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Structure–Activity Relationships of Cyclic Enediynes Related to Dynemicin A—I. Synthesis and Antitumor Activity of 9-Acetoxy Enediynes Equipped with Aryl Carbamate Moieties

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Abstract—A series of the 9-acetoxy enediyne compounds, **6a–k** which were simplified from natural dynemicin A, and designed to be equipped with various aryl carbamate moieties, was synthesized and evaluated for DNA-cleaving ability, in vitro cytotoxicity, and in vivo antitumor activity. As a result of this study of the structure–activity relationships (SAR) with regard to the R^1 substituent, both compounds **6a** and **6f** with the phenyl carbamate and 4-chlorophenyl carbamate moiety, respectively, were found to exhibit significant activity (T/C > 200%) against murine P388 leukemia in mice, in spite of having IC_{50} values in the micromolar range. In particular, compound **6f** showed the most potent activity with a maximum T/C of 256% at a daily dosage of 4.0 mg/kg for four days. Furthermore, both compounds **6a** and **6f** were effective against Meth A sarcoma in mice and inhibited 71 and 77% of the tumor growth at 2.0 and 3.0 mg/kg dosages, respectively. In contrast to **6f**, compound **6i** possessing the 2-nitrophenyl carbamate moiety showed only a slight in vivo activity, while it had about one order of magnitude higher in vitro cytotoxicity than **6f**. For the stereochemistry–activity relationships at the C9 position, the (9*R**)-isomers of **6c**, **6g**, and **6j** were found to show higher in vitro and in vivo potencies than the corresponding (9*S**)-isomers. © 1997 Elsevier Science Ltd.

Introduction

The cyclic enediynes, a new growing class of antitumor antibiotics,[1] are promising chemotherapeutic agents that exhibit a strong DNA-cleaving ability and extremely potent antitumor activity. Members of this family include dynemicin A (**1**, Fig. 1),[2] calicheamicins,[3] esperamicins,[4] neocarzinostatin chromophore,[5] kedarcidin chromophore,[6] C-1027 chromophore,[7] and maduropeptin chromophore.[8] Important features of the cyclic enediynes are as follows: (a) a delivery system that is responsible for targeting DNA, (b) a triggering device that, after activation under physiological conditions, initiates the reactions to form the phenylene diradical, and (c) an enediyne ring that generates the reactive diradicals.

Dynemicin A (**1**), a metabolite isolated from the fermentation broth of *Micromonospora chersina*, is unique in possessing features of both the cyclic enediyne antibiotics and anthracycline antibiotics.[9] For the structural novelty, complexity, and high potent activity, the mechanistic and synthetic studies of dynemicin A (**1**) have been rapidly extended.[1] Recently, the excellent total syntheses of dynemicin A (**1**) and its derivatives have been achieved by the three groups of Schreiber,[10] Myers,[11] and Danishefsky.[12] The mechanism of action by which dynemicin A (**1**) exerts its antitumor activity is believed to be due to its ability to break DNA strands.[13] It is presumed that the DNA cleavage by **1** is attributed to the reactive phenylene diradical **1d** which is generated by Bergman cycloaromatization[14] as shown in Figure 2. The opening of the epoxide ring in **1** causes a conformational change such that the distance between the two terminal carbons of the 1,5-diyne-3-ene system (*cd* distance) is shortened from 3.48 Å in **1** to 3.23 Å in the *cis*-diol **1c**, based on a molecular orbital calculation using PM3.[15] This enhances the strain energy in the cyclic enediyne system, and thus allows the formation of the phenylene diradical **1d** via Bergman cycloaromatization at ambient temperature. In this context, dynemicin A (**1**) is considered to be a natural prodrug equipped with a triggering device which can be activated under physiological conditions.

Based on the concept of prodrug activation, some groups have reported the strategies that enable the generation of reactive enediynes from the stable precursors.[16] Nicolaou et al. have performed significant studies in this area.[17] They have reported that the dynemicin A analogue **2** with the 2-(phenylsulfonyl)-

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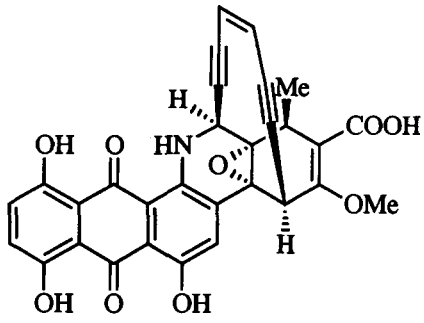
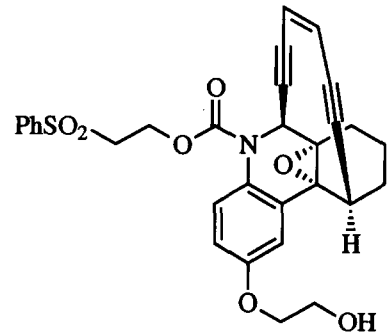
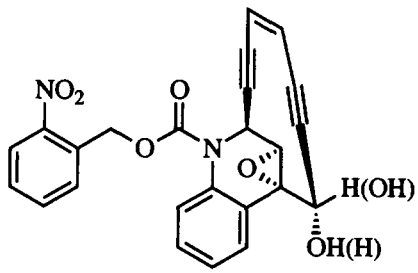


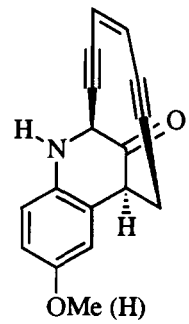
Dynemicin A (1)



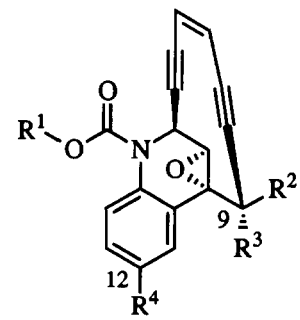
Nicolaou's enediyne (2)



Wender's enediyne (3)



Magnus' enediyne (4)



5 : R^1 = Ph, R^2 = Me, R^3 = OH, R^4 = H
6 : R^1 = Ar, R^2 = H (OAc),
R^3 = OAc (H), R^4 = H

Figure 1. Dynemicin A (**1**) and its functional analogues **2–6.**

ethoxycarbonyl group as a triggering device shows DNA-cleaving activity and highly potent cytotoxicity against various cell lines.[17c] However, the in vivo data for compound **2** have not yet been reported and remain unclear. Wender et al. have reported dynemicin A analogues **3** with the 2-nitrobenzyl carbamate moiety which can be activated by photochemical deprotection.[18] Danishefsky et al. have shown that enediyne quinone imines, which can be bioreductively activated in a similar manner as in the case of dynemicin A (**1**), exhibit remarkable cytotoxicity against various tumor cell lines and significantly reduce tumor volume in mice bearing solid tumors.[12c,19] Denny et al. have shown that the 4-nitrobenzyl carbamate moiety is a suitable triggering device which can be enzymatically activated by the *Escherichia coli* nitroreductase.[20] In contrast to these compounds **2** and **3**, Magnus et al. have shown that the dynemicin A analogue **4** undergoes the cycloaromatization via a nondiradical pathway and exhibits cytotoxicity and in vivo antitumor activity.[21]

As a part of our studies[22] aiming at the molecular design of the simple functional analogues of **1** and the identification of the key structural features responsible for the biological activity, we have recently found that the novel enediyne compound **5** equipped with the phenyl carbamate moiety showed effective antitumor activity against both murine P388 leukemia and Lewis lung carcinoma in mice despite exhibiting only a slight DNA-cleaving activity and having an IC_{50} value in the micromolar range.[22g] This finding suggested that the phenyl carbamate moiety in **5** played an important role in the in vivo antitumor activity. With a view to application in chemotherapy, we selected **5** as our leading compound, and planned to optimize the R^1, R^2, R^3, and R^4 substituents of the cyclic enediyne core. First, on the basis of our finding, we introduced the various aryl (as R^1 substituent) carbamate moieties onto the cyclic enediyne core such as the 9-acetoxy enediyne compounds **6**. Secondly, modification of the acetoxy function at the C9 position in **6** was compared with the *tert*-alcohol in **5**.

In addition with this paper as well as the continuing paper, we discuss the structure–activity relationships (SAR) with regard to the R^1, R^2, R^3, and R^4 substituents of a series of simple dynemicin A analogues with the aryl carbamate moiety. In this paper, we describe the syntheses of such 9-acetoxy enediyne compounds **6** that are equipped with various aryl carbamate moieties, and the evaluation for DNA-cleaving ability, in vitro cytotoxicity, and in vivo antitumor activity. Particularly, we describe the SAR with regard to the R^1 substituent and the stereochemistry–activity relationships at the C9 position of the enediyne ring system.

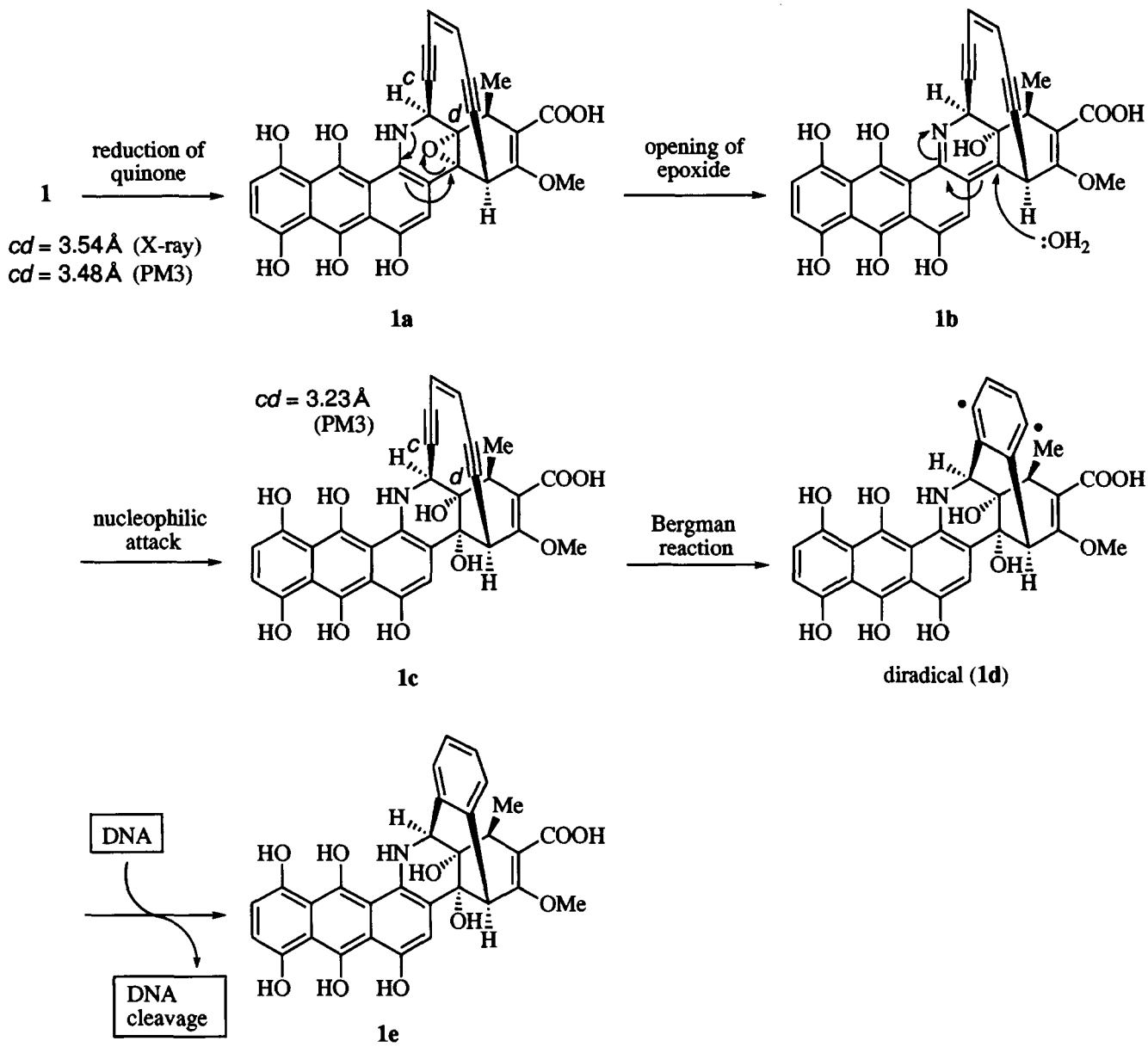


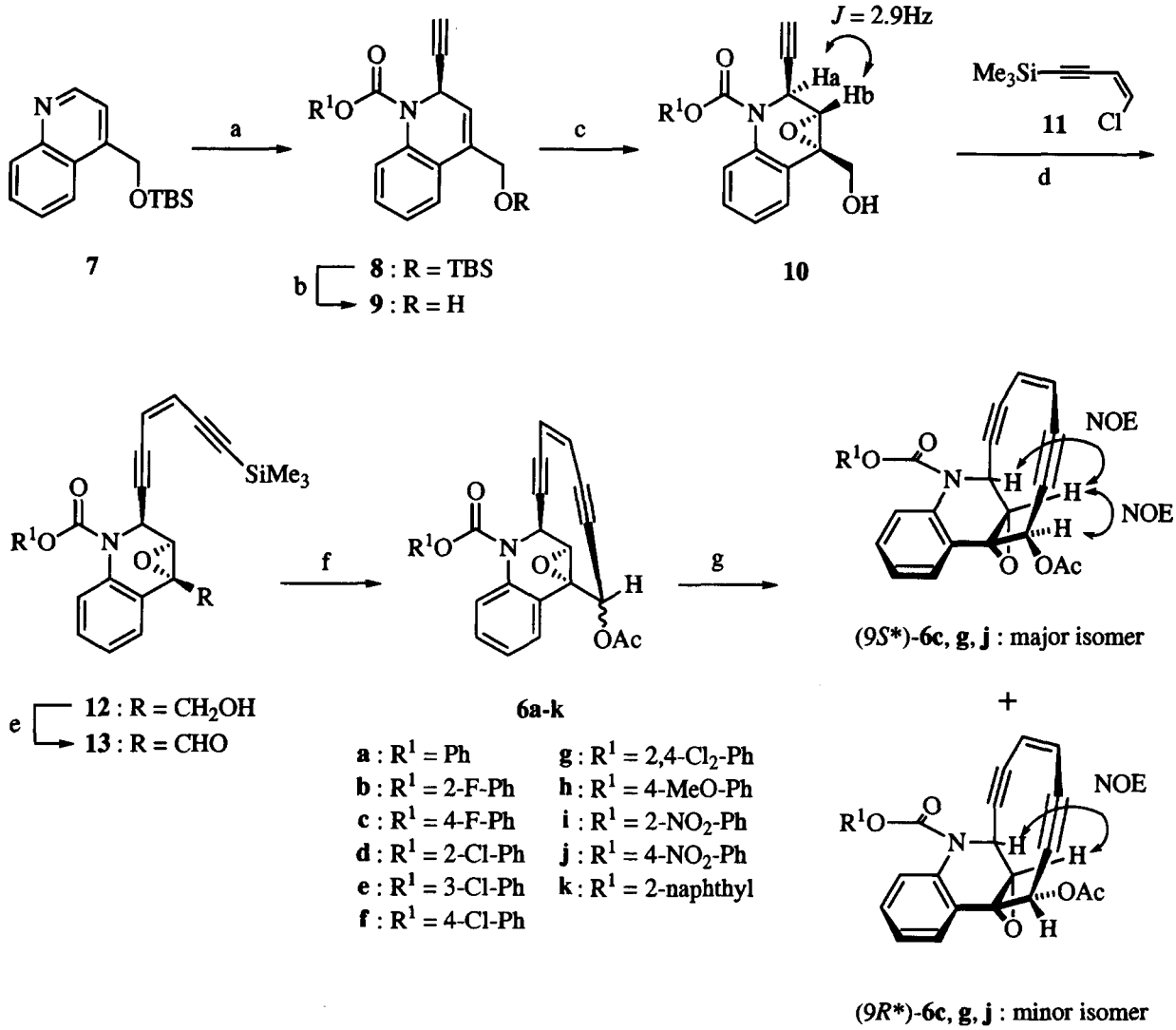
Figure 2. Proposed mechanism of action for dynemicin A (**1**).

