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Synthetic Studies on Antibiotic Dynemicin A. Synthesis of Cyclic Enediyne Model Compound of Dynemicin A

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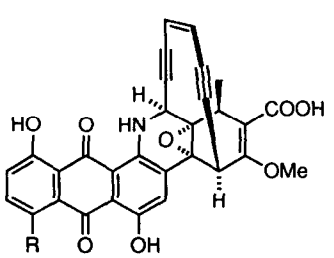
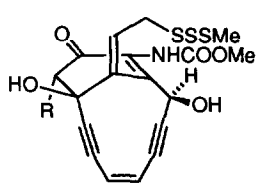
Abstract: Dynemicin A, a potent antitumor antibiotic has novel 10-membered cyclic enediyne moiety. The bicyclo[7.3.1]-tridecadiyne system having aniline moiety of this antibiotic was designed and synthesized from lepidine in 10 steps. The synthesized compound can be cycloaromatized to Bergman product *via* pinacol rearrangement under acidic condition, and also exhibited DNA cleaving activity.

Recently, a new class of novel antitumor antibiotics possessing an unprecedented bicyclic enediyne unit have been discovered.[1] In 1989, Konishi and co-workers at Research Institute of Bristol-Myers in Tokyo reported the structure of dynemicin A (**1**), that was isolated from fermentation broth of *Micromonospora chersina*.[2] This compound (**1**) can be considered as a hybrid antibiotic between two types of antitumor agents, anthracycline such as daunomycin and cyclic enediyne antibiotics such as esperamicin (**3**)[3] and calicheamicin (**4**).[4] Low production of **1** by microorganism prevents from further biological studies although **1** shows potent *in vivo* antitumor effect and weaker acute toxicity than other type of enediyne antibiotics **3** and **4**. So that the structure of dynemicin A as well as other enediyne antibiotics has attracted attention for chemical synthesis.[1,5] We became interested in the synthesis of dynemicin A analogues to explore biologically potent compounds.[6]



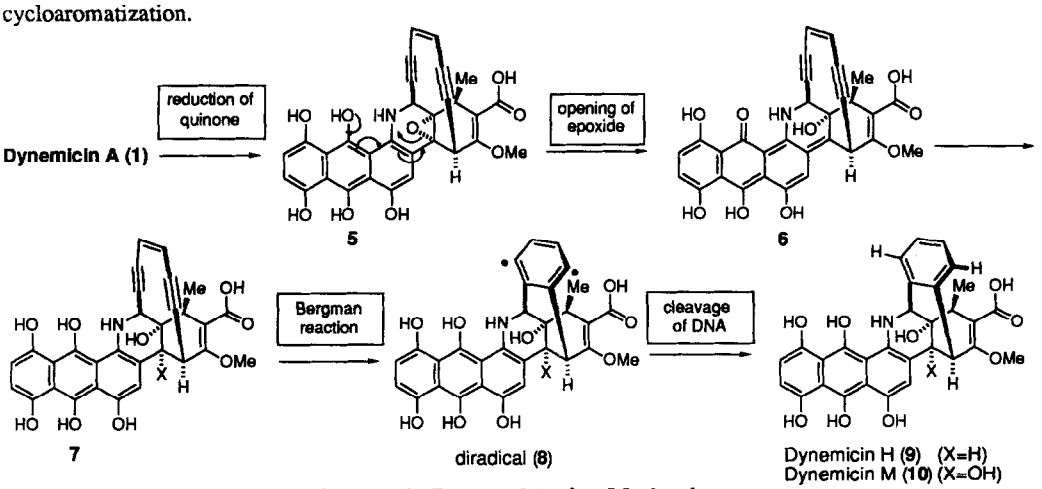
Dynemicin A (**1**) R = OH
deoxy-Dynemicin A (**2**) R = H



Esperamicin aglycon (**3**) R = OH
Calicheamicin aglycon (**4**) R = H

Figure 1. Structures of Cyclic Enediyne Antibiotics

Previous studies on the mechanism of action of esperamicin/calicheamicin[1] and anthracycline antibiotics[7] suggested a multi-step mechanism of DNA cleavage by **1** (Scheme 1):[8] thus, (i) intercalation of anthraquinone moiety to double strand DNA, (ii) bio-reduction of the quinone subunit in **1** to hydroquinone (**5**), (iii) epoxide opening to quinone methide formation (**5**→**6**), (iv) nucleophilic attack of water or protonation to form sp^3 carbon which enhances the strain in the system (**6**→**7**), (v) Bergman cycloaromatization to generate phenylene diradical (**7**→**8**), (vi) abstraction of hydrogen atoms from the sugar phosphate backbone of DNA (**8** →**9**[8d] or **10**[2]) and (vii) cleavage of the DNA chain. The anthraquinone moiety plays an important role in coordination with DNA, and the quinone reduction-epoxide ring opening is a device which triggers Bergman reaction. The enediyne ring is necessary part for generation of phenylene diradical by Bergman reaction and existence of epoxide ring prohibits Bergman cycloaromatization.



Scheme 1. Proposed Action Mechanism

This paper deals with the synthesis of dynemicin A model compounds[9] and an evaluation of their biological activity in an *in vitro* DNA cleavage assay.

Molecular Design of Active Model Compounds

Simplification of dynemicin structure by leaving the bicyclo-enediyne ring system as well as the triggering epoxide had led us to consider the Model A (Fig. 2). This Model A would have the critical distance between the two terminal carbons of the 1,5-diyne-3-ene system *(c-d distance)* to be about 3.4-3.5Å according to the molecular mechanics calculation using Biograf (employing Dreiding force field). This value may suggest Model A being rather stable.[10] We have calculated the five analogs which have been reported to be stable from X-ray crystallographic data.[11]

Our preliminary report on the synthesis of Model A has already shown that compound **11** is fairly stable, and that its treatment with acid resulted, in fact, in the opening of epoxide but at the different position. We have isolated an isomerized alcohol **12**, which possessed the bridge-head double bond.[12] This product is quite similar as esperamicin/calicheamicin type bicyclic system, that is prohibited from undergoing spontaneous Bergman reaction due to ring strain (presence of bridgehead double bond). These preliminary experiments suggested that the aromatic ring should be present to ensure regiospecific opening

of the epoxide ring at the benzylic position as the case for dynemicin A. The Model B was, thus, designed to have an aromatic ring and nitrogen function at the corresponding position to natural system.

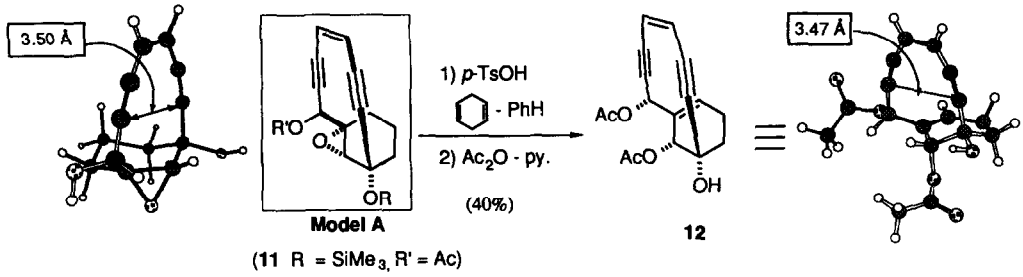
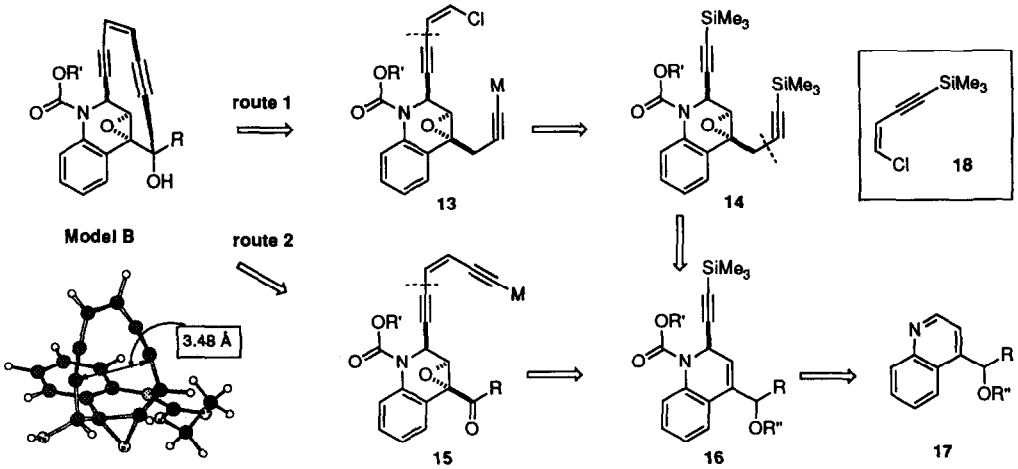


Figure 2

Synthetic Plan

The retrosynthetic plan for Model B is shown in Scheme 2. The crucial step is a 10-membered enediyne ring closure which is rendered difficult because of high strain of the ring. Two routes 1 and 2 to Model B were envisaged. Route 1 included intramolecular coupling that would be mediated by palladium as a template under neutral condition.[13] The precursor (**13**) for this cyclization was bisacetylene (**14**). Route 2 included intramolecular attack of the acetylide anion to the carbonyl group which had been used to construct the enediyne ring in esperamicin /calicheamicin type of compounds.[11a, 14] The precursor of this cyclization was an acyclic enediyne **15** which was retrosynthesized into **16** and **18**.[14] Common intermediate of route 1 and 2 was the acetylene alcohol **16** which would be synthesized from quinoline derivative (**17**).



Scheme 2. Retrosynthetic Plan

In all the four intermediates (**13**, **14**, **15** and **16**), each acetylenic group was analyzed to occupy a pseudo axial orientation on the 6-membered ring. This is due to A-strain effect between acetylene group and N-acyl group.[15] This preferential conformation of **16** was supported by molecular mechanics calculation using Biograf.[11] Axial conformation of **16** is 5.6 kcal/mol more stable than equatorial one.

This axial conformer is neccesary for cyclization of the 10-membered enediyne ring as it is axial in the cyclization product (Figure 3).

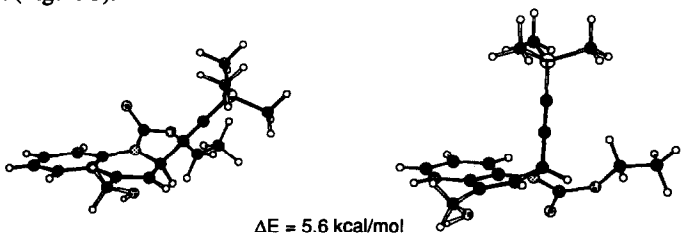


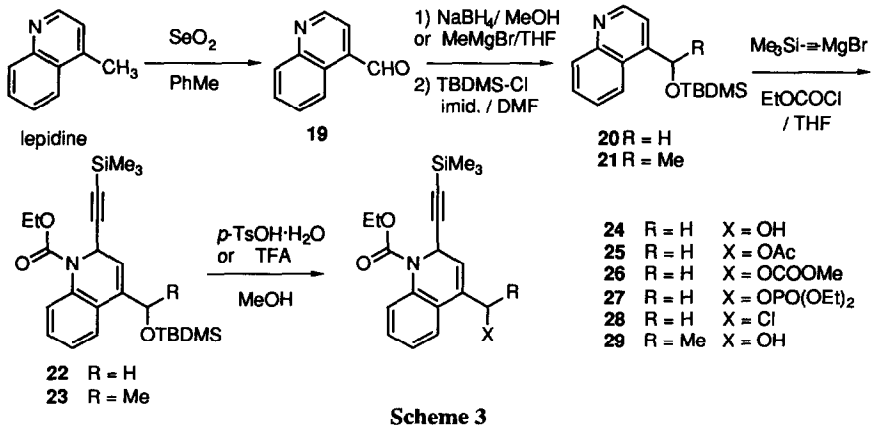
Figure 3

Synthesis of Model B Compound

(1) Synthesis of Common Synthetic Intermediate

We started from lepidine which was easily oxidized with SeO_2 into 4-quinolinecarboxaldehyde (**19**, cinchoninaldehyde).[16] Reduction of the aldehyde (**19**) with $NaBH_4$ and subsequent protection of the resulting alcohol with TBDMS-Cl afforded the silylether (**20**) in 93 % yield. An acetylenic group was regioselectively introduced into the quinoline nucleus by Yamaguchi protocol[17] to obtain **22** in 90 % yield. Selective desilylation of the TBDMS group in **22** under acidic condition (*p*-TsOH/MeOH, 94 %) afforded the alcohol (**24**) which was treated with Ph_3P/CCl_4 to give the chloride (**28**) in 92 %. This chloride did not react with lithium acetylide under established conditions[18] due to the unstability of **28** in basic medium.

