Synthesis and Reaction of Novel Tricyclic Dynemicin A Models with Methyl Group

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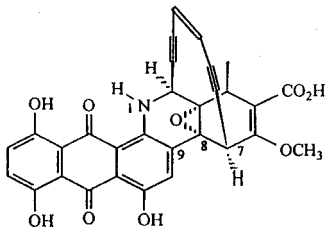
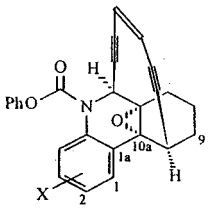
New dynemicin A mimics with methyl group **2a** and **2b** were synthesized, and acid-induced hydrolyzed to see an electronic effect of substituent for epoxide opening. The model **2a** with methyl group at C3 position was more rapidly transformed to diol **16a** than **2b** with methyl group at C2. This result suggests that any substituent at C3 position plays more important role than any substituent at C2 position in the dynemicin A mimic activation.

Introduction

A new type of antibiotics, esperamicin and calicheamicin, was reported by Lederle laboratories[1] and Bristol-Meyers' researchers,[2] respectively in 1987. These drugs have been received increasing attention because of their extremely potent antitumor activity and unusual structure containing enediyne system.[3] The dynemicin A (**1**)[4] isolated from *micromonospora chersina* also showed a potent antitumor activity *in vitro* and *in vivo*. Structurally, this drug was characterized as a hybrid molecule of two typical chemotypes of antineoplastic agents, enediyne and anthraquinone. The pronounced cytotoxic activity of these compounds has been attributed to their ability to undergo Bergman cyclization to give a phenylene diradical which initiates DNA cleavage.[5] Cycloaromatization for **1** is triggered by epoxide opening induced by developing electron density at C-9. This suggestion that epoxide opening is a critical step of the drug activation has been supported by the results of molecular modeling and mechanistic studies.[6,7] Accordingly, for the model compound (*i.e.*, **2a**) the use of proper substituent on benzene ring will give an effect on electron density of C10a and then, epoxide opening and cycloaromatization will be able to be controlled. In this paper, we describe the syntheses and acid-induced Bergman cyclization of tricyclic dynemicin A models **2a** and **2b**.



Dynemicin A (**1**)

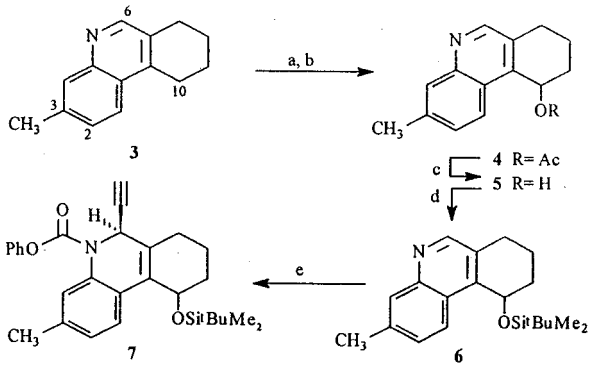


2a X= 3-CH 3
2b X= 2-CH 3

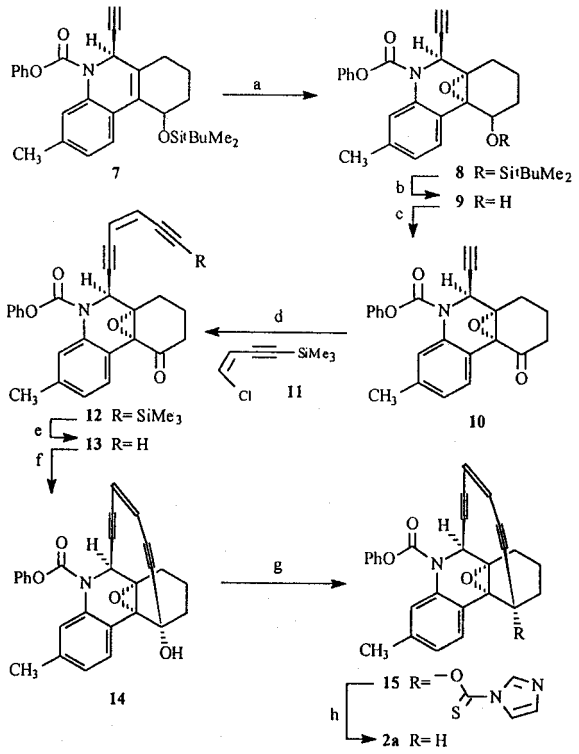
Results and Discussion

Synthesis of Dynemicin A Models. Scheme 1 and 2 summarize the construction of new dynemicin A model **2a** starting 3-methyl-7,8,9,10-tetrahydrophenanthridine (**3**)[8] using a typical preparation method[9,10] for the dynemicin A model compounds.

