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Synthesis and Reactivity of Cinnoline-Fused Cyclic Enediyne

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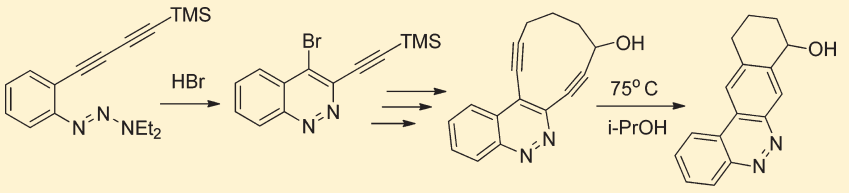
Supporting Information

ABSTRACT:



A short and efficient synthesis of cinnoline-fused cyclic enediyne is reported. Richter cyclization of *o*-(1,3-butadiynyl)phenyltriazene produced 3-alkynyl-4-bromocinnoline. The Sonogashira coupling of the latter with 5-hexyn-1-ol was employed for the introduction of a second acetylenic moiety. The crucial cyclization step was achieved under Nozaki−Hiyama−Kishi conditions. Cinnoline-fused 10-membered ring enediyne is more reactive than corresponding carbocyclic analog and produces good yield of the Bergman cyclization product upon mild heating. This enediyne induces single-strand dDNA scissions upon incubation at 40 °C.

Natural antibiotics belonging to the enediyne family are among the most potent antineoplastic agents ever discovered.[1] The cytotoxicity of these natural products is attributed to the ability of the (*Z*)-3-ene-1,5-diyne fragment to undergo Bergman cyclization[2] and produce DNA-damaging *p*-benzyne diradical.[1] The development of methods to control cycloaromatization reactions and direct powerful DNA-cleaving activity of enediyne antibiotics toward cancerous cells represents an important goal in current medicinal chemistry.[3] In addition, enediyne cycloaromatization is used in the development of selective nucleases,[4] enzyme inhibitors,[5] high-performance linear aromatic polymers,[6] and polymer initiators[7] and in the synthesis of polyaromatic compounds.[8] Natural enediynes are too scarce for practical use; therefore, there is a significant interest in developing efficient syntheses of simpler enediyne compounds. High temperatures required to induce cyclization of acyclic enediynes make them unsuitable for a majority of applications, especially in biology and biochemistry. Among cyclic enediynes, 11- or larger ring systems possess reactivity similar to that of the acyclic analogus,[9] while nine-membered ring enediynes are virtually unknown because of fast spontaneous cyclization.[10,11] The rate of the Bergman cyclization of 10-membered ring enediyne compounds strongly depends on both the ring strain of enediyne-containing cycle[12] and the electronic properties of substituents.[13,14] While fusion with heterocycles provides an alternative strategy for the control of electronic properties of the enediyne system, only few examples of heterocycle-fused enediynes are known.[15] Nitrogen heterocycles, such as cinnoline discussed in this report, can be protonated, thus broadening the range of the electronic density modulation of the enediyne π-system. In addition, conjugation with cinnolines provides enediyne-based nucleases with an additional benefit: enhanced dDNA affinity via intercalation mechanism.[16,17] Finally, cinnoline-based compounds structurally similar to the compound **10** (vide infra) have been recently shown to inhibit topoisomerase I activity, even in multidrug resistant cancer cells.[18] This feature can be employed for the development of antibiotics with dual antineoplastic activity mode. Initial enediyne cycloaromatization produces *p*-benzyne diradical, which abstract hydrogen from DNA inducing strand scission. The TOPO I inhibition by the stable product of the first step further increases the cytotoxic effect of the drug. Here, we report an efficient synthesis of a model cinnoline-fused 10-membered enediyne system, as well as preliminary studies of its cycloaromatization and nuclease activity.