The homologue (**29**) was synthesized in a similar manner. Addition of MeMgBr to **19** and subsequent silylation of the resulting alcohol provided **21** in 95% yield. Acetylenic group was introduced to quinoline derivative (**21**) in quantitative yield. Product (**23**) of this reaction was diastereomixture, the ratio being ca. 1:2 from ^1H NMR data. Selective removal of silyl ether in **23** under acidic condition (TFA/MeOH, 79 %) afforded the allylic alcohol (**29**).



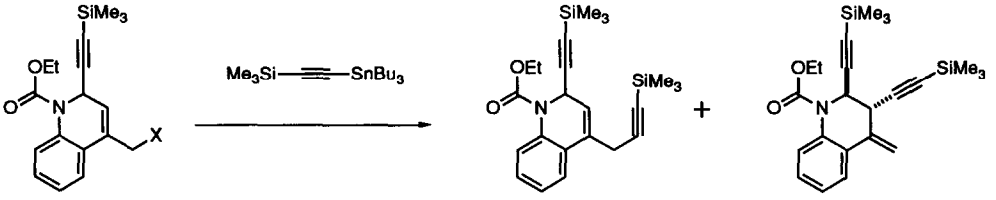
Scheme 3

(2) Route I

For introduction of the second acetylenic group, we developed a new method using palladium as catalyst for coupling between allylic derivatives and tin acetylene.[19] Because the Pd mediated reaction

could proceed under neutral condition, the allylic derivatives (**25-28**) could be employed. The acetate, carbonate and phosphate, however, gave only unsatisfied results (entry 1-3 in **Table 1**). Extensive screening of reaction conditions including the solvents, Pd reagents, ligands, ratio of ligand to Pd, led us to find that dimethylfumarate (dmf) accelerated this reaction to give the highest yield in stead of the phosphine ligand[20] (entry 5). Fair yields were also obtained using trifurylphosphine (TFP) ligand[21] (entry 6). Along with the desired product (**31**), the rearrangement product (**32**) was formed as a single stereoisomer.[22]

Table 1. Palladium Catalyzed Coupling of Allylic Derivarives with Tin Acetylene.



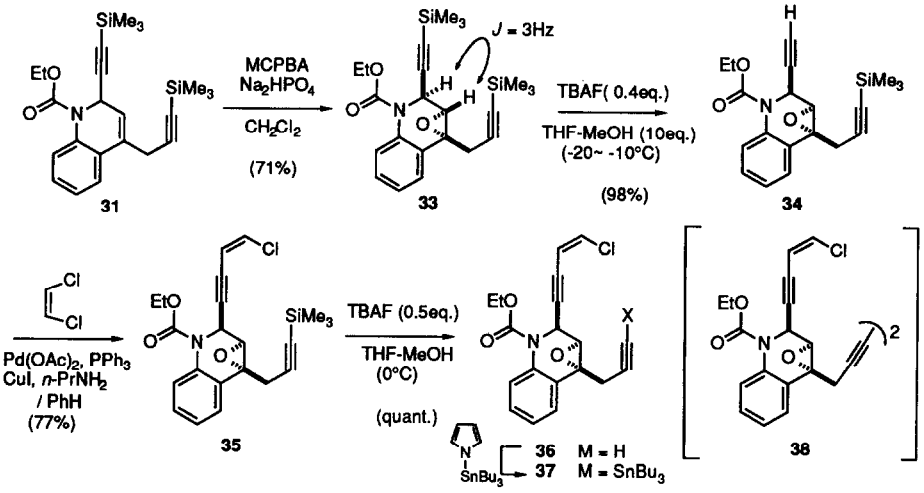
25~28 **31** **32**

entry	substrate	X	catalyst[a]	solvent	temp.	time	yield (%)[b]	ratio[c] (31:32)
1	**25**	OAc	$Pd_2[dba]_3{\cdot}CHCl_3$, PPh_3	NMP	80 °C	44 h	27	7:1
2	**26**	OCOOMe	$Pd_2[dba]_3{\cdot}CHCl_3$, PPh_3, LiCl	PhH	45-55 °C	5 days	23	11:1
3	**27**	$OPO(OEt)_2$	$Pd_2[dba]_3{\cdot}CHCl_3$, dmf	PhH	45 °C	46 h	22	6:1
4	**28**	Cl	$Pd_2[dba]_3{\cdot}CHCl_3$, PPh_3	NMP	70 °C	12 h	35	15:1
5	**28**	Cl	$Pd_2[dba]_3{\cdot}CHCl_3$, dmf	PhH	60 °C	4 days	68	16:1
6	**28**	Cl	$Pd_2[dba]_3{\cdot}CHCl_3$, TFP	THF	60-65 °C	6 days	47	10:1

[a] Me_3Si-≡-$SnBu_3$ (1.1 eq.), $Pd_2[dba]_3{\cdot}CHCl_3$ (3 mol %), Ph_3P (12 mol %), LiCl (2 eq.), dimethylfumarate (20 mol %), TFP (12 mol %). [b] Isolated yields. [c] Ratio determined by integration value of ^1H NMR.

Epoxidation of **31** gave **33** as a single stereoisomer which was deduced to have *anti*-epoxide to acetylene substituent (Scheme 4). Coupling constant between the propargylic and epoxidic protons was 3 Hz indicating *anti* stereochemistry. This assumption was supported by molecular mechanics calculation (*anti*- and *syn*- epoxide gave J = 3.9 and 8.5 Hz, respectively).[23] Control element of this selectivity was due to steric hindrance of pseudo-axial acetylenic moiety. Next steps was a regioselective desilylation of one of the two trimethysilylacetylenes in **33** for Pd coupling with (*Z*)-dichloroethylene. We found that limited use of TBAF (0.4-0.5 eq.) at -20~-10 °C gave **34**.[24] Terminal acetylene of **34** was coupled with (*Z*)-dichloroethylene under Sonogashira's condition[25] to give an eneyne (**35**) which was further desilylated at 0°C into **36**, the precursor for cyclization.

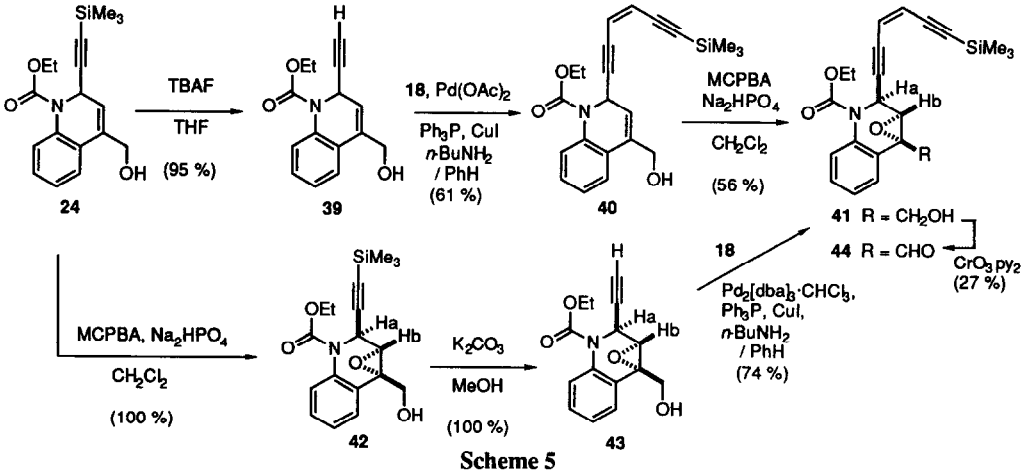
All attempts to cyclize **36** by using Pd-CuI catalyst failed. The only isolated product was dimer (**38**).[26] To avoid this dimerization, **36** was converted to tin acetylene[27] (**37**) by using N-tributyltin-pyrrole.[28] Even in the case of tin acetylene (**37**), cyclization product was not obtained. Therefore we abandoned the route 1 for synthesis of Model B.



Scheme 4

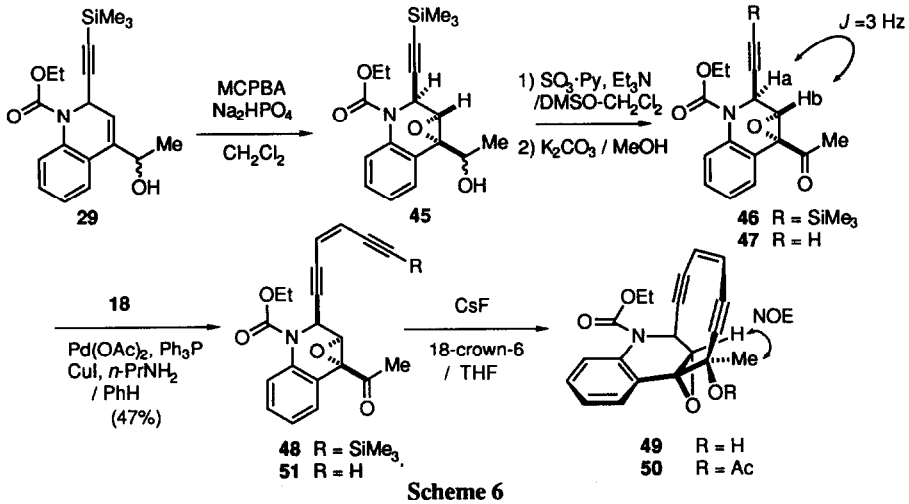
(3) Route 2

The other possible route to the bicyclic enediyne ring system (such as **15** in Scheme 2) involves inintramolecular addition of the terminal acetylide to the carbonyl group as a key step. This was first anticipated from the epoxyaldehyde (**44**) *via* the 2 routes from **24**, into **41** through **39** → **40**, or **42** → **43** shown in Scheme 5. In reality, the epoxy aldehyde intermediate (**44**) was extremely difficult to obtain from the epoxy alcohol (**41**) by oxidation under various conditions; *e.g.* PCC, Collins oxidation, SO_3-Py-DMSO, etc.[29] Extremely high selectivity in the epoxidation of the ring olefin, on the other hand, was observed during the synthesis of **41**; *e.g.* in the step from **24** and from **40**. The conformation of **41** had been predicted to have axial-like orientation of the acetylenic group (see Figure 3), which is important for cyclization. This conformation was supported from its ^{1}H NMR data (observed, J= 3 Hz) to have good harmony with one of the calculated values *anti* (J= 3.9 Hz) but not with *syn* (J= 8.5 Hz).[23] These findings prompted us to continue the same intramolecular cyclization using a higher homologue, such as **48** instead of **44**.