The first strategy to make **2a** is the C6 and C10 functionalization of compound **3**. The treatment of **3** with *m*-chloroperoxybenzoic acid (*m*CPBA) in dichloromethane gave the *N*-oxide, which was vigorously stirred to give the acetate **4**. This acetate was converted to the silyl ether **6** in overall high yield by conventional method *via* base hydrolysis of product **5**. Introduction of acetylene at C6 with ethynylmagnesium bromide and protection of N5 with phenyl chloroformate transformed compound **6** to diastereomeric mixture **7**. Continuously, treatment of **7** with mCPBA yielded the epoxide **8**, which was converted to the ketone **10** *via* alcohol **9** by desilylation, followed by oxidation with pyridinium dichlorochromate (PCC) (Scheme 2). Coupling of compound **10** and vinyl chloride **11** using Pd(0)-Cu(I) catalysis afforded an enediyne product **12**. On the other hand, even though direct cyclization of **12** with CsF to give alcohol **14** *via* **13** was tried, only desilylated product **13** was isolated in relatively good yield.[11] Treatment of **13** with lithium diisopropylamide (LDA) resulted in the formation of 10-membered enediyne cyclic adduct **14**. Finally, the tertiary hydroxy group in **14** was removed to obtain a closer model of dynemicin A. The treatment of alcohol **14** with thiocarbonyldiimidazole



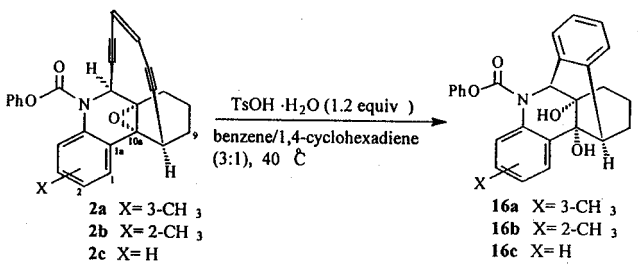
Scheme 1. C6 and C10 functionalization of tricyclic compound. Reagents and conditions: (a) 1.2 equiv of *m*CPBA, CH_2Cl_2, 25 ℃, 2 h, 95%; (b) Ac_2O, 25 ℃, 1 h, 74%; (c) K_2CO_3 (catalytic), MeOH, 25 ℃, 3 h, 92%; (d) 1.1 equiv of $^tBuMe_2SiOSO_2CF_3$, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 ℃, 30 min, 94%; (e) 1.1 equiv of ethynylmagnesium bromide, 1.1 equiv of PhOCOCl, THF, −78 ℃ to 25 oC, 30 min, 88%.



Scheme 2. Synthesis of a Dynemicin A Model.
Reagents and conditions: (a) 1.5 equiv of *m*CPBA, CH_2Cl_2, 25 ℃, 1 h, 91%; (b) 1.2 equiv of $^nBu_4NF$, THF, 25 ℃, 4 h, 99%; (c) 1.8 equiv of PCC, 4-Å molecular sieves, CH_2Cl_2, 25 ℃, 1 h, 78%; (d) 1.6 equiv of **11**, 0.06 equiv of $Pd(PPh_3)_4$, 0.24 equiv of CuI, 2.0 equiv of $^nBuNH_2$, benzene, 25 ℃, 1 h, 54%; (e) 3.5 equiv of CsF, 2.0 equiv of Ac_2O, 1.0 equiv of $NaHCO_3$, CH_3CN, 60 ℃, 10 min, 79%; (f) 1.0 equiv of LDA, toluene, −78 ℃, 30 min, 88% based on 22% recover of **13**; (g) 3.0 equiv of thiocarbonyldiimidazole, 0.5 equiv of DMAP, CH_2Cl_2, 25 ℃, 48 h, 92% based on 28% recover of **14**; (h) 2.0 equiv of *n*-Bu_3SnH, AIBN (cat.), toluene, 80 ℃, 2 h, 54%.

in the presence of 4-(dimethylamino)pyridine (DMAP) gave the compound **15**, which was reduced to the desired compound **2a** by *n*-Bu_3SnH and 2,2′-azobis(isobutyronitrile) (AIBN).