Results and Discussion

Synthesis of the 9-acetoxy enediyne compounds 6a–k

The general synthetic procedure for 11 analogues of the 9-acetoxy enediyne compounds **6a–k** with various aryl carbamate moieties is shown in Scheme 1. The key step in the synthesis of **6** is the formation of a strained 10-membered ring. Various methods have been reported for this cyclization,[23] which include the acetylide coupling with the aldehyde,[24] the Pd(0)-mediated double cross-coupling,[25] the Nicholas reaction,[26] the trans-annular Diels–Alder reaction,[27] and the Cr(II)-mediated coupling[28] as a key step. We have previously established the useful cyclization method by coupling between trimethylsilylacetylene and carbonyl groups in the presence of CsF and 18 crown-6.[22c,29] Wender et al. have also reported a similar CsF-promoted cyclization in the presence of Ac_2O to give a cyclic enediyne core such as **6** in high yield.[18b,30] This CsF-promoted cyclization avoids the desilylation step as well as the use of any strong base required for the acetylide formation; thus, the CsF-promoted cyclization is an advanced method for the cyclic enediyne ring construction.

Synthesis of the aldehydes **13**, the precursors of **6**, commenced from the reaction with three components, the silyl ether **7**,[18c,22e] ethynylmagnesium bromide and aryl chloroformate, to provide **8** which were deprotected to the corresponding alcohols **9**. Epoxidation of **9** with *m*CPBA selectively gave the epoxy alcohols **10**, and the stereochemistry was confirmed by the coupling constant of 2.9 Hz between Ha and Hb.[22e] Coupling of **10** with the vinyl chloride **11**[24a] in the presence of Pd(0)–Cu(I)[31] catalyst gave the alcohols **12** which were



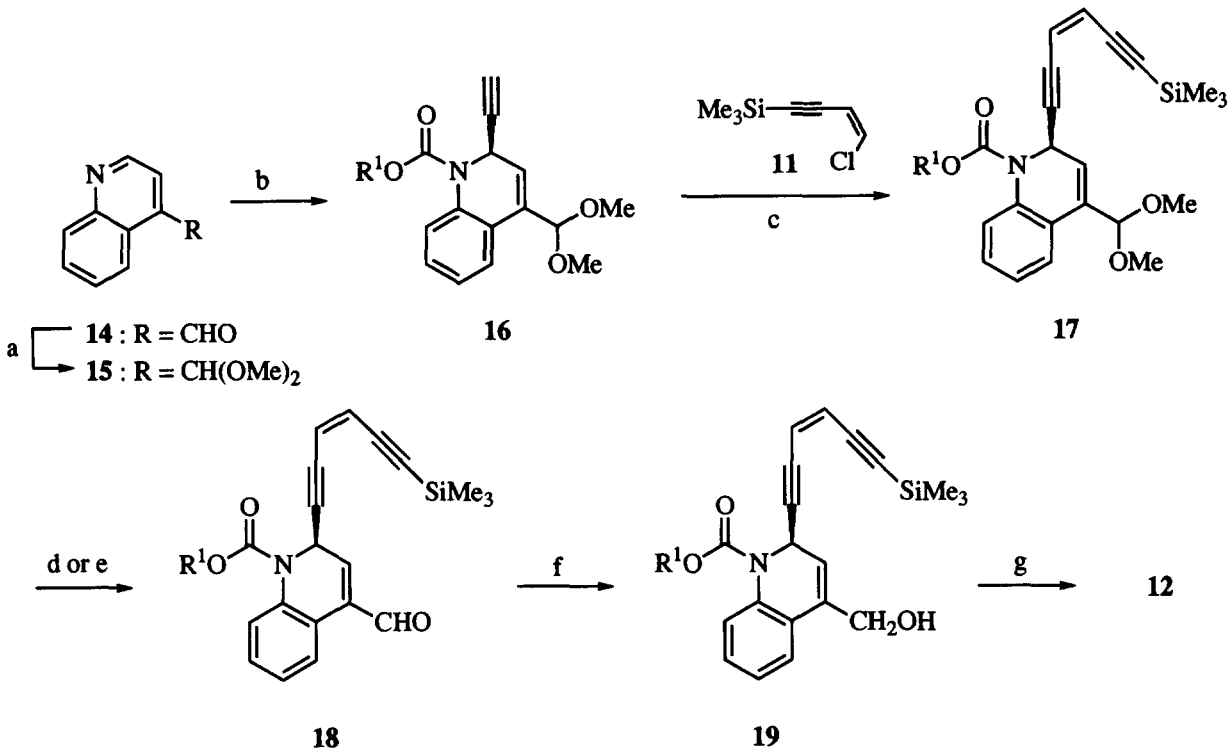
Scheme 1. General synthetic procedure for the 9-acetoxy enediyne compounds **6**: Method A. Reagents and conditions: (a) HC≡CMgBr, R^1OCOCl, THF, −70 °C to 0 °C, 1 h; (b) *p*TsOH·H_2O, MeOH-CH_2Cl_2, 0 °C, 1.5 h; (c) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C, 1 h; (d) **11**, $Pd_2(dba)_3$·$CHCl_3$, Ph_3P, CuI, *n*-$BuNH_2$, THF, rt, 2 h; (e) Dess–Martin periodinane, py, CH_2Cl_2, rt, 2 h; (f) CsF, Ac_2O, CH_3CN, 0 °C, 2–4 h; (g) silica gel chromatography.

oxidized with Dess–Martin periodinane reagent[32] to the aldehydes **13**. Alternative synthetic procedure for the same intermediates **12** is shown in Scheme 2. In this route, synthesis of **12** started from the protection of a commercially available aldehyde **14**, and the resulting acetal **15** was converted to compounds **17** using the same procedure as those described above. Compounds **17** were deprotected with a catalytic amount of $SnCl_4$ and $ZnCl_4$ or excess BF_3 etherate to the aldehydes **18**. Treatment of **18** with $NaBH_4$ in the presence of $CeCl_3$[33] gave 1,2-reduction products **19** which were epoxidized to **12** with *m*CPBA. Finally, the CsF-promoted cyclization of **13** in the presence of Ac_2O proceeded smoothly to provide **6** as a 2:1 mixture of diastereomers which, however, could not be separated except for **6c**, **6g** and **6j** as shown in Table 1. The stereochemical assignment for a major product (9*S**)-**6c**[34] and a minor product (9*R**)-**6c** was based on NOE difference spectroscopy in which irradiation of the epoxy proton in (9*S**)-**6c** produced an enhancement (22%) of the C9 proton while no enhancement was observed in the corresponding experiment with (9*R**)-**6c**. Both isomers exhibited an NOE enhancement at the C2 proton when the epoxy proton was irradiated.

Furthermore, in order to establish a concise route for **6a**, we planned to synthesize a novel dienediyne compound **20** as a precursor of **6a** (Scheme 3). The CsF-promoted cyclization of **18a** in the presence of Ac_2O proceeded smoothly and clearly provided **20** (90%) as a diastereomeric mixture (ca. 2:1, by ^1H NMR). This compound **20** was stable in diluted $CDCl_3$ solution below 0 °C, whereas it was extremely unstable without solvent to decompose during storage at −20 °C. Attempted epoxidation of **20** did not give **6a** under various epoxidation in neutral media[35,36] because of decomposition of **20**.

DNA cleavage with the enediynes[37]

The DNA-cleaving activity of the 9-acetoxy enediyne compounds **6a**, **6f**, (9*S**)-**6j**, and (9*R**)-**6j** was examined

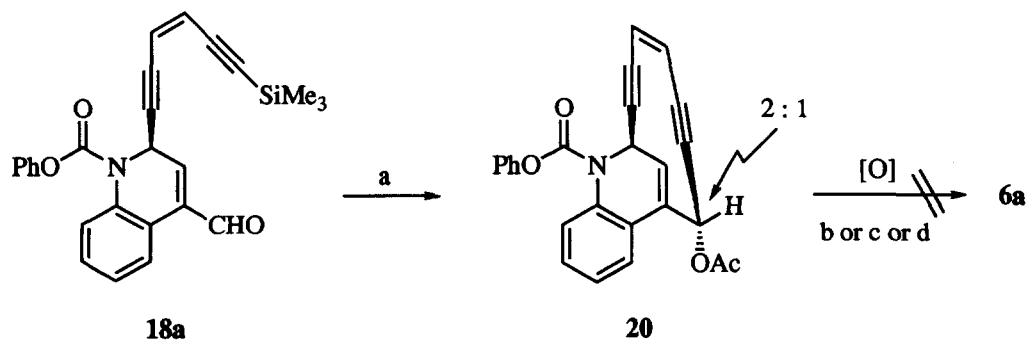


Scheme 2. General synthetic procedure for the intermediates **12**: Method B. Reagents and conditions: (a) $CH(OMe)_3$, *p*TsOH·H_2O, MeOH, reflux, 24 h, 96%; (b) HC≡CMgBr, R^{1}OCOCl, THF, −70 °C to 0 °C, 1 h; (c) **11**, $Pd_2(dba)_3$·$CHCl_3$, Ph_3P, CuI, *n*-$BuNH_2$, benzene, rt, 2 h; (d) $SnCl_4$, $ZnCl_2$, CH_2Cl_2, 0 °C, 2 h; (e) BF_3·OEt_2, CH_2Cl_2, −78 °C, 1 h; (f) $NaBH_4$, $CeCl_3$·$7H_2O$, CH_2Cl_2-EtOH, −78 °C, 20 min; (g) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C, 1.5 h.

with supercoiled ΦX174 DNA (Form I) and analyzed by agarose gel electrophoresis. Figure 3 shows the DNA cleavage profiles of these compounds at a 1 mM concentration incubated at 37 °C for 18 h in pH 7.4 buffer solution. The Form II band represents the nicked open circular DNA. None of the tested compounds caused DNA cleavage (Form I → Form II), and their activities were less potent than that of **5** previously reported.[22f] It was apparent that their low activities resulted from the chemical stability of the aryl carbamate moieties which could not be deprotected to generate a diradical intermediate (equivalent to **1d**) under such neutral conditions as this assay. In fact, we have previously reported that the phenyl carbamate moiety in **5** could not be deprotected under the weakly basic conditions (pH 9.3).[22g]

In vitro cytotoxicity of the enediynes[38]

The in vitro cytotoxicity of the 9-acetoxy enediyne compounds **6a–k** against the human carcinoma KB cell line is shown in Table 1. Among **6a**, **6b**, **6d–f**, and **6h–k**, though being a 2:1 mixture of diastereomers, compound **6i**, possessing the 2-nitrophenyl carbamate moiety, showed the most potent activity (IC_{50} = 0.17 μM) and compound **6j** possessing the 4-nitrophenyl carbamate moiety was slightly less potent (IC_{50} = 0.49 μM) than **6i**. Other compounds resulted in almost the same IC_{50} values between 1.5 and 5.6 μM. These results indicate that incorporation of a strong electron-withdrawing group such as the nitro group into the phenyl carbamate moiety in **6a** can significantly increase its in vitro potency. Therefore, it is considered that an electronic



Scheme 3. Synthesis of the dienediyne compound **20**. Reagents and conditions: (a) CsF, Ac_2O, CH_3CN, 0 °C, 1 h, 90%; (b) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C, 2 h; (c) Cl_3CCN, 30% H_2O_2, CH_2Cl_2·H_2O (pH 6.8), rt, 8 h; (d) dimethyldioxirane, acetone, rt, 2h.

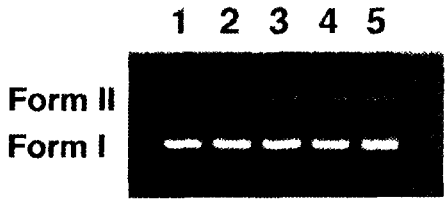


Figure 3. Attempted DNA cleavage by compounds **6a**, **6f**, (9*S**)-**6j**, and (9*R**)-**6j**. The ΦX174 DNA (Form I, 250 μM/base pair) was incubated at 37 °C for 18 h with 1 mM (final concentration) of each compound in 50 mM phosphate buffer (pH 7.4) containing 10% DMSO and analyzed by electrophoresis (1% agarose gel, ethidium bromide strain). Lane 1, DNA alone; lane 2, compound **6a**; lane 3, compound **6f**; lane 4, compound (9*S**)-**6j**; lane 5, compound (9*R**)-**6j**. Key: Form I, supercoiled DNA; Form II, nicked DNA.

property of aryl carbamate moieties in **6** significantly influences their cytotoxicities.

Furthermore, with regard to the stereochemistry–activity relationships at the C9 position, compound (9*R**)-**6j** showed the most potent activity (IC_{50} = 0.12 μM) among **6a–k**, and was found to be 10-fold more potent than the corresponding (9*S**)-isomer. Other (9*R**)-isomers of **6c** and **6g** also showed higher potency than the corresponding (9*S**)-isomers. These results apparently indicate that the stereochemistry at the C9 position in **6** significantly affects the in vitro cytotoxicity.

In vivo antitumor activity of the enediynes[39]

The 9-acetoxy enediyne compounds **6a–k** were evaluated for antitumor activity in mice inoculated intraperitoneally (ip) with murine P388 leukemia, and the results are shown in Table 1. A T/C 125% was taken as the criterion of activity. Compound **6f** possessing the 4-chlorophenyl carbamate moiety showed the most potent activity with a T/C of 221% and 256% at a daily dosage of 2.0 and 4.0 mg/kg for four days, respectively. Compound **6a** possessing the phenyl carbamate moiety also showed significant activity with a T/C of 202% (2.0 mg/kg). Surprisingly, these compounds exhibited significant in vivo efficacy despite showing IC_{50} values in the micromolar range, and in addition, these activities considerably increased compared to that of **5**. This difference in activity between **5** and **6a** resulted from substituents at the C9 position; thus, it is apparent that the R^2 or R^3 substituents at the C9 position significantly influence the in vivo activity of the 9-acetoxy enediyne compounds **6**. On the other hand, although a high in vitro cytotoxicity was observed with **6i** and **6j**, these compounds showed only modest in vivo efficacy (T/C = 151% and 157% at 2.0 mg/kg, respectively). Thus, the in vivo antitumor activity of the enediyne compounds with an aryl carbamate moiety was not parallel with their in vitro cytotoxicity as was often observed. This inconsistency is considered to be due to an absorption or a metabolism of **6**.

For the stereochemistry–activity relationships about the C9 position, the (9*R**)-isomers of **6c**, **6g**, and **6j** showed higher potency than the corresponding (9*S**)-isomers, and this result was consistent with that of the in vitro cytotoxicity. In case of a daily dosage of 2.0 mg/kg for four days, compound (9*R**)-**6j** did not exhibit any life-prolongation judging from the fact that the average body weight was considerably reduced in mice. This toxicity observed in case of the (9*R**)-isomers tended to be more serious than that of the corresponding (9*S**)-isomers.

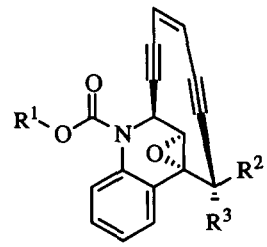
Compounds **6a** and **6f** were further evaluated against various solid tumors (Meth A sarcoma, Colon 26 adenocarcinoma, and Lewis lung carcinoma) in mice as shown in Table 2. Both compounds **6a** and **6f** were effective against the Meth A sarcoma in mice, causing 71 and 77% inhibition of the tumor growth at dosages of 2.0 and 3.0 mg/kg, respectively, whereas these compounds were only slightly or not effective against both the Colon 26 adenocarcinoma and Lewis lung carcinoma in mice.