The first step of the target cinnolinoenediyne **8** synthesis employs recently developed method for the preparation of 3-alkynyl-4-halocinnolines (Scheme 1).[19] Reaction of diethylamine with *o*-iodobenzenediazonium chloride, produced in situ by diazotization of *o*-iodoaniline, gave triazene **1** in 94% yield. Sonogashira cross-coupling[20] of the latter with mono TMS-potected buta-1,3-diyne led to *o*-(trimethylsilylbuta-1,3-diynyl)-phenyltriazene **2** in an excellent yield. HBr-induced cleavage of **2**, followed by Richter-type cyclization of the resulting arenediazonium salt, produced 4-bromo-3-(trimethylsilylethynyl)cinnoline (**3**, Scheme 1). The bromine atom in **3** was replaced with 5-hexyn-1-ol under Sonogashira conditions to introduce the second acetylenic moiety. To synthesize the cyclic analogue of the cynnolinoenediyne **4**, we decided to employ Nozaki−Hiyama−Kishi reaction,[21] adapted to iodoacetylenes by Crevisy and

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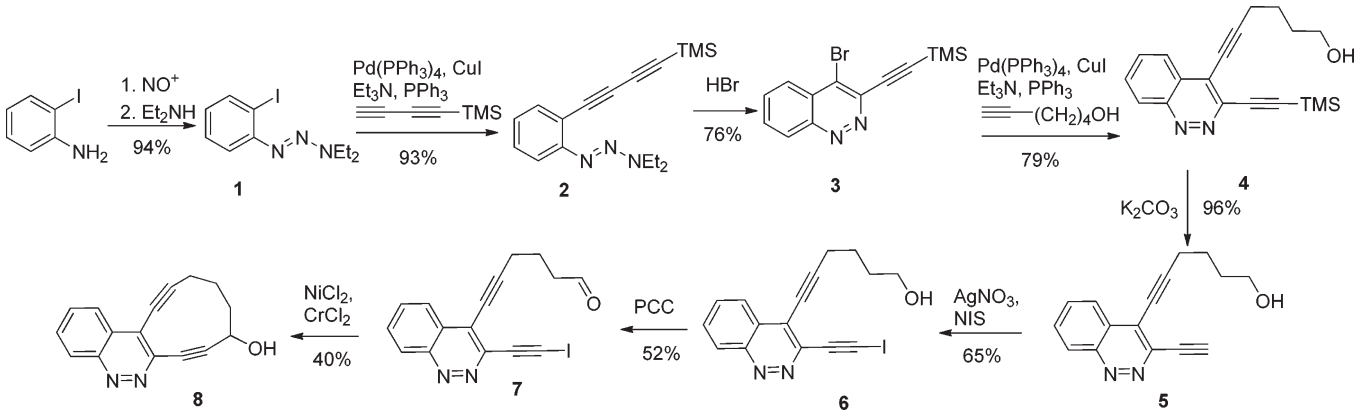
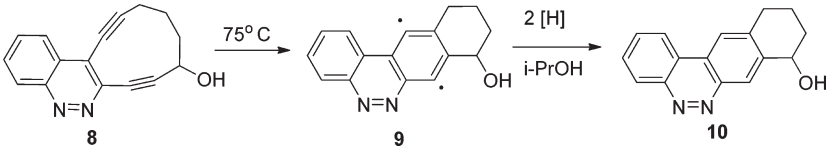
Scheme 1. Synthesis of Cinnolinoenediyne 8



Scheme 2. Thermally Induced Bergman Cyclization of Enediyne 8



Beau[22] (Scheme 1). Iodoacetylene component for this reaction was prepared by removing trimethylsyl protecting group in **4** and subsequent treating of the resulting terminal acetylene **5** with NIS in the presence of $AgNO_3$.[23] The hydroxyl group of in **6** was oxidized by PCC to corresponding aldehyde **7** in 52% yield.[24]