Activation of Dynemicin A models. The tandem acid-induced epoxide opening and Bergman cyclization of new models was performed to examine an electronic effect by methyl group (Scheme 3). Compounds **2a** and **2b** with methyl group at C3 and C2 positions were treated with *p*-toluenesulfonic acid in benzene/1,4-cyclohexadiene (3/1) at 40 ℃. Expectedly, **2a** and **2b** gave the aromatized products **16a** and **16b**, respectively *via* tandem epoxide opening and Bergman cyclization. Table 1 shows the reaction time and yields for the enediyne models. The unsubstituted compound 2c was also activated to compare the reaction profile with two methyl substituted models under the same condition.[10] Interestingly, epoxide opening for the three compounds showed a significant rate difference. The order of reactivity was **2a, 2b** and **2c**. Moreover, compound **2a** with methyl group at para position to the internal epoxide underwent epoxide opening more rapidly than **2b** with methyl group at meta position. These results suggest that the methyl group particiPates in the epoxide opening as an activator, and confirm a known mechanism that epoxide opening triggers Bergman cyclization in dynemicin A chemistry.



Scheme 3.

Table 1. *

Substrate	Reaction time (min)	Product	Yield (%)
2a	10	**16a**	52
2b	40	**16b**	51
2c	80	**16c**	46

*All reactions were run in duplicate and averaged. Reaction progress was checked every five minute by TLC.

In summary, two tricyclic dynemicin A model compounds were easily synthesized from methyl substituted 7,8,9,10-tetrahydrophenanthridine. In acidic condition, the epoxide of these methyl derivatives was opened with different rate and then, Bergman cyclized to give the aromatized compounds. The fact that **2a** is more rapidly hydrolyzed to diol than **2b** suggests that C3 position could have priority to C2 in the choice of any substituent for new dynemicin mimic development.

Experimental Section

Genenral Techiques. Melting points were recorded on a Büchi 512 capillary melting point appratus and were not corrected. NMR spectra were recorded on a Varian Unity Plus FT-300 instrument. IR spectra were recorded on a Perkin Elmer 1430 IR spectrophotometer.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) under UV light. Preparative thin layer chromatography was performed on 0.5 mm×20 cm×20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography.

3-Methyl-7,8,9,10-tetrahydrophenanthridine *N*-Oxide (3a). A solution of (6.87 g, 34.8 mmol) in dichloromethane (140 mL) was treated at 25 ℃ with *m*CPBA (12.19 g of a 55% sample, 38.9 mmol) and stirred for 2 h. The solution was poured into saturated sodium bicarbonate solution (250 mL) and extracted. The aqueous layer was extracted with further dichloromethane (2×250 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica, 10% methanol in ethyl acetate) to give the *N*-Oxide **3a** (7.05 g, 95%) as a white cryatalline solid: mp 73-74 ℃; R_f=0.38 (silica, 10% methanol in ethyl acetate); IR (KBr) ν_{max} 2870, 1580, 1420, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):

δ=8.49 (s, 1H, H4), 8.23 (s, 1H, H6), 7.74 (d, *J*=8.7 Hz, 1H, H1), 7.39 (d, *J*=8.4 Hz, 1H, H2), 2.95 (t, *J*=5.7 Hz, 2H, H10), 2.71 (t, *J*=5.7 Hz, 2H, H7), 2.51 (s, 3H, CH_3), 1.92-1.85 and 1.84-1.79 (m, 4H, H8 and H9); ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.6, 139.2, 136.3, 132.6, 130.3, 129.2, 127.5, 122.9, 119.0, 26.9, 24.5, 22.1, 21.9, 21.6.