Conclusion

The 9-acetoxy enediyne compounds **6a–k**, simple dynemicin A (**1**) analogues equipped with aryl carbamate moieties, were synthesized using a CsF-promoted cyclization method. DNA-cleaving ability of these compounds was evaluated with in vitro cytotoxicity against the human carcinoma KB cell line, and in vivo antitumor activity against murine P388 leukemia and various solid tumors. Both compounds **6a** and **6f** possessing the phenyl and 4-chlorophenyl carbamate moieties, respectively, showed significant activity (T/C > 200%) against the murine P388 leukemia in mice, in spite of having IC_{50} values in the micromolar range. In particular, compound **6f** exhibited the most potent activity with a maximum T/C of 256% at a daily dosage of 4.0 mg/kg for four days. In contrast to **6f**, compound **6i** possessing the 2-nitrophenyl carbamate moiety showed only a slight in vivo activity (T/C = 151% at 2.0 mg/kg × 4), although it had about one order of magnitude higher in vitro cytotoxicity than **6f**. These results show that the aryl carbamate moiety in **6** plays an important role in the in vivo antitumor activity, and that the 4-chlorophenyl carbamate in **6f** is the most effective *N*-protecting group. For the stereochemistry–activity relationships at the C9 position, the (9*R**)-isomers of **6c**, **6g**, and **6j** showed higher in vitro and in vivo potencies than the corresponding (9*S**)-isomers. Thus, we found that the stereochemistry of the C9 position significantly affected the biological activity of **6**. Furthermore, both compounds **6a** and **6f** were effective against the Meth A sarcoma in mice, which inhibited 71 and 77% of the tumor growth at dosages of 2.0 and 3.0 mg/kg, respectively.

Recently, some examples supporting different mechanisms from radical one for biological activity of the synthetic enediyne compounds have been reported. Magnus et al. have shown that the dynemicin A analogue **4** undergoes cycloaromatization via a nondiradical pathway and exhibits both in vitro and in vivo

Table 1. Preparation and biological data of the 9-acetoxy enediyne compounds **6a–k**



Compd No	R^1	R^2	R^3	Synthetic method	Formula[a]	In vitro cytotoxicity against KB cells IC_{50} (μM)[b]	In vivo antitumor activity against P388 leukemia[c] Dose (mg/kg)	AWC[d] (g)	T/C[e] (%)
6a	Ph	H	OAc[f]	B	$C_{25}H_{17}NO_5$	2.3	0.25	−0.54	128
							0.5	−1.57	147
							1.0	−1.71	154
							2.0	−3.17	202
6b	2-F-Ph	H	OAc[f]	A	$C_{25}H_{16}FNO_5$	3.5			NT
(9*S**)-**6c**	4-F-Ph	H	OAc	A	$C_{25}H_{16}FNO_5$	4.0	2.0	−1.77	157
(9*R**)-**6c**	4-F-Ph	OAc	H	A	$C_{25}H_{16}FNO_5$	1.1	2.0	−3.39	183
6d	2-Cl-Ph	H	OAc[f]	A	$C_{25}H_{16}ClNO_5$	3.1	2.0	−2.09	154
6e	3-Cl-Ph	H	OAc[f]	A	$C_{25}H_{16}ClNO_5$	1.5	2.0	−2.99	176
6f	4-Cl-Ph	H	OAc[f]	A, B	$C_{25}H_{16}ClNO_5$	3.6	0.5	−0.40	144
							1.0	−0.31	144
							2.0	−1.94	221
							4.0	−2.56	256
(9*S**)-**6g**	2,4-Cl_2-Ph	H	OAc	A	$C_{25}H_{15}Cl_2NO_5$	4.2	2.0	−1.15	160
(9*R**)-**6g**	2,4-Cl_2-Ph	OAc	H	A	$C_{25}H_{15}Cl_2NO_5$	3.3	2.0	−1.44	176
6h	4-MeO-Ph	H	OAc[f]	A	$C_{26}H_{19}NO_6$	2.3	2.0	−2.07	157
6i	2-NO_2-Ph	H	OAc[f]	A	$C_{25}H_{16}N_2O_7$	0.17	2.0	−1.86	151
6j	4-NO_2-Ph	H	OAc[f]	A	$C_{25}H_{16}N_2O_7$	0.49	2.0	−1.21	157
(9*S**)-**6j**	4-NO_2-Ph	H	OAc	A	$C_{25}H_{16}N_2O_7$	1.1	2.0	−3.01	182
(9*R**)-**6j**	4-NO_2-Ph	OAc	H	A	$C_{25}H_{16}N_2O_7$	0.12	1.25	−2.89	179
							2.0	−3.73	114(toxic)
6k	2-Naphthyl	H	OAc[f]	B	$C_{29}H_{19}NO_5$	5.6	2.0	−1.03	164
5	Ph	Me	OH	—	—	5.0	2.0	−1.77	165

[a]Analysis for C, H, and N are within 0.4% of theory. [b]Inhibiting concentration (μM) of 50% cellular growth. [c]CDF_1 mice were inoculated intraperitoneally (ip) with 1×10^6 cells/mouse of P388 on day 0, and the test compound was administered ip once daily for 4 days from day 1 to 4. [d]Average weight changes (AWC) were measured on day 4. [e]The T/C represents the ratio of mean survival time of the treated to the control mice × 100. The T/C values over 125% are considered indicative of significant activity. [f]A 2:1 mixture of diastereomers.

antitumor activity.[21] It has been concluded that the diradical formation in **4** is not necessary for the antitumor activity. Nicolaou et al. have shown that the cytotoxicity of the enediyne compound such as **2** results from a potent induction of apoptosis primarily in human leukemic cells.[40] Zein et al. have also reported that the synthetic enediyne compound, the simple core of the calicheamicins and esperamicins, causes protein damage to several cellular proteins.[41] In the mechanistic studies, the 9-acetoxy enediyne compounds **6** scarcely showed DNA-cleaving activity, because the aryl carbamate moiety in these enediyne compounds could not be deprotected under neutral conditions. In contrast to the natural enediyne compounds, the relatively high concentrations of the synthetic enediyne compounds required for DNA cleavage suggest that other mechanisms might contribute to the observation of both the in vitro and in vivo activity.

Experimental

Melting points were measured on a Yanaco MP-l apparatus without correction. Infrared (IR) spectra were recorded on a Jasco FT/IR-8000 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM GSX-270 (270 MHz) spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM GSX-270 (67.9 MHz) spectrometer. 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, m = multiplet, br = broad. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on JEOL JMS-DX300 and JMS-SX1020 spectrometers. Elemental analyses were performed with a Yanaco CHN CORDER MT-3.

Table 2. Antitumor activity of compounds **6a** and **6f** against solid tumors in mice

Compound No	Dose (mg/kg)	Meth A sarcoma[a] AWC(g)	Meth A sarcoma[a] Avg tumor weight (T/C)	Colon 26 adenocarcinoma[a] AWC (g)	Colon 26 adenocarcinoma[a] Avg tumor weight (T/C)	Lewis lung carcinoma[b] AWC (g)	Lewis lung carcinoma[b] Avg tumor weight (T/C)
Control		+0.57	1.00	+0.46	1.00	+0.46	1.00
6a	1.0	−0.28	0.52±0.09	−0.98	0.76±0.04	−0.48	0.72±0.26
	2.0	−1.33	0.29±0.10	−1.64	0.41±0.05	−1.40	0.46±0.05
6f	1.0			−0.49	0.94+0.12		
	2.0	−1.05	0.44±0.09	−1.71	0.56±0.09	−1.02	0.57±0.08
	3.0	−2.12	0.23±0.06				
	4.0					−1.66	toxic

[a]CDF_1 mice were inoculated subcutaneously (sc) with 1×10^6 cells/mouse of Meth A sarcoma and Colon 26 adenocarcinoma on day 0, respectively, and the test compound was administered intraperitoneally (ip) once daily for 4 days from day 1 to 4. Average weight changes (AWC) were measured on day 4, and the average tumor weights were measured on day 15. [b]BDF_1 mice were inoculated sc with 5×10^5 cells/mouse of Lewis lung carcinoma on day 0, and the test compound was administered ip once daily for 4 days from day 1 to 4. Average weight changes (AWC) were measured on day 4, and the average tumor weights were measured on day 14.

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-*tert*-Butyldimethylsilyloxymethyl-2-ethynyl-1-(2-fluorophenyloxycarbonyl)-1,2-dihydroquinoline (8b): representative procedure .A solution of silyl ether **7**[18c,22e] (7.69 g, 28.2 mmol) in dry THF (60 mL) was cooled to −70 °C and treated with ethynylmagnesium bromide (Aldrich, 68.0 mL of a 0.5 M solution in THF, 33.8 mmol). The solution was briefly warmed to 0 °C and cooled to −70 °C again, and 2-fluorophenyl chloroformate[42] (5.90 g, 33.8 mmol) was added, and then the reaction mixture was allowed to slowly warm to 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated NH_4Cl solution (20 mL), extracted with AcOEt (150 mL × 2). The combined organic layers were washed with saturated $NaHCO_3$ solution (40 mL), brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2:*n*-hexane = 2:1) to give **8b** (12.3 g, quantitative) as a colorless gum. ^1H NMR ($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.95 (9H, s, *t*-Bu), 2.25 (1H, d, *J* = 2.4 Hz, C≡C*H*), 4.55 and 4.71 (each 1H, d, *J* = 14.2 Hz, O–CH_2), 6.01 (1H, dd, *J* = 6.8, 2.4 Hz, N–C*H*), 6.20 (1H, d, *J* = 6.8 Hz, C=C*H*), 7.1–7.4 (7H, m, aromatic), 7.78 (1H, d, *J* = 7.5 Hz, aromatic). MS (EI) *m/z*: 437 (M^+). HRMS for $C_{25}H_{28}FNO_3Si$ (M^+) calcd 437.1822, found 437.1830.

The following compounds were prepared by a procedure similar to that described for **8b**.

4-*tert*-Butyldimethylsilyloxymethyl-2-ethynyl-1-(4-fluorophenyloxycarbonyl)-1,2-dihydroquinoline (8c). Yield: 10.0 g (quantitative) as a colorless gum. ^1H NMR($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.95 (9H, s, *t*-Bu), 2.24 (1H, d, *J* = 2.4 Hz, C≡C*H*), 4.54 and 4.70 (each 1H, d, *J* = 14.2 Hz, O–CH_2), 6.01 (1H, dd, *J* = 6.8, 2.4 Hz, N–C*H*), 6.19 (1H, d, *J* = 6.8, 2.4 Hz, C=C*H*), 7.0–7.4 (7H, m, aromatic), 7.73 (1H, br d, *J* = 7.5 Hz, aromatic). MS (EI) *m/z*: 437 (M^+). HRMS for $C_{25}H_{28}FNO_3Si$ (M^+) calcd 437.1822, found 437.1832.

4-*tert*-Butyldimethylsilyloxymethyl-1-(2-chlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydroquinoline (8d). Yield: 13.8 g (quantitative) as a colorless gum. ^1H NMR ($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.95 (9H, s, *t*-Bu), 2.25 (1H, d, *J* = 2.4 Hz, C≡C*H*), 4.55 and 4.71 (each 1H, d, *J* = 14.2 Hz, O–CH_2), 6.07 (1H, m, N–C*H*), 6.20 (1H, d, *J* = 6.8 Hz, C=C*H*), 7.1–7.5 (7H, m, aromatic), 7.78 (1H, d, *J* = 7.8 Hz, aromatic). MS (EI) *m/z*: 453 (M^+; ^{35}Cl), 455 (M^+; ^{37}Cl). HRMS for $C_{25}H_{28}ClNO_3Si$ (M^+) calcd 453.1527, found 453.1536.

4-*tert*-Butyldimethylsilyloxymethyl-1-(3-chlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydroquinoline (8e). Yield: 11.6 g (quantitative) as a colorless gum. ^1H NMR ($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.95 (9H, s, *t*-Bu), 2.25 (1H, d, *J* = 2.4Hz, C≡C*H*), 4.54 and 4.70 (each 1H, d, *J* = 14.2 Hz, O–CH_2), 6.00 (1H, d, *J* = 6.8 Hz, N–C*H*), 6.19 (1H, d, *J* = 6.8 Hz, C=C*H*), 7.1–7.4 (7H, m, aromatic), 7.72 (1H, br d, *J* = 7.5 Hz, aromatic). MS (EI) *m/z*: 453 (M^+; ^{35}Cl), 455 (M^+; ^{37}Cl). HRMS for $C_{25}H_{28}ClNO_3Si$ (M^+) calcd 453.1527, found 453.1530.

4-*tert*-Butyldimethylsilyloxymethyl-1-(4-chlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydroquinoline (8f). Yield: 10.0 g (quantitative) as a colorless gum. ^1H NMR ($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.95 (9H, s, *t*-Bu), 2.23 (1H, d, *J* = 2.4 Hz, C≡C*H*), 4.54 and 4.70 (each 1H, d, *J* = 14.2 Hz, O–CH_2), 6.00 (1H, d, *J* = 6.8 Hz, N–C*H*), 6.19 (1H, d, *J* = 6.8 Hz, C=C*H*), 7.1–7.4 (7H, m, aromatic), 7.71 (1H, br d, *J* = 7.5 Hz, aromatic). MS (EI) *m/z*: 453 (M^+; ^{35}Cl), 455 (M^+; ^{37}Cl). HRMS for $C_{25}H_{28}ClNO_3Si$ (M^+) calcd 453.1527, found 453.1520.

4-*tert*-Butyldimethylsilyloxymethyl-1-(2,4-dichlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydroquinoline (8g). Yield: 12.0 g (quantitative) as a colorless gum. ^1H NMR ($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.95 (9H, s, *t*-Bu), 2.23 (1H, d, *J* = 2.4 Hz, C≡C*H*), 4.55 and 4.71 (each

1H, d, J = 14.2 Hz, O–CH_2), 6.04 (1H, m, N–C*H*), 6.20 (1H, d, J = 6.8 Hz, C=C*H*), 7.1–7.5 (6H, m, aromatic), 7.84 (1H, d, J = 7.8 Hz, aromatic). MS (EI) m/z: 487 (M^+), 489 [$(M+2)^+$], 491 [$(M+4)^+$]. HRMS for $C_{25}H_{27}Cl_2NO_3Si$ (M^+) calcd 487.1137, found 487.1131.

4-*tert*-Butyldimethylsilyloxymethyl-2-ethynyl-1-(4-methoxyphenyloxycarbonyl)-1,2-dihydroquinoline (8h). Yield: 14.7 g (quantitative) as a colorless gum. ^{1}H NMR ($CDCl_3$) δ 0.09 (6H, s, $SiMe_2$), 0.90 (9H, s, t-Bu), 2.19 (1H, d, J = 2.4 Hz, C≡C*H*), 3.75 (3H, s, OMe), 4.52 and 4.66 (each 1H, dd, J = 14.2, 1.5 Hz, O–CH_2), 5.99 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.14 (1H, d, J = 6.8 Hz, C=C*H*), 6.8–7.4 (7H, m, aromatic), 7.71 (1H, br d, J = 7.5 Hz, aromatic). MS (EI) m/z: 449 (M^+). HRMS for $C_{26}H_{31}NO_4Si$ (M^+) calcd 449.2022, found 449.2036.

4-*tert*-Butyldimethylsilyloxymethyl-2-ethynyl-1,2-dihydro-1-(2-nitrophenyloxycarbonyl)quinoline (8i). Yield: 13.3 g (quantitative) as a colorless gum. ^{1}H NMR ($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.92 (9H, s, t-Bu), 2.27 (1H, d, J = 2.4 Hz, C≡C*H*), 4.56 (1H, d, J = 14.2 Hz, O–C*H*H), 4.72 (1H, dd, J = 14.2, 1.5 Hz, O–CH*H*), 6.01 (1H, m, N–C*H*), 6.21 (1H, dt, J = 6.8, 1.5 Hz, C=C*H*), 7.2–7.5 (4H, m, aromatic), 7.41 (1H, m, aromatic), 7.66 (1H, t, J = 7.8 Hz, aromatic), 7.81 (1H, dd, J = 8.3, 1.5 Hz, aromatic), 7.88 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) m/z: 464 (M^+). HRMS for $C_{25}H_{28}N_2O_5Si$ (M^+) calcd 464.1767, found 464.1783.

