≡C), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: [Major product] 0.10 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.48 (3H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 2.22 (1H, d, J = 2.4 Hz, C≡CH), 4.73 (1H, q, J = 6.4 Hz, $CH_3C\underline{H}$), 5.95 (1H, dd, J = 6.8, 2.4 Hz, CHC≡C), 6.04 (1H, d, J = 6.8Hz, olefinic), 7.15—7.80 (9H, m, aromatic). [Minor product] 0.11 (6H, s, $Si(CH_3)_2$), 0.95 (9H, s, $SiC(CH_3)_3$), 1.35 (3H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 2.22 (1H, d, J = 2.4 Hz, C≡CH), 5.01 (1H, dq, J = 6.4, 1.4 Hz, $CH_3C\underline{H}$), 5.95 (1H, dd, J = 6.8, 2.4 Hz, CHC≡C), 6.04 (1H, dd, J = 6.8, 1.4 Hz, olefinic), 7.15—7.80 (9H, m, aromatic). MS (EI) m/z: 433 (M^+). HR-MS Calcd for $C_{26}H_{31}NO_3Si$ (M^+): 433.2073. Found 433.2080.

2-Ethynyl-1,2-dihydro-4-(1-hydroxyethyl)-1-phenoxycarbonylquinoline (5) A solution of silyl ether **4** (16.5 g, 36.2 mmol) in MeOH (200 ml) was treated with pTsOH·H_2O (3.44 g, 18.1 mmol). The mixture was stirred at 22 °C for 5 h, then treated with pyridine (1.43 g, 18.1 mmol), and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (200 ml) and the solution was washed with water (100 ml) and brine (50 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica, n-hexane/ether = 1 : 1) to give **5** (10.4 g, 90%, *ca.* 2 : 1 mixture of isomers). IR (KBr) cm^{-1}: 2110 (C≡C), 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: [Major product] 1.57 (3H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 1.74 (1H, d, J = 6.4 Hz, $CHO\underline{H}$), 2.24 (1H, d, J = 2.4 Hz, C≡CH), 4.94 (1H, m, $CH_3C\underline{H}$), 6.01 (1H, dd, J = 6.8, 2.4 Hz, CHC≡C), 6.19 (1H, d, J = 6.8 Hz, olefinic), 7.15—7.84 (9H, m, aromatic). [Minor product] 1.44 (3H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 1.72 (1H, d, J = 6.4 Hz, $CHO\underline{H}$), 2.24 (1H, d, J = 2.4 Hz, C≡CH), 5.06 (1H, m, $CH_3C\underline{H}$), 6.03 (1H, dd, J = 6.8, 2.4 Hz, CHC≡C), 6.28 (1H, dd, J = 6.8, 1.4 Hz, olefinic), 7.15—7.84 (9H, m, aromatic). MS (EI) m/z: 319 (M^+), 275, 242 (base peak). HR-MS Calcd for $C_{20}H_{17}NO_3$ (M^+): 319.1208. Found 319.1219.

3,4-Epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-(1-hydroxyethyl)-1-phenoxycarbonylquinoline (6) A solution of allyl alcohol **5** (10.2 g, 31.9 mmol) and anhydrous Na_2HPO_4 (13.6 g, 95.7 mmol) in CH_2Cl_2 (200 ml) cooled to 0 °C was treated with mCPBA (16.5 g, 47.9 mmol). The mixture was stirred at 0 °C for 2 h, diluted with CH_2Cl_2 (200 ml), washed with aqueous $Na_2S_2O_3$ (100 ml), aqueous $NaHCO_3$ (100 ml) and brine (50 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica, $Et_2O : CHCl_3 = 1 : 1$) to give **6** (11.4 g, 99%, *ca.* 2 : 1 mixture of isomers). IR (KBr) cm^{-1}: 2120 (C≡C), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: [Major product] 1.44 (3H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 1.54 (1H, s, $CHO\underline{H}$), 2.20 (1H, d, J = 2.4 Hz, C≡CH), 4.10 (1H, d, J = 2.4 Hz, epoxide), 4.82 (1H, q, J = 6.4 Hz, $CH_3C\underline{H}$), 5.93 (1H, t, J = 2.4 Hz, CHC≡C), 7.05—7.62 (9H, m, aromatic). [Minor product] 1.54 (3H, d, J = 6.4 Hz, $C\underline{H}_3CH$), 1.92 (1H, d, J = 6.4 Hz, $CHO\underline{H}$), 2.24 (1H, d, J = 2.4 Hz, C≡CH), 4.07 (1H, d, J = 2.4 Hz, epoxide), 4.41 (1H, m, $CH_3C\underline{H}$), 5.89 (1H, t, J = 2.4 Hz, CHC≡C), 7.05—7.62 (8H, m, aromatic), 7.86 (1H, d, J = 7.4 Hz, aromatic). MS (EI) m/z: 335 (M^+, base peak), 242, 198. HR-MS Calcd for $C_{20}H_{17}NO_4$ (M^+): 335.1157. Found 335.1144.