The crucial cyclization of iodoacetylene **7**, conducted under conventional Nozaki–Hiyama–Kishi cross-coupling conditions in THF, initially failed to produce the target compound. According to DIP-MS analysis, the insoluble precipitate formed in this reaction contained some of the cyclized product but all our isolation attempts yielded only small amounts of **8**. Since cinnolines are known to from complexes with various transition metals,[25] we suspected that insoluble product was a complex of cinnoline moiety in **8** and Ni or Cr. To alleviate this problem, we have performed Nozaki–Hiyama–Kishi coupling in DMF. The consumption of starting material was somewhat slower in this medium, but we were able to isolate the target enediyne **8** in 40% yield. In addition, using DMF as a reaction medium allowed for the 10-fold increase in concentration of the precursor **7** without significant formation of the dimer. We have also tried to conduct the reaction in DMSO but obtained only trace amounts the product.

Upon heating to 75 °C in 2-propanol, enediyne **8** undergoes smooth Bergman cycloaromatization producing, upon double hydrogen abstraction from the solvent, a single product, benzo[*c*]cinnoline derivative **10**, which was isolated in 60% yield (Scheme 2).

To evaluate the influence of cinnoline heterocycle on the reactivity of 10-membered ring enediyne, we have compared the rate of the Bergman cyclization of **8** with that of 3,4-benzocyclodeca-1,5-diyne (**11**, Figure 1). The accurate rate measurements of the cyclization reactions of **8** and **11** at 75 °C in 2-propanol were conducted by following the decay of starting material and formation of the products using HPLC. The reaction follows the first-order equation well as shown on the insert in Figure 1.

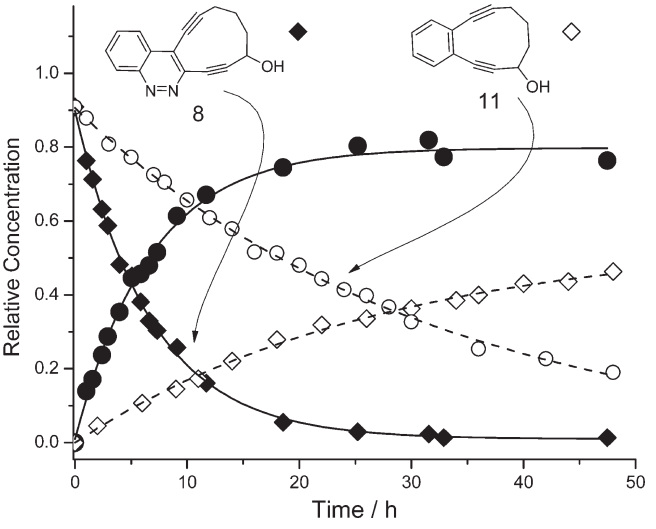


Figure 1. HPLC traces of the cycloaromatization reaction of 1 mM solutions of enediynes **8** (filled squares) and **11** (empty circles) in 2-propanol at 75 °C. Growth of the concentration of corresponding cyclized products (**10**, filled circles, and 1,2,3,4-tetrahydro-1-anthracenol, empty squares) is also shown. The lines were drawn using parameters obtained by least-squares fitting of the data to a single exponential equation.

The rates of the Bergman cyclization of cinnolinoenediyne **8** determined from the decay of the starting material ($k_{decay} = (4.15 \pm 0.19) \times 10^{-5}\ s^{-1}$) and the formation of the product ($k_{form} = (4.13 \pm 0.19) \times 10^{-5}\ s^{-1}$) are in excellent agreement. Enediyne **8** is four times more reactive than benzo-fused analogue **11** ($k_{decay} = (9.14 \pm 0.28) \times 10^{-6}\ s^{-1}$ and $k_{form} = (1.01 \pm 0.07) \times 10^{-5}\ s^{-1}$). In fact, proper assessment of the cinnoline rate enhancement effect comes from the comparison of the reactivity