4-*tert*-Butyldimethylsilyloxymethyl-2-ethynyl-1,2-dihydro-1-(4-nitrophenyloxycarbonyl)quinoline (8j). Yield: 23.3 g (quantitative) as a colorless gum. ^{1}H NMR ($CDCl_3$) δ 0.14 (6H, s, $SiMe_2$), 0.95 (9H, s, t-Bu), 2.27 (1H, d, J = 2.4 Hz, C≡C*H*), 4.55 (1H, d, J = 14.2 Hz, O–C*H*H), 4.71 (1H, dd, J = 14.2, 1.5 Hz, O–CH*H*), 5.99 (1H, m, N–C*H*), 6.21 (1H, d, J = 6.8 Hz, C=C*H*), 7.2–7.4 (5H, m, aromatic), 7.73 (1H, m, aromatic), 8.27 (2H, m, aromatic). MS (EI) m/z: 464 (M^+). HRMS for $C_{25}H_{28}N_2O_5Si$ (M^+) calcd 464.1767, found 464.1779.

2-Ethynyl-1-(2-fluorophenyloxycarbonyl)-1,2-dihydro-4-hydroxymethylquinoline (9b): representative procedure. To a solution of silyl ether **8b** (9.10 g, 20.8 mmol) in MeOH (100 mL) and CH_2Cl_2 (30 mL) was added pTsOH·H_2O (2.60 g, 13.7 mmol), followed by stirring at 0 °C for 1 h. The reaction mixture was treated with pyridine (1.08 g, 13.7 mmol), and then evaporated in vacuo. The residue was dissolved in AcOEt (300 mL) and the solution was washed with water (100 mL), brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **9b** (6.3 g, 93%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.25 (1H, d, J = 2.4 Hz, C≡C*H*), 4.59 (2H, s, CH_2OH), 6.00 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.19 (1H, d, J = 6.8 Hz, C=C*H*), 7.0–7.4 (7H, m, aromatic), 7.78 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) m/z: 323 (M^+). HRMS for $C_{19}H_{14}FNO_3$ (M^+) calcd 323.0958, found 323.0963.

The following compounds were prepared by a procedure similar to that described for **9b**.

2-Ethynyl-1-(4-fluorophenyloxycarbonyl)-1,2-dihydro-4-hydroxymethylquinoline (9c). Yield: 9.0 g (95%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.73 (1H, s, O*H*), 2.25 (1H, d, J = 2.4 Hz, C≡C*H*), 4.62 (2H, s, CH_2OH), 6.02 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.20 (1H, d, J = 6.8 Hz, C=C*H*), 7.0–7.4 (7H, m, aromatic), 7.74 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) m/z: 323 (M^+). HRMS for $C_{19}H_{14}FNO_3$ (M^+) calcd 323.0958, found 323.0970.

1-(2-Chlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydro-4-hydroxymethylquinoline (9d). Yield: 8.4 g (97%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.26 (1H, d, J = 2.4 Hz, C≡C*H*), 4.58 (2H, s, CH_2OH), 6.06 (1H, m, N–C*H*), 6.22 (1H, d, J = 6.8 Hz, C=C*H*), 7.1–7.5 (7H, m, aromatic), 7.88 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) m/z: 339 (M^+; ^{35}Cl), 341 (M^+; ^{37}Cl). HRMS for $C_{19}H_{14}ClNO_3$ (M^+) calcd 339.0662, found 339.0658.

1-(3-Chlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydro-4-hydroxymethylquinoline (9e). Yield: 8.0 g (93%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.71 (1H, s, O*H*), 2.26 (1H, d, J = 2.4 Hz, C≡C*H*), 4.63 (2H, s, CH_2OH), 6.00 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.22 (1H, d, J = 6.8 Hz, C=C*H*), 7.1–7.5 (7H, m, aromatic), 7.72 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) m/z: 339 (M^+; ^{35}Cl), 341 (M^+; ^{37}Cl). HRMS for $C_{19}H_{14}ClNO_3$ (M^+) calcd 339.0662, found 339.0677.

1-(4-Chlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydro-4-hydroxymethylquinoline (9f). Yield: 7.0 g (98%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.87 (1H, br t, J = 5.9 Hz, O*H*), 2.23 (1H, d, J = 2.4 Hz, C≡C*H*), 4.60 (2H, d, J = 5.9 Hz, CH_2OH), 6.01 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.19 (1H, d, J = 6.8 Hz, C=C*H*), 7.0–7.4 (7H, m, aromatic), 7.75 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) m/z: 339 (M^+; ^{35}Cl), 341 (M^+; ^{37}Cl). HRMS for $C_{19}H_{14}ClNO_3$ (M^+) calcd 339.0662, found 339.0666.

1-(2,4-Dichlorophenyloxycarbonyl)-2-ethynyl-1,2-dihydro-4-hydroxymethylquinoline (9g). Yield: 9.4 g (95%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.79 (1H, s, O*H*), 2.26 (1H, d, J = 2.4 Hz, C≡C*H*), 4.61 (2H, s, CH_2OH), 6.03 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.20 (1H, d, J = 6.8 Hz, C=C*H*), 7.1–7.5 (6H, m, aromatic), 7.85 (1H, d, J = 7.8 Hz, aromatic). MS (EI) m/z: 373 (M^+), 375 [$(M+2)^+$], 377 [$(M+4)^+$]. HRMS for $C_{19}H_{13}Cl_2NO_3$ (M^+) calcd 373.0272, found 373.0281.

2-Ethynyl-1,2-dihydro-4-hydroxymethyl-1-(4-methoxyphenyloxycarbonyl)quinoline (9h). Yield: 11.3 g (98%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.73 (1H, br s, O*H*), 2.25 (1H, d, J = 2.4 Hz, C≡C*H*), 3.80 (3H, s, OMe), 4.63 (2H, s, CH_2OH), 6.04 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.20 (1H, d, J = 6.8 Hz, C=C*H*), 6.9–7.4 (7H, m, aromatic), 7.76 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) m/z: 335 (M^+). HRMS for $C_{20}H_{17}NO_4$ (M^+) calcd 335.1157, found 335.1151.

2-Ethynyl-1,2-dihydro-4-hydroxymethyl-1-(2-nitrophenyloxycarbonyl)quinoline (9i). Yield: 7.9 g (93%) as a colorless solid. ^{1}H NMR($CDCl_3$) δ 2.27 (1H, d, J = 2.4 Hz, C≡C*H*), 4.62 (2H, s, CH_2OH), 6.02 (1H, m, N–C*H*), 6.22 (1H, dt, J = 6.8, 1.5 Hz, C=C*H*), 6.9–7.4 (5H, m, aromatic), 7.67 (1H, m, aromatic), 7.88 (1H, dd, J = 7.8, 1.5 Hz, aromatic), 8.14 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) m/z: 350 (M^+). HRMS for $C_{19}H_{14}N_2O_5$ (M^+) calcd 350.0902, found 350.0912.

2-Ethynyl-1,2-dihydro-4-hydroxymethyl-1-(4-nitrophenyloxycarbonyl)quinoline (9j). Yield: 12.0 g (96%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.90 (1H, br s, O*H*), 2.27 (1H, d, J = 2.4 Hz, C≡C*H*), 4.63 (2H, s, CH_2OH), 6.00 (1H, dd, J = 6.8, 2.4 Hz, N–C*H*), 6.22 (1H, d, J = 6.8 Hz, C=C*H*), 7.2–7.4 (5H, m, aromatic), 7.71 (1H, m, aromatic), 8.27 (2H, m, aromatic). MS (EI) m/z: 350 (M^+). HRMS for $C_{19}H_{14}N_2O_5$ (M^+) calcd 350.0902, found 350.0917.

3,4-Epoxy-2-ethynyl-1-(2-fluorophenyloxycarbonyl)-1,2-,3,4-tetrahydro-4-hydroxymethylquinoline (10b): representative procedure. To a solution of allyl alcohol **9b** (6.70 g, 20.7 mmol) and anhydrous Na_2HPO_4 (8.82 g, 62.1 mmol) in CH_2Cl_2 (120 mL) cooled to 0 °C was added *m*CPBA (7.70 g, 31.1 mmol), followed by stirring at 0 °C for 2h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with aqueous $Na_2S_2O_3$ (100 mL) and 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 gel, CH_2Cl_2:ether = 20:1) to give **10b** (3.6 g, 92%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.21 (1H, br s, C≡C*H*), 2.38 (1H, m, O*H*), 4.10 (1H, d, J =2.4 Hz, epoxide), 4.15 (1H, m, C*H*HOH), 4.44 (1H, dd, J = 12.7, 4.9 Hz, CH*H*OH), 5.88 (1H, m, N–C*H*), 7.0–7.3 (5H, m, aromatic), 7.3–7.5 (1H, m, aromatic), 8.22 (2H, m, aromatic). MS (EI) m/z: 339 (M^+). HRMS for $C_{19}H_{14}FNO_4$ (M^+) calcd 339.0907, found 339.0914.

The following compounds were prepared by a procedure similar to that described for **10b**.

3,4-Epoxy-2-ethynyl-1-(4-fluorophenyloxycarbonyl)-1,2,3,4-tetrahydro-4-hydroxymethylquinoline (10c). Yield: 9.3 g (98%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.20 (1H, br s, C≡C*H*), 2.32 (1H, dd, J = 7.8, 5.4 Hz, O*H*), 4.10 (1H, d, J = 2.4 Hz, epoxide), 4.13 and 4.45 (each 1H, dd, J = 12.7, 5.4 Hz, CH_2OH), 5.88 (1H, m, N–C*H*), 7.0–7.1 (4H, m, aromatic), 7.26 (1H, dt, J = 7.3, 1.5 Hz, aromatic), 7.39 (1H, dt, J = 7.3, 1.5 Hz, aromatic), 7.55 (1H, d, J = 7.3 Hz, aromatic). MS (EI) m/z: 339 (M^+). HRMS for $C_{19}H_{14}FNO_4$ (M^+) calcd 339.0907, found 339.0919.

1-(2-Chlorophenyloxycarbonyl)-3,4-epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-hydroxymethylquinoline (10d). Yield: 9.7 g (97%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.94 (1H, dd, J = 8.3, 5.4 Hz, O*H*), 2.22 (1H, br s, C≡C*H*), 4.13 (1H, d, J = 2.4 Hz, epoxide), 4.14 (1H, dd, J = 12.7, 8.3 Hz, C*H*HOH), 4.51 (1H, dd, J = 12.7, 5.4 Hz, CH*H*OH), 5.93 (1H, m, N–C*H*), 7.1–7.5 (6H, m, aromatic), 7.57 (1H, d, J = 7.3 Hz, aromatic), 7.72 (1H, d, J = 7.3 Hz, aromatic). MS (EI) m/z: 355 (M^+; ^{35}Cl), 357 (M^+; ^{37}Cl). HRMS for $C_{19}H_{14}ClNO_4$ (M^+) calcd 355.0611, found 355.0605.

1-(3-Chlorophenyloxycarbonyl)-3,4-epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-hydroxymethylquinoline (10e). Yield: 7.9 g (93%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.97 (1H, m, O*H*), 2.22 (1H, br s, C≡C*H*), 4.12 (1H, d, J = 2.4 Hz, epoxide), 4.13 (1H, dd, J = 12.7, 7.8 Hz, C*H*HOH), 4.48 (1H, dd, J = 12.7, 3.9 Hz, CH*H*OH), 5.87 (1H, m, N–C*H*), 7.04 (1H, m, aromatic), 7.20 (2H, dd, J = 7.8, 1.5 Hz, aromatic), 7.32 (2H, dt, J = 7.8, 1.5 Hz, aromatic), 7.44 (1H, m, aromatic), 7.57 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) m/z: 355 (M^+; ^{35}Cl), 357 (M^+; ^{37}Cl). HRMS for $C_{19}H_{14}ClNO_4$ (M^+) calcd 355.0611, found 355.0622.

1-(4-Chlorophenyloxycarbonyl)-3,4-epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-hydroxymethylquinoline (10f). Yield: 7.1 g (99%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.17 (1H, br s, O*H*), 2.20 (1H, br s, C≡C*H*), 4.10 (1H, d, J = 2.4 Hz, epoxide), 4.13 (1H, dd, J = 12.7, 7.8 Hz, C*H*HOH), 4.46 (1H, dd, J = 12.7, 3.9 Hz, CH*H*OH), 5.88 (1H, m, N–C*H*), 7.07 (2H, br d, J = 7.8 Hz, aromatic), 7.2–7.4 (4H, m, aromatic), 7.40 (2H, dt, J = 7.8, 1.5 Hz, aromatic), 7.44 (1H, m, aromatic), 7.55 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) m/z: 355 (M^+; ^{35}Cl), 357 (M^+; ^{37}Cl). HRMS for $C_{19}H_{14}ClNO_4$ (M^+) calcd 355.0611, found 355.0618.

1-(2,4-Dichlorophenyloxycarbonyl)-3,4-epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-hydroxymethylquinoline (10g). Yield: 7.9 g (95%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.06 (1H, dd, J = 7.8, 5.4 Hz, O*H*), 2.22 (1H, br s, C≡C*H*), 4.12 (1H, d, J = 2.4 Hz, epoxide), 4.16 (1H, dd, J = 12.7, 7.8 Hz, C*H*HOH), 4.46 (1H, dd, J = 12.7, 5.4 Hz, CH*H*OH), 5.89 (1H, m, N–C*H*), 7.0–7.4 (5H, m, aromatic), 7.56 (1H, d, J = 7.8 Hz, aromatic), 7.67 (1H, dd, J = 7.8, 1.8 Hz, aromatic). MS (EI) m/z: 389 (M^+), 391 [$(M+2)^+$], 393 [$(M+4)^+$]. HRMS for $C_{19}H_{13}Cl_2NO_4$ (M^+) calcd 389.0221, found 389.0202.

3,4-Epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-(4-methoxyphenyloxycarbonyl)quinoline (10h). Yield: 9.4 g (80%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.05 (1H, m, O*H*), 2.21 (1H, br s, C≡C*H*), 3.78 (3H, s, OMe), 4.11 (1H, d, J = 2.4 Hz, epoxide), 4.06 and 4.48 (each 1H, dd, J = 12.7, 5.4 Hz, CH_2OH), 5.91 (1H, m, N–C*H*), 6.87 (2H, m, aromatic), 7.08 (2H, d, J = 8.8 Hz, aromatic), 7.26 (1H, m, aromatic), 7.40 (1H, dt, J = 7.3, 1.5 Hz, aromatic), 7.56 (2H, m, aromatic). MS (EI) m/z: 351 (M^+). HRMS for $C_{20}H_{17}NO_5$ (M^+) calcd 351.1106, found 351.1123.

3,4-Epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-(2-nitrophenyloxycarbonyl)quinoline (10i). Yield: 9.2 g (98%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.97 (1H, dd, J = 7.8, 5.4 Hz, O*H*), 2.23 (1H, br s, C≡C*H*), 4.13 (1H, d, J = 2.4 Hz, epoxide), 4.17 (1H, dd, J = 12.7, 7.8 Hz, C*H*HOH), 4.51 (1H, dd, J = 12.7, 5.4 Hz, CH*H*OH), 5.87 (1H, m, N–C*H*), 7.2–7.5 (5H, m,

aromatic), 7.59 (1H, m, aromatic), 7.68 (1H, dd, J = 7.8, 1.5 Hz, aromatic), 8.11 (1H, d, J = 7.8 Hz, aromatic). MS (EI) m/z: 366 (M^+). HRMS for $C_{19}H_{14}N_2O_5$ (M^+) calcd 366.0852, found 366.0858.