Scheme 5

In Scheme 6, the homologous alcohol (**29** from Scheme 3) was converted into the carbonyl intermediate through 4 steps including epoxidation (**45**),[30] oxidation with SO_3·Py-DMSO[31] (**46**,[32] 76% in 2 steps), desilylation (**47**, 85%) and palladium mediated coupling with **18**[14] to yield the enediyne ketone (**48**, 47%). All the steps worked smoothly as had been studied in the previous schemes. The crucial cyclization of **48** was best achieved to give **49** in 20% yield with CsF[33] (catalytic amount) in the presence of 18-crown-6 in THF solvent.[34] This condition was employed to avoid the enolization of the carbonyl methyl group by addition of a base into the desilylated equivalent (**51**).[35] Another fluoride anion reagent such as tetrabutylammonium fluoride (TBAF),[36] benzyltrimethylammonium fluoride (BTAF) and Wender's condition (CsF/CH_3CN)[5c] gave only desilylated product (**51**). The cyclized product **49** was largely a single isomer (>95:5, by ^1H NMR) about the new stereogenic center, which was assigned by NOE data observed between the methyl group and epoxy proton.



29 **45** **46** R = $SiMe_3$, **47** R = H

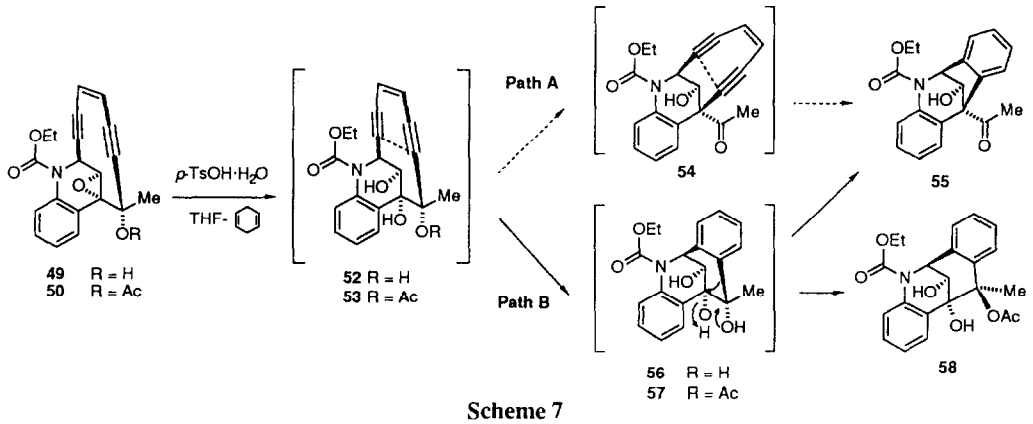
48 R = $SiMe_3$, **51** R = H **49** R = H, **50** R = Ac

Scheme 6

Bergman Reaction

Acid treatment of **49** in the presence of 1,4-cyclohexadiene gave a benzene derivative as expected through Bergman cycloaromatization (Scheme 7). The product however was not the triol (**56**), but the ketone (**55**) judging from the Me signal in ^1H NMR (δ 2.51 ppm). This fact suggested that pinacol-pinacolone rearrangement occured before or after Bergman reaction. The c-d distance of the intermediate (**52**) was estimated to be 3.29 Å, and the distance of pinacol-pinacolone rearrangement product **54** was 3.01 Å.[11] These two intermediates **52** and **54** have the distances short enough to cycloaromatize under this condition. It is unlikely that Path A was operative due to the low migration aptitude of acetylenic group,[37] and involvement of the more strained 9-membered enediyne (**54**).[38]

This speculation was supported by the fact that the *tert*-acetate (**50**) did not rearrange to the methyl ketone, but underwent Bergman reaction to afford **58**. This fact indicated that the intermediate (**53**) retained enough ability to undergo cycloaromatization at room temperature. From above discussion, we conclude that Path B is more plausible than Path A.



Scheme 7

DNA-Cleaving Activity

The synthetic enediynes (**49**, **50** and **59**[39]) were subjected to DNA cleaving activity although we did not expect much activity because of triggering device locked by stable N-protective group.[40] Surprisingly, **49**, **50** and **59** showed considerable cleaving activity toward supercoiled DNA (form I) to nicked DNA (form II) under neutral condition (Figure 4). These are the first examples to exhibit DNA cleavage activity with such compounds having stable N-protective group such as ethoxy and phenyl carbamate.[41] These results have encouraged us for further studies on synthesis of other model compounds.[42]

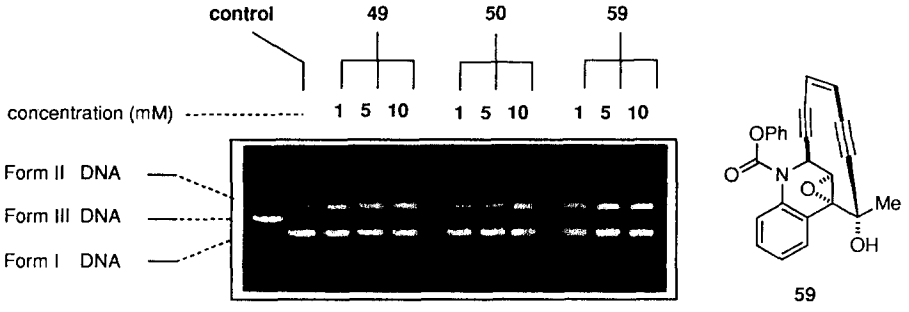


Figure 4

In conclusion, dynemicin A model compounds having DNA cleaving ability have been synthesized. Further synthesis of both enantiomers of Model B and another model compound having an anthraquinone moiety are in progress.

Experimental Section

General: Melting points were measured with a Yanaco MP-S3 melting point apparatus and are not corrected. Infrared spectra were recorded on a JASCO FT/IR spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on JEOL FX-200 (200 MHz), JEOL EX-270 (270 MHz), Varian VXR 500 (500 MHz) spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL FX-200 (50 MHz), JEOL EX-270 (67.9 MHz), Varian VXR 500 (125 MHz) spectrometer. Low resolution mass spectra (EI) were recorded JEOL JMS-D 100 spectrometer and reported in m/z. High-resolution mass spectra (HRMS) were recorded on a JEOL DX-705L spectrometer and reported in m/z. Elemental analyses were performed by Analytical Laboratory at School of Agriculture, Nagoya University to which the authors gratefully acknowledge. Unless otherwise noted, non aqueous reaction were carried out under nitrogen atmosphere. THF was distilled from potassium metal/benzophenone ketyl. Benzene was dried over Na metal and used without distillation. DMF and CH_2Cl_2 were dried over MS 4Å. Pyridine was dried over KOH and used without distillation. DMSO, *n*-$PrNH_2$ and *n*-$BuNH_2$ were distilled from CaH_2. CCl_4 was distilled from P_2O_5. Ethylchloroformate was distilled under N_2 atmosphere. All other commercially obtained reagents were used as received. Analytical thin-layer chromatography (TLC) was carried out by precoated silica gel plates (Art 5715). Preparative thin-layer chromatography (TLC) was carried out by precoated silica gel plates (Art 5774), or prepared silica gel (Art 7747). Silica gel for column chromatography were supplied from Fuji Devison (BW 820-MH).

TBDMS-ether (20). To a solution of 4-quinolinecarboxaldehyde **19** (14.0 g, 89.0 mmol) in MeOH (300 mL) cooled to 0 °C was added $NaBH_4$ (1.68 g, 44.5 mmol) portionwise followed by stirring at 0 °C for 10 min. The reaction mixture was quenched with acetic acid (2 mL), removed solvent under reduced pressure. The residue was dissolved with water, extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude product 14.8 g. This material was sufficiently pure for use in the next reaction. The resulting alcohol was dissolved in DMF (200 mL), cooled to 0 °C was mixed with imidazole (18.17 g, 267 mmol), *t*-butyldimethylchlorosilane (16.09 g, 106.8 mmol), followed by stirring at 0 °C for 30 min. The reaction mixture was warmed to rt, stirred for 1 h, poured into ice-water (300 mL) extracted with AcOEt (200 mL x3). Combined organic layers were washed with water (300 mL x3), brine (300 mL x2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 500 g, ether/hexane, 1:3) to give silylether **20** (22.6 g, 93 %): IR (KBr) ν_{max} 2956, 2858, 1597, 1470, 1258, 1123 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (6H s, $Si(CH_3)_2$), 0.98 (9H, s, $SiC(CH_3)_3$), 5.21 (2H, s, CH_2O), 7.47-7.61 (2H, m, aromatic), 7.69 (1H, t, J = 7.5 Hz, aromatic), 7.85 (1H, d, J = 8 Hz, aromatic), 8.14 (1H, d, J = 7.5 Hz), 8.92 (1H, br s, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -5.4, 18.2, 25.7, 61.5, 117.4, 122.2, 125.3, 126.1, 128.7, 130.0, 146.3, 147.5, 150.3. Anal. Calcd for $C_{16}H_{23}NOSi$: C, 70.28; H, 8.48; N, 5.12. Found: C, 70.30; H, 8.50; N, 5.08.

Ethyl carbamate (22). To a solution of trimethylsilylacetylene in dry THF (330 mL) cooled to 0 °C was added dropwise ethylmagnesium bromide (49 mL of 3 M solution of THF, 148 mmol). The solution was stirred at rt for 30 min and cooled to 0 °C again. To the resultant solution were added a solution of quinoline **20** (22.6 g, 82.6 mmol) in THF (80 mL) over 10 min, and then a solution of ethyl chloroformate (17.8 mL, 185 mmol) in THF (30 mL) at 0 °C. After stirring for 3 h, the mixture was quenched with sat. NH_4Cl solution, extracted with EtOAc (250 mL x3). Combined organic layers were washed with water (500 mL x2), brine (500 mL x2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. Crystallization of the residue from hexane afford **22** (30.83 g, 89.8 %): IR (KBr) ν_{max}2953, 2856, 2165, 1705, 1495, 1324, 1287, 1257, 1103, 1039 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, $C{\equiv}C\text{-}Si(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 4.27 (2H, m, OCH_2CH_3), 4.48 (1H, dt, J = 14, 1.5 Hz, CH_AH_B-OH), 4.66 (1H, dd, J = 14, 1 Hz, CH_AH_B-OH), 5.90 (1H, br d, J = 7.5 Hz, NCH-C≡C), 6.08 (1H, td, J = 7.5, 1.5 Hz, olefinic), 7.11 (1H, td, J = 7, 1 Hz, aromatic), 7.22 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67. 9 MHz, $CDCl_3$) δ -5.2, -5.1, -0.2, 14.4, 18.3, 25.9, 44.5, 62.3, 62.4, 88.1, 101.7, 120.8, 122.6, 124.1, 124.6, 126.1, 127.4, 134.0, 134.2, 153.6. Anal. Calcd for $C_{24}H_{37}O_3NSi_2$: C, 64.96; H, 8.40; N, 3.15. Found: C, 65.17; H, 8.51; N, 3.17.

Allyl alcohol (24). To a solution of TBDMS ether **22** (20.0 g, 48.1 mmol) in MeOH (300 mL) was added *p*-TsOH·H_2O (4.57 g, 24 mmol), followed by stirring at rt for 2 h. After the reaction mixture was diluted with AcOEt (400 mL), aq. $NaHCO_3$ solution (400 mL) and water (200 mL) were successively added. The mixture was extracted with AcOEt (200 mL x2). Combined organic layers were washed with water

(500 mL x2), brine (400 mL x2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crystalization of the residue gave alcohol **24** (14.9 g, 94 %): IR (KBr) ν_{max} 3448, 2964, 2168, 1717, 1493, 1377, 1304, 1261, 1036 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, $Si(CH_3)_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 4.27 (2H, m, OCH_2CH_3), 4.56 (2H, s, CH_2OH), 5.90 (1H, d, J = 6 Hz, olefinic or N-C*H*-C≡C), 6.10 (1H, d, J = 6 Hz, olefinic or N-C*H*-C≡C), 7.14 (1H, br t, J = 8 Hz, aromatic), 7.23-7.38 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.4, 44.3, 62.2, 62.5, 88.3, 101.4, 121.9, 122.9, 124.8, 125.7, 127.7, 134.3, 134.4, 153.5. MS (EI) m/z 329 (M^+), 300, 298. HRMS (EI) for $C_{18}H_{23}O_3NSi$ (M^+), calcd 329.1447, found 329.1459.