10-Acetoxy-3-methyl-7,8,9,10-tetrahydrophenanthridine (4). A solution of the *N*-Oxide **3a** (7.05 g, 33.1 mmol) in acetic anhydride (62.3 mL) was treated at 25 ℃ for 3 h, evaporated to dryness, dissolved in dichloromethane (250 mL), and washed with saturated sodium bicarbonate solution (200 mL). The aqueous layer was extracted with dichloromethane (2×100 mL). The combined organic layers were dried (Na_2SO_4), evaporated in vacuo, and the residue was purified by flash chromatography (silica, 20% ethyl acetate in hexane) to give the acetate **4** (6.22 g, 74%) as a white cryatalline solid: mp 130-131 ℃; R_f=0.31 (silica, 20% ethyl acetate in hexane); IR (KBr) ν_{max} 2950, 2880, 1720, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.67 (s, 1H, H6), 7.86 (s, 1H, H4), 7.66 (d, *J*=8.4 Hz, 1H, H1), 7.37 (dd, *J*=6.6, 1.8 Hz, 1H, H2), 6.55 (br s, 1H, H10), 3.01 (br d, *J*=14.4 Hz, 1H, H7), 2.89-2.83 (m, 1H, H7), 2.54 (s, 3H, CH_3), 2.27 (br d, *J*=6.0 Hz, 1H, H9), 2.09 (s, 3H, $COCH_3$), 2.05-1.95 (m, 3H, H8 and H9); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.2, 152.3, 147.2, 138.4, 136.5, 130.2, 129.3, 129.1, 124.5, 122.1, 64.5, 28.7, 26.6, 21.5, 21.1, 17.3.

10-Hydroxy-3-methyl-7,8,9,10-tetrahydrophenanthridine (5). A solution of **4** (1.52 g, 5.95 mmol) in methanol (25 mL) was treated with potassium carbonate (120 mg, catalytic) and stirred at 25 ℃ for 30 min. The solution was concentrated to *ca.* 7 mL, poured into water (200 mL), and extrated with dichloromethane (2×200 mL). The combined organic layer were evaporated in vacuo, and residue was filtered with glass filter, and washed with ether to give alcohol **5** (1.17 g, 92%) as a white cryatalline solid: mp 164-165 ℃; R_f=0.34 (silica, 50% ethyl acetate in hexane); IR (KBr) ν_{max} 3570, 2880, 1640, 1470, 1320, 1170 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=8.63 (s, 1H, H6), 8.19 (d, *J*=8.4 Hz, 1H, H1), 7.78 (s, 1H, H4), 7.46 (dd, *J*=6.9, 1.8 Hz, 1H, H6), 5.41 (br s, 1H, H10), 3.40 (br s, 1H, OH), 2.97-2.55 (m, 2H, H7), 2.53 (s, 3H, CH_3), 2.12-1.78 (m, 4H, H8 and H9); ^{13}C NMR (75 MHz, DMSO-d_6): δ=147.4 142.0, 136.4, 132.5, 123.8, 123.4, 123.3, 120.1, 119.4, 56.2, 26.9, 21.7, 16.3, 11.9.

10-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-7,8,9,10-tetrahydrophenanthridine (6). A stirred solution of **5** (3.62 g, 17.0 mmol) in dry dichloromethane (50 mL) was cooled to 0 ℃ and treated with 2,6-lutidine (1.82 mL, 25.5 mmol) and *tert*-butyldimethylsilyl triflate (4.29 mL, 18.7 mmol). After 30 min at 0 ℃, methanol (3.1 mL) was added and continued to stir for 5 min. The reaction mixture was poured into saturated sodium bicarbonate solution (100 mL) and extracted. The aqueous layer was extracted with further dichloromethane (2×100 mL), the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash chromatography (silica, 25% ethyl acetate in hexane) to generate silyl ether **6** (5.23 g, 94%) as a white semi-solid: R_f=0.65 (silica, 25% ethyl acetate in hexane); IR (KBr) ν_{max} 2960, 2880, 1490, 1350, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.63 (s, 1H, H6), 7.96 (d, *J*=9.0 Hz, 1H, H1), 7.84 (s, 1H, H4), 7.37 (dd, *J*=6.9, 1.8 Hz, 1H, H2), 5.43 (t, *J*=3.0 Hz, 1H, H10), 3.02-2.94 (m, 1H, H7), 2.85-2.74 (m, 1H, H7), 2.55 (s, 3H, CH_3), 2.23-2.08 (m, 2H, H8 or H9), 1.90-1.75 (m, 2H, H8 or H9), 0.85 (s, 9H, *t*-Bu), 0.22 (d, *J*=2.4 Hz, 6H, Si(CH_3)$_2$).

