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The synthesis and evaluation of 10- and 12-membered ring benzofused enediyne amino acids

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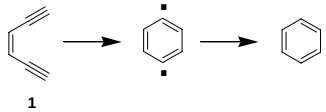
Abstract—The enediyne moiety is a versatile functional group found in natural anticancer and anti-infective agents, undergoing the Bergman cyclization reaction to afford a diradical which cleaves double-stranded DNA. We have incorporated the enediyne group into 10- (**4**–**10**) and 12-membered ring (**11**) cyclic amino acids and dipeptides, respectively, and explored their relative reactivity toward cyclization, varying N-substitution in the case of the 10-membered ring substrate, which gave the expected cyclization products in good yields when using either thermal conditions in the presence or absence of microwave irradiation. The *N*-tosyl substituted derivative (**4**) was shown to nick double-stranded supercoiled DNA. N-Arylsulfonyl substitution on the ring promoted the cyclization, when compared to N-mesyl or acyl substitution, possibly because of a π–π stacking effect as an *endo*-relationship of the aryl group with the enediyne was demonstrated in both the solid state and in solution. The 12-membered ring enediyne dipeptide (**11**) was inert to the Bergman cyclization under a variety of conditions. When this substrate was irradiated with ultraviolet light, regio- and stereospecific reduction was observed in which one of the alkynes was reduced to a *Z*-olefin (**47**).

1. Introduction

cis-1,2-Enediyne anticancer and antibiotic agents such as calicheamicin γ, dynemicin, and neocarzinostatin have attracted much interest because the enediyne system **1** undergoes the Bergman aromatization reaction forming a diradical intermediate which nicks and cleaves double-stranded DNA.[1] The Bergman reaction is promoted either thermally, photochemically, or by metal catalysis, and the study of substituted model enediynes has provided insight into the factors which influence reactivity and selectivity.[2] In addition to the well-studied nicking of double-stranded DNA, proteins are also attractive targets for enediyne radical-mediated cleavage. Enediynes have been attached to a substructure which directs the reactive portion to a specific molecular target such as conjugation with steroids and then binding and inactivation of the human estrogen A receptor.[3] Few enediynes incorporating amino acids or peptides have been prepared. In one example, Basak et al. found that the association of two pendant tripeptide chains via the β-sheet hydrogen bonding of **2** promoted the thermal Bergman cyclization of the central core enediyne.[4] Jones and co-workers described an acyclic enediyne **3** bearing a tri-aspartic acid side chain that cleaved the basic protein histone I specifically into one observed component.[5]



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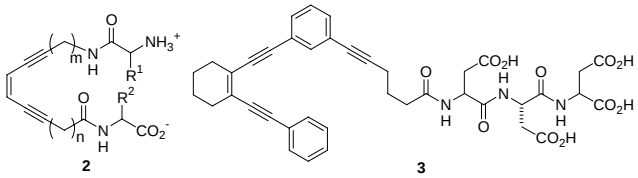

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Keywords: Enediynes; Bergman cyclization; Peptidomimetics; Microwave-assisted chemistry.
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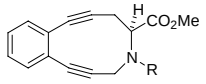
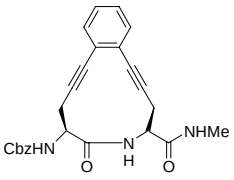
As part of a program looking at constrained peptidomimetics and structure-function relationships,[6] we reasoned that incorporation of an enediyne into a cyclic peptide scaffold might afford useful structures with defined and characteristic secondary structures such as the β-turn. In addition, cyclic enediyne amino acids may display affinity for biological targets such as receptors or transcriptional regulators thereby promoting nicking and degradation. Such interactions could also provide information as to the location of ligand binding by inspection of where the target is cleaved. We have investigated the incorporation of benzofused enediynes into 10- and 12-membered cyclic α-amino acids **4**–**10** and dipeptide **11**, respectively, and examined their reactivity and conformational preferences.