Allyl acetate (25). A solution of alcohol **24** (1.93 g, 5.85 mmol) in Ac_2O (25 mL) and pyridine (25 mL) was stirred at rt for 12 h. The mixture was evaporated *in vacuo*. The residue was purified by column chromatography (silica 80 g, ether/hexane, 1:2) to give acetate **25** (2.18 g, 100 %). IR (KBr) ν_{max} 2962, 2172, 1742, 1716, 1495, 1378, 1324, 1033 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, $Si(CH_3)_3$), 1.33 (3H, t, J = 7 Hz, OCH_2CH_3), 2.09 (3H, s, $OCOCH_3$), 4.28 (2H, m, OCH_2CH_3), 4.90 (1H, br d, J = 13 Hz, CH_ACH_B-OAc), 5.08 (1H, br d, J = 13 Hz, CH_ACH_B-OAc), 5.90 (1H, br d, J = 6.5 Hz, N-C*H*-C≡C or olefinic), 6.11 (1H, br d, J = 6.5 Hz, N-C*H*-C≡C or olefinic), 7.14 (1H, br t, J = 7.5 Hz, aromatic), 7.23-7.33 (2H, m, aromatic), 7.6 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR δ -0.3, 14.4, 20.9, 44.3, 62.5, 63.0, 88.7, 101.1, 123.0, 124.4, 124.6, 124.8, 125.5, 128.0, 130.1, 134.5, 153.5, 170.6. Anal. Calcd for $C_{20}H_{25}O_4NSi$: C, 64.69; H, 64.70; N, 3.77. Found: C, 64.70; H, 6.82; N, 3.73.

Allyl carbonate (26). To a solution of alcohol **24** (1.64 g, 5.00 mmol) and pyridine (1.6 mL, 20 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C was added methyl chloroformate (0.77 mL, 10 mmol) followed by stirring at 0 °C for 30 min. The mixture was poured into ice-cold 1N HCl solution, extracted with CH_2Cl_2 (x2). Combined organic layers were washed with 1N HCl solution (x2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 60g, ether/hexane, 1:2) to give allyl carbonate **26** (1.80 g, 93 %). IR (KBr) ν_{max} 2962, 2170, 1750, 1705, 1494, 1378, 1272 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (9H, s, $Si(CH_3)_3$), 1.31 (3H, t, J = 7Hz, OCH_2CH_3), 3.79 (3H, s, $OCOOCH_3$), 4.27 (2H, m, OCH_2CH_3), 4.97 (1H, br d, J = 13 Hz, $MeOCOOCH_AH_B$), 5.11 (1H, br d, J = 13 Hz, $MeOCOOCH_AH_B$), 5.91 (1H, d, J = 8 Hz, N-C*H*-C≡C), 6.15 (1H, d, J = 8 Hz, olefinic), 7.14 (1H, td, J = 8, 1 Hz, aromatic), 7.24-7.32 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.4, 14.3, 44.2, 54.8, 62.4, 66.4, 88.6, 100.8, 122.9, 124.3, 124.7, 124.9, 125.1, 127.9, 129.5, 134.3, 153.3, 155.3. Anal. Calcd for $C_{20}H_{25}O_5NSi$: C, 62.02; H, 6.46; N, 3.62. Found: C, 61.97; H, 6.58; N, 3.51.

Allyl phosphate (27). To a solution of alcohol **24** (1.64 g, 5.00 mmol) and pyridine (1.0 mL, 7.5 mmol) in CH_2Cl_2 (25 mL) cooled to 0 °C was added diethyl chlorophosphate (1.0 mL, 7.5 mmol). After stirring at rt for 1.5 h, pyridine (0.5 mL, 7.5 mmol) and diethyl chlorophosphate (0.5 mL, 3.7 mmol) was added. The mixture was warmed to rt for 1 h, poured into ice-cold water, extracted with CH_2Cl_2 (x2). Combined organic layers were washed with 1N HCl (x2), brine (x2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 120 g, EtOAc/hexane, 1:1) to give allyl phosphate **27** (1.96 g, 84 %). IR (KBr) ν_{max} 2983, 2171, 1705, 1493, 1377, 1264, 1027 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.22 (9H, s, $Si(CH_3)_3$), 1.26-1.35 (9H, m, OCH_2CH_3, $PO(OCH_2CH_3)_2$), 4.02-4.16 (4H, m, $PO(OCH_2CH_3)_2$), 4.27 (2H, m, OCH_2CH_3), 4.88 (1H, dd, J = 12.5, 7 Hz, CH_AH_B-OP), 4.97 (1H, dd, J = 12.5, 7 Hz, CH_AH_B-OP), 5.91 (1H, d, J = 6.5, 1.5 Hz, N-C*H*-C≡C or olefinic), 6.16 (1H, d, J = 6.5 Hz, N-C*H*-C≡C or olefinic), 7.14 (1H, td, J = 7.5 Hz, aromatic), 7.24-7.36 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). Anal. Calcd for $C_{22}H_{32}O_6NSiP$: C, 56.76; H, 6.96; N, 3.01. Found: C, 56.79; H, 6.96; N, 2.89.

Allyl chloride (28). A solution of alcohol **24** (3.05 g, 9.25 mmol) and Ph_3P (3.39 g, 12.9 mmol) in CCl_4 (30 mL) was heated under reflux for 12 h. After reaction mixture was cooled to rt, the mixture was diluted with hexane (20 mL), filtrated through the pad of Super-Cel®, washed with hexane. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica 150 g, ether/hexane, 1:10) to give chloride **28** (3.02 g, 92 %): IR (KBr) ν_{max} 2962, 2168, 1707, 1490, 1379, 1323, 1262, 1046 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, $Si(CH_3)_3$), 1.33 (3H, t, J = 7 Hz, OCH_2CH_3), 4.29 (2H, m, OCH_2CH_3), 4.36 (1H, d, J = 12 Hz, CH_AH_BCl), 4.54 (1H, br d, J = 12 Hz, CH_AH_BCl), 5.91 (1H, br d, J = 6.5 Hz, N-C*H*-CH=C or N-CH-C*H*=C), 6.17 (1H, br d, J = 6.5 Hz, N-C*H*-CH=C or N-CH-C*H*=C), 7.18 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.31 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.39 (1H, dd, J = 7.5, 1.5 Hz, aromatic), 7.65 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.3, 14.4, 43.3, 44.4, 62.6, 88.9, 100.8, 123.3, 124.3, 124.9, 125.0, 125.5, 128.1, 131.6, 134.6, 153.4. MS (EI) m/z 349 (M^+:

^{37}Cl), 347 (M^+: ^{35}Cl), 320, 318, 298. Anal. Calcd for $C_{18}H_{22}NO_2SiCl$: C, 62.14; H, 6.37; N, 4.03. Found C, 62.37; H, 6.28; N, 3.95.

TBDMS-ether (21). To a solution of 4-quinolinecarboxaldehyde **19** (6.53 g, 41.5 mmol) in THF cooled to -40 °C was added MeMgBr (3.0 M in ether, 18.0 mL, 54.0 mmol). After stirring at -40 °C for 1.5 h, the solution was poured into sat. NH_4Cl solution, and extracted with AcOEt (x3). Organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude product. This material was sufficiently pure for use in the next reaction. The resulting residue was dissolved with CH_2Cl_2 (120 mL) and DMF (24 mL). To this solution were added imidazole (8.44 g, 124 mmol) and TBDMS-Cl (9.33 g, 61.9 mmol). After stirring at rt for 16 h, the reaction mixture was partitioned between water and CH_2Cl_2. The organic layers were washed with water (x2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica 450 g, ether/hexane, 1:2) to give the silylether **21** (11.26 g, 94.5 % in 2 steps): IR (KBr) ν_{max} 2954, 2858, 1593, 1570, 1471 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.11 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.55 (3H, d, J = 6.5 Hz, CH_3CHOSi), 5.53 (1H, q, J = 6.5 Hz, CH_3CHOSi), 7.48 (1H, ddd, J = 8.2, 7.0, 1.5 Hz, aromatic), 7.55 (1H, d, J = 4.6 Hz, aromatic), 7.64 (1H, ddd, J = 8.2, 7.0, 1.5 Hz, aromatic), 7.95 (1H, br d, J = 8.2 Hz, aromatic), 8.09 (1H, br d, J = 8.2 Hz, aromatic), 8.83 (1H, d, J = 4.6 Hz, aromatic) ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -4.9, 18.3, 25.9, 26.4, 67.3, 117.3, 123.1, 125.2, 126.3, 128.9, 130.4, 148.2, 150.6, 152.3. MS (EI) m/z 287 (M^+), 272. HRMS (EI) for $C_{17}H_{25}NOSi$ (M^+), calcd 287.1705, found 287. 1709. Anal. Calcd for $C_{17}H_{25}NOSi$: C, 71.08; H, 8.71; N, 4.89. Found: C, 71.01; H, 8.76; N, 4.64.

Ethyl carbamate (23). To an ice-cooled solution of trimethylsilyl acetylene (11.0 mL, 77.6 mmol) in THF (175 mL) was added EtMgBr (3M in ether, 24.6 mL, 73.7 mmol). The solution was stirred at rt for 30 min and cooled to 0°C, and silylether **21** (11.4g, 38.8 mmol) in THF (45 mL) was added, followed by ethyl chloroformate (9.27 mL, 97 mmol). The solution was stirred for 40 min without the cooling bath. After stirring at rt for 1 h, the solution was poured into sat. NH_4Cl solution and extracted with AcOEt (x3). The organic layer was washed with brine (x2), dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and the residue was purified by column chromatography (silica 600 g, ether/hexane, 1:8) to give the acetylene adduct **23** (17.6 g, 99.5 %): IR (KBr) ν_{max} 2958, 2169, 1710, 1569, 1490, 1379 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$),* δ 0.05-0.25 (15H, m, $Si(CH_3)_3$, $Si(CH_3)_2$), 0.87-0.95 (9H, m, $SiC(CH_3)_3$), 1.25-1.45 (6H, m, CH_3CHOSi, OCH_2CH_3), 4.25 (2H, m, OCH_2CH_3), 4.64 [4.96] (1H, q [qd], J = 6.5 Hz [J = 6.5, 1.5 Hz], CH_3CHOSi), 5.80 [5.85] (1H, d, J = 6.5 Hz, propargylic), 5.93 [6.18] (1H, d [dd], J = 6.5 Hz [J = 6.5, 1.5 Hz], olefinic), 7.09 (1H, br t, J = 8.0 Hz, aromatic), 7.23 (1H, br t, J = 8.0 Hz, aromatic), 7.59 [7.65] (1H, br d, J = 8.0 Hz, aromatic), 7.85 (1H, dd, J = 8.0, 1.5 Hz, aromatic). * [ ] shows data of minor isomer, major : minor = 2 : 1 (Detected by integration of ^1H NMR). EIMS m/z 457 (M^+), 442 (M^+-Me). HRMS(EI) for $C_{25}H_{39}NO_3Si$ (M^+), calcd 457.2468, found 457.2453.