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6-ethynyl-3-methyl-5,6,7,8,9,10-hexahydrophenanthridine (7).** A solution of quinoline **6** (6.04 g, 19.0 mmol) in THF (93 mL) was cooled to −78 ℃ and treated with ethynyl magnesiumbromide (41.7 mL of a 0.5 M solution in THF, 20.9 mmol), and then phenyl chloroformate (2.6 mL, 20.9 mmol) was added. The reaction mixture was allowed to slowly warm up to 25 ℃ over 30 min, quenched with saturated ammonium chloride solution (500 mL), and extracted. The aqueous layer was extracted with ethyl acetate (2×300 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica, 14% ethyl acetate in hexane) to give the carbamate **7** (7.73 g, 88%) as a white semi-solid: R_f=0.41 (silica, 14% ethyl acetate in hexane); IR (KBr) ν_{max} 3190, 2950, 2880, 2140, 1720, 1520, 1420, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.55 (d, *J*=7.8 Hz, 1H, aromatic), 7.40 (td, 2H, *J*=8.1, 1.5 Hz, 2H, aromatic), 7.30-7.19 (m, 4H, aromatic), 6.98 (br d, *J*=7.2 Hz, 1H, aromatic), 5.65 (d, *J*=2.4 Hz, 1H, H6, major isomer), 5.61 (d, *J*=1.8 Hz, 1H, H6, minor isomer), 4.98 (t, *J*=5.1 Hz, 1H, H10, major isomer), 4.67 (br s, 1H, H10, minor isomer), 2.36 (s, 3H, CH_3), 2.28-1.63 (m, 7H, H7, H8, H9 and C≡CH), 0.95 and 0.83 (2s, 9H, *t*-Bu), 0.27, 0.20, 0.10 and 0.08 (singlets, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=151.0, 136.7, 133.4, 130.0, 129.5, 129.3, 125.7, 123.8, 121.7, 121.6, 80.1, 71.5, 71.4, 64.1, 48.9, 32.7, 28.1, 26.0, 25.9, 21.5, 18.3, 18.2, 18.0, −3.1, −3.6, −4.2, −4.4.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6a,10a-epoxy-6-ethynyl-3-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (8).** A solution of **7** (500 mg, 1.06 mmol) in dichloromethane (3.19 mL) was treated with *m*CPBA (70%, 390 mg, 1.58 mmol) and stirred at 25 ℃ for 1 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL) and extracted with dichloromethane (2×100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 14% ethyl acetate in hexane) to produce 472 mg of **8** (91%) as a white solid: mp 143-144 ℃; R_f=0.33 (silica, 14% ethyl acetate in hexane); IR (KBr) ν_{max} 3190, 2950, 2135, 1720, 1520, 1420, 1180 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.78 and 7.55 (dd, *J*=7.8, 6.0 Hz, 1H, aromatic), 7.42-7.07 (m, 7H, aromatic), 5.60 (d, *J*=1.5 Hz, 1H, H6, major isomer), 5.67 (d, *J*=1.5 Hz, H6, minor isomer), 4.96 (br s, 1H, H10, minor isomer), 4.84 (dd, *J*=9.9, 4.5 Hz, 1H, H10, major isomer), 2.40 (s, 3H, CH_3), 2.35 (br d, *J*=6.0 Hz, 1H, CH_2), 2.14 (s, 1H, C≡CH), 1.99-1.61 (m, 5H, H7, H8 and H9), 0.94 and 0.87 (2s, 9H, *t*-Bu), 0.31, 0.26, 0.21, 0.12 and 0.05 (singlets, 6H, Si(CH_3)$_2$).

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-6-ethynyl-10-hydroxy-3-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (9).** A solution of **8** (7.47 g, 15.3 mmol) in THF (100 mL) was treated with *tetra-n*-butylammonium fluoride (TBAF) (19.1 mL, 1.0 M in THF, 19.1 mmol) at 25 ℃ for 4 h and the solvent was evaporated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica, 25% ethyl acetate in hexane) to give 5.94 g of alcohol **9** (99%) as a white semi-solid: R_f=0.16 (silica,

25% ethyl acetate in hexane); IR (KBr) ν_{max} 3320, 3180, 2950, 2880, 2150, 1720, 1420, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.79 (d, J=8.1 Hz, 1H, aromatic), 7.34 (d, J=7.8 Hz, 2H, aromatic), 7.26-7.08 (m, 5H, aromatic), 5.62 (d, J=2.4 Hz, 1H, H6), 4.69 (t, J=6.0 Hz, 1H, H10), 2.37 (s, 3H, *CH*$_3$), 2.32-1.40 (m, 6H, H7, H8 and H9).