4-Acetyl-3,4-epoxy-2-ethynyl-1,2,3,4-tetrahydro-1-phenoxycarbonylquinoline (7) The epoxy alcohol **6** (10.2 g, 30.7 mmol) was dissolved in dry CH_2Cl_2 (80 ml), dry DMSO (160 ml) and Et_3N (46.6 g, 460 mmol), and the solution was cooled to 0 °C. Then SO_3·Py (48.9 g, 310 mmol) was added portionwise over 30 min. The reaction mixture was stirred at 24 °C for 1.5 h, cooled to 0 °C, poured into 1 N HCl (400 ml), and extracted with EtOAc (700 ml × 2). The combined organic layers were washed with water (700 ml × 2) and brine (100 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica, CH_2Cl_2) to give **7** (8.80 g, 87%). mp 154—155 °C. IR (KBr) cm^{-1}: 2122 (C≡C), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.27 (1H, d, J = 2.4 Hz, C≡CH), 2.29 (3H, s, CH_3CO), 4.04 (1H, d, J = 2.4 Hz, epoxide), 5.99 (1H, br t, J = 2.4 Hz, CHC≡C), 7.11—7.44 (7H, m, aromatic), 7.58 (1H, d, J = 7.4 Hz, aromatic), 7.69 (1H, d, J = 7.4 Hz, aromatic). MS (EI) m/z: 333 (M^+, base peak), 290, 240. HR-MS Calcd for $C_{20}H_{15}NO_4$ (M^+): 333.1001. Found 333.1015.

4-Acetyl-3,4-epoxy-1,2,3,4-tetrahydro-1-phenoxycarbonyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (9) A mixture of (*Z*)-1-chloro-4-trimethylsilyl-1-buten-3-yne (**8**) (7.61 g, 48.0 mmol), $Pd_2(dba)_3$·$CHCl_3$ (310 mg, 0.30 mmol), PPh_3 (315 mg, 1.20 mmol) and CuI (229 mg, 1.20 mmol) in dry, degassed benzene (160 ml) was stirred under argon at 25 °C for 1 h. The resulting dark red solution was cooled to 0 °C, and the epoxy ketone **7** (4.00 g, 12.0 mmol) in dry, degassed benzene (60 ml) was added, followed by n-butylamine (3.51 g, 48.0 mmol). The reaction mixture was stirred at 25 °C for 1.5 h, then the reaction was quenched with saturated NH_4Cl solution (250 ml), and the whole was extracted with EtOAc (250 ml × 2). The combined organic layers were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica, CH_2Cl_2) to give **9** (3.51 g, 64%). IR (KBr) cm^{-1}: 2140 (C≡C), 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.22 (9H, s, $Si(CH_3)_3$), 2.36 (3H, s, CH_3CO), 4.05 (1H, d, J = 2.4 Hz, epoxide), 5.68 (1H, dd, J = 11.2, 1.5 Hz, $C\underline{H}$=CHC≡CSi), 5.83 (1H, d, J = 11.2 Hz, CH=$C\underline{H}$C≡CSi), 6.22 (1H, dd, J = 2.4, 1.5 Hz, CHC≡C), 7.10—7.45 (9H, m, aromatic). MS (EI) m/z: 455 (M^+). HR-MS Calcd for $C_{27}H_{25}NO_4Si$ (M^+): 455.1553. Found 455.1541.

Phenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-9-Hydroxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (2a)** A CsF powder (376 mg, 2.48 mmol) was placed in a dried three-necked flask and heated at 100 °C for 1 h *in vacuo*. It was cooled to room temperature, then dry THF (250 ml) was added. To this suspension were added the enediyne ketone **9** (1.13 g, 2.48 mmol) in dry THF (25 ml) and 18-crown-6 (655 mg, 2.48 mmol) in dry THF (10 ml). The mixture was stirred for 3 h, the reaction was quenched with saturated NH_4Cl solution (200 ml), and the whole was extracted with EtOAc (250 ml × 2). The combined organic layers were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica, $CHCl_3 : Et_2O = 3 : 1$) to give **2a** (175 mg, 18%) as colorless crystals. mp 93—95 °C (dec.). IR (KBr) cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.74 (3H, s, $C(OH)C\underline{H}_3$), 4.07 (1H, d, J = 2.4 Hz, epoxide), 5.66 (1H, dd, J = 11.2, 1.5 Hz, NCHC≡$CC\underline{H}$=CH), 5.82 (1H, d, J = 11.2 Hz, NCHC≡CCH=$C\underline{H}$), 5.89 (1H, dd, J = 2.4, 1.5 Hz, CHC≡C), 7.10—7.70 (8H, m, aromatic), 8.80 (1H, dd, J = 7.8, 1.4 Hz, aromatic). MS (EI) m/z: 383 (M^+, base peak), 340, 146. *Anal.* Calcd for $C_{24}H_{17}NO_4$: C, 75.19; H, 4.47; N, 3.65. Found: C, 75.05; H, 4.66; N, 3.52.

Phenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-9-Methoxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (10)** A mixture of the enediyne **2a** (100 mg, 0.26 mmol), Cs_2CO_3 (168 mg, 51.8 mmol), MeI (367 mg, 15.5 mmol) and 18-crown-6 (41.0 mg, 15.5 mmol) in dry CH_3CN (3 ml) was stirred at 24 °C for 4 h. It was diluted with EtOAc (30 ml), washed with saturated NH_4Cl solution (30 ml), saturated $NaHCO_3$ (30 ml) and brine (30 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica, benzene : EtOAc = 20 : 1) to give **10** (59 mg, 57%) as a colorless amorphous powder, with recovery of 26 mg (26%) of **2a**. IR (KBr) cm^{-1}: 1722 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s, CCH_3), 3.50 (3H, s, CH_3O), 4.01 (1H, d, J = 2.4 Hz, epoxide), 5.66 (1H, dd, J = 11.2, 1.5 Hz, NCHC≡$CC\underline{H}$=CH), 5.82 (1H, d, J = 11.2 Hz,

$\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 5.89 (1H, dd, *J*=2.4, 1.5 Hz, $\mathrm{CHC{\equiv}C}$), 7.10—7.55 (8H, m, aromatic), 8.58 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 397 ($\mathrm{M^+}$, base peak). HR-MS Calcd for $\mathrm{C_{25}H_{19}NO_4}$ ($\mathrm{M^+}$): 397.1314. Found 397.1321.

Phenyl (2R*,5Z,9S*,10S*,16R*)-9-Methyl-9-trimethylsilyloxy-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (11) A mixture of the enediyne **2a** (77 mg, 0.20 mmol) and bis(trimethylsilyl)trifluoroacetamide (2.0 ml, 7.5 mmol) in dry pyridine (2 ml) was stirred at 25 °C for 44 h. The reaction mixture was diluted with toluene (20 ml) and evaporated *in vacuo* to afford **11** (102 mg, quantitative) as a colorless oil. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1720 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 0.29 (9H, s, $\mathrm{Si(CH_3)_3}$), 1.70 (3H, s, $\mathrm{CCH_3}$), 4.06 (1H, d, *J*=2.4 Hz, epoxide), 5.63 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.81 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 5.86 (1H, dd, *J*=2.4, 1.5 Hz, $\mathrm{CHC{\equiv}C}$), 7.10—7.45 (8H, m, aromatic), 7.49 (1H, d, *J*=7.8 Hz, aromatic), 8.69 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 455 ($\mathrm{M^+}$), 440, 412, 73 (base peak). HR-MS Calcd for $\mathrm{C_{27}H_{25}NO_4Si}$ ($\mathrm{M^+}$): 455.1553. Found 455.1559.

2-(Phenylthio)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Hydroxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (12) 2-(Phenylthio)ethanol (50 mg, 0.12 mmol) was added to a suspension of NaH (60%, 10 mg, 0.25 mmol) in dry THF (1 ml) cooled to 0 °C, followed by stirring at 0 °C for 10 min. This solution was cooled to −15 °C, and stirred a solution of **2a** (50 mg, 0.12 mmol) in dry THF (1 ml) was added. The mixture was stirred at −10 °C for 1 h, the reaction was quenched with saturated $\mathrm{NH_4Cl}$ (10 ml), and the whole was extracted with EtOAc (20 ml), washed with brine (10 ml), dried over anhydrous $\mathrm{Na_2SO_4}$, and evaporated *in vacuo*. The residue was purified by preparative TLC (silica, $\mathrm{CH_2Cl_2:Et_2O=4:1}$) to give **12** (18 mg, 31%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1710 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.69 (3H, s, $\mathrm{CCH_3}$), 3.16 (2H, m, $\mathrm{SCH_2}$), 3.92 (1H, d, *J*=2.4 Hz, epoxide), 4.20—4.42 (2H, m, $\mathrm{SCH_2C\underline{H}_2O}$), 5.63 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.75 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.79 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 7.14—7.42 (8H, m, aromatic), 8.74 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 443 ($\mathrm{M^+}$). HR-MS Calcd for $\mathrm{C_{26}H_{21}NO_4S}$ ($\mathrm{M^+}$): 443.1191. Found 443.1182.