Allyl alcohol (29). To a solution of silyl ether **23** (17.32 g, 37.9 mmol) in MeOH (250 mL) cooled to 0°C was added TFA (100 mL) over 1 h, followed by stirring at rt for 15 h. The reaction mixture was diluted with toluene and evaporated *in vacuo* without heating. The residue was purified by column chromatography (silica 500 g, ether/hexane, 1:2) to give alcohol **29** (10.32 g, 79.4 %): IR (KBr) ν_{max} 3389, 2977, 2172, 1703, 1603, 1488, 1381 cm^{-1}. ^1H-NMR (270 MHz, $CDCl_3$),* δ 1.27 [1.29] (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.48 [1.33] (3H, d, J = 6.5 Hz, CH_3CHOH), 4.23 (2H, m, OCH_2CH_3), 4.82 [4.94] (1H, q [qd], J = 6.5 Hz [J = 6.5, 1.5 Hz], CH_3CHOH), 5.83 [5.85] (1H, d, J = 6.5 Hz, propargylic), 6.05 [6.14] (1H, d, J = 6.5 Hz [J = 6.5, 1.5 Hz], olefinic), 7.10 [7.08] (1H, br t, J = 8.0 Hz, aromatic), 7.23 (1H, br t, J = 8.0 Hz, aromatic), 7.50 (1H, dd, J = 8.0, 1.5 Hz, aromatic), 7.59 (1H, br d, J = 8.0 Hz, aromatic). * [ ] shows data of minor isomer, major : minor = 2 : 1 (Detected by integration of ^1H NMR). MS (EI) m/z 343 (M^+). HRMS (EI) for $C_{19}H_{25}NO_3Si$ (M^+), calcd 343.1604, found 343.1598.

Bis acetylene (31) and (32). In a dry two necked flask was placed allyl chloride **28** (1.43g, 4.12 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (106 mg, 0.10 mmol), dimethyl fumarate (119 mg, 0.82 mmol), and benzene (25 mL) and the whole mixture was degassed by two freeze-thaw cycles and covered with argon. After stirring until reaction mixture became yellow, tributylstannyl(trimethylsilyl)ethyne (1.75 g, 4.53 mmol) was added and was stirred at 60 °C for 5 days. Concentration of the mixture under reduced pressure provided an oil. The residue was purified by column chromatography (silica 150 g, ether/hexane, 1:10) to give **31** (1.07 g, 64 %) and **32** (67 mg, 4 %). **31**: IR (KBr) ν_{max} 2961, 2903, 2177, 1706, 1492, 1379, 1264, 1034 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (9H, s, $Si(CH_3)_3$), 0.20 (9H, s, $Si(CH_3)_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 3.31 (1H, dt, J = 20, 1 Hz, CH_AH_B-C≡C), 3.52 (1H, dd, J = 20, 2 Hz, CH_AH_B-C≡C), 4.28 (2H, m, CH_2CH_3), 5.91 (1H, d, J = 6.5 Hz, N-CH-CH=C), 6.22 (1H, dt, J = 6.5, 1 Hz, olefinic), 7.14 (1H, br t, J = 7 Hz, aromatic), 7.20-7.32 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz,

$CDCl_3$) δ -0.2, 0.0, 14.4, 23.1, 44.7, 62.4, 88.1, 88.9, 101.7, 102.3, 122.6, 122.7, 124.3, 124.6, 126.9, 127.7, 129.8, 134.3, 153.5. MS (EI) m/z 409 (M^+), 394, 380. Anal. Calcd for $C_{23}H_{31}O_2NSi_2$: C, 67.43; H, 7.62; N, 3.41. Found: C, 67.40; H, 7.77; N, 3.29. **32:** IR (KBr) ν_{max} 2963, 2176, 1709, 1488, 1378, 1310, 1250, 1034 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ -0.06 (9H, s, $Si(CH_3)_3$), 0.06 (9H, s, $Si(CH_3)_3$), 1.35 (3H, t, J = 7 Hz, OCH_2CH_3), 3.64 (1H, d, J = 3Hz, N-CH-CH), 4.26 (2H, m, OCH_2CH_3), 5.16 (1H, d, J = 0.5 Hz, $C{=}CH_AH_B$), 5.61 (1H, d, J = 3 Hz, N-CH-CH), 5.76 (1H, s, $C{=}CH_AH_B$), 7.08 (1H, td, J = 7.5, 2 Hz, aromatic), 7.25 (1H, ddd, J = 9, 7, 2 Hz, aromatic), 7.63 (1H, dd, J = 8, 1.5 Hz, aromatic), 7.67 (1H, dd, J = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.4, -0.2, 14.5, 41.1, 49.6, 62.3, 101.8, 103.3, 112.6, 123.9, 124.0, 124.9, 125.0, 128.1, 134.6, 136.8. MS (EI) m/z 409 (M^+), 336. HRMS (EI) for $C_{23}H_{31}O_2NSi$ (M^+), calcd 409.1893, found 409.1891.

Epoxide (33). To a solution of enediyne **31** (1.00 g, 2.44 mmol) and anhydrous Na_2HPO_4 (1.97 g, 13.8 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C was added MCPBA (70 %, 1.10 g, 4.88 mmol). After stirring at 0 °C for 4 h 20 min, sat. Na_2SO_3 solution was added until KI starch paper became negative. The aqueous layer was extracted with CH_2Cl_2 (x2) and combined organic layers were washed with sat. $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 75 g, ether/hexane, 1:10 → 1:5) to give epoxide **33** (696 mg, 67 %). IR (KBr) ν_{max} 2963, 2181, 1715, 1496, 1250, 1044 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.00 (9H, s, $Si(CH_3)_3$), 0.14 (9H, s, $Si(CH_3)_3$), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.05 (1H, d, J = 17 Hz, $C{\equiv}C\text{-}CH_AH_B$), 3.20 (1H, d, J = 17 Hz, $C{\equiv}C\text{-}CH_AH_B$), 3.99 (1H, d, J = 3 Hz, epoxide), 4.20 (2H, m, OCH_2CH_3), 5.76 (1H, br s, N-CH-C≡C), 7.20 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.33 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.42 (1H, br, aromatic), 7.59 (1H, br d, J = 7.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.4, -0.1, 14.3, 24.5, 44.1, 54.4, 62.6, 65.6, 88.6, 90.8, 99.1, 100.0, 124.9, 126.4, 126.9, 127.0, 128.3, 135.1. MS (EI) m/z 425 (M^+), 410, 396, 380, 352. HRMS (EI) for $C_{23}H_{31}O_3NSi_2$ (M^+), calcd 425.1842, found 425.1835.

Mono-TMS acetylene (34). To a solution of bistrimethylsilylacetylene **33** (145 mg, 0.341 mmol) in THF (7 mL) and MeOH (0.13 mL, 3.4 mmol) cooled to -20 °C was added to *n*-Bu_4NF (1.0 M solution of THF, 0.13 mL, 0.13 mmol). After stirring at -20 °C for 1 h, aq. NH_4Cl solution was added, extracted with CH_2Cl_2 (x3) , dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 7 g, ether/hexane, 1:10) to give **34** (118 mg, 98 %): IR (KBr) ν_{max} 3283, 2963, 2182, 1712, 1496, 1321, 1251 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (9H, s, $Si(CH_3)_3$), 1.13 (3H, t, J = 7 Hz, OCH_2CH_3), 2.15 (1H, d, J = 2.5 Hz, C≡C-H), 3.00 (1H, d, J = 17 Hz, $C{\equiv}C\text{-}CH_AH_B$), 3.24 (1H, d, J = 17 Hz, $C{\equiv}C\text{-}CH_AH_B$), 4.02 (1H, d, J = 3 Hz, epoxide), 4.26 (2H, m, OCH_2CH_3), 5.81 (1H, br s, N-CH-C≡C), 7.21 (1H, td, J = 7, 1.5 Hz, aromatic), 7.36 (1H, td, J = 8, 1.5 Hz, aromatic), 7.44 (1H, br d, J = 7 Hz, aromatic), 7.58 (1H, dd, J = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.18, 14.3, 24.3, 43.2, 54.4, 62.6, 65.2, 73.5, 77.6. 88.8, 99.9, 125.0, 126.1, 126.8, 127.0, 128.5, 134.9. MS (EI) 353 (M^+), 324. HRMS (EI) for $C_{20}H_{23}NO_3Si$ (M^+), calcd 353.1447, found 353.1429.

Enediyne (35). A suspension of acetylene **34** (360 mg, 1.02 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), Ph_3P (26 mg, 0.10 mmol), CuI (19 mg, 0.101 mmol) in benzene (18 mL) was degassed by three freeze-thaw cycles and covered under argon atmosphere. To this mixture were successively added (Z)-dichloroethylene (0.38 mL, 5.05 mmol) and *n*-propylamine (0.16 mL, 2.03 mmol). The mixture was stirred at rt for 1 h 10 min, poured into ice-cold aq. NH_4Cl solution, and extracted. The aqueous layer was extracted with AcOEt (x2), the combined organic layers were washed with aq. NH_4Cl solution (x2), brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 25 g, ether/hexane, 1:10→1:5) to give the enediyne **35** (322 mg, 77 %): ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (9H, $Si(CH_3)_3$), 0.20 (3H, t, J = 7 Hz, OCH_2CH_3), 1.97 (1H, d, J = 17 Hz, $CH_AH_B\text{-}C{\equiv}C\text{-}Si$), 2.16 (1H, d, J = 17 Hz, $CH_AH_B\text{-}C{\equiv}C\text{-}Si$), 2.99 (1H, d, J = 3Hz, epoxide), 3.16 (2H, m, OCH_2CH_3), 4.62 (1H, dd, J = 7.5, 2 Hz, CH=CHCl), 4.91 (1H, br s, N-CH-C≡C), 5.24 (1H, d, J = 7.5 Hz, CH=CHCl), 6.12 (1H, td, J = 8, 1 Hz, aromatic), 6.24 (1H, td, J = 8, 1 Hz, aromatic), 6.37 (1H, br d, J = 8 Hz, aromatic), 6.51 (1H, dd, J = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 14,3, 24.3, 44.1, 54.4, 62.6, 65.3, 79.1, 88.7, 91.2, 99.8, 111.0, 125.0, 126.2, 127.0, 128.5, 130.0, 135.0. MS (EI) m/z 415 (M^+: ^{37}Cl), 413 (M^+: ^{35}Cl).

Enediyne (36). To a solution of silylacetylene **35** (322 mg, 0.777 mmol) in THF (10 mL) and MeOH (0.15 mL, 3.88 mmol) cooled to 0 °C was added *n*-Bu_4NF (1.0 M in THF solution , 0.38 mL, 0.38 mmol). After stirring at 0 °C for 2 h, the mixture was poured into ice-cold aq. NH_4Cl, extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 15g, ether/hexane, 1:2) to give terminal acetylene **36** (265 mg, 100 %): IR (KBr) ν_{max} 3289, 3084, 2985, 2123, 1709, 1496, 1262 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7 Hz,

OCH_2CH_3), 2.13 (1H, t, J = 3 Hz, C≡C-H), 3.04 (1H, dd, J = 17, 3 Hz, CH_AH_B-C≡C-H), 3.19 (1H, dd, J = 17, 3 Hz, CH_AH_B-C≡C-H), 4.09 (1H, d, J = 3 Hz, epoxide), 4.24 (2H, m, OCH_2CH_3), 5.70 (1H, dd, J = 7, 2 Hz, CH=CHCl), 5.98 (1H, br s, N-CH-C≡C), 6.32 (1H, d, J = 7 Hz, CH=CHCl), 7.21 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.35 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.44 (1H, m, aromatic), 7.58 (1H, dd, J = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.3, 23.1, 44.1, 54.5, 62.7, 65.5, 72.0, 77.8, 79.3, 91.0, 111.0, 125.1, 126.0, 126.9, 127.1, 128.6, 130.1, 135.1. MS (EI) m/z 341 (M^+: ^{37}Cl), 343 (M^+: ^{35}Cl). HRMS (EI) for $C_{19}H_{16}NO_3{}^{37}Cl$ (M^+), calcd 341.0818, found 341.0829.