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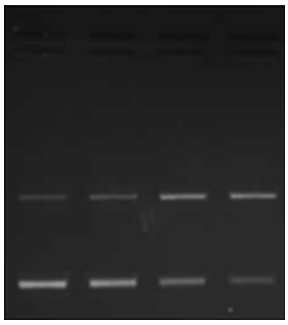

Figure 2. Cleavage of φX174 plasmid DNA by enediyne **8**: lane 1, DNA alone incubated for 24 h at 40 °C; lanes 2−4, DNA incubated with **8** (200 μM, 2 mM, and 4 mM).

of **8** with naphthalene-fused 10-membered ring enediynes, which are stable below 100 °C.[13b] In other words, the electron-poor cinnoline moiety significantly enhances the rate of enediyne cycloaromatization.

Evaluation of enediyne **8** nuclease activity was carried out using supercoiled plasmid DNA cleavage assay.[24] Three forms of this DNA, native (RF I), circular relaxed (RF II, produced by single-strand cleavage), and linear (RF III, formed by scission of both strand in close proximity), are readily separated by the agarose gel electrophoresis. Solutions of φX174 plasmid DNA in aqueous TE buffer (pH = 7.6) were incubated in the presence of various concentration of enediyne **8** for 24 h at 40 °C. Agarose gel electrophoresis results are shown in Figure 2.

Cinnolinoenediyne **8** induces substantial single strand cleavage of φX174 DNA (RF II), while linearized form (RF III) was not observed under experimental conditions. Integration of fluorescence of bands on the gel shown in Figure 2, allowed us to evaluate the relative abundance of the native and circular forms of φX174 DNA. Thus, incubation of the latter with the 200 μM of enediyne **8** produces 8% of single strand cleavage (corrected for blank experiment). At 2 and 4 mM concentrations of **8**, DNA-cleavage efficiency grows to 43 and 50% correspondingly (lanes 3 and 4, Figure 2). While efficient DNA scission requires relatively high concentrations of **8**, one should take into account that overall conversion of enediyne **8** during incubation time is about 3%. Our group has previously synthesized analogues of benzocyclodecadiyne **11**, which undergo fast spontaneous cyclization under ambient conditions.[26] We expect that similar structural features incorporated in the structure **8**, will turn it into an efficient nuclease. We also explore structural modification that would allow enhance topoisomerase I binding affinity of the cyclization product **10**.

EXPERIMENTAL SECTION

General Methods. All organic solvents were dried and freshly distilled before use. Flash chromatography was performed using 40−63 μm silica gel. All NMR spectra were recorded in $CDCl_3$ and referenced to TMS unless otherwise noted. Melting points are uncorrected. Tetrahydrofuran was distilled from sodium/benzophenone ketyl; ether and hexanes were distilled from sodium. Other reagents were obtained from commercial sources and used as received unless otherwise noted.

Materials. 1,4-Bis(trimethylsilyl)buta-1,3-diyne, 1-(trimethylsilyl)-buta-1,3-diyne, and 4,5-benzocyclodeca-2,6-diyne-1-ol (**11**) were prepared according to the literature procedurs.[24]