2-(Phenylthio)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Methoxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (13) Compound **13** was obtained from **10** (50 mg, 0.12 mmol) by a procedure similar to that described for **12**. Yield: 32 mg (57%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1710 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.62 (3H, s, $\mathrm{CCH_3}$), 3.17 (2H, m, $\mathrm{SCH_2}$), 3.46 (3H, s, $\mathrm{CH_3O}$), 3.92 (1H, d, *J*=2.4 Hz, epoxide), 4.20—4.42 (2H, m, $\mathrm{SCH_2C\underline{H}_2O}$), 5.63 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.75 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.79 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 7.14—7.42 (8H, m, aromatic), 8.54 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 457 ($\mathrm{M^+}$), 441, 321, 137 (base peak). HR-MS Calcd for $\mathrm{C_{27}H_{23}NO_4S}$ ($\mathrm{M^+}$): 457.1348. Found 457.1372.

2-(Phenylthio)ethyl (2R*,5Z,9S*,10R*,16R*)-9-Methyl-9-trimethylsilyloxy-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (14) Compound **14** was obtained from **11** (43 mg, 0.094 mmol) by a procedure similar to that described for **12**. Yield: 30 mg (62%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1711 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 0.27 (9H, s, $\mathrm{Si(CH_3)_3}$), 1.67 (3H, s, $\mathrm{CCH_3}$), 3.15 (2H, m, $\mathrm{SCH_2}$), 3.46 (3H, s, $\mathrm{CH_3O}$), 3.98 (1H, d, *J*=2.4 Hz, epoxide), 4.23—4.38 (2H, m, $\mathrm{SCH_2C\underline{H}_2O}$), 5.61 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.75 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.78 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 7.16—7.40 (8H, m, aromatic), 8.66 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 515 ($\mathrm{M^+}$), 379, 254, 137 (base peak). HR-MS Calcd for $\mathrm{C_{29}H_{29}NO_4SSi}$ ($\mathrm{M^+}$): 515.1587. Found 515.1608.

2-(4-Chlorophenylthio)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Methyl-9-trimethylsilyloxy-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (15) Compound **15** was obtained from **11** (45 mg, 0.10 mmol) by a procedure similar to that described for **12**. Yield: 35 mg (63%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1710 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 0.27 (9H, s, $\mathrm{Si(CH_3)_3}$), 1.67 (3H, s, $\mathrm{CCH_3}$), 3.05—3.25 (2H, m, $\mathrm{SCH_2}$), 3.98 (1H, d, *J*=2.4 Hz, epoxide), 4.15—4.39 (2H, m, $\mathrm{SCH_2C\underline{H}_2O}$), 5.61 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.74 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.78 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 7.16—7.45 (7H, m, aromatic), 8.65 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 551 ($\mathrm{M^+}$; ^{37}Cl), 549 ($\mathrm{M^+}$; ^{35}Cl), 379, 143 (base peak). HR-MS Calcd for $\mathrm{C_{29}H_{28}ClNO_4SSi}$ ($\mathrm{M^+}$): 549.1197. Found 549.1192.

2-(Methylthio)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Methyl-9-trimethylsilyloxy-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (16) Compound **16** was obtained from **11** (40 mg, 0.088 mmol) by a procedure similar to that described for **12**. Yield: 26 mg (65%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1712 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 0.26 (9H, s, $\mathrm{Si(CH_3)_3}$), 1.68 (3H, s, $\mathrm{CCH_3}$), 2.10 (3H, s, $\mathrm{SCH_3}$), 2.70—2.78 (2H, m, $\mathrm{SCH_2}$), 4.00 (1H, d, *J*=2.4 Hz, epoxide), 4.24—4.39 (2H, m, $\mathrm{SCH_2C\underline{H}_2O}$), 5.60 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.76 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.78 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 7.16 (1H, td, *J*=7.8, 1.4 Hz, aromatic), 7.27 (1H, td, *J*=7.8, 1.4 Hz, aromatic), 7.35 (1H, d, *J*=7.8 Hz, aromatic), 8.65 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 453 ($\mathrm{M^+}$), 379, 348, 75 (base peak). HR-MS Calcd for $\mathrm{C_{24}H_{27}NO_4SSi}$ ($\mathrm{M^+}$): 453.1430. Found 453.1436.