3,4-Epoxy-2-ethynyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-(4-nitrophenyloxycarbonyl)quinoline (10j). Yield: 7.5 g (98%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.07 (1H, dd, J = 7.8, 5.4 Hz, O*H*), 2.23 (1H, br s, C≡C*H*), 4.13 (1H, d, J = 2.4 Hz, epoxide), 4.17 (1H, dd, J = 12.7, 7.8 Hz, C*H*HOH), 4.50 (1H, dd, J = 12.7, 5.4 Hz, CH*H*OH), 5.88 (1H, m, N–C*H*), 7.2–7.6 (5H, m, aromatic), 7.60 (1H, d, J = 7.8 Hz, aromatic), 8.24 (2H, m, aromatic). MS (EI) m/z: 366 (M^+). HRMS for $C_{19}H_{14}N_2O_6$ (M^+) calcd 366.0852, found 366.0864.

3,4-Epoxy-1-(2-fluorophenyloxycarbonyl)-1,2,3,4-tetrahydro-4-hydroxymethyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12b): representative procedure. A mixture of (*Z*)-1-chloro-4-trimethylsilyl-1-buten-3-yne (**11**)[24a] (3.18 g, 20.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$[43] (260 mg, 0.25 mmol), PPh_3 (260 mg, 1.00 mmol) and CuI (190 mg, 1.00 mmol) in dry, degassed THF (100 mL) was stirred under argon at 25 °C for 1 h. The resulting dark red solution was cooled to 0 °C, and the epoxy alcohol **10b** (3.40 g, 10.0 mmol) in dry, degassed THF (50 mL) was added, followed by *n*-butylamine (1.46 g, 20.0 mmol). The reaction mixture was stirred at 25 °C for 2 h and quenched with saturated NH_4Cl solution (50 mL), extracted with AcOEt (150 mL × 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **12b** (1.4 g, 36%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 2.10 (1H, dd, J = 8.3, 5.4 Hz, O*H*), 4.13 (1H, d, J = 2.9 Hz, epoxide), 4.14 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.48 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.67 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.80 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.13 (1H, m, N–C*H*), 7.2–7.6 (5H, m, aromatic), 7.39 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.58 (2H, m, aromatic). MS (EI) m/z: 461 (M^+). HRMS for $C_{26}H_{24}FNO_4Si$ (M^+) calcd 461.1458, found 461.1451.

The following compounds were prepared by a procedure similar to that described for **12b**.

3,4-Epoxy-1-(4-fluorophenyloxycarbonyl)-1,2,3,4-tetrahydro-4-hydroxymethyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12c). Yield: 3.8 g (50%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 2.07 (1H, dd, J = 8.3, 5.4 Hz, O*H*), 4.12 (1H, d, J = 2.9 Hz, epoxide), 4.13 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.48 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.66 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.81 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.13 (1H, m, N–C*H*), 7.0–7.2 (4H, m, aromatic), 7.26 (1H, m, aromatic), 7.38 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.56 (2H, br d, J = 7.8 Hz, aromatic). MS (EI) m/z: 461 (M^+). HRMS for $C_{26}H_{24}FNO_4Si$ (M^+) calcd 461.1458, found 461.1445.

1-(2-Chlorophenyloxycarbonyl)-3,4-epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12d). Yield: 2.9 g (38%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 1.94 (1H, dd, J = 8.3, 5.4 Hz, O*H*), 4.15 (1H, d, J = 2.9 Hz, epoxide), 4.16 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.51 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.68 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.81 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.16 (1H, m, N–C*H*), 7.1–7.3 (4H, m, aromatic), 7.3–7.5 (2H, m, aromatic), 7.57 (1H, d, J = 7.8 Hz, aromatic), 7.71 (1H, d, J = 8.8 Hz, aromatic). MS (EI) m/z: 477 (M^+; ^{35}Cl), 479 (M^+; ^{37}Cl). HRMS for $C_{26}H_{24}ClNO_4Si$ (M^+) calcd 477.1163, found 477.1175.

1-(3-Chlorophenyloxycarbonyl)-3,4-epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12e). Yield: 2.5 g (39%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.23 (9H, s, $SiMe_3$), 1.88 (1H, br, O*H*), 4.14 (1H, d, J = 2.9 Hz, epoxide), 4.16 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.51 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.68 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.82 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.12 (1H, m, N–C*H*), 7.1–7.3 (5H, m,aromatic), 7.40 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.58 (2H, m, aromatic). MS (EI) m/z: 477 (M^+; ^{35}Cl), 479 (M^+; ^{37}Cl). HRMS for $C_{26}H_{24}ClNO_4Si$ (M^+) calcd 477.1163, found 477.1181.

1-(4-Chlorophenyloxycarbonyl)-3,4-epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12f). Yield: 3.5 g (49%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 2.07 (1H, br, O*H*), 4.12 (1H, d, J = 2.9 Hz, epoxide), 4.17 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.47 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.66 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.80 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.12 (1H, m, N–C*H*), 7.12 (2H, d, J = 8.8 Hz, aromatic), 7.2–7.4 (3H, m, aromatic), 7.38 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.5–7.6 (2H, m, aromatic). MS (EI) m/z: 477 (M^+; ^{35}Cl), 479 (M^+; ^{37}Cl). HRMS for $C_{26}H_{24}ClNO_4Si$ (M^+) calcd 477.1163, found 477.1159.

1-(2,4-Dichlorophenyloxycarbonyl)-3,4-epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12g). Yield: 4.4 g (53%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 1.88 (1H, dd, J = 8.3, 5.4 Hz, O*H*), 4.15 (1H, d, J = 2.9 Hz, epoxide), 4.16 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.51 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.66 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.82 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.13 (1H, m, N–C*H*), 7.0–7.5 (5H, m, aromatic), 7.57 (1H, d, J = 7.8 Hz, aromatic), 7.67 (1H, dd, J = 8.3, 1.5 Hz, aromatic). MS (EI) m/z: 511 (M^+), 513 [$(M+2)^+$], 515 [$(M+4)^+$]. HRMS for $C_{26}H_{23}Cl_2NO_4Si$ (M^+) calcd 511.0773, found 511.0779.

3,4-Epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-1-(4-methoxyphenyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12h). Yield: 6.9 g (63%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 1.89 (1H, dd, J = 7.8, 5.4 Hz, O*H*), 3.79 (3H, s, OMe),

4.14 (1H, d, J = 2.9 Hz, epoxide), 4.15 (1H, dd, J = 12.2, 7.8 Hz, C*H*HOH), 4.51 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.66 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.81 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.15 (1H, m, N–C*H*), 6.87 (2H, m, aromatic), 7.08 (2H, br d, J = 8.8 Hz, aromatic), 7.27 (1H, m, aromatic), 7.39 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.56 (2H, br d, J = 7.8 Hz, aromatic). MS (EI) *m/z*: 473 (M^+). HRMS for $C_{27}H_{27}NO_5Si$ (M^+) calcd 473.1658, found 473.1671.

3,4-Epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-1-(2-nitrophenyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12i). Yield: 2.1 g (34%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 1.88 (1H, dd, J = 8.3, 5.4 Hz, O*H*), 4.15 (1H, d, J = 2.9 Hz, epoxide), 4.16 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.51 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.68 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.81 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.11 (1H, m, N–C*H*), 7.1–7.5 (5H, m, aromatic), 7.59 (1H, m, aromatic), 7.66 (1H, dd, J = 7.8, 1.5 Hz, aromatic), 7.71 (1H, d, J = 6.8 Hz, aromatic). MS (EI) *m/z*: 488 (M^+). HRMS for $C_{26}H_{24}N_2O_6Si$ (M^+) calcd 488.1403, found 488.1419.

3,4-Epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-1-(4-nitrophenyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12j). Yield: 3.9 g (46%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 2.01 (1H, m, O*H*), 4.15 (1H, d, J = 2.9 Hz, epoxide), 4.16 (1H, dd, J = 12.2, 8.3 Hz, C*H*HOH), 4.50 (1H, dd, J = 12.2, 5.4 Hz, CH*H*OH), 5.67 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.83 (1H, d, J = 11.2 Hz, CH=C*H*C≡CSi), 6.11 (1H, m, N–C*H*), 7.2–7.6 (6H, m, aromatic), 8.24 (2H, d, J = 8.8 Hz, aromatic). MS (EI) *m/z*: 488 (M^+). HRMS for $C_{26}H_{24}N_2O_6Si$ (M^+) calcd 488.1403, found 488.1422.

4-Dimethoxymethylquinoline (15). To a solution of aldehyde **14** (25.0 g, 159 mmol) in MeOH (150 mL) was added $CH(OMe)_3$ (84.8 g, 800 mmol) and *p*TsOH·H_2O (15.1 g, 80.0 mmol), followed by refluxing for 24 h. The reaction mixture was evaporated in vacuo and the resulting residue was dissolved in AcOEt (800 mL). The solution was washed with aqueous $NaHCO_3$ (300 mL), water (200 mL), brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was distilled under reduced pressure to give **15** (31.1 g, 96%) as a pale yellow oil, bp 130–132 °C (3 mmHg). ^{1}H NMR ($CDCl_3$) δ 3.37 (6H, s, OMe × 2), 5.95 (1H, s, C*H*OMe), 7.50 (1H, m, aromatic), 7.63 (1H, d, J = 4.4 Hz, aromatic), 7.75 (1H, m, aromatic), 8.14 (1H, d, J = 8.3 Hz, aromatic), 8.25 (1H, d, J = 8.3 Hz, aromatic), 8.94 (1H, d, J = 4.4 Hz, aromatic). MS (EI) *m/z*: 203 (M^+).

4-Dimethoxymethyl-2-ethynyl-1,2-dihydro-1-phenyloxycarbonylquinoline (16a). Prepared from **15** (10.2 g, 50.0 mmol) by a procedure similar to that described for **8b**. Purified by column chromatography (silica gel, CH_2Cl_2) to give **16a** (17 g, quantitative) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.23 (1H, d, J = 2.4 Hz, C≡C*H*), 3.34 (3H, s, OMe), 3.40 (3H, s, OMe), 5.30 (1H, s, C*H*-OMe), 6.05 (1H, dd, J = 6.3, 2.4 Hz, N–C*H*), 6.41 (1H, d, J = 6.3 Hz, C=C*H*), 7.1–7.4 (7H, m, aromatic), 7.66 (1H, dd, J = 7.8, 1.5 Hz, aromatic), 7.74 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) *m/z*: 349 (M^+). HRMS for $C_{21}H_{19}NO_4$ (M^+) calcd 349.1314, found 349.1310.

4-Dimethoxymethyl-2-ethynyl-1,2-dihydro-1-(2-naphthyloxycarbonyl)quinoline (16k). Prepared from **15** (2.00 g, 9.84 mmol) by a procedure similar to that described for **8b**. Purified by column chromatography (silica gel, CH_2Cl_2) to give **16k** (3.6 g, quantitative) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.25 (1H, d, J = 2.4 Hz, C≡C*H*), 3.35 (3H, s, OMe), 3.41 (3H, s, OMe), 5.31 (1H, s, C*H*–OMe), 6.10 (1H, dd, J = 6.3, 2.4 Hz, N–C*H*), 6.43 (1H, d, J = 6.3 Hz, C=C*H*), 7.23 (1H, t, J = 6.4 Hz, aromatic), 7.34 (2H, dt, J = 7.5, 1.5 Hz, aromatic), 7.4–7.6 (2H, m, aromatic), 7.64 (1H, d, J = 1.9 Hz, aromatic), 7.66 (1H, d, J = 7.5 Hz, aromatic), 7.8–8.0 (4H, m, aromatic). MS (EI) *m/z*: 399 (M^+). HRMS for $C_{25}H_{21}NO_4$ (M^+) calcd 399.1470, found 399.1488.

4-Dimethoxymethyl-1,2-dihydro-1-phenyloxycarbonyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (17a). Prepared from **16a** (7.0 g, 20.0 mmol) by a procedure similar to that described for **12b**. Purified by column chromatography (silica gel, CH_2Cl_2) to give **17a** (5.5 g, 58%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.19 (9H, s, $SiMe_3$), 3.31 (3H, s, OMe), 3.40 (3H, s, OMe), 5.31 (1H, s, C*H*-OMe), 5.71 (1H, dd, J = 11.2, 1.5 Hz, C*H*=C*H*–C≡CSi), 5.77 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.28 (1H, dd, J = 6.3, 1.5 Hz, N–C*H*), 6.42 (1H, d, J = 6.3 Hz, C=C*H*), 7.1–7.4 (7H, m, aromatic), 7.6–7.7 (2H, m, aromatic). MS (EI) *m/z*: 471 (M^+). HRMS for $C_{28}H_{29}NO_4Si$ (M^+) calcd 471.1866, found 471.1875.

4-Dimethoxymethyl-1,2-dihydro-1-(2-naphthyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (17k). Prepared from **16k** (6.25 g, 39.4 mmol) by a procedure similar to that described for **12b**. Purified by column chromatography (silica gel, CH_2Cl_2:*n*-hexane = 1:1) to give **17k** (2.1 g, 40%) as a brown foam. ^{1}H NMR ($CDCl_3$) δ 0.20 (9H, s, $SiMe_3$), 3.33 (3H, s, OMe), 3.42 (3H, s, OMe), 5.33 (1H, s, C*H*–OMe), 5.74 (1H, dd, J = 11.2, 1.5 Hz, C*H*=CH–C≡CSi), 5.78 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.33 (1H, dd, J = 6.3, 1.5 Hz, N–C*H*), 6.45 (1H, d, J = 6.3 Hz, C=C*H*), 7.1–7.9 (11H, m, aromatic). MS (EI) *m/z*: 521 (M^+). HRMS for $C_{32}H_{31}NO_4Si$ (M^+) calcd 521.2022, found 521.2010.

4-Formyl-1,2-dihydro-1-phenyloxycarbonyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (18a). A suspension of $SnCl_4$ (110 mg, 0.42 mmol) and $ZnCl_2$ (57 mg, 0.42 mmol) in dry CH_2Cl_2 (50 mL) was stirred at rt for 30 min and then a solution of acetal **17a** (1.00 g, 2.12 mmol) in dry CH_2Cl_2 (50 mL) was added to this solution. After stirring at 22 °C for 1 h, the reaction mixture was quenched with aqueous $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were washed with H_2O (20 mL), brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo.

The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **18a** (900 mg, quantitative) as a yellow foam. ^1H NMR ($CDCl_3$) δ 0.19 (9H, s, $SiMe_3$), 5.72 (1H, dd, J = 11.2, 1.5 Hz, C*H*=CH–C≡CSi), 5.82 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.52 (1H, dd, J = 6.3, 1.5 Hz, N–C*H*), 6.93 (1H, d, J = 6.3 Hz, C=C*H*), 7.1–7.4 (6H, m, aromatic), 7.6–7.7 (2H, m, aromatic), 8.26 (1H, dd, J = 7.8, 1.5 Hz, aromatic), 9.80 (1H, s, C*H*O). MS (EI) *m/z*: 425 (M^+). HRMS for $C_{26}H_{23}NO_3Si$ (M^+) calcd 425.1447, found 425.1458.

4-Formyl-1,2-dihydro-1-(2-naphthyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (18k). A solution of acetal **17k** (1.86 g, 3.57 mmol) in dry CH_2Cl_2 (50 mL) was cooled to −78 °C and $BF_3{\cdot}OEt_2$ (3.02 g, 21.2 mmol) was added to this solution. After stirring at −78 °C for 1 h, the reaction mixture was quenched with H_2O (20 mL), extracted with CH_2Cl_2 (50 mL × 2). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL), brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **18k** (1.55 g, 91%) as a yellow foam. ^1H NMR ($CDCl_3$) δ 0.19 (9H, s, $SiMe_3$), 5.72 (1H, dd, J = 11.2, 1.5 Hz, C*H*=CH–C≡CSi), 5.82 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.55 (1H, dd, J = 6.3, 1.5 Hz, N–C*H*), 6.92 (1H, d, J = 6.3 Hz, C=C*H*), 7.1–7.6 (5H, m, aromatic), 7.6–7.9 (5H, m, aromatic), 8.28 (1H, dd, J = 6.4, 1.5 Hz, aromatic), 9.79 (1H, s, C*H*O). MS (EI) *m/z*: 475 (M^+). HRMS for $C_{30}H_{25}NO_3Si$ (M^+) calcd 475.1604, found 475.1617.