3,3-Diethyl-1-(2-iodophenyl)triazene (1).[26] *o*-Iodoaniline (25.402 g, 115.99 mmol) was added to a solution of concentrated HCl (29 mL) in water (50 mL), stirred vigorously for 10 min, and cooled to −2 °C, and a solution of $NaNO_2$ (8.625 g, 125.0 mmol) in water (20 mL) was slowly added. The reaction mixture was stirred at ca. −5 °C for 20 min, and then diethylamine (14.0 mL, 135.6 mmol) was added dropwise. The reaction mixture was brought to rt, stirred for 30 min, and neutralized by addition of aqueous NaOH solution (2 M, 110 mL). A dark oily product was extracted with ether (3 × 100 mL). Combined ethereal solutions were washed with brine (100 mL), dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. Crude product was purified by flash chromatography (hexanes, R_f = 0.05) to afford pure **1** (33.011 g, 108.95 mmol, 94%) as a yellow oil. ^{1}H NMR (300 MHz): 1.31 (t, J = 7.2 Hz, 6H), 3.79 (q, J = 7.2 Hz, 4H), 6.79−6.85 (m, 1H), 7.23−7.29 (m, 1H), 7.33−7.36 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.82−7.85 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H). ^{1}C NMR (75 MHz): 10.98 (broad s), 14.51 (broad s), 42.01 (broad s), 53.40 (broad s), 96.54, 117.50, 126.45, 128.59, 139.00, 150.39. FW calcd for $C_{10}H_{14}IN_3$: 303. MS found: 303 (15) [M^+], 231 (45), 203 (100), 184 (3), 118 (1), 104 (3), 91 (10), 76 (61), 72 (29), 62 (10), 56 (17), 50 (25).

3,3-Diethyl-1-(2-[(4-trimethylsilyl)buta-1,3-diynyl]phenyl)triazene (2). A degassed solution of triazene **1** (0.033 mol, 10 g), $Pd(PPh_3)_4$ (3.6 mmol, 4.2 g), PPh_3 (3.6 mmol, 944 mg), 1-(trimethylsilyl)buta-1,3-diyne (0.072 mol, 8.8 g), and CuI (7.2 mmol, 1.4 g) in Et_3N (170 mL) was stirred at 45 °C overnight. The reaction mixture was diluted with hexanes, passed through a short layer of silica gel (5% of EtOAc in hexanes), and concentrated in vacuum. The residue was purified by chromatography (hexanes/Et_3N/EtOAc 100:1:0 → 100:2:0 → 100:2:1) to give 9.1 g (93%) of **2** as yellow oil. ^{1}H NMR (400 MHz): 0.22 (s, 9H), 1.31 (s, 6H), 3,79 (q, 4H, J = 7.2 Hz), 7.03 (dt, 1H, J^3 = 7.2 Hz, J^4 = 1.2 Hz), 7.27 (dt, 1H, J^3 = 7.2 Hz, J^4 = 1.6 Hz), 7.37 (dd, 1H, J^3 = 8.0 Hz, J^4 = 0.8 Hz), 7.47 (dd, 1H, J^3 = 7.6 Hz, J^4 = 1.6 Hz). ^{13}C NMR (100 MHz): −0.1, 76.0, 77.9, 88.7, 90.3, 116.1, 117.4, 124.7, 129.1, 134.0, 154.6. EIMS m/z: 268 (M^+ − Et, 29), 197 (M^+ −N_3Et_2, 76), 167 (M^+ − N_3Et_2 − $2CH_3$, 100). HRMS: calcd for $C_{17}H_{23}N_3Si$ [M + H^+] 298.1734, found 298.1731.

4-Bromo-2-(trimethylsilylethynyl)cinnoline (3). Concentrated hydrobromic acid (0.15 mol, 13 mL) was added to a solution of the triazene **2** (0.025 mol, 7.4 g) in acetone (100 mL) at 0 °C and the mixture stirred for 10 min. The cooling bath was removed, the reaction mixture was stirred for 1.5 h at rt and was quenched with brine, and aqueous layer was extracted with ethyl acetate (30 × 3 mL). The combined organic layers were dried over $MgSO_4$, solvent was evaporated in vacuum, and the residue was purified by column chromatography (EtOAc (1 → 25%) in hexanes) to give 5.8 g (76%) of **3** as colorless crystals. Mp: 62−63 °C. ^{1}H NMR (400 MHz): 0.36 (s, 9H), 7.85−7.92 (m, 2H), 8.19 (dd, 1H, J^3 = 7.2 Hz, J^4 = 2.0 Hz), 8.57 (dd, 1H, J^3 = 7.6 Hz, J^4 = 2.0 Hz). ^{13}C NMR (100 MHz): −0.2, 98.8, 105.3, 123.3, 124.1, 130.4, 131.7, 132.7, 137.0, 140.1, 149.0. EIMS: m/z 306 (M^{+2}, 62), 304 (M^+, 66), 291 (M^{+2} − CH_3, 14), 289 (M^+ − CH_3), 263 (M^{+2} − N_2, 29), 261 (M^+ − N_2, 23), 225 (M^+ − Br, 78), 197 (M^+ − Br-N_2, 100), 182 (M^+ − Br-N_2-CH_3, 9), 167 (31), 152 (16). HRMS: calcd for $C_{13}H_{13}BrN_2Si$ [M + H^+] 305.0110, 307.0089, found 305.0103, 307.0083.