2-(4-Chlorophenylsulfinyl)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Methyl-9-trimethylsilyloxy-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (17) A solution of **15** (2 mmg, 0.050 mmol) and anhydrous $\mathrm{Na_2HPO_4}$ (15 mg, 0.10 mmol) in $\mathrm{CH_2Cl_2}$ (4 ml) was cooled to 0 °C, *m*CPBA (18 mg, 0.050 mmol) was added, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with $\mathrm{CH_2Cl_2}$ (20 ml), washed with aqueous $\mathrm{Na_2S_2O_3}$ (2 ml), aqueous $\mathrm{NaHCO_3}$ (2 ml) and brine (2 ml), dried over anhydrous $\mathrm{Na_2SO_4}$, and evaporated *in vacuo*. The residue was purified by preparative TLC (silica, $\mathrm{CH_2Cl_2:Et_2O=5:1}$) to give **17** (10 mg, 65%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1715 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 0.28 (9H, s, $\mathrm{Si(CH_3)_3}$), 1.67 (3H, s, $\mathrm{CCH_3}$), 2.95—3.20 (2H, m, $\mathrm{SOCH_2}$), 4.00 (1H, d, *J*=2.4 Hz, epoxide), 4.35—4.62 (2H, m, $\mathrm{SOCH_2C\underline{H}_2O}$), 5.62 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.74 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.79 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 7.19—7.65 (7H, m, aromatic), 8.66 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (EI) *m*/*z*: 567 ($\mathrm{M^+}$; ^{37}Cl), 565 ($\mathrm{M^+}$; ^{35}Cl), 335, 292, 73 (base peak). HR-MS Calcd for $\mathrm{C_{29}H_{28}ClNO_5SSi}$ ($\mathrm{M^+}$): 565.1146. Found 565.1150.

2-(4-Chlorophenylsulfinyl)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Hydroxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (18) A 1 M solution of tetrabutyl ammonium fluoride and AcOH in THF (60 μl, 0.060 mmol) was added to a solution of **17** (16 mg, 0.028 mmol) in dry THF (2 ml) at 0 °C, and the mixture was stirred at 0 °C for 20 min, then evaporated *in vacuo*. The residue was purified by preparative TLC (silica, $\mathrm{CH_2Cl_2:Et_2O=3:1}$) to give **18** (12 mg, 86%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1714 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.70 (3H, s, $\mathrm{CCH_3}$), 2.95—3.20 (2H, m, $\mathrm{SOCH_2}$), 4.00 (1H, d, *J*=2.4 Hz, epoxide), 4.35—4.62 (2H, m, $\mathrm{SOCH_2C\underline{H}_2O}$), 5.64 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.74 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.80 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 7.19—7.65 (7H, m, aromatic), 8.77 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (FAB) *m*/*z*: 495 ($\mathrm{(M+H)^+}$; ^{37}Cl), 493 ($\mathrm{(M+H)^+}$; ^{35}Cl). HR-MS Calcd for $\mathrm{C_{26}H_{20}ClNO_5S}$ ($\mathrm{(M+H)^+}$): 493.0751. Found 493.0760.

2-(Phenylsulfonyl)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Hydroxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (19) A solution of **12** (36 mg, 0.080 mmol) and anhydrous $\mathrm{Na_2HPO_4}$ (57 mg, 0.40 mmol) in $\mathrm{CH_2Cl_2}$ (4 ml) was treated with *m*CPBA (62 mg, 0.20 mmol) at 0 °C and the mixture was stirred at the same temperature for 1 h, then diluted with $\mathrm{CH_2Cl_2}$ (20 ml), washed with aqueous $\mathrm{Na_2S_2O_3}$ (2 ml), aqueous $\mathrm{NaHCO_3}$ (2 ml) and brine (2 ml), dried over anhydrous $\mathrm{Na_2SO_4}$, and evaporated *in vacuo*. The residue was purified by preparative TLC (silica, $\mathrm{CH_2Cl_2:Et_2O=4:1}$) to give **19** (6 mg, 23%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1715 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.70 (3H, s, $\mathrm{CCH_3}$), 3.48 (2H, m, $\mathrm{SO_2CH_2}$), 3.94 (1H, d, *J*=2.4 Hz, epoxide), 4.38—4.60 (2H, m, $\mathrm{SO_2CH_2C\underline{H}_2O}$), 5.63 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.65 (1H, m, $\mathrm{CHC{\equiv}C}$), 5.79 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 7.15—7.31 (3H, m, aromatic), 7.51—7.69 (3H, m, aromatic), 7.80—8.00 (2H, m, aromatic), 8.72 (1H, dd, *J*=7.8, 1.4 Hz, aromatic). MS (FAB) *m*/*z*: 476 ($\mathrm{(M+H)^+}$). HR-MS Calcd for $\mathrm{C_{26}H_{22}NO_6S}$ ($\mathrm{(M+H)^+}$): 476.1168. Found 476.1161.