1,2-Dihydro-4-hydroxymethyl-1-phenyloxycarbonyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (19a). To a solution of aldehyde **18a** (800 mg, 1.88 mmol) and $CeCl_3{\cdot}7H_2O$ (910 mg, 2.44 mmol) in EtOH (20 mL) and CH_2Cl_2 (20 mL) was added $NaBH_4$ (126 mg, 3.00 mmol), followed by stirring at −78 °C for 20 min. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL), extracted with CH_2Cl_2 (40 mL × 2). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **19a** (800 mg, quantitative) as a pale yellow foam. ^1H NMR ($CDCl_3$) δ 0.19 (9H, s, $SiMe_3$), 1.72 (1H, br t, J = 5.9 Hz, O*H*), 4.61 (2H, m, C*H*$_2$OH), 5.72 (1H, dd, J = 11.2, 1.5 Hz, C*H*=CH–C≡CSi), 5.78 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.20 (1H, d, J = 6.3 Hz, C=C*H*), 6.27 (1H, d, J = 6.3 Hz, N–C*H*), 7.1–7.4 (8H, m, aromatic), 7.76 (1H, br d, J = 7.8 Hz, aromatic). MS (EI) *m/z*: 427 (M^+). HRMS for $C_{26}H_{25}NO_3Si$ (M^+) calcd 427.1604, found 427.1621.

1,2-Dihydro-4-hydroxymethyl-1-(2-naphthyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (19k). Prepared from **18k** (1.70 g, 3.57 mmol) by a procedure similar to that described for **19a**. Purified by column chromatography (silica gel, ether:*n*-hexane = 1:1) to give **19k** (1.1 g, 64%) as a yellow foam. ^1H NMR ($CDCl_3$) δ 0.19 (9H, s, $SiMe_3$), 1.62 (1H, br s, O*H*), 4.62 (2H, s, C*H*$_2$OH), 5.74 (1H, dd, J = 11.2, 1.5 Hz, C*H*=CH–C≡CSi), 5.80 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.20 (1H, d, J = 6.3 Hz, C=C*H*), 6.27 (1H, d, J =6.3 Hz, N–C*H*), 7.1–7.6 (5H, m, aromatic), 7.66 (1H, br d, J = 2.0 Hz, aromatic), 7.7–7.9 (5H, m, aromatic). MS (EI) *m/z*: 477 (M^+). HRMS for $C_{30}H_{27}NO_3Si$ (M^+) calcd 477.1760, found 477.1766.

3,4-Epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-1-phenyloxycarbonyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (12a). Prepared from **19a** (2.80 g, 5.93 mmol) by a procedure similar to that described for **10b**. Purified by column chromatography (silica gel, CH_2Cl_2) to give **12a** (2.78 g, 96%) as a pale yellow foam. ^1H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 2.05 (1H, br s, O*H*), 4.12 (1H, d, J = 2.4 Hz, epoxide), 4.12 and 4.47 (each 1H, d, J = 12.7 Hz, C*H*$_2$OH), 5.67 (1H, dd, J = 11.2, 1.5 Hz, C*H*=CH–C≡CSi), 5.80 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.15 (1H, m, J = 6.3 Hz, N–C*H*), 7.1–7.6 (9H, m, aromatic). MS (EI) *m/z*: 443 (M^+). HRMS for $C_{26}H_{25}NO_4Si$ (M^+) calcd 443.1553, found 443.1562.

3,4-Epoxy-1,2,3,4-tetrahydro-4-hydroxymethyl-1-(2-naphthyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (12k). Prepared from **19k** (520 mg, 1.10 mmol) by a procedure similar to that described for **10b**. Purified by column chromatography (silica gel, CH_2Cl_2) to give **12k** (510 mg, 95%) as a pale yellow foam. ^1H NMR ($CDCl_3$) 0.24 (9H, s, $SiMe_3$), 1.98 (1H, br s, O*H*), 4.17 (1H, d, J = 2.4 Hz, epoxide), 4.17 and 4.51 (each 1H, d, J = 12.7 Hz, C*H*$_2$OH), 5.70 (1H, dd, J = 11.2, 1.5 Hz, C*H*=CH–C≡CSi), 5.83 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.20 (1H, m, J = 6.3 Hz, N–C*H*), 7.2–8.0 (11H, m, aromatic). MS (EI) *m/z*: 493 (M^+). HRMS for $C_{30}H_{27}NO_4Si$ (M^+) calcd 493.1709, found 493.1718.

3,4-Epoxy-4-formyl-1,2,3,4-tetrahydro-1-phenyloxycarbonyl-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (13a): representative procedure. The epoxy alcohol **12a** (1.30 g, 2.95 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and pyridine (890 mg, 11.3 mmol), and the solution was cooled to 0 °C. To this solution was added Dess–Martin periodinane (1.80 g, 4.23 mmol) in dry CH_2Cl_2 (20 mL) portionwise over 30 min. After stirring at 23 °C for 2 h, the reaction mixture was diluted with ether (250 mL), washed with aqueous $Na_2S_2O_3$ (50 mL) and aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2:ether = 40:1) to give **13a** (1.0 g, 75%) as a pale yellow foam. IR (KBr) ν_{max} 2962, 2144, 1730, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.21 (9H, s, $SiMe_3$), 4.21 (1H, d, J = 2.9 Hz, epoxide), 5.64 (1H, dd, J = 11.2, 2.0 Hz, C*H*=CH–C≡CSi), 5.81 (1H, d, J = 11.2 Hz, CH=C*H*–C≡CSi), 6.30 (1H, t, J = 2.0 Hz, N–C*H*), 7.1–7.4 (7H, m, aromatic), 7.58 (1H, br d, J = 7.8 Hz, aromatic), 8.26 (1H, d, J = 7.8 Hz, aromatic), 9.26 (1H, s, C*H*O). MS (EI) *m/z*: 441 (M^+). HRMS for $C_{26}H_{23}NO_4Si$ (M^+) calcd 441.1396, found 441.1410.

The following compounds were prepared by a procedure similar to that described for **13a**.

3,4-Epoxy-1-(2-fluorophenyloxycarbonyl)-4-formyl-1,2,3,4-tetrahydro-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13b). Yield: 1.1 g (80%) as a pale yellow foam. IR (KBr) ν_{max} 2961, 2145, 1730, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.21 (9H, s, $SiMe_3$), 4.23 (1H, d, *J* = 2.4 Hz, epoxide), 5.66 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.83 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.28 (1H, m, N–C*H*), 7.1–7.3 (4H, m, aromatic), 7.43 (1H, dt, *J* = 7.8, 1.5 Hz, aromatic), 7.62 (1H, d, *J* = 7.8 Hz, aromatic), 8.27 (1H, d, *J* = 7.8 Hz, aromatic), 9.28 (1H, s, C*H*O). MS (EI) *m/z*: 459 (M^+). HRMS for $C_{26}H_{22}FNO_4Si$ (M^+) calcd 459.1302, found 459.1315.

3,4-Epoxy-1-(4-fluorophenyloxycarbonyl)-4-formyl-1,2,3,4-tetrahydro-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13c). Yield: 1.8 g (52%) as a pale yellow foam. IR (KBr) ν_{max} 2961, 2145, 1730, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 4.22 (1H, d, *J* = 2.4 Hz, epoxide), 5.66 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.83 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.28 (1H, m, N–C*H*), 7.0–7.2 (4H, m, aromatic), 7.2–7.6 (3H, m, aromatic), 8.27 (1H, d, *J* = 7.8 Hz, aromatic), 9.28 (1H, s, C*H*O). MS (EI) *m/z*: 459 (M^+). HRMS for $C_{26}H_{22}FNO_4Si$ (M^+) calcd 459.1302, found 459.1310.

1-(2-Chlorophenyloxycarbonyl)-3,4-epoxy-4-formyl-1,2,3,4-tetrahydro-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13d). Yield: 2.5 g (88%) as a pale yellow foam. IR (KBr) ν_{max} 2959, 2140, 1731, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.21 (9H, s, $SiMe_3$), 4.24 (1H, d, *J* = 2.4 Hz, epoxide), 5.67 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.83 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.31 (1H, m, N–C*H*), 7.1–7.5 (6H, m, aromatic), 7.71 (1H, d, *J* = 6.8 Hz, aromatic), 8.27 (1H, d, *J* = 7.8 Hz, aromatic), 9.30 (1H, s, C*H*O). MS (EI) *m/z*: 475 (M^+; ^{35}Cl), 477 (M^+; ^{37}Cl). HRMS for $C_{26}H_{22}ClNO_4Si$ (M^+) calcd 475.1006, found 475.1019.

1-(3-Chlorophenyloxycarbonyl)-3,4-epoxy-4-formyl-1,2,3,4-tetrahydro-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13e). Yield: 1.9 g (80%) as a pale yellow foam. IR (KBr) ν_{max} 2959, 2140, 1731, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 4.23 (1H, d, *J* = 2.4 Hz, epoxide), 5.67 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.84 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.27 (1H, m, N–C*H*), 7.05 (1H, br d, *J* = 7.8 Hz, aromatic), 7.1–7.4 (4H, m, aromatic), 7.44 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic), 7.54 (1H, m, aromatic), 8.28 (1H, d, *J* = 7.8 Hz, aromatic), 9.29 (1H, s, C*H*O). MS (EI) *m/z*: 475 (M^+; ^{35}Cl), 477 (M^+; ^{37}Cl). HRMS for $C_{26}H_{22}ClNO_4Si$ (M^+) calcd 475.1006, found 475.1025.

1-(4-Chlorophenyloxycarbonyl)-3,4-epoxy-4-formyl-1,2,3,4-tetrahydro-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13f). Yield: 2.7 g (76%) as a pale yellow foam. IR (KBr) ν_{max} 2959, 2140, 1731, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.21 (9H, s, $SiMe_3$), 4.25 (1H, d, *J* = 2.4 Hz, epoxide), 5.65 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.83 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.27 (1H, m, N–C*H*), 7.07 (2H, d, *J* = 7.8 Hz, aromatic), 7.2–7.6 (5H, m, aromatic), 8.27 (1H, d, *J* = 7.8 Hz, aromatic), 9.28 (1H, s, C*H*O). MS (EI) *m/z*: 475 (M^+; ^{35}Cl), 477 (M^+; ^{37}Cl). HRMS for $C_{26}H_{22}ClNO_4Si$ (M^+) calcd 475.1006, found 475.1022.

1-(2,4-Dichlorophenyloxycarbonyl)-3,4-epoxy-4-formyl-1,2,3,4-tetrahydro-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (13g). Yield: 3.2 g (74%) as a pale yellow foam. IR (KBr) ν_{max} 2961, 2140, 1731, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.21 (9H, s, $SiMe_3$), 4.23 (1H, d, *J* = 2.4 Hz, epoxide), 5.66 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.83 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.27 (1H, m, N–C*H*), 7.0–7.4 (4H, m, aromatic), 7.6–7.7 (2H, m, aromatic), 8.28 (1H, d, *J* = 7.8 Hz, aromatic), 9.28 (1H, s, C*H*O). MS (CI) *m/z*: 510 [$(M+1)^+$], 512 [$(M+3)^+$], 514 [$(M+5)^+$]. HRMS for $C_{26}H_{22}Cl_2NO_4Si$ (M+H) calcd 510.0695, found 510.0710.

3,4-Epoxy-4-formyl-1,2,3,4-tetrahydro-1-(4-methoxyphenyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)quinoline (13h). Yield: 4.9 g (72%) as a pale yellow foam. IR (KBr) ν_{max} 2960, 2145, 1730, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.21 (9H, s, $SiMe_3$), 3.80 (3H, s, OMe), 4.21 (1H, d, *J* = 2.4 Hz, epoxide), 5.66 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.82 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.29 (1H, m, N–C*H*), 6.86 (2H, m, aromatic), 7.29 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic), 7.42 (1H, dt, *J* = 7.8, 1.5 Hz, aromatic), 7.56 (1H, br d, *J* = 7.8 Hz, aromatic), 8.25 (1H, d, *J* = 7.8 Hz, aromatic), 9.28 (1H, s, C*H*O). MS (EI) *m/z*: 471 (M^+). HRMS for $C_{27}H_{25}NO_5Si$ (M^+) calcd 471.1502, found 471.1519.

3,4-Epoxy-4-formyl-1,2,3,4-tetrahydro-1-(2-nitrophenyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13i). Yield: 1.6 g (81%) as a pale yellow foam. IR (KBr) ν_{max} 2959, 2140, 1734, 1523 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.20 (9H, s, $SiMe_3$), 4.23 (1H, d, *J* = 2.4 Hz, epoxide), 5.67 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.83 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.26 (1H, m, N–C*H*), 7.2–7.5 (6H, m, aromatic), 8.12 (1H, d, *J* = 7.8 Hz, aromatic), 8.28 (1H, d, *J* = 7.8 Hz, aromatic), 9.29 (1H, s, C*H*O). MS (EI) *m/z*: 486 (M^+). HRMS for $C_{26}H_{22}N_2O_6Si$ (M^+) calcd 486.1247, found 486.1235.

3,4-Epoxy-4-formyl-1,2,3,4-tetrahydro-1-(4-nitrophenyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13j). Yield: 1.0 g (42%) as a pale yellow foam. IR (KBr) ν_{max} 2959, 2140, 1734, 1523 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 4.25 (1H, d, *J* = 2.4 Hz, epoxide), 5.66 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CHC≡CSi), 5.85 (1H, d, *J* = 11.2 Hz, CH=C*H*C≡CSi), 6.27 (1H, m, N–C*H*), 7.0–7.4 (3H, m, aromatic), 7.44 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic), 7.50 (1H, m, aromatic), 8.26 (3H, m, aromatic), 9.29 (1H, s, C*H*O). MS (EI) *m/z*: 486 (M^+). HRMS for $C_{26}H_{22}N_2O_6Si$ (M^+) calcd 486.1247, found 486.1240.

3,4-Epoxy-4-formyl-1,2,3,4-tetrahydro-1-(2-naphthyloxycarbonyl)-2-((*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl)-quinoline (13k). Yield: 420 mg (65%) as a pale yellow foam. IR (KBr) ν_{max} 2961, 2145, 1730, 1510 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.22 (9H, s, $SiMe_3$), 4.25 (1H, d, *J* = 2.9 Hz, epoxide), 5.68 (1H, dd, *J* = 11.2, 2.0 Hz, C*H*=CH–C≡CSi), 5.84 (1H, d, *J* = 11.2 Hz, CH=C*H*–C≡CSi), 6.35 (1H, m, N–C*H*), 7.2–7.9 (9H, m, aromatic), 8.28 (1H, d, *J* = 7.8 Hz, aromatic), 8.63 (1H, m, aromatic), 9.31 (1H, s, C*H*O). MS (EI) *m/z*: 491 (M^+). HRMS for $C_{30}H_{25}NO_4Si$ (M^+) calcd 491.1553, found 491.1566.