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-6-ethynyl-10-oxo-3-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (10).** The alcohol **9** (6.59 g, 17.6 mmol) was dissolved in dichlomethane (140 mL) and treated with activated 4 Å molecular sieves (powder, 6.25 g) and pyridinium chlorochromate (6.43 g, 29.8 mmol). The suspension was stirred for 1 h at 25 ℃, diluted with ethyl ether (100 mL), filtered through celite, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 67% dichloromethane in hexane) to give ketone **10** (3.78 g, 78%) as a white crystalline solid: mp 170-171 ℃; R_f=0.61 (silica, 67% dichloromathane in hexane); IR (KBr) ν_{max} 3180, 2950, 2130, 1720, 1520, 1410, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.23 (d, J=8.1 Hz, 1H, armatic), 7.38-7.06 (m, 7H, aromatic), 5.71 (d, J=2.1 Hz, 1H, H6), 2.78-2.69 (m, 1H, H9), 2.63-2.53 (m, 1H, H9), 2.36 (s, 3H, CH_3), 2.34-2.22 (m, 3H, C≡*CH* and H7 or H8), 2.06-1.98 (m, 2H, H7 or H8); ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.1, 151.0, 139.1, 135.6, 130.0, 129.3, 127.0, 125.7, 121.5, 120.0, 106.4, 106.3, 77.7, 74.7, 74.3, 57.6, 47.5, 38.7, 23.7, 21.3, 18.4.

***N*-[(Phenyloxy)carbonyl]-6-[6-(trimethylsilyl)-3(Z)-hexene-1,5-diynyl]-6a,10a-epoxy-6-ethynyl-10-oxo-3-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (12).** To a solution of **11** (500 mg, 1.34 mmol) in dry degassed benzene (10 mL) was added copper(I) iodide (61 mg, 0.32 mmol). To the resulting mixture was added the (Z)-chloroenyne **11** (340 mg, 2.14 mmol), followed by *n*-butylamine (266 μL, 2.68mmol) and tetrakis(triphenylphosphine)palladium(0) (93 mg, 0.08 mmol) in dry degassed benzene (5 mL). The reaction mixture was stirred at 25 ℃ for 1 h, diluted with ethyl ether (50 mL), poured into saturated ammonium chloride solution (100 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl ether (2× 100 mL), the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash chromatography (silica, 33% ethyl acetate in hexane) to give 358 mg of **12** (54%) as a white semi-solid: R_f=0.40 (silica, 33% ethyl acetate in hexane); IR (KBr) ν_{max} 3060, 2960, 1720, 1465, 1350, 1200, 840, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.23 (d, J=8.1 Hz, 1H, aromatic), 7.36 (t, J=7.8 Hz, 3H, aromatic), 7.21 (t, J=7.2 Hz, 1H, aromatic), 7.13 (br d, J=7.2 Hz, 2H, aromatic), 7.05 (dd, J=8.1, 1.2 Hz, 1H, aromatic), 5.97 (d, J=1.5 Hz, 1H, H6), 5.82 (d, 11.1 Hz, 1H, olefinic), 5.67 (dd, J=8.1, 1.2 Hz, 1H, olefinic), 2.78-2.65 (m, 2H, H9), 2.36 (s, 3H, *CH*$_3$), 2.33-2.26 (m, 2H, H7), 2.03-1.88 (m, 2H, H8), 0.23 (s, 9H, Si(*CH*$_3$)$_3$).