2-(Phenylsulfonyl)ethyl (2R*,5Z,9S*,10S*,16R*)-9-Methoxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[b]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (20) Compound **20** was obtained from **13** (20 mg, 0.044 mmol) by a procedure similar to that described for **19**. Yield: 20 mg (96%) as a colorless amorphous powder. IR ($\mathrm{CHCl_3}$) $\mathrm{cm^{-1}}$: 1715 (C=O). ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.60 (3H, s, $\mathrm{CCH_3}$), 3.46 (3H, s, $\mathrm{CH_3O}$), 3.48 (2H, m, $\mathrm{SO_2CH_2}$), 3.88 (1H, d, *J*=2.4 Hz, epoxide), 4.46—4.60 (2H, m, $\mathrm{SO_2CH_2C\underline{H}_2O}$), 5.63 (1H, dd, *J*=11.2, 1.5 Hz, $\mathrm{NCHC{\equiv}CC\underline{H}{=}CH}$), 5.75 (1H, br s, $\mathrm{CHC{\equiv}C}$), 5.79 (1H, d, *J*=11.2 Hz, $\mathrm{NCHC{\equiv}CCH{=}C\underline{H}}$), 7.15—7.31 (3H, m, aromatic), 7.51—7.62 (3H, m, aromatic), 7.89 (2H, m, aromatic), 8.50 (1H, dd, J=7.8, 1.4 Hz, aromatic). MS (EI) m/z: 489 (M^+), 473, 460, 125 (base peak). HR-MS Calcd for $C_{27}H_{23}NO_6S$ (M^+): 489.1249. Found 489.1246.

2-(Phenylsulfonyl)ethyl (2*R,5*Z*,9*S**,10*R**,16*R**)-9-Methyl-9-trimethyl-silyloxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (21)** Compound **21** was obtained from **14** (24 mg, 0.045 mmol) by a procedure similar to that described for **19**. Yield: 18 mg (71%) as a colorless amorphous powder. IR ($CHCl_3$) cm^{-1}: 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.28 (9H, s, $Si(CH_3)_3$), 1.66 (3H, s, CCH_3), 3.47 (2H, t, J=5.6 Hz, SO_2CH_2), 3.93 (1H, d, J=2.4 Hz, epoxide), 4.38—4.59 (2H, m, $SO_2CH_2C\underline{H}_2O$), 5.60 (1H, dd, J=11.2, 1.5 Hz, $NCHC\equiv CC\underline{H}=CH$), 5.62 (1H, m, CHCC), 5.78 (1H, d, J=11.2 Hz, $NCHC\equiv CCH=C\underline{H}$), 7.15—7.32 (3H, m, aromatic), 7.45—7.65 (3H, m, aromatic), 7.89 (2H, d, J=4.4 Hz, aromatic), 8.62 (1H, dd, J=7.8, 1.4 Hz, aromatic). MS (EI) m/z: 547 (M^+), 519, 504, 77 (base peak). HR-MS Calcd for $C_{29}H_{29}NO_6SSi$ (M^+): 547.1484. Found 547.1472.

2-(4-Chlorophenylsulfonyl)ethyl (2*R,5*Z*,9*S**,10*S**,16*R**)-9-Hydroxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (22)** Compound **22** was obtained from **18** (20 mg, 0.05 mmol) by a procedure similar to that described for **17**. Yield: 10 mg (48%) as a colorless amorphous powder. IR ($CHCl_3$) cm^{-1}: 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, CCH_3), 3.49 (2H, t, J=5.6 Hz, SO_2CH_2), 3.93 (1H, d, J=2.4 Hz, epoxide), 4.54 (2H, t, J=5.6 Hz, $SO_2CH_2C\underline{H}_2O$), 5.63 (1H, dd, J=11.2, 1.5 Hz, $NCHC\equiv CC\underline{H}=CH$), 5.74 (1H, br s, $C\underline{H}C\equiv C$), 5.79 (1H, d, J=11.2 Hz, $NCHC\equiv CCH=C\underline{H}$), 7.19—7.85 (7H, m, aromatic), 8.76 (1H, dd, J=7.8, 1.4 Hz, aromatic). MS (FAB) m/z: 512 ($(M+H)^+$; ^{37}Cl), 510 ($(M+H)^+$; ^{35}Cl). HR-MS Calcd for $C_{26}H_{21}ClNO_6S$ ($(M+H)^+$): 510.0778. Found 510.0773.