Dimer (38). A suspension of $Pd(OAc)_2$ (2.3 mg, 0.011 mmol), Ph_3P (5.6 mg, 0.021 mmol), CuI (4.0 mg, 0.021 mmol) in benzene (30 mL) was degassed by three freeze-thaw cycles and covered in argon. To this mixture was added successively acetylene **36** (73 mg, 0.21 mmol) in THF (5 mL), *n*-propylamine (35 μL, 0.42 mmol) in benzene (0.5 mL). The solution was stirred at rt for 2 h 10 min, poured into ice-cold aq. NH_4Cl solution, and extracted. The aqueous layer was extracted with AcOEt (x2), the combined organic layers were washed with water (x2), brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 10 g, ether/hexane, 1:1) to give unreacted **36** (45 mg, 62 %) and the dimer **38** (11.4 mg, 7.8 %): IR (KBr) ν_{max} 2982, 1796, 1377, 1319, 1259 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7Hz, OCH_2CH_3), 1.27 (3H, t, J = 7Hz, OCH_2CH_3), 3.05 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 3.06 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 3.22 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 3.25 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 4.01 (1H, d, J = 3 Hz, epoxide), 4.02 (1H, d, J = 3 Hz, epoxide), 4.08-4.34 (4H, m, OCH_2CH_3 x2), 5.64 (1H, dd, J = 7.5, 2Hz, CH=CHCl), 5.65 (1H, dd, J = 7.5, 2Hz, CH=CHCl), 5.95 (2H, br s, N-CH-C≡C x2), 6.24 (1H, d, J = 7.5 Hz, CH=CHCl), 6.26 (1H, d, J = 7.5 Hz, CH=CHCl), 7.21 (2H, td, J = 7.5, 1 Hz, aromatic), 7.35 (2H, td, J = 7.5, 1 Hz, aromatic), 7.44 (2H, br d, J = 7.5 Hz, aromatic), 7.52 (2H, br d, J = 7.5 Hz, aromatic). MS (FAB) m/z 681 (M+H).

Tin acetylene (37). To a solution of acetylene **36** (265 mg, 0.775 mmol) in THF (0.5 mL) was added N-tributyltin-pyrrole (0.49 mL, 1.55 mmol). After stirring at 80 °C for 96 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica 40 g, ether/hexane, 1:10→1:5) to give unreacted **36** (73 mg, 27 %) and tin acetylene **37** (214 mg, 44 %): IR (KBr) ν_{max} 2957, 2157, 1710, 1496, 1377, 1316, 1258 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84-0.98 (15H, m, $SnCH_2(CH_2)_2CH_3$ x 3), 1.22-1.38 (9H, Sn-CH_2-CH_2-CH_2-CH_3 x3, OCH_2CH_3), 1.52 (6H, m, Sn-CH_2-CH_2-CH_2-CH_3 x3), 3.10 (1H, d, J = 17 Hz, CH_AH_B-C≡C-Sn), 3.23 (1H, d, J = 17 Hz, CH_AH_B-C≡C-Sn), 4.09 (1H, d, J = 3 Hz, epoxide), 4.23 (2H, m, OCH_2CH_3), 5.68 (1H, dd, J = 7.5, 2 Hz, CH=CHCl), 5.97 (1H, br s, N-CH-C≡C), 6.31 (1H, d, J = 7.5 Hz, CH=CHCl), 7.17 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.32 (1H, td, J = 8, 1.5 Hz, aromatic), 7.43 (1H, br d, J = 8H, aromatic), 7.63 (1H, dd, J = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 10.9, 13.6, 14.3, 24.6, 26.9, 28.8, 44.2, 54.7, 62.6, 65.3, 79.0, 86.6, 91.4, 103.8, 111.1, 124.9, 126.5, 126.9, 127.2, 128.3, 129.9, 135.0. MS (FAB) m/z 632 (M+H).

Alcohol (39). To a solution of **24** (4.15 g, 10.0 mmol) in THF (80 mL) and MeOH (4.0 mL, 100 mmol) cooled to -78 °C was added TBAF (1.0 M solution of THF, 10 mL, 10.0 mmol), followed by stirring at -78 °C for 15 min. The mixture was stirred at 0 °C for 2 h, poured into sat. NH_4Cl solution, extracted with AcOEt (x3). Combined organic layers were washed with water (x2), brine (x2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 100 g, ether/hexane, 2:1) to give **29** (2.45 g, 95 %): IR (KBr) ν_{max} 3404, 3287, 2980, 2112, 1698, 1492 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, t, J = 7 Hz, OCH_2CH_3), 2.20 (1H, d, J = 2.5 Hz, C≡C-H), 4.29 (2H, m, OCH_2CH_3), 4.58 (2H, br s, CH_2-OH), 5.93 (1H, dd, J = 6, 2.5 Hz, N-CH-C≡C), 6.13 (1H, br d, J = 6 Hz, olefinic), 7.17 (1H, td, J = 8, 2 Hz, aromatic), 7.25-7.40 (2H, m, aromatic), 7.66 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.2, 43.3, 61.7, 62.6, 71.5, 80.1, 121.0, 123.0, 124.4, 125.6, 127.8, 134.0, 134.8, 153.4. MS (EI) m/z 257 (M^+), 228, 184. HRMS (EI) for $C_{15}H_{15}O_3N$ (M^+), calcd 257.1051, found 257.1061.

Epoxide (42). To a solution of allyl alcohol **24** (1.00 g, 3.03 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C was added MCPBA (70 %, 1.48 g, 6.06 mmol), followed by stirring at 0 °C for 1.5 h. The mixture was diluted with $CHCl_3$ (30 mL), washed with aq. Na_2SO_3 solution (x2), aq. $NaHCO_3$ solution (x2) and brine (x2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 50 g, ether/hexane, 1:1) to give epoxide **42** (1.05 g, 100 %): IR (KBr) ν_{max} 3455, 2962, 2175, 1709, 1498, 1256, 1047 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ -0.01 (9H, s, $Si(CH_3)_3$), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 1.94 (1H, dd, J = 8.5, 5 Hz, CH_2-OH), 4.04 (1H, d, J = 3 Hz, epoxide), 4.10 (1H, dd, J = 12.5, 8.5 Hz, CH_AH_B-OH), 4.23 (2H, m, OCH_2CH_3), 4.46 (1H, dd, J = 12.5, 5 Hz, CH_AH_B-OH), 5.78 (1H, br s, N-CH-C≡C), 7.20 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.35 (1H, td, J = 8, 1.5 Hz, aromatic), 7.43 (1H, br d, J = 8 Hz, aromatic), 7.48 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9

MHz, $CDCl_3$) δ -0.4, 14.3, 44.0, 56.5, 61.0, 62.6, 63.9, 91.1, 98.8, 125.2, 125.4, 126.5, 127.1, 128.5, 135.2. MS (EI) m/z 345 (M^+), 327, 314, 298. Anal. Calcd for $C_{18}H_{23}NO_4Si$; C; 62.57, H; 6.71, N; 4.05. Found C; 62.69, H; 6.89, N; 4.07.

Epoxide (43). To a solution of silylacetylene **42** (280 mg, 0.81 mmol) in MeOH (8 mL) was added anhydrous K_2CO_3. The mixture was stirred at rt for 20 min, poured into aq. $NaHCO_3$ solution, extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 15 g, ether/hexane, 1:1) to give **43** (216 mg, 100 %): IR (KBr) ν_{max} 3504, 3291, 2973, 2120, 1702, 1497 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7 Hz, OCH_2CH_3), 2.03 (1H, dd, J = 8.5 Hz, CH_2-O*H*), 2.16 (1H, d, J = 2.5 Hz, C≡C-*H*), 4.06 (1H, d, J = 3 Hz, epoxide), 4.12 (1H, dd, J = 12.5, 8 Hz, CH_AH_B-OH), 4.24 (2H, m, OCH_2CH_3), 4.44 (1H, dd, J = 12.5, 5 Hz, CH_AH_B-OH), 5.84 (1H, br s, N-C*H*-C≡C), 7.22 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.37 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.46 (1H, br d, J = 7.5 Hz, aromatic), 7.51 (1H, br d, J = 7.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.3, 43.1, 56.4, 60.9, 62.8, 63.8, 73.7, 77.5, 125.2, 125.3, 126.8, 127.0, 128.7, 135.0. MS (EI) m/z 273 (M^+), 242. HRMS (EI) for $C_{15}H_{15}O_4N$ (M^+), calcd 273.1000, found 273.1013.

Enediyne (40). A suspension of $Pd(OAc)_2$ (106 mg, 0.476 mmol), Ph_3P (249 mg, 0.952 mmol), CuI (181 mg, 0.952 mmol) in benzene (50 mL) was degassed by three freeze-thaw cycles and covered in argon. To this mixture were added successively acetylene **39** (2.45 g, 9.52 mmol) in benzene (8 mL)-THF (2 mL), vinyl chloride **18** (2.26 g, 14.2 mmol) in benzene (7 mL) and *n*-propylamine (2.34 mL, 28.5 mmol). The solution was stirred at rt for 1.5 h, poured into ice-cold aq. NH_4Cl solution, and extracted. The aqueous layer was extracted with ether (x2), the combined organic layer was washed with aq. NH_4Cl solution (x2), water (x2), brine (x2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 120 g, ether/hexane, 2:1) to give the enediyne **40** (2.22 g, 61 %): IR (KBr) ν_{max} 3427, 2963, 2148, 1697, 1491, 1379, 1261 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (9H, s, $Si(CH_3)_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 4.27 (2H, m, OCH_2CH_3), 4.54 (2H, br s, CH_2OH), 5.68 (1H, dd, J = 11, 1 Hz, CH-C≡C-C*H*=CH), 5.73 (1H, d, J = 11 Hz, C=C*H*-C≡C-Si), 6.08-6.17 (2H, m, C=C*H*-C*H*-N), 7.13 (1H, td, J = 8, 1 Hz, aromatic), 7.24-7.34 (2H, m, aromatic), 7.68(1H, br d, J = 8 Hz). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.4, 44.4, 62.1, 62.6, 80.5, 93.5, 101.6, 103.0, 119.7, 120.0, 121.4, 123.1, 124.5, 124.7, 125.6, 127.9, 134.3, 134.6, 153.5. MS (EI) m/z 379 (M^+), 350, 348, 306. HRMS (EI) for $C_{22}H_{25}O_3NSi$ (M^+), calcd 379.1603, found 379.1618.