6-[3-(Trimethylsilylethynyl)cinnolin-4-yl]hex-5-yn-1-ol (4). A degassed solution of cinnoline **3** (19 mmol, 5.8 g), hex-5-yn-1-ol (23 mmol, 2.54 mL), CuI (2.2 mmol, 417 mg), and $Pd(PPh_3)_4$ (1.1 mmol, 1.27 g) in Et_3N (50 mL) was stirred at 50 °C for 17 h., diluted with hexane (100 mL), and filtered through a short layer of silica gel (30% hexane in EtOAc). The resulting solution was concentrated in vacuo, and the residue was purified by chromatography (EtOAc in hexanes (5 → 75%)) to give 4.8 g (79%) of **4** as yellow oil. ^{1}H NMR (400 MHz): 0.34 (s, 9H), 1.52 (bs, 1H), 1.85−1.88 (m, 4H), 2.73 (t, 2H, J = 6.4 Hz), 3.77 (t, 2H, J = 6.4 Hz), 7.75−7.84 (m, 2H), 8.14 (d, 1H, J = 8.0 Hz), 8.51 (d, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz): 0.1, 20.2, 25.0, 32.1,

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62.4, 74.5, 101.2, 102.4, 107.9, 122.4, 125.2, 125.3, 130.4, 131.2, 132.0 142.0, 147.8. EIMS m/z 322 (M^+, 64), 307 ($M^+ - CH_3$, 58), 291 ($M^+ - CH_2OH$, 32), 277 ($M^+ - 3CH_3$, 100), 233 (34), 190 (21). HRMS: calcd for $C_{19}H_{22}N_2OSi$ [M + H$^+$] 323.1580, found 323.1570.

6-(3-Ethynylcinnoline-4-yl)hex-5-yn-1-ol (5). K_2CO_3 (15.4 mmol, 2.13 g) was added to a solution of cinnoline **4** (14 mmol, 4.51 g) in 120 mL MeOH, and reaction mixture was stirred at for 2 h at rt. EtOAc (150 mL) and brine (200 mL) were added to the reaction mixture. Layers were separated, and aqueous layer was extracted with ethyl acetate (3 × 30 mL). Combined organic layers were washed with brine, dried over $MgSO_4$, and solvent removed in vacuum. The residue was purified by column chromatography (hexanes/EtOAc 6:1 → hexanes/EtOAc/MeOH 1:1:0.01) to give 3.4 g (96%) of enediyne **6** as colorless crystals. Mp: 59−62 °C. ^{1}H NMR (400 MHz): 1.73 (bs, 1H), 1.85−1.88 (m, 4H), 2.74 (t, J = 6.4 Hz, 2H), 3.64 (s, 1H), 3.77 (t, J = 5.6 Hz), 7.77−7.87 (m, 2H), 8.16 (d, J = 8.4 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz): 20.2, 24.9, 32.0, 62.4, 74.4, 80.6, 83.7, 108.3, 123.0, 125.2 130.4, 131.4, 132.2, 141.3, 148.0. EIMS m/z: 250 (M^+, 100), 222 ($M^+ - N_2$, 64), 163 ($M^+ - N_2$-$CH_2CH_2CH_2OH$, 92). HRMS: calcd for $C_{16}H_{15}N_2O$ [M + H$^+$] 251.1184, found 251.1177.