2-(Methylsulfonyl)ethyl (2*R,5*Z*,9*S**,10*S**,16*R**)-9-Methyl-9-trimethyl-silyloxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (23)** Compound **23** was obtained from **16** (36 mg, 0.078 mmol) by a procedure similar to that described for **19**. Yield: 21 mg (54%) as a colorless amorphous powder. IR ($CHCl_3$) cm^{-1}: 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.25 (9H, s, $Si(CH_3)_3$), 1.67 (3H, s, CCH_3), 2.52 (3H, br s, SO_2CH_3), 3.13—3.40 (2H, m, SO_2CH_2), 4.01 (1H, d, J=2.4 Hz, epoxide), 4.48, 4.75 (each 1H, m, $SO_2CH_2C\underline{H}_2O$), 5.60 (1H, dd, J=11.2, 1.5 Hz, $NCHC\equiv CC\underline{H}=CH$), 5.74 (1H, br s, $CHC\equiv C$), 5.79 (1H, d, J=11.2 Hz, $NCHC\equiv CCH=C\underline{H}$), 7.15—7.38 (3H, m, aromatic), 8.64 (1H, dd, J=7.8, 1.4 Hz, aromatic). MS (CI) m/z: 486 ($(M+H)^+$), 368, 107 (base peak). HR-MS Calcd for $C_{24}H_{28}NO_6SSi$ ($(M+H)^+$): 486.1406. Found 486.1411.

2-(Methylsulfonyl)ethyl (2*R,5*Z*,9*S**,10*S**,16*R**)-9-Hydroxy-9-methyl-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (24)** Compound **24** was obtained from **23** (18 mg, 0.036 mmol) by a procedure similar to that described for **18**. Yield: 15 mg (98%) as a colorless amorphous powder. IR ($CHCl_3$) cm^{-1}: 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, CCH_3), 2.50 (3H, br s, SO_2CH_3), 3.11—3.38 (2H, m, SO_2CH_2), 4.01 (1H, d, J=2.4 Hz, epoxide), 4.48, 4.74 (2H, m, $SO_2CH_2C\underline{H}_2O$), 5.64 (1H, dd, J=11.2, 1.5 Hz, $NCHC\equiv CC\underline{H}=CH$), 5.76 (1H, br s, $CHC\equiv C$), 5.80 (1H, d, J=11.2 Hz, $NCHC\equiv CCH=C\underline{H}$), 7.17—7.40 (3H, m, aromatic), 8.74 (1H, dd, J=7.8, 1.4 Hz, aromatic). MS (FAB) m/z: 414 ($(M+H)^+$). HR-MS Calcd for $C_{21}H_{20}NO_6S$ ($(M+H)^+$): 414.1011. Found 414.1017.

4-(*tert*-Butyldimethylsilyloxy)benzyl (2*R,5*Z*,9*S**,10*S**,16*R**)-9-Methyl-9-trimethylsilyloxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (25)** Compound **25** was obtained from **11** (40 mg, 0.088 mmol) by a procedure similar to that described for **12**. Yield: 20 mg (37%) as a colorless amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.20 (6H, s, $Si(CH_3)_2$), 0.26 (9H, s, $Si(CH_3)_3$), 0.98 (9H, s, $SiC(CH_3)_3$), 1.67 (3H, s, CCH_3), 4.00 (1H, d, J=2.4 Hz, epoxide), 5.06, 5.22 (each 1H, d, J=11.7 Hz, CH_2O), 5.60 (1H, dd, J=11.2, 1.5 Hz, $NCHC\equiv CC\underline{H}=CH$), 5.78 (1H, d, J=11.2 Hz, $NCHC\equiv CCH=C\underline{H}$), 5.79 (1H, br s, $CHC\equiv C$), 6.80 (2H, d, J=8.3 Hz, aromatic), 7.15—7.40 (5H, m, aromatic), 8.64 (1H, d, J=7.8 Hz, aromatic). MS (EI) m/z: 599 (M^+). HR-MS Calcd for $C_{34}H_{41}NO_5Si_2$ (M^+): 599.2523. Found 599.2530.