4 R = Ts
5 R = H
6 R = Ac
7 R = Ms
8 R = Ns
9 R = 4-(MeO)PhSO$_2$
10 R = 3,4-(MeO)$_2$PhSO$_2$



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2. Results and discussion

2.1. Ten membered cyclic enediyne amino acids

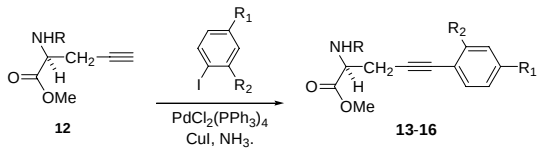
Cyclic enediynes containing a 10-membered ring have been the most widely investigated because the distances between their terminal alkyne carbons are optimally disposed for Bergman cyclization (2.9–3.2 Å).[7] Among the enediyne model systems that have been prepared are carbocyclic with pendant substitution[5c,8] and incorporation of a heteroatom directly into the ring as an ether,[3,9] secondary amine,[10] thioether,[11] or sulfone.[12] Insertion of the enediyne into a ring has proven to be a general way to change strain energy and modulate enediyne reactivity.[13] In the calicheamycin system, addition of a thiol to an sp^2 center transformed it to sp^3 which altered the conformation of the ring sufficiently enough to promote the reaction.[1] A similar effect was recently reported in the transannular reaction of a reactive functionality to give a bicyclic system which facilitated the Bergman reaction.[14]

We envisioned that construction of enediyne **4** could be achieved by using either Sonogashira alkynyl coupling or C–N bond formation as the key step. Although intramolecular Sonogashira coupling has been used in the construction of enediyne 10-membered rings, the yields were modest (ca. 30%).[15] Alternatively, C–N bond formation during the construction of an enediyne ring has been accomplished by sulfonamide displacement of a mesylate.[10] We decided to explore the use of the Mitsonobu reaction to form the required C–N bond because it is simple and compatible with diverse functional groups.[16] Intramolecular Mitsonobu reactions have been used to prepare three- to six-membered cyclic amines and β-lactams even when the amine or amide precursors were not activated,[17] but it had not yet been used in the preparation of enediynes. We reasoned that the required acyclic enediyne precursor to the Mitsonobo reaction could be assembled by two consecutive Sonogashira couplings of both propargyl glycine derivative **12** and propargyl alcohol with 1,2-diiodobenzene.

Sonogashira coupling is an efficient way to prepare conjugated enynes from alkenyl halides or triflates with 1-alkynes.[18] Applications of this method to the coupling of propargyl amino acid derivatives with phenyl or vinyl halides has been reported when using Pd(PPh$_3$)$_4$,[19] PdCl$_2$(dppf)$_2$,[20] and Pd/C.[21] Recently, it was reported that certain alkynes could couple with aryl halides under the catalysis of PdCl$_2$(PPh$_3$)$_2$ in THF at room temperature using aqueous ammonia as base.[22] We have used these later conditions on the amino acid substrate **12** in coupling to aryl iodides with either electron withdrawing or donating substitution to afford enynes **13**–**16** in good yields (Table 1). When 1,2-diiodobenzene was used, the use of DME was found to be preferred over MeCN and THF (entries 4–6).

Alkyne **16** was coupled in a second Sonogashira reaction with propargyl alcohol to form 1,2-diynylbenzene **17** (Fig. 1, 94%). Intramolecular Mitsunobu reaction of **17** conducted at 0 °C provided enediyne **4** (90%). Compound **4** and 1,4-cyclohexadiene (100 mol equiv) were dissolved in DMF, and subjected to microwave irradiation producing cyclized product **18** in 84% yield after

Table 1. Sonogashira coupling of L-propargylglycine **12** with iodobenzenes



12 **13-16**

Entry	R_1	R_2	Solvent	Time (h)	Product	Yield (%)
1	H	H	THF	14	**13**	80
2	OMe	H	THF	14	**14**	55
3	CF_3	H	THF	14	**15**	77
4	H	I	THF	24	**16**	50
5	H	I	CH_3CN	24	**16**	50
6	H	I	DME	4	**16**	60

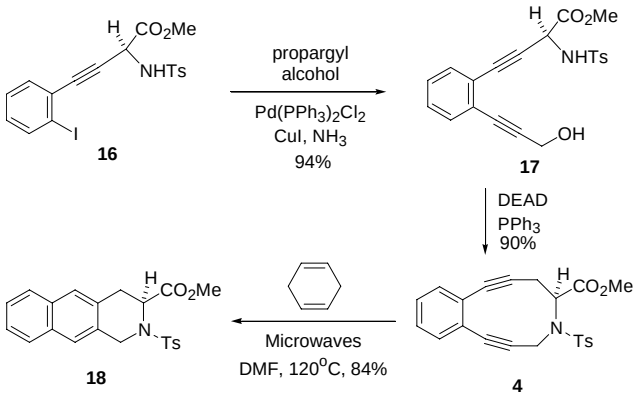


Figure 1. Synthesis of 10-membered cyclic enediyne amino acid **4**.