Enediyne (41). To a solution of allylic alcohol **40** (445 mg, 1.17 mmol) and Na_2HPO_4 (232 mg, 1.64 mmol) in CH_2Cl_2 cooled to 0 °C was added MCPBA (80 %, 354 mg, 1.64 mmol), followed by stirring at 0 °C for 4 h 50 min. To this mixture at 0 °C was added Na_2HPO_4 (33 mg, 0.23 mmol) and MCPBA (80 %, 40 mg, 0.23 mmol). After stirring at 0 °C for 2.5 h, the mixture was treated with aq. Na_2SO_3 solution, and extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4 concentrated under reduced pressure. The residue was purified by column chromatography (silica 25 g, ether/hexane, 1:1) to give epoxide **41** (159 mg, 56 %): IR (KBr) ν_{max} 3508, 2959, 2144, 1701, 1498, 1140, 1028 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.23 (9H, s, $Si(CH_3)_3$), 1.29 (3H, t, J = 7 Hz, OCH_2CH_3), 1.89 (1H, m, O*H*), 4.08 (1H, d, J = 3H, epoxide), 4.04-4.36 (3H, m, OCH_2CH_3, CH_AH_B-OH), 4.46 (1H, dd, J = 13, 3 Hz, CH_AH_B-OH), 5.65 (1H, dd, J = 11, 2 Hz, CH=C*H*-C≡C-CH), 5.79 (1H, d, J = 11 Hz, Si-C≡C-C*H*=C), 6.07 (1H, br s, N-C*H*-C≡C), 7.20 (1H, td, J = 8, 2 Hz, aromatic), 7.35 (1H, td, J = 8, 2 Hz, aromatic), 7.41-7.57 (2H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 14.3, 44.0, 56.5, 61.1, 62.7, 63.9, 82.3, 90.6, 101.4, 103.5, 119.2, 120.5, 125.1, 125.2, 126.8, 126.9, 128.6, 135.0. MS (EI) m/z 395 (M^+), 377, 364, 348. HRMS (EI) for $C_{22}H_{25}O_4N$ Si (M^+), calcd 395.1552, found 395.1539.

Enediyne (41) from 43. A suspension of $Pd_2[dba]_3 \cdot CHCl_3$ (9.5 mg, 0.0184 mmol), Ph_3P (9.6 mg, 0.036 mmol) and CuI (7.0 mg, 0.036 mmol) in benzene (5 mL) was degassed by three freeze-thaw cycles and covered in argon. To this mixture were added successively acetylene **42** (94 mg, 0.34 mmol) in THF (2 mL), vinyl chloride **18** (117 mg, 0.738 mmol) in benzene (1.5 mL) and *n*-propylamine (2.34 mL) in benzene (0.6 mL). The solution was stirred at rt for 1.5 h, poured into ice-cold aq. NH_4Cl solution and extracted. The aqueous layer was extracted with AcOEt (x2), the combined organic layers were washed with aq. NH_4Cl solution (x2), water (x2), brine (x2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 15 g, ether/hexane, 1:1 → 2:1) to give the enediyne **41** (101 mg, 74 %).

Epoxyaldehyde(44). To a solution of epoxyalcohol **41** (70 mg, 0.176 mmol) in CH_2Cl_2 cooled to 0 °C was added $CrO_3 \cdot Py_2$ (ca. 500 mg), followed by stirring at 0 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 (2 mL), mixed with Super-Cel® and ether (5 mL), filtrated through the pad of Hyflo

Super-Cel ® and washed with AcOEt. The filtrate was concentrated under reduced pressure and purified by short column chromatography (silica, ether) to give epoxyaldehyde **44** (19 mg, 27 %). IR (KBr) ν_{max} 2962, 2144, 1733, 1709, 1495, 1258 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.21 (1H, s, $Si(CH_3)_3$), 1.28 (3H, t, J = 7 Hz, OCH_2CH_3), 4.16 (1H, d, J = 3 Hz, epoxide), 4.25 (2H, m, OCH_2CH_3), 5.64 (1H, dd, J = 11, 2 Hz, CH=CH-C≡C-Si), 5.80 (1H, d, J = 11 Hz, CH=CHC≡C-Si), 6.22 (1H, br s, N-CH-C≡C), 7.24 (1H, td, J = 7.5 Hz, 1.5 Hz, aromatic), 7.35-7.52 (2H, m, aromatic), 8.19 (1H, dd, J = 7.5, 1.5 Hz, aromatic), 9.25 (1H, s, CHO). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.3, 43.5, 56.9, 63.0, 64.8, 83.0, 89.1, 101.2, 103.9, 118.8, 120.7, 121.1, 125.4, 126.9, 128.3, 129.2, 134.8, 194.5. MS (EI) m/z 393 (M^+), 364. HRMS (EI) for $C_{22}H_{23}O_4NSi$ (M^+), calcd 393.1396, found 393.1380.

Epoxy ketone (46). (i) To a solution of alcohol **29** (10.20 g, 29.7 mmol) and anhydrous Na_2HPO_4 (12.65 g, 89.1 mmol) in CH_2Cl_2 (200 mL) cooled to 0 °C was added MCPBA (80 %, 9.63 g, 44.6 mmol) over 25 min. After stirring at 0 °C for 3 h 20 min, sat. Na_2SO_3 solution was added until KI starch paper became negative. The aqueous layer was extracted with CH_2Cl_2 (x2) and extracts were washed with sat. $NaHCO_3$ solution, water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude epoxide (**45**). (ii) The resulting residue was dissolved with CH_2Cl_2 (80 mL), DMSO (160 mL), Et_3N (54.9 mL) and cooled to 0 °C. To this solution was added SO_3·Py (41.76 g, 262.0 mmol) portionwise over 40 min. After stirring at rt for 1h 30 min, the reaction mixture was cooled to 0 °C, poured into sat. NH_4Cl solution, extracted with ether (x3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica 380 g, ether/hexane, 1:4) to give epoxy ketone **46** (8.02 g, 75. 8 % in 2 steps): IR (KBr) ν_{max} 2961, 2175, 1713, 1607, 1583, 1496 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.22 (9H, s, $Si(CH_3)_3$), 1.27 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.29 (3H, s, $C(O)CH_3$), 3.93 (1H, d, J = 2.9 Hz, epoxide), 4.22 (2H, m, OCH_2CH_3), 5.71 (1H, d, J = 2.9 Hz, propargylic), 7.13 (1H, br t, J = 7.8 Hz, aromatic), 7.30 (1H, td, J = 7.8, 1.5 Hz, aromatic), 7.38 (1H, br d, J = 7.8 Hz, aromatic), 7.56 (1H, br d, J = 7.8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.5, 14.3, 26.6, 43.6, 60.1, 62.8, 65.1, 92.2, 97.9, 122.1, 125.1, 127.2, 128.5, 128.8, 135.2, 154.7, 202.6. EIMS m/z 357 (M^+), 314. Anal. Calcd for $C_{19}H_{23}NO_4Si$: C, 63.87; H, 6.44; N, 3.92. Found: C, 63.95; H, 6.43; N, 3.74.

Acetylene (47). To a solution of epoxy ketone **46** (5.06 g, 14.2 mmol) in MeOH (150 mL) was added anhydrous K_2CO_3 (1.19 g) followed by stirring at rt for 1 h. Cooled (0 °C) sat. NH_4Cl solution was added to the mixture, followed by extraction with CH_2Cl_2 (x3). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and evaporated to a crude product. The residue was purified by column chromatography (silica 160 g, ether/hexane, 2:3) to give **47** (3.64 g, 85.2 %): Mp 114.5 - 116.0 °C. IR (KBr) ν_{max} 3278, 2987, 2126, 1704, 1581, 1497 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.20 (1H, d, J = 2.4 Hz, C≡C-H) , 2.30 (3H, s, $C(O)CH_3$), 3.96 (1H, d, J = 2.9 Hz, epoxide), 4.22 (2H, m, OCH_2CH_3), 5.86 (1H, br t, J = 2.4 Hz, propargylic), 7.17 (1H, td, J = 8.0, 1.8 Hz, aromatic), 7.34 (1H, td, J = 8.0, 1.8 Hz, aromatic), 7.40 (1H, br d, J = 8.0 Hz, aromatic), 7.58 (1H, br d, J = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.3, 26.5, 42.7, 59.9, 62.9, 64.9, 74.5, 99.4, 121.8, 125.3, 127.1, 128.6, 129.0, 134.9, 154.6, 202.7. MS (EI) m/z 285 (M^+), 242. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.26; N, 4.91. Found: C, 67.50; H, 5.11; N, 4.73.

Enediyne (48). A mixture of acetylene **47** (1.05 g, 3.7 mmol), $Pd(OAc)_2$ (41.5 mg, 0.185 mmol), PPh_3 (96.9 mg, 0.370 mmol) and CuI (70.4 mg, 0.37 mmol) in dried benzene (30 mL) was degassed by two freeze-thaw cycles and covered under argon atmoshpere. The (Z)-1-chloro-4-trimethylsilyl-1-buten-3-yne **18** (6.11 mL, 37.0 mmol) and *n*-$PrNH_2$ (0.76 mL, 9.25 mmol) was added, followed by stirring at rt for 1.5 h. The reaction mixture was quenched with sat. NH_4Cl solution, extracted with ether (x3). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 130 g, ether/hexane, 1:3) to give enediyne **48** (1.17 g, 77.6 %): IR (KBr) ν_{max} 2961, 2216, 2143, 1710, 1607, 1582, 1494 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.20 (9H, s, $Si(CH_3)_3$), 1.27 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.30 (3H, s, $C(O)CH_3$), 3.96 (1H, d, J = 2.9 Hz, epoxide), 4.22 (2H, m, OCH_2CH_3), 5.64 (1H, dd, J = 11.1, 1.8 Hz, CH=CHC≡CSi), 5.78 (1H, d, J = 11.1 Hz, CH=CHC≡CSi), 6.11 (1H, dd, J = 2.9, 1.8 Hz, propargylic), 7.16 (1H, br t, J = 8.0 Hz, aromatic), 7.25-7.48 (2H, m, aromatic), 7.61 (1H, br d, J = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.3, 26.6, 43.6, 60.0, 62.9, 64.9, 82.9, 89.4, 101.4, 103.7, 119.1, 120.9, 121.7, 125.2, 127.1, 128.6, 129.0, 135.0, 154.7, 202.7. MS (EI) m/z 407 (M^+), 364. HRMS (EI) for $C_{23}H_{25}NO_4Si$ (M^+), calcd 407.1553, found 407.1539.

Cyclic enediyne (49). In a dried two-necked flask was placed CsF (5.2 mg, 0.17 mmol), followed by heating at 100 °C for 1.5 h in *vacuo*. After cooling to rt, THF (2.5 mL), enediyne **48** (69 mg, 0.17 mmol) in

THF (1.5 mL) was added under Argon. After stirring for 30 min, 18-crown-6 (76.1 mg, 0.288 mmol) in THF(1.0 mL) was added. The reaction mixture was stirred at rt for 21 h, poured into sat. NH_4Cl solution and extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (silica, ether/hexane, 1:1) to give cyclic enediyne **49** (11 mg, 20 %) and desilylated product **51** (12 mg, 21 %). **49**: IR (KBr) ν_{max} 3428, 2985, 2193, 2699, 1606, 1579, 1493 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.69 (3H, s, $CC{\equiv}C(OH)CH_3$), 4.02 (1H, d, J = 3.0 Hz, epoxide), 4.23 (2H, m, OCH_2CH_3), 5.64 (1H, dd, J = 10.0, 1.5 Hz, $CH{=}CHC{\equiv}CC(OH)CH_3$), 5.80 (1H, d, J = 10.0 Hz, $CH{=}CHC{\equiv}CC(OH)CH_3$), 5.82 (1H, m, propargylic), 7.19 (1H, br t, J = 8.0 Hz, aromatic), 7.31 (1H, td, J = 8.0, 1.5 Hz, aromatic), 7.37 (1H, br d, J = 8.0 Hz, aromatic), 8.75 (1H, br d, J = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.5, 25.4, 45.3, 61.9, 62.8, 66.2, 72.4, 89.0, 90.3, 93.0, 102.1, 122.3, 124.5, 125.1, 126.6, 126.8, 128.2, 131.7, 135.7. MS (EI) m/z 335 (M^+). HRMS(EI) for $C_{20}H_{17}NO_4$ (M^+), calcd 335.1157, found 335.1160. **51**: IR (KBr) ν_{max} 3287, 2980, 1711, 1494 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.30 (3H, s, $C(OH)CH_3$), 3.15 (1H, m, C≡C-*H*), 4.00 (1H, d, J = 2.9 Hz, epoxide), 4.24 (2H, m, OCH_2CH_3), 5.73 (2H, m, olefinic), 6.08 (1H, m, propargylic), 7.17 (1H, br t, J = 8.0 Hz, aromatic), 7.34 (1H, br t, J = 8.0, aromatic), 7.44 (1H, br d, J = 8.0 Hz, aromatic), 7.62 (1H, br d, J = 8.0 Hz, aromatic). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 26.6, 43.7, 60.1, 62.9, 65.0, 79.9, 82.7, 85.5, 89.4, 120.2, 120.6, 122.0, 125.0, 127.2, 128.2, 128.6, 135.2, 202.3 ppm. MS (EI) m/z 335 (M^+), 292. HRMS(EI) for $C_{20}H_{17}NO_4$ (M^+), 335.1157, found 335.1169.