Anthraquinone-2-methyl (2*R,5*Z*,9*S**,10*S**,16*R**)-9-Methyl-9-trimethyl-silyloxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate (26)** Compound **26** was obtained from **11** (40 mg, 0.088 mmol) by a procedure similar to that described for **12**. Yield: 10 mg (12%) as a colorless amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.27 (9H, s, $Si(CH_3)_3$), 1.69 (3H, s, CCH_3), 4.03 (1H, d, J=2.4 Hz, epoxide), 5.34, 5.41 (each 1H, d, J=14.2 Hz, CH_2O), 5.61 (1H, dd, J=11.2, 1.5 Hz, $NCHC\equiv CC\underline{H}=CH$), 5.79 (1H, br s, $CHC\equiv C$), 5.79 (1H, d, J=11.2 Hz, $NCHC\equiv CCH=C\underline{H}$), 7.15—7.40 (3H, m, aromatic), 7.72 (1H, m, aromatic), 7.80 (1H, d, J=5.9 Hz, aromatic), 7.81 (1H, d, J=5.9 Hz, aromatic), 8.23—8.40 (4H, m, aromatic), 8.68 (1H, d, J=7.8 Hz, aromatic). MS (EI) m/z: 599 (M^+), 368, 69 (base peak). HR-MS Calcd for $C_{36}H_{29}NO_6Si$ (M^+): 599.1764. Found 599.1760.

(2*R,5*Z*,9*S**,10*S**,16*R**)-9-Methyl-9-trimethylsilyloxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne (27)** The enediyne **11** (2.4 mg, 5.4 μmol) in THF (0.3 ml) was treated at 0 °C with $LiAlH_4$ (14 μl of a 1.0 M solution in THF, 14 μmol). The mixture was stirred for 30 min, then the reaction was quenched with saturated $NaHCO_3$ (0.5 ml) and the whole was diluted with ether (2 ml). The organic layer was dried over anhydrous Na_2SO_4, and evaporated *in vacuo* at 0 °C to give **27** (1.5 mg, 83%) as a crude oil. ^{1}H-NMR (DMSO-d_6) δ: 0.28 (9H, s, $Si(CH_3)_3$), 1.52 (3H, s, CCH_3), 5.35 (1H, m, $CHC\equiv C$), 5.83 (1H, dd, J=11.2, 1.5 Hz, $NCHC\equiv CC\underline{H}=CH$), 5.93 (1H, d, J=11.2 Hz, $NCHC\equiv CCH=C\underline{H}$), 6.55—6.65 (2H, m, aromatic), 7.05 (1H, dt, J=7.8, 1.4 Hz, aromatic), 8.40 (1H, dd, J=7.8, 1.4 Hz, aromatic). MS (FAB) m/z: 336 ($(M+H)^+$). HR-MS Calcd for $C_{20}H_{22}NO_2Si$ ($(M+H)^+$): 336.1420. Found 336.1435.

Biological Assays *In Vitro* Cytotoxicity: Human epidermoid carcinoma KB cells were cultured in Eagle's minimum essential medium containing 10% fetal bovine serum at a density of 5×10^4 cells/ml on day 0. After culture with test compounds for 48 h from day 1 to day 3, the number of viable cells was counted with a Coulter counter on day 3. Other cell lines, human T cell leukemia MOLT-4, murine leukemia L1210, murine leukemia P388 and P388/ADM (doxorubicin-resistant P388 subline) were cultured with test compounds in RPMI1640 medium containing 10% fetal bovine serum at a density of 1.0×10^5 cells/ml (MOLT-4), 2.5×10^4 cells/ml (L1210), and 5×10^4 cells/ml (P388, P388/ADM) for 48 h from day 0 to day 2, respectively. The number of viable cells was counted with a Coulter counter on day 2.

In Vivo Antitumor Activity: For the evaluation of the antitumor activity against P388 leukemia, CDF_1 mice were inoculated intraperitoneally with 1×10^6 cells/mouse of P388 on day 0, and 2 mg/kg of test compound was administered intraperitoneally once daily for 4 d from day 1 to day 4. Survival was recorded for 30 d. The T/C values reported refer to the relative mean survival times of drug-treated to control mice (expressed as a percentage). T/C values over 125% are considered significant.

For the evaluation of the antitumor activity against Lewis lung carcinoma (LLC, murine lung carcinoma), BDF_1 mice were inoculated subcutaneously with 5×10^5 cells/mouse of LLC on day 0, and the test compound (1.0, 1.5 or 2.0 mg/kg) was administered intraperitoneally once daily for 4 d from day 1 to day 4. The mice were killed on day 14. Each tumor was excised and its weight was measured. The reduction of tumor weight in a treated group relative to the untreated control was expressed as percent inhibition of tumor growth. Inhibition of over 58% is considered significant.

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