Mixture of phenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclo-dodeca-5-ene-3,7-diyne-1-carboxylate and (9*R**) isomer (6a): representative procedure.** A CsF powder (370 mg, 2.18 mmol) was placed in a dried three-necked flask and heated at 100 °C for 1 h in vacuo. After cooling to rt, dry CH_3CN (200 mL) was added, followed by Ac_2O (440 mg, 4.36 mmol). To this suspension was added the aldehyde **13a** (960 mg, 2.18 mmol) in dry CH_3CN (50 mL) at 25 °C during 30 min. After stirring for 2 h, the reaction mixture was filtered and the filtrate was evaporated in vacuo. The resulting residue was dissolved with AcOEt (300 mL), and the organic layer were washed with saturated NH_4Cl solution (50 mL), H_2O (50 mL), brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **6a** (470 mg, 53%, ca. 2:1 mixture of diastereomers) as a colorless solid. ^1H NMR ($CDCl_3$) [(9*S**)-isomer] 2.26 (3H, s, OAc), 3.99 (1H, d, *J* = 2.9 Hz, epoxide), 5.60 (1H, s, propargylic), 5.74 (1H, d, *J* = 10.2 Hz, NCHC≡CC*H*=CH), 5.85 (1H, d, *J* = 10.2 Hz, NCHC≡CCH=C*H*), 6.01 (1H, m, N–C*H*), 7.1–7.4 (7H, m, aromatic), 7.55 (1H, br d, *J* = 7.8 Hz, aromatic), 8.22 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.17 (3H, s, OAc), 4.31 (1H, d, *J* = 2.9 Hz, epoxide), 5.82 (2H, s, C≡CC*H*=C*H*), 5.96 (1H, m, N–C*H*), 6.47 (1H, s, propargylic), 7.1–7.4 (7H, m, aromatic), 7.55 (1H, br d, *J* = 7.8 Hz, aromatic), 7.67 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 411 (M^+). HRMS for $C_{25}H_{17}NO_5$ (M^+) calcd 411.1106, found 411.1115. Anal. calcd for $C_{25}H_{17}NO_5$: C, 72.99; H, 4.16; N, 3.40. Found: C, 72.71; H, 4.36; N, 3.19.

The following compounds were prepared by a procedure similar to that described for **6a**.

Mixture of 2-fluorophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate and (9*R**) isomer (6b).** Purified by column chromatography (silica gel, CH_2Cl_2) to give **6b** (620 mg, 66%, ca. 2:1 mixture of diastereomers) as a colorless solid. ^1H NMR ($CDCl_3$) δ [(9*S**)-isomer] 2.27 (3H, s, OAc), 4.00 (1H, d, *J* = 2.4 Hz, epoxide), 5.60 (1H, s, propargylic), 5.75 (1H, dd, *J* = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.85 (1H, d, *J* = 10.2 Hz, NCHC≡CCH=C*H*), 5.99 (1H, m, N–C*H*), 7.1–7.3 (5H, m, aromatic), 7.41 (1H, m, aromatic), 7.59 (1H, d, *J* = 6.8 Hz, aromatic), 8.23 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.18 (3H, s, OAc), 4.32 (1H, d, *J* = 2.4 Hz, epoxide), 5.83 (2H, s, C≡CC*H*=C*H*), 5.97 (1H, m, N–C*H*), 6.47 (1H, s, propargylic), 7.1–7.3 (5H, m, aromatic), 7.41 (1H, m, aromatic), 7.66 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic), 8.23 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 429 (M^+). HRMS for $C_{25}H_{16}FNO_5$ (M^+) calcd 429.1012, found 429.1019. Anal. calcd for $C_{25}H_{16}FNO_5$: C, 69.93; H, 3.76; N, 3.26. Found: C, 69.70; H, 3.99; N, 3.02.

4-Fluorophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate [(9*S**)-6c] and (9*R**)-isomer [(9*R**)-6c].** Purified by column chromatography (silica gel, CH_2Cl_2:*n*-hexane = 2:1) to gave (9*S**)-**6c** (290 mg, 17%), (9*R**)-**6c** (120 mg, 7%), and a mixture of diastereomers (420 mg, 25%) as a colorless solid, respectively. (9*S**)-**6c**: mp 102–105 °C (dec). IR (KBr) ν_{max} 2932, 1732, 1606, 1504, 1377 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.26 (3H, s, OAc), 3.99 (1H, d, *J* = 2.4 Hz, epoxide), 5.60 (1H, s, propargylic), 5.74 (1H, dd, *J* = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.85 (1H, d, *J* = 10.2 Hz, NCHC≡CCH=C*H*), 5.99 (1H, m, N–C*H*), 7.0–7.1 (4H, m, aromatic), 7.29 (1H, m, aromatic), 7.40 (1H, dt, *J* = 7.8, 1.5 Hz, aromatic), 7.53 (1H, br d, *J* = 7.8 Hz, aromatic), 8.23 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.9, 45.9, 58.6, 66.5, 70.0, 90.6, 91.0, 92.2, 95.7, 115.9, 116.2, 122.9, 123.0, 124.4, 125.2, 125.9, 126.8, 127.0, 128.3, 128.9, 130.0, 135.1, 146.7, 158.5, 162.1, 169.4. MS (EI) *m/z*: 429 (M^+). HRMS for $C_{25}H_{16}FNO_5$ (M^+) calcd 429.1012, found 429.1025. Anal. calcd for $C_{25}H_{16}FNO_5$: C, 69.93; H, 3.76; N, 3.26. Found: C, 69.65; H, 4.02; N, 2.99. (9*R**)-**6c**: mp 91–94 °C (dec). IR (KBr) ν_{max} 2932, 1730, 1606, 1505, 1377 cm^{-1}. ^1H NMR ($CDCl_3$) 2.17 (3H, s, OAc), 4.31 (1H, d, *J* = 2.4 Hz, epoxide), 5.83 (2H, s, C≡CC*H*=C*H*), 5.94 (1H, m, N–C*H*), 6.47 (1H, s, propargylic), 7.0–7.1 (4H, m, aromatic), 7.29 (1H, m, aromatic), 7.41 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic), 7.55 (1H, br d, *J* = 7.8 Hz, aromatic), 7.67 (1H, dd, *J* = 7. 8, 1.5 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.6, 45.4, 57.2, 59.8, 62.8, 90.4, 91.0, 93.2, 95.3, 115.9, 116.2, 122.9, 123.0, 124.4, 125.3, 126.0, 127.0, 129.2, 134.5, 146.7, 158.5, 162.1, 169.3. MS (EI) *m/z*: 429 (M^+). HRMS for $C_{25}H_{16}FNO_5$ (M^+) calcd 429.1012, found 429.1016. Anal. calcd for $C_{25}H_{16}FNO_5$: C, 69.93; H, 3.76; N, 3.26. Found: C, 69.73; H, 4.00; N, 3.09.

Mixture of 2-chlorophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate and (9*R**)-isomer (6d).** Purified by column chromatography (silica gel, AcOEt:*n*-hexane = 1:4) gave **6d** (1.6 g, 74%, ca. 2:1 mixture of diastereomers) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ [(9*S**)-isomer] 2.27 (3H, s, OAc), 4.00 (1H, d, *J* = 2.4 Hz, epoxide), 5.60 (1H, s, propargylic), 5.74 (1H, dd, *J* = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.85 (1H, d, *J* = 10.2 Hz, NCHC≡CCH=C*H*), 6.02 (1H, m, N–C*H*), 7.1–7.5 (5H, m, aromatic), 7.72 (1H, m, aromatic), 8.23 (1H, dd, *J* = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.18 (3H, s, OAc), 4.32 (1H, d, *J* = 2.4 Hz, epoxide), 5.83 (2H, s, C≡CC*H*=C*H*), 5.97 (1H, m,

N–C*H*), 6.47 (1H, s, propargylic), 7.1–7.5 (6H, m, aromatic), 7.72 (1H, m, aromatic), 8.23 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 445 (M^+; ^{35}Cl), 447 (M^+; ^{37}Cl). HRMS for $C_{25}H_{16}ClNO_5$ (M^+) calcd 445.0717, found 445.0705. Anal. calcd for $C_{25}H_{16}ClNO_5$:C, 67.35; H, 3.62; N, 3.14. Found: C, 67.02; H, 3.81; N, 3.00.

Mixture of 3-chlorophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate and (9*R**)-isomer (6e).** Purified by column chromatography (silica gel, AcOEt:*n*-hexane = 1:4) gave **6e** (1.2 g, 70%, ca. 2:1 mixture of diastereomers) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ [(9*S**)-isomer] 2.27 (3H, s, OAc), 4.00 (1H, d, J = 2.4 Hz, epoxide), 5.60 (1H, s, propargylic), 5.74 (1H, dd, J = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.86 (1H, d, J = 10.2 Hz, NCHC≡CCH=C*H*), 5.98 (1H, m, N–C*H*), 7.05 (1H, br d, J = 6.8 Hz, aromatic), 7.2–7.7 (6H, m, aromatic), 8.23 (1H, dd, J = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.18 (3H, s, OAc), 4.32 (1H, d, J = 2.4 Hz, epoxide), 5.84 (2H, s, C≡CC*H*=C*H*), 5.93 (1H, m, N–C*H*), 6.47 (1H, s, propargylic), 7.05 (1H, br d, J = 6.8 Hz, aromatic), 7.1–7.5 (6H, m, aromatic), 8.23 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 445 (M^+; ^{35}Cl), 447 (M^+; ^{37}Cl). HRMS for $C_{25}H_{16}ClNO_5$ (M^+) calcd 445.0717, found 445.0723. Anal. calcd for $C_{25}H_{16}ClNO_5$: C, 67.35; H, 3.62; N, 3.14. Found: C, 67.07; H, 3.91; N, 2.89.

Mixture of 4-chlorophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate and (9*R**)-isomer (6f).** Purified by column chromatography (silica gel, CH_2Cl_2) gave **6f** (1.5 g, 64%, ca. 2:1 mixture of diastereomers) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ [(9*S**)-isomer] 2.26 (3H, s, OAc), 4.01 (1H, d, J = 2.4 Hz, epoxide), 5.60 (1H, s, propargylic), 5.73 (1H, dd, J = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.84 (1H, d, J = 10.2 Hz, NCHC≡CCH=C*H*), 5.97 (1H, m, N–C*H*), 7.07 (2H, dd, J = 7.3, 1.5 Hz, aromatic), 7.2–7.4 (4H, m, aromatic), 7.51 (1H, br d, J = 7.3 Hz, aromatic), 8.22 (1H, dd, J = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.17 (3H, s, OAc), 4.31 (1H, d, J = 2.4 Hz, epoxide), 5.82 (2H, s, C≡CC*H*=C*H*), 5.93 (1H, m, N–C*H*), 6.47 (1H, s, propargylic), 7.07 (2H, dd, J = 7.3, 1.5 Hz, aromatic), 7.2–7.4 (4H, m, aromatic), 7.51 (1H, br d, J = 7.3 Hz, aromatic), 7.67 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 445 (M^+; ^{35}Cl), 447 (M^+; ^{37}Cl). HRMS for $C_{25}H_{16}ClNO_5$ (M^+) calcd 445.0717, found 445.0712. Anal. calcd for $C_{25}H_{16}ClNO_5$: C, 67.35; H, 3.62; N, 3.14. Found: C, 67.12; H, 3.77; N, 2.88.

2,4-Dichlorophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate [(9*S**)-6g] and (9*R**)-isomer [(9*R**)-6g].** Purified by column chromatography (silica gel, CH_2Cl_2:*n*-hexane = 2:1) gave (9*S**)-**6g** (150 mg, 12%), (9*R**)-**6g** (80 mg, 7%), and a mixture of diastereomers (600 mg, 48%) as a colorless solid, respectively. (9*S**)-**6g**: mp 105–107 °C (dec). IR (KBr) ν_{max} 2935, 1732, 1607, 1507, 1376 cm^{-1} . ^1H NMR ($CDCl_3$) δ 2.27 (3H, s, OAc), 4.00 (1H, d, J = 2.4 Hz, epoxide), 5.60 (1H, s, propargylic), 5.74 (1H, dd, J = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.86 (1H, d, J = 10.2 Hz, NCHC≡CCH=C*H*), 5.99 (1H, m, N–C*H*), 7.1–7.3 (3H, m, aromatic), 7.42 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.45 (1H, d, J = 2.4 Hz, aromatic), 7.65 (1H, d, J = 6.8 Hz, aromatic), 8.23 (1H, dd, J = 7.8, 1.5 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.9, 46.1, 58.6, 66.3, 70.0, 90.7, 91.0, 92.0, 95.7, 123.0, 124.5, 124.8, 125.2, 126.1, 127.9, 129.0, 130.0, 132.0, 134.8, 145.8, 169.4. MS (CI) *m/z*: 480 [$(M+1)^+$], 482 [$(M+3)^+$], 484 [$(M+5)^+$]. HRMS for $C_{25}H_{15}Cl_2NO_5$ (M^+) calcd 479.0327, found 479.0320. Anal. calcd for $C_{25}H_{15}Cl_2NO_5$: C, 62.52; H, 3.15; N, 2.92. Found: C, 62.40; H, 3.35; N, 2.70. (9*R**)-**6g**: mp 95–98 °C (dec). IR (KBr) ν_{max} 2935, 1732, 1607, 1507, 1376 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.18 (3H, s, OAc), 4.32 (1H, d, J = 2.4 Hz, epoxide), 5.83 (2H, s, C≡CC*H*=C*H*), 5.94 (1H, m, N–C*H*), 6.47 (1H, s, propargylic), 7.0–7.4 (4H, m, aromatic), 7.44 (1H, d, J = 2.4 Hz, aromatic), 7.67 (2H, d, J = 7.8 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.6, 45.7, 57.2, 59.7, 62.6, 90.5, 91.9, 92.9, 95.3, 122.3, 124.5, 124.8, 125.3, 126.1, 126.9, 127.8, 127.9, 127.9, 129.2, 130.0, 132.0, 134.2, 145.8, 169.2. MS (CI) *m/z*: 480 [$(M+1)^+$], 482 [$(M+3)^+$], 484 [$(M+5)^+$]. HRMS for $C_{25}H_{15}Cl_2NO_5$ (M^+) calcd 479.0327, found 479.0335. Anal. calcd for $C_{25}H_{15}Cl_2NO_5$: C, 62.52; H, 3.15; N, 2.92. Found: C, 62.45; H, 3.39; N, 2.78.

Mixture of 4-methoxyphenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate and (9*R**)-isomer (6h).** Purified by column chromatography (silica gel, CH_2Cl_2:*n*-hexane = 2:1) gave **6h** (1.2 g, 48%, ca. 2:1 mixture of diastereomers) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ [(9*S**)-isomer] 2.26 (3H, s, OAc), 3.99 (1H, d, J = 2.4 Hz, epoxide), 5.59 (1H, s, propargylic), 5.74 (1H, dd, J = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.85 (1H, d, J = 10.2 Hz, NCHC≡CCH=C*H*), 6.01 (1H, m, N–C*H*), 6.86 (2H, d, J = 9.3 Hz, aromatic), 7.04 (2H, dd, J = 9.3, 2.4 Hz, aromatic), 7.27 (1H, m, aromatic), 7.40 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.55 (1H, br d, J = 7.8 Hz, aromatic), 8.22 (1H, d, J = 7.8 Hz, aromatic). [(9*R**)-isomer] 2.17 (3H, s, OAc), 4.31 (1H, d, J = 2.4 Hz, epoxide), 5.83 (2H, s, C≡CC*H*=C*H*), 5.96 (1H, m, N–C*H*), 6.45 (1H, s, propargylic), 6.86 (2H, d, J = 9.3 Hz, aromatic), 7.04 (2H, dd, J = 9.3, 2.4 Hz, aromatic), 7.27 (1H, m, aromatic), 7.40 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.55 (1H, br d, J = 7.8 Hz, aromatic), 7.66 (1H, d, J = 7.8 Hz, aromatic). MS (EI) *m/z*: 441 (M^+). HRMS for $C_{26}H_{19}NO_6$ (M^+) calcd 441.1212, found 441.1215. Anal. calcd for $C_{26}H_{19}NO_6$: C, 70.74; H, 4.34; N, 3.17. Found: C, 70.58; H, 4.63; N, 2.95.