***N*-[(Phenyloxy)carbonyl]-6-[3(Z)-hexene-1,5-diynyl]-6a,10a-epoxy-6-ethynyl-10-oxo-3-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (13).** Compound **12** (443 mg, 0.89 mmol), CsF (475 mg, 3.13 mmol), and dry $NaHCO_3$ (75 mg, 0.89 mmol) was dissolved in dry CH_3CN (40 mL) and treated with acetic anhydride (168 μL, 1.79 mmol) at 60 ℃. After 10 min stirring, the suspension was filtered through celite, and concentrated *in vacuo*, and the residue was purified by flash chromatography (silica, 33% ethyl acetate in hexane) to generate 300 mg of **13** (79%) as a white semi-solid: R_f=0.31 (silica 33% ethyl acetate in hexane); IR (KBr) ν_{max} 3280, 3020, 2960, 1715, 1375, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.23 (d, J=8.1 Hz, 1H, aromatic), 7.35 (t, J=8.1 Hz, 3H, aromatic), 7.20 (t, J=7.2 Hz, 1H, aromatic), 7.13 (br d, J=7.2 Hz, 2H, aromatic), 7.05 (d, J=8.1 Hz, 1H, aromatic), 5.91 (d, J=1.2 Hz, 1H, H6), 5.77 (s, 2H, olefinic), 3.15 (d, J=1.2 Hz, 1H, C≡*CH*), 2.78-2.63 (m, 2H, H9), 2.35 (s, 3H, *CH*$_3$), 2.33-2.07 (m, 2H, H7), 2.05-1.89 (m, 2H, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ=201.4, 151.0, 138.9, 135.7, 129.7, 129.3, 126.8, 125.7, 121.5, 120.4, 120.0, 111.0, 90.7, 85.1, 82.7, 80.3, 75.0, 57.6, 48.4, 38.8, 29.7, 23.9, 21.3, 18.5.

Compound 14. A solution of **13** (300 mg, 0.708 mmol) in dry toluene (60 mL) was cooled to −78 ℃ and treated with LDA (1.5 M in cyclohexane, 472 μL, 0.708 mmol) and then, stirred for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (24 mL), extracted with ethyl ether (2×100 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 50% ethyl ether in hexane) to give the recovered **13** (65 mg, 22%) and 209 mg of **14** (69% based on 22% recovery of **13**) as a white solid: mp 122-123 ℃; R_f=0.32 (silica, 50% ethyl ether in hexane); IR (KBr) ν_{max} 3460, 3020, 2950, 2180, 1715, 1490, 1360, 1200, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=8.53 (d, J=8.4 Hz, 1H, aromatic), 7.41 (t, J=7.5 Hz, 2H, aromatic), 7.25 (t, J=7.2 Hz, 2H, aromatic), 7.16 (d, J=8.7 Hz, 2H, aromatic), 7.03 (d, J=7.5 Hz, 1H, aromatic), 6.07 (d, J=10.2 Hz, 1H, olefinic), 5.87 (dd, J=10.2, 1.5 Hz, 1H, olefinic), 5.51 (br s, ^1H, NC*H*C≡C), 2.28 (s, 3H, CH_3), 2.24-1.65 (m, 7H, CH_2CH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ=153.0, 150.9, 137.2, 135.5, 131.3, 129.6, 126.6, 126.0, 125.9, 125.3, 122.3, 121.8, 102.8, 94.1, 92.8, 88.9, 73.0, 71.9, 63.9, 50.3, 34.4, 23.0, 20.9, 18.9.

Compound 15. A mixture of **14** (187 mg, 0.440 mmol), thiocarbonyldiimidazole (235 mg, 1.319 mmol), and DMAP (27 mg, 0.220 mmol) in CH_2Cl_2 (2 mL) was stirred at 25 ℃ for 48 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 67% ethyl ether in hexane) to afford **15** (155 mg, 66%), together with recovery of **14** (53 mg, 28%) as a white solid: mp ℃; R_f=0.43 (silica, 67% ethyl ether in hexane); IR (KBr) ν_{max} 3020, 2950, 1720, 1380, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.38 (br s, 1H, imidazole), 7.64 (br s, 1H, aromatic), 7.53 (d, J=7.5 Hz, 1H, aromatic or imidazole), 7.42-7.17 (m, 6H, aromatic and imidazole), 7.04 (br s, 1H, aromatic), 6.95 (d, J=3.9 Hz, 1H, aromatic), 5.94 (d, J=5.1 Hz, 1H, olefinic), 5.75 (dd, J=9.6, 1.8 Hz, 1H, olefinic), 5.58 (d, J=1.8 Hz, 1H, *CH*N), 3.08 (br d, J=5.1 Hz, 1H, CH_2CH_2), 2.46-2.07 (m, 4H, CH_2CH_2) 2.33 (s, 3H, *CH*$_3$), 1.87-1.80 (m, 1H, CH_2CH_2).