6-(3-Iodoethynylcinnoline-4-yl)hex-5-yn-1-ol (6). Enediyne **5** (13 mmol, 3.25 g) and $AgNO_3$ (1.5 mmol, 255 mg) were added to a solution of NIS (15 mmol, 3.37 g) in 40 mL of acetone and reaction mixture was stirred for 1.5 h at r.t. Acetone was evaporated in vacuum and the residue was purified by chromatography (hexanes/EtOAc 2:1 → 1:2) to yield 3.2 g (65%) of **6** as colorless crystals. Mp > 97 °C dec); ^{1}H NMR (400 MHz, DMSO-d_6): 1.68−1.75 (m, 4H), 2.75 (t, J = 6.0 Hz, 2H), 3.52 (td, J = 5.6, 5.2 Hz, 2H), 4.50 (q, J = 5.2 Hz, 1 H), 7.95−8.02 (m, 2H), 8.14 (dd, J^3 = 5.2 Hz, J^4 = 1.6 Hz, 1H), 8.49 (dd, J^3 = 5.2 Hz, J^4 = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 19.3, 24.6, 28.3, 31.6, 60.2, 73.6, 90.0, 109.1, 122.0, 124.3, 124.7, 129.7, 132.1, 133.0, 141.4, 147.0. EIMS m/z: 376 (M^+, 100), 249 (M^+ − I, 41), 221 ($M^+ - I$-N_2, 71). HRMS: calcd for $C_{16}H_{13}IN_2O$ [M + H$^+$] 377.0151, found 377.0140.

6-(3-Iodoethynylcinnoline-4-yl)hex-5-ynal (7). PCC (12 mmol, 2.59 g) was added to a solution of alcohol **6** (8 mmol, 3.00 g) in 300 mL of CH_2Cl_2, and the reaction mixture was stirred for 2 h at rt. The resulting solution was passed through a short layer of silica gel (20 → 50% EtOAc in hexanes) and solvent removed under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexanes 1:5 → EtOAc/hexanes/CH_2Cl_2 1:1:2) to give 1.6 g (52%) of **7** as colorless crystals. Mp > 111 °C dec. ^{1}H NMR (400 MHz): 2.07 (quint, J = 6.8 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 2.84 (td, J = 7.2, 0.8 Hz, 2H), 7.77−7.86 (m, 2H), 8.11 (dd, J^3 = 8.0 Hz, J^4 = 0.8 Hz, 1H), 8.51 (dd, J^3 = 8.0 Hz, J^4 = 0.8 Hz, 1H), 9.92 (s, 1H). ^{13}C NMR (100 MHz): 17.2, 19.6, 20.8, 42.7, 75.0, 91.7, 106.8, 122.9, 125.0, 125.1, 130.4, 131.5, 132.3, 142.1, 147.8, 201.5. EIMS: m/z 374 (M^+, 68), 346 ($M^+ - N_2$, 11), 247 (M^+ − I, 32), 219 ($M^+ - I$-N_2, 100). HRMS: calcd for $C_{16}H_{11}IN_2O$ [M + H$^+$] 374.9994, found 375.0002.