Mixture of 2-nitrophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate and (9*R**)-isomer (6i).** Purified by column chromatography (silica gel, AcOEt:*n*-hexane = 1:4) gave **6i** (860 mg, 61%, ca. 2:1 mixture of diastereomers) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ [(9*S**)-isomer] 2.27 (3H, s, OAc), 4.00 (1H, d, J = 2.4 Hz, epoxide), 5.61 (1H, s, propargylic),

5.75 (1H, dd, J = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.85 (1H, d, J = 10.2 Hz, NCHC≡CCH=C*H*), 5.97 (1H, m, N–C*H*), 7.2–7.5 (4H, m, aromatic), 7.5–7.7 (2H, m, aromatic), 8.13 (1H, dd, J = 7. 8, 1.5 Hz, aromatic), 8.23 (1H, dd, J = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.18 (3H, s, OAc), 4.32 (1H, d, J = 2.4 Hz, epoxide), 5.84 (2H, s, C≡CC*H*=C*H*), 5.92 (1H, m, N–C*H*), 6.45 (1H, s, propargylic), 7.2–7.5 (4H, m, aromatic), 7.5–7.7 (2H, m, aromatic), 8.13 (1H, dd, J = 7.8, 1.5 Hz, aromatic), 8.23 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 456 (M^+). HRMS for $C_{25}H_{16}N_2O_7$ (M^+) calcd 456.0957, found 456.0940. Anal. calcd for $C_{25}H_{16}N_2O_7$: C, 65.79; H, 3.53; N, 6.14. Found: C, 65.65; H, 3.79; N, 5.95.

4-Nitrophenyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate [(9*S**)-6j] and (9*R**)-isomer [(9*R**)-6j].** Purified by column chromatography (silica gel, CH_2Cl_2:*n*-hexane = 2:1) gave (9*S**)-**6j** (50 mg, 4%), (9*R**)-**6j** (25 mg, 2%), and a mixture of diastereomers (420 mg, 30%) as a colorless solid, respectively. (9*S**)-**6j**: mp 110–112 °C (dec). IR (KBr) ν_{max} 2937, 1732, 1616, 1523, 1493, 1379 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.27 (3H, s, OAc), 4.01 (1H, d, J = 2.4 Hz, epoxide), 5.61 (1H, s, propargylic), 5.75 (1H, dd, J = 10.2, 1.5 Hz, NCHC≡CC*H*=CH), 5.87 (1H, d, J = 10.2 Hz, NCHC≡CCH=C*H*), 5.97 (1H, m, N–C*H*), 7.32 (3H, m, aromatic), 7.43 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.50 (1H, br s, aromatic), 8.26 (3H, m, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.9, 46.0, 59.6, 66.1, 69.8, 90.8, 90.9, 91.6, 95.6, 122.2, 122.8, 124.5, 125.1, 125.3, 126.3, 126.6, 126.7, 127.0, 129.0, 129.2, 130.1, 134.6, 145.2, 155.4, 169.3. MS (EI) *m/z*: 456 (M^+). HRMS for $C_{25}H_{16}N_2O_7$ (M^+) calcd 456.0957, found 456.0975. Anal. calcd for $C_{25}H_{16}N_2O_7$: C, 65.79; H, 3.53; N, 6.14. Found: C, 65.60; H, 3.80; N, 6.00. (9*R**)-**6j**: mp 103–105 °C (dec). IR (KBr) ν_{max} 2935, 1734, 1616, 1523, 1493, 1377 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.18 (3H, s, OAc), 4.33 (1H, d, J = 2.4 Hz, epoxide), 5.84 (2H, s, C≡CC*H*=C*H*), 5.92 (1H, m, N–C*H*), 6.48 (1H, s, propargylic), 7.33 (3H, m, aromatic), 7.43 (1H, dt, J = 7.8, 1.5 Hz, aromatic), 7.50 (1H, br s, aromatic), 7.70 (1H, d, J = 7.8 Hz, aromatic), 8.25 (2H, d, J = 9.3 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.5, 45.6, 57.3, 59.7, 62.5, 90.7, 91.1, 92.6, 95.3, 122.3, 124.6, 125.2, 125.6, 126.4, 126.9, 127.1, 129.3, 134.1, 145.3, 155.5, 169.2. MS (EI) *m/z*: 456 (M^+). HRMS for $C_{25}H_{16}N_2O_7$ (M^+) calcd 456.0957, found 456.0970. Anal. calcd for $C_{25}H_{16}N_2O_7$: C, 65.79; H, 3.53; N, 6.14. Found: C, 65.73; H, 3.76; N, 6.01.

Mixture of 2-naphthyl (2*R,5*Z*,9*S**,10*S**,16*R**)-(±)-9-acetoxy-10,2,10-(epoxymetheno)-1-benz[*b*]azacyclododeca-5-ene-3,7-diyne-1-carboxylate and (9*R**)-isomer (6k).** Purified by column chromatography (silica gel, CH_2Cl_2) gave **6k** (220 mg, 57%, ca. 2:1 mixture of diastereomers) as a colorless solid. ^1H NMR ($CDCl_3$) δ [(9*S**)-isomer] 2.26 (3H, s, OAc), 4.01 (1H, d, J = 2.9 Hz, epoxide), 5.62 (1H, s, propargylic), 5.73 (1H, d, J = 10.2 Hz, NCHC≡CC*H*=CH), 5.84 (1H, d, J = 10.2 Hz, NCHC≡CCH=C*H*), 6.05 (1H, m, N–C*H*), 7.2–7.9 (10H, m, aromatic), 8.24 (1H, dd, J = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.17 (3H, s, OAc), 4.33 (1H, d, J = 2.9 Hz, epoxide), 5.82 (2H, s, C≡CC*H*=C*H*), 6.01 (1H, m, N–C*H*), 6.49 (1H, s, propargylic), 7.2–7.9 (10H, m, aromatic), 8.24 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 461 (M^+). HRMS for $C_{29}H_{19}NO_5$ (M^+) calcd 461.1263, found 461.1277. Anal. calcd for $C_{29}H_{19}NO_5$: C, 75.48; H, 4.15; N, 3.04. Found: C, 75.69; H, 4.43; N, 2.95.

Mixture of phenyl (1(13)*E*,2*R,5*Z*,9*S**)-(±)-2-acetoxy-11,12-benzo-10-azabicyclo[7.3.1]tridec-5,1(13)-diene-3,7-diyne-1-carboxylate and (9*R**)-isomer (20).** A CsF powder (32 mg, 0.21 mmol) was placed in a dried three-necked flask and heated at 100 °C for 1 h in vacuo. After cooling to rt, dry CH_3CN (10 mL) was added, followed by Ac_2O (43 mg, 0.42 mmol). To this suspension was added the aldehyde **18a** (90 mg, 0.21 mmol) in dry CH_3CN (5 mL) at 0 °C during 10 min. After stirring at 0 °C for 1 h, the reaction mixture was evaporated in vacuo. The resulting residue was dissolved with AcOEt (40 mL), and the organic layer was washed with saturated NH_4Cl solution, H_2O, brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **20** (85 mg, 90%, ca. 2:1 mixture of diastereomers) as a brown foam. ^1H NMR ($CDCl_3$) [(9*S**)-isomer] 2.32 (3H, s, OAc), 3.30 (1H, dd, J = 1.5, 1.0 Hz, N–C*H*), 5.82 (1H, dd, J = 10.2, 2.4 Hz, NCHC≡CC*H*=CH), 6.07 (1H, dd, J = 10.2, 1.0 Hz, NCHC≡CCH=C*H*), 6.53 (1H, d, J = 1.0 Hz, propargylic), 7.1–7.5 (8H, m, aromatic), 7.99 (1H, dd, J = 7.8, 1.5 Hz, aromatic). [(9*R**)-isomer] 2.28 (3H, s, OAc), 3.30 (1H, dd, J = 1.5, 1.0 Hz, N–C*H*), 5.85 (1H, dd, J = 10.2, 2.4 Hz, NCHC≡CC*H*=CH), 6.09 (1H, dd, J = 10.2, 1.0 Hz, NCHC≡CCH=C*H*), 7.1–7.5 (9H, m, aromatic and propargylic), 7.92 (1H, dd, J = 7.8, 1.5 Hz, aromatic). MS (EI) *m/z*: 395 (M^+). HRMS for $C_{25}H_{17}NO_5$ (M^+) calcd 411.1106, found 411.1115.

Biological assays

DNA-cleaving assay. Supercoiled ΦX174 DNA (Form I, 250 μM/base pair) was incubated at 37 °C for 18 h with 1 mM (final concentration) of each compound in 50 mM phosphate buffer (pH 7.4) containing 10% DMSO and analyzed by electrophoresis (1% agarose gel) to separate the various forms of DNA. DNA bands were visualized with ethidium bromide binding and UV illumination.

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. IC_{50} values were determined graphically from plots of residual activity versus drug concentration.

In vivo antitumor activity. For the evaluation of the antitumor activity against P388 leukemia, CDF_1 mice were inoculated intraperitoneally (ip) with 1×10^6 cells/

mouse of P388 on day 0, and the test compound was administered ip once daily for four days from day 1 to day 4. Survival was recorded for 30 days. The T/C values reported refer to the relative mean survival times of drug-treated to control mice (expressed as a percentage). The T/C values over 125% are considered to be significant. For the evaluation of the antitumor activity against solid tumors (Meth A sarcoma, Colon 26 adenocarcinoma, and Lewis lung carcinoma), CDF_1 mice were inoculated subcutaneously (sc) with 1×10^6 cells/mouse of Meth A sarcoma and Colon 26 adenocarcinoma on day 0, respectively, and BDF_1 mice were inoculated sc with 5×10^5 cells/mouse of LLC on day 0. The test compound was administered ip once daily for four days from day 1 to day 4. Body-weight changes were measured on day 4 and the mice were killed on day 14 (LLC) and day 15 (Meth A sarcoma and Colon 26 adenocarcinoma), respectively. Each tumor was excised and its weight was measured.

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References

1. For reviews of the cyclic enediynes, see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387. (b) Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5881. (c) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453.

2. (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Kamei, T.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Kamei, H.; Nishiyama, Y.; Takahashi, A.; Obi, Y.; Oki, T. *J. Antibiot.* **1991**, *44*, 1306. (c) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

3. (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

4. (a) Golik, J.; Clardy, J.; Dubay, G.; Groennewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groennewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

5. Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331.

6. Leet, J. E.; Schroeder, D. R.; Hofstead, S.; Golik, J. J.; Colson, K. L.; Huang, S.; Klohr, S. E.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 7946.

7. Yoshida, K.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett.* **1993**, *34*, 2637.

8. (a) Hanada, M.; Ohkuma, H.; Yonemoto, T.; Tomita, K.; Ohbayashi, M.; Kamei, H.; Miyaki, T.; Konishi, M.; Kawaguchi, H.; Forenza, S. *J. Antibiot.* **1991**, *44*, 403. (b) Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Zein, N.; Langley, D. R.; Lee, M. S.; Matson, J. A.; Doyle, T. W. *J. Am. Chem. Soc.* **1994**, *116*, 9531.

9. Arcamone F., *Medicinal Chemistry Series: Doxorubicin*; Academic Press: London, 1981; Vol. 17.

10. For the synthesis of methylated dynemicin A, see: Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378.

11. For the total synthesis of (+)-dynemicin A, see: (a) Myers, A. G.; Fraley, M. E.; Tom, N. J.; Cohen, S. B.; Madar, D. *J. Chem. Biol.* **1995**, *2*, 33. (b) Myers, A. G.; Fraley, M. E.; Tom, N. J. *J. Am. Chem. Soc.* **1994**, *116*, 11556.

12. For the total synthesis of (±)-dynemicin A, see: (a) Shair, M. D.; Yoon, T. Y.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1721. (b) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16, and references cited therein. (c) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509.

13. For studies on the action mechanism, see: (a) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, *34*, 1521. (b) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 3831. (c) Snyder, J. P.; Tipsword, G. E. *J. Am. Chem. Soc.* **1990**, *112*, 4040. (d) Kusakabe, T.; Maekawa, K.; Ichikawa, A.; Uesugi, M.; Sugiura, Y. *Biochem.* **1993**, *32*, 11669.

14. (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T. P.; Gomita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. (c) Darby, N.; Kim, C. U.; Salaun, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *J. Chem. Soc. Chem. Commun.* **1971**, 1516.

15. The molecular orbital calculations (PM3) were carried out with the quantum chemistry program package MOPAC (QCPE program # 455) version 6.0 (Stewart, J. J. P. *J. Comp.-Aided Mol. Design*, **1990**, *4*, 1) running on a graphics workstation Indigo 2 (Silicon Graphics).

16. For review, see: Maier, M. E. *Synlett* **1995**, 13, and references cited therein.

17. (a) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106. (b) Nicolaou, K. C.; Hong, Y.-P.; Torisawa, Y.; Tasy, S.-C.; Dai, W.-M. *J. Am. Chem. Soc.* **1991**, *113*, 9878. (c) Nicolaou, K. C.; Maligres, P.; Suzuki, T.; Wendborn, S. V.; Dai, W.-M.; Chadha, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8890. (d) Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908. (e) Nicolaou, K. C.; Dai, W.-M.; Tsay, S. C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172. (f) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Wrasidlo, W. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1155.

18. (a) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. (b) Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E. *J. Org. Chem.* **1993**, *58*, 5867. (c) Wender, P. A.; Beckham, S.; O'Leary, J. G. *Synthesis* **1994**, 1278.

19. Shair, M. D.; Yoon, T. Y.; Chou, D.; Danishefsky, S. *J. Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2477.

20. Hay, M. P.; Wilson, W. R.; Denny, W.A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2829.

21. Magnus, P.; Eisenbeis, S. A.; Rose, W. C.; Zein, N.; Solomon, W. *J. Am. Chem. Soc.* **1993**, *115*, 12627.

22. (a) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 99. (b) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. (c) Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. *Chem. Lett.* **1991**, 1271. (d) Isobe, M.; Nishikawa, T.; Yamamoto, N.; Tsukiyama, T.; Ino, A.; Okita, T. *J. Heterocycl. Chem.* **1992**, *29*, 619. (e) Nishikawa, T.; Ino, A.; Isobe, M. *Tetrahedron* **1994**, *50*, 1449. (f) Nishikawa, T.; Yoshikai, M.; Obi, K.;

Kawai, T.; Unno, R.; Jomori, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 9339. (g) Unno, R.; Michishita, H.; Inagaki, H.; Baba, Y.; Jomori, T.; Nishikawa, T.; Isobe, M. *Chem. Pharm. Bull.* **1997**, *45*, 125.

23. For review, see: Konig, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 165, and references cited therein.

24. (a) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. (b) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S. *J. Am. Chem. Soc.* **1988**, *110*, 6890.

25. Shair, M. D.; Yoon, T. Y.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755.

26. Magnus, P.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1991**, 544.

27. Porco, J. A.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410.

28. Brandstetter, T.; Maier, M. E. *Tetrahedron* **1994**, *50*, 1435.

29. Nishikawa, T.; Shibuya, S.; Isobe, M. *Synlett* **1994**, 482.

30. Wender, P. A.; Beckham, S.; Mohler, D. L. *Tetrahedron Lett.* **1995**, *36*, 209.

31. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

32. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

33. (a) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (b) Danishefsky, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 4368.

34. The (9*S**)-isomer and (9*R**)-isomer represent the (2*R**,9*S**,10*S**,16*R**)-(±)-isomer and (2*R**,9*R**,10*S**,16*R**)-(±)-isomer, respectively.

35. For the epoxidation with trichloroacetonitrile and hydrogen peroxide, see: Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888.

36. For the epoxidation with dimethyldioxirane, see: Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Lett.* **1990**, *31*, 331.

37. For the DNA-cleavage studies on dynemicin A analogues, see: (a) Myers, A. G.; Cohen, S. B.; Tom, N. J.; Madar, D. J.; Fraley, M. E. *J. Am. Chem. Soc.* **1995**, *117*, 7574. (b) refs 17, 18, 19, 22e, 22f, and 22g.

38. For the studies on the in vitro cytotoxicity of dynemicin A analogues, see refs 12c, 17, 19, 20, 21, and 22g.

39. For the studies on the in vivo antitumor activity of dynemicin A analogues, see refs 12c, 19, 21, and 22g.

40. Nicolaou, K. C.; Stabila, P.; Esmaeli-Azad, B.; Wrasidlo, W.; Hiatt, A. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 3142.

41. Zein, N.; Solomon, W.; Casazza, A. M.; Kadow, J. F.; Krishnan, B. S.; Tun, M. M.; Vyas, D. M.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1351.

42. Zabik, M. J.; Schuetz, R. D. *J. Org. Chem.* **1967**, *32*, 300.

43. Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

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