Compound 2a. A solution of thionoimidazolide **15** (140 mg, 0.261 mmol) in toluene (5 mL) was treated with *n*-Bu_3SnH (103 μL, 0.523 mmol) and AIBN (10 mg, 7.2 mol%) and stirred at 80 ℃ for 2 h. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, 50% ethyl ether in hexane) to give the deoxygenated compound **2a** (57.9 mg, 54%) as a white solid: R_f=0.58 (silica, 50% ethyl ether in hexane); IR (KBr) ν_{max} 3020, 2940, 2180, 1720, 1505, 1370, 1300, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.48 (d, J=3.9 Hz, 1H, aromatic), 7.39-7.33 (m, 3H, aromatic), 7.25-7.13 (m, 3H, aromatic), 7.03 (br d, J=3.9 Hz, 1H, aromatic), 5.78 (dd, J=10.2, 1.8 Hz, 1H,

olefinic), 5.66 (dd, J=10.2, 1.8 Hz, 1H, olefinic), 5.51 (br d, J=1.8 Hz, 1H, *CH*N), 3.77 (br s, 1H, CH_2CH), 2.44-2.37 (m, 1H, CH_2) 2.33 (s, 3H, CH_3), 2.28-2.20 (m, 1H, CH_2), 2.05-1.77 (m, 3H, CH_2CH_2), 1.64-1.58 (m, 1H, CH_2).

Compound 2b. Obtained in 71% yield in a similar manner as that described for **2a, 2b** as a white solid: R_f=0.79 (silica, 50% ethyl ether in hexane); IR (KBr) ν_{max} 3020, 2940, 2180, 1720, 1510, 1360, 1320, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.40-7.32 (m, 4H, aromatic), 7.26-7.11 (m, 5H, aromatic), 5.73 (ddd, J=36.6, 9.3, 1.5 Hz, 2H, olefinic), 5.50 (d, J=1.5 Hz, 1H, *CH*N), 3.79 (br s, 1H, CH_2CH), 2.45-2.40 (m, 1H, CH_2) 2.37 (s, 3H, CH_3), 2.31-2.17 (m, 1H, CH_2), 2.09-1.89 (m, 2H, CH_2CH_2), 1.85-1.78 (m, 1H, CH_2), 1.64-1.55 (m, 1H, CH_2).

Diol 16a. A solution of enediyne **2a** (20.4 mg, 0.05 mmol) in 1,4-cyclohexadiene (0.5 mL) and benzene (1.5 mL) was treated with *p*-toluenesulfonic acid (11.4 mg, 0.06 mmol) stirred at 40 ℃ for 10 min. The solvent was removed *in vacuo* and the residue was purified by preparative thin layer chromatography (silica gel, 33% ethyl acetate in hexane) to give **16a** (11.2 mg, 52%) as a white semi-solid: R_f=0.31 (silica, 67% ethyl ether in hexane); IR (KBr) ν_{max} 3470, 3030, 2930, 2870, 1710, 1490, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.55-7.34 (m, 4H, aromatic), 7.28-7.12 (m, 6H, aromatic), 6.89 (t, J=7.8 Hz, 2H, aromatic), 5.81 (s, 1H, *CH*N), 3.33 (s, 1H, CH_2CH), 2.78 (br s, 1H, *OH*), 2.32-2.20 (m, 1H, CH_2CH_2), 2.18 (s, 3H, CH_3), 1.81 (br dd, J=12.9, 4.2 Hz, 1H, CH_2CH_2), 1.60 (br s, 1H, *OH*), 1.41 (br t, J=15.0 Hz, 2H, CH_2CH_2), 0.92-0.86 (m, 1H, CH_2CH_2).

Diol 16b. Prepared from **2b** in 51% yield in a similar manner as that described for **16a, 16b** as a white semi-solid: R_f=0.42 (silica, 67% ethyl ether in hexane); IR (KBr) ν_{max} 3470, 3020, 2920, 2870, 1710, 1490, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.49-7.33 (m, 4H, aromatic), 7.28-7.12 (m, 6H, aromatic), 6.91-6.87 (m, 2H, aromatic), 5.79 (s, 1H, *CH*N), 3.33 (s, 1H, CH_2CH), 2.82 (br s, 1H, *OH*), 2.31 (br s, 1H, CH_2CH_2), 2.26 (s, 3H, CH_3), 2.15 (td, J=12.8, 3.0 Hz, 1H, CH_2CH_2) 1.79 (br dd, J=13.5, 5.1 Hz, 1H, CH_2CH_2), 1.61 (br s, 1H, *OH*), 1.40 (br t, J=13.5 Hz, 2H, CH_2CH_2), 0.94-0.83 (m, 1H, CH_2CH_2).

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