Cyclic enediyne (49) and *t*-acetate (50). In a dried two-necked flask were placed CsF (74.6 mg, 0.50 mmol), followed by heating at 100°C for 1.5 h *in vacuo*. After cooling to rt, THF (20 mL) , enediyne **48** (100 mg, 0.245 mmol) in THF (2.5 mL) was added under Argon. After stirring for 30 min, 18-crown-6 (65 mg, 0.25 mmol) in THF (2.0 mL) was added. The reaction mixture was stirred for 18 h at rt and poured into sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (silica, ether/hexane, 2:1) to give cyclic enediyne **49** (5.8 mg, 7.0 %), *t*-acetate **50** (9.5 mg, 10 %) and desilylated product **51** (6.5 mg, 7.9 %). **50**: IR (KBr) ν_{max} 2982, 2196, 1750, 1705, 1579, 1491 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.29 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.80 (3H, s, $C(OAc)$-CH_3), 2.21 (3H, s, $OC(O)CH_3$), 4.09 (1H, d, J = 3.0 Hz, epoxide), 4.23 (2H, m, OCH_2CH_3), 5.66 (1H, dd, J = 9.5, 1.5 Hz, $CH{=}CHC{\equiv}CC(CH_3)$), 5.83 (1H, d, J = 9.5 Hz, $CH{=}CHC{\equiv}CC(CH_3)$), 5.84 (1H, m, propargylic), 7.17 (1H, m, aromatic), 7.32 (1H, td, J = 8.0, 1.5 Hz, aromatic), 7.39 (1H, br d, J = 8.0, aromatic), 8.00 (1H, br d, J = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.5, 20.1, 22.0, 45.2, 61.0, 62.9, 65.4, 77.3, 90.5, 92.9, 99.3, 104.4, 122.9, 124.7, 125.0, 126.5, 127.2, 128.3, 130.0, 135.9, 169.1. MS (EI) m/z 377 (M^+). HRMS (EI) for $C_{22}H_{19}NO_5$ (M^+), calcd 377.1263, found 377.1251.

***t*-Acetate (50).** To a solution of **49** (17.1 mg, 0.051 mmol) in pyridine (0.8 mL) was added Ac_2O (0.8 mL) followed by stirring at rt for 34 h. The reaction mixture was diluted with toluene and evaporated *in vacuo*. The residue was purified by preparative TLC to give acetate **50** (8.2 mg, 43 %) and recovered **49** (4.8 mg, 28 %).

Bergman product (55). To s solution of enediyne **49** (5.0 mg, 0.15 mmol) and 1,4-cyclohexadiene (0.12 mL) was added $TsOH{\cdot}H_2O$ (2.9 mg, 0.15 mmol) in THF (0.25 mmol), followed by stirring at rt for 24 h. The reaction mixture was subjected to short column (Na_2SO_4- SiO_2-Na_2SO_4), washed with AcOEt and concentrated. The residue was purified by preparative TLC (ether/hexane, 2:1) to give **55** (3.9 mg, 78 %): IR (KBr) ν_{max} 3415, 2992, 1700, 1484 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.45 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.51 (3H, s, $C(O)CH_3$), 2.61 (1H, d, J = 9.5 Hz, CHO*H*), 4.36 (2H, m, OCH_2CH_3), 4.52 (1H, dd, J = 9.5, 4.5 Hz, C*H*OH), 5.75 (1H, d, J = 4.5 Hz, benzylic), 6.96-7.10 (2H, m, aromatic), 7.18-7.31 (3H, m, aromatic), 7.40 (1H, br d, J = 7.0, aromatic), 7.58 (1H, br d, J = 7.0 Hz, aromatic), 8.23 (1H, d, J = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.6, 29.4, 60.6, 62.7, 64.6, 72.1, 122.2, 123.9, 124.0, 124.9, 125.5, 126.6, 128.2, 128.5, 129.6, 134.8, 135.0, 145.1, 154.5, 207.4. MS (EI) m/z 337 (M^+), 294. HRMS(EI) for $C_{20}H_{19}NO_4$ (M^+), calcd 337.1314, found 337.1305.

Bergman product (58). To a solution of **50** (8.2 mg, 0.022 mmol) and 1,4-cyclohexadiene in THF (0.85 mmol) was added $TsOH{\cdot}H_2O$ (4.6 mg, 0.024 mmol) in THF (0.25 mL) followed by stirring at rt for 21 h. The mixture was quenched with sat. $NaHCO_3$ solution and extracted with AcOEt (x3). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC to give **58** (6.5 mg, 75 %): IR (KBr) ν_{max} 3457, 3397, 2977, 1699, 1490 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.93 (3H, s, $C(OAc)CH_3$), 2.16 (3H, s, $OCOCH_3$), 3.04 (1H, br s, C-O*H*), 4.26 (1H, d, J = 4.5 Hz, C*H*OH), 4.36 (2H, q, J = 7.0 Hz,

OCH_2CH_3), 6.03 (1H, d, J = 4.5 Hz, benzylic), 6.55 (1H, s, O*H*), 7.00 (1H, br t, J = 8.0 Hz, aromatic), 7.15 (1H, br t, J = 8.0 Hz, aromatic), 7.22-7.38 (4H, m, aromatic), 7.54 (1H, m, aromatic), 7.68 (1H, br d, J = 8.0 Hz, aromatic). MS (EI) m/z 397 (M^+), 337. HRMS(EI) for $C_{22}H_{23}NO_6$ (M^+), 397.1525, found 397.1535.

Cyclic enediyne (59). IR (KBr) ν_{max} 2254, 2195, 2145, 1943, 1718 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.73 (3H, s, C(OH)C*H*$_3$), 4.07 (1H, d, J = 3 Hz, epoxide), 5.67 (1H, dd, J = 10, 2 Hz, N-CH-C≡C-C*H*=CH), 5.82 (1H, d, J = 10 Hz, N-CH-C≡C-CH=C*H*), 5.89 (1H, dd, J = 3, 2 Hz, propargylic), 7.14 (2H, br d, aromatic), 7.20-7.28 (2H, m, aromatic), 7.31-7.41 (3H, m, aromatic), 7.51 (1H, br d, J = 8 Hz, aromatic), 8.80 (1H, dd, J = 8, 1.5 Hz, aromatic). HRMS (EI) for $C_{24}H_{17}O_4N$ (M^+), 383.1157, found 383.1156.

DNA cleaving assay of compound 49, 50, 59. Supercoiled ΦX174 DNA (90 % form I, 250 μM/bp) was incubated with a variety of concentration (1, 5, 10 mM, final concentration) of indicated enediyne (**49, 50, 59**) in buffer solution (50 mM phosphate buffer, pH 7.4) at 37 °C for 18 h and analyzed by agarose gel electrophoresis to separate the various forms of DNA. The DNA bands were visualized with ethidium bromide binding and UV illumination

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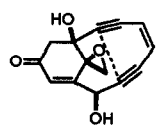
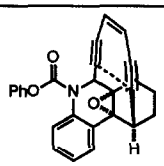
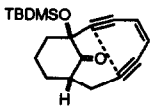
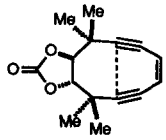
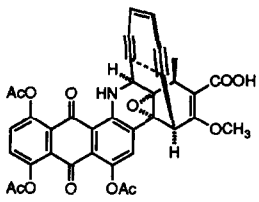
Biograf (Dreiding)	X-ray	ref	Biograf (Dreiding)	X-ray	ref
 c-d = 3.48 Å	3.44 Å	11a	 3.48 Å	3.59 Å	11d
 3.40 Å	3.39 Å	11b			
 3.45 Å	3.42 Å	11c	 3.47 Å	3.54 Å	2b

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21. Farina, V.; Baker, S. F.; Benigni, D. A.; Hauck, S. I.; Sapino, Jr, C. *J. Org. Chem.* **1990**, *55*, 5833-5847.

22. The structure of allylic rearranged product (**32**) was assigned from mechanistic consideration.

23. The coupling constants were calculated as following: (i) energy minimization by Dreiding force field (Biograf) (ii) transfer of the obtained coordinates to MacroModel (V3.1) (iii) calculation of coupling constants were performed in MacroModel. We gratefully acknowledge Prof. W. C. Still (Columbia University) for providing MacroModel software.

24. Scope and limitation of this selective mono-desilylation is currently under investigation. Selective mono-desilylation of bis-trimethylsilylacetylene compound with $NaBH(OMe)_3$ was reported. see: Myers, A. G.; Harrington, P. M. ; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694-695.

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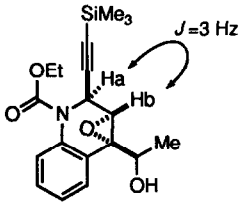
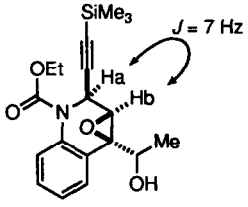
29. Wender *et al.* however reported the oxidation of the epoxyalcohol such as **41** with Dess-Martin periodinane in fair yield.

30. The mixture **45** contained at least 3 isomers in which two isomers **45a**, **45b** were isolated by TLC. The stereochemistry of these two epoxide were determined by coupling constants of **45a**, **45b** as shown below (see: ref. 23). The stereochemistry of *sec*-alcohol in **45a** and **45b**, were pure but not determined.



45 a (*anti*)



45 b (*syn*)

31. Parikh, J. R.; E. Doering, W. V. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

32. The product (**46**) was a single stereoisomer. This result indicated that *syn*-epoxide **45 b** might be unstable under SO_3-Py-DMSO condition.

33. For a review on importance of Cs ion in macrocyclization, see : Galli, G. *Org. Prep. Proced. Int.* **1992**, 287-307.

34. The use of excess CsF gave *t*-acetate (**50**) as a major product. The structure of **50** was confirmed by conversion of **49** to **50** (Ac_2O-Py, 43 %). Although the mechanism of this reaction is unclear, the origin of acetyl group is presumed methyl ketone in **48**.

35. In fact, attempts to cyclize terminal acetylene **51** with LDA have failed. The quenching experiment with D_2O afforded products which was deuterized at methylketone and terminal acetylene.

36. (a) Nakamura, E.; Kuwajima, I. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 498-499. (b) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975-982. (c) Holmes, A. B.; Jenning-White, C. L. D.; Schulthess, A. H.; Akinde, B.; Walton, D. R. M. *Chem. Commun.* **1979**, 840-842.

37. For low migratory aptitude of alkynyl group, see: Suzuki, K.; Ohkuma, T.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 373-376.

38. Nicolaou *et al.* reported a similar pinacol-pinacolone rearrangement of their model compounds of dynemicin A, see: Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106-3114.

39. **59** was synthesized from **21** in a similar manner. Details of the synthesis of **59** will be described elsewhere.

40. Nicolaou, K. C.; Smith, A. L; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106-3114.

41. Studies on antitumor activities (*in vitro*) of **49**, **50** and **59** are now in progress.

42. For biological activities of various dynemicin A model compounds. see: Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172-1178.

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