Cinnolino[5,4-*c*]cyclodeca-4-ene-2,6-diyn-1-ol (8). A solution of aldehyde **7** (0.4 mmol, 150 mg) in 5 mL of DMF was added dropwise over 2 min to a suspension of $CrCl_2$ (1.6 mmol, 197 mg) and $NiCl_2$ (0.04 mmol, 5 mg) in 40 mL of dry degassed DMF under argon and stirred vigorously overnight at rt. Et_2O (50 mL) and brine (50 mL) were added to the reaction mixture, the layers were separated, and the aqueous layer was extracted with ether. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuum. The residue was purified by column chromatography (EtOAc/hexanes/CH_2Cl_2 1:1:0.1 → 3:1:0.1) to produce 40 mg (40%) of the target enediyne **8** as colorless solid. Mp: 72−74 °C. ^{1}H NMR (400 MHz): 1.91−1.99 m (1H), 2.20−2.38 (m, 3H), 2.60−2.75 (m, 2H), 4.81 (dd, J = 8.2 Hz, J = 2.8 Hz, 1H), 7.76−7.87 (m, 2H), 8.05 (dd, J^3 = 7.2 Hz, J^4 = 0.8 Hz), 8.50 (d, J = 8.0 Hz). ^{13}C NMR (100 MHz): 22.0, 23.3, 37.3, 62.8, 78.4, 82.8, 103.0, 112.0, 123.8, 125.1, 126.9, 130.1, 131.3, 131.8, 145.6, 148.3. EIMS m/z: 248 (M^+, 16), 230 ($M^+ - H_2O$, 91), 202 ($M^+ - H_2O$-N_2, 100). HRMS: calcd for $C_{16}H_{12}N_2O$ [M + H$^+$] 249.1028, found 249.1034. UV (*i*-PrOH, 25 °C, c = 1.82 × 10^{-5} M): λ = 263 (ε = 55000), λ = 308 (ε = 5600), λ = 321 (ε = 5900), λ = 351 (ε = 5200).

8,9,10,11-Tetrahydrodibenzo[*c*,*g*]cinnolin-8-ol (10). A solution of enediyne **8** (0.06 mmol, 15 mg) in 5 mL of 2-propanol was incubated at 75 °C for 24 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/hexanes/CH_2Cl_2 1:1:1) to give 9 mg (60%) of **10** as white solid. Mp: 196−198 °C. ^{1}H NMR (400 MHz): 1.94−2.09 (m, 3H), 2.15−2.23 (m, 2H), 3.04−3.24 (m, 2H), 5.14 (dd, J = 5.2 Hz, J = 10.4 Hz, 1H), 7.88−7.90 (m, 2H), 8.27 (s, 1H), 8.52−8.54 (m, 1H), 8.70−8.74 (m, 1H), 8.33 (s, 1H). ^{13}C NMR (100 MHz,): 19.1, 30.2, 32.2, 68.5, 120.2, 120.7, 120.9, 121.5, 129.2, 130.5, 131.4, 131.5, 141.8, 142.2, 144.7, 145.3. EIMS m/z: 250 (M^+, 100), 232 ($M^+ - H_2O$, 25), 222 ($M^+ - N_2$, 25), 203 (16), 194 (16), 178 (11), 165 (38), 152 (9), 101 (18). HRMS: calcd for $C_{16}H_{14}N_2O$ [M + H$^+$] 251.1184, found 251.1182. UV (*i*-PrOH, 25 °C, c = 6 × 10^{-5}): λ = 260 (ε = 16000).

DNA Cleavage Experiments. Solutions of enediyne **8** in DMSO (15 μL) (0 mM, 0.54 mM, 5.4 mM, 10.8 mM) were added to 25 μL of aqueous solution of φX174 plasmid DNA (10 ng/μL, in TE buffer [pH = 7.6]). The solutions were incubated for 24 h in 40 °C. Incubated samples were mixed with a glycerol-based loading buffer (7 μL) containing xylene cyanol loading dye and loaded onto a 1% agarose gel containing 0.5 μg/mL of ethidium bromide. Gel was developed at 80 V (400 mA) for 2 h and photographed on the UV transilluminator. The relative intensities of fluorescent bands on the developed gel were calculated using Alpha Ease FC software package by Alpha Innotech, Inc.

■ ASSOCIATED CONTENT

Supporting Information. Preparation of known synthetic intermediates and NMR spectra of the newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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