10 min at 120 °C. Although microwaves have been used in organic synthesis extensively,[23] this appears to be their first application to the Bergman reaction. Alternatively, the reaction was also achieved under heating in the absence of microwaves. We compared the conversion of **4** to **18** by either heating or microwave irradiation at different temperatures during a 10 min period. Although it appeared that the use of microwaves accelerated the reaction to a modest extent when compared with thermal conditions alone, there was not a dramatic difference between the two.

Compound **4** was stable for several months at room temperature in the solid state. We carefully monitored the rate of conversion of **4** to **18** at 0.1 mM in DMF with 1,4-cyclohexadiene (100 mol equiv), and determined that the half-life ($t_{1/2}$) for depletion of **4** and formation of **18** was 131 h at 37 °C and 9.5 h at 55 °C without any other products being detected. A single-crystal X-ray structure of **4** was obtained and revealed that the tosyl group adopts an *endo*-orientation placing it above the enediyne ring (Fig. 2). A NOESY NMR experiment of **4** in $CDCl_3$ was conducted revealing a positive NOE between hydrogens on the tosylate methyl and phenyl hydrogens on the benzo group of the fused enediyne ring, as well as the phenyl hydrogens *ortho* to sulfonyl of the tosylated with methylene hydrogens of the enediyne ring. Therefore, the *endo*-conformation revealed in the X-ray structure of **4** in the solid state was also observed for the compound in solution.

To investigate the possibility that **4** could cleave double-stranded DNA, we incubated it with supercoiled DNA at 37 °C for a period of 24 h while varying the

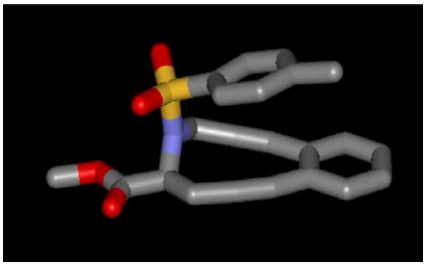


Figure 2. X-ray crystal structure of **4** revealing an *endo*-orientation of the tosylate group with the enediyne ring.

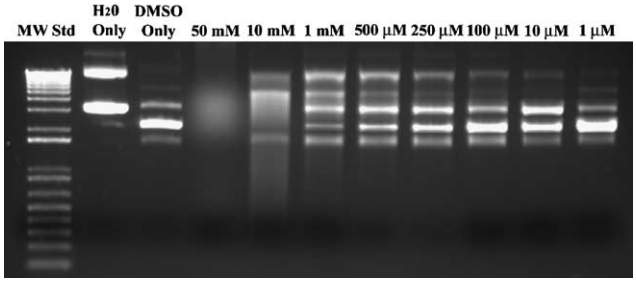


Figure 3. Cleavage of ϕ-X DNA mediated by differing concentrations of **4**. The compound was dissolved in 100% DMSO and incubated with the DNA for 24 h followed by analysis on a 1% agarose gel and visualization using ethidium bromide.

concentration from 1 μM to 50 mM and evaluated the progress of the reaction by agarose gel electrophoresis (Fig. 3).[24] Cleavage of supercoiled DNA was seen at concentrations 10 μM and higher, with many fragments being observed at the highest concentrations.

Several factors are known to influence Bergman cyclization such as the distance between the bond-forming alkynyl carbons, electronic effects, and strain energy. However, the effect of pendant substitution on stabilization of a diradical intermediate is not well characterized. We prepared NH compound **5** and *N*-substituted derivatives **6**–**10** to complement **4**, to investigate the effect of N-substitution upon the Bergman cyclization. Since the tosylate of **4** was in an *endo*-orientation relative to the enediyne ring by X-ray structure determination and in solution, we reasoned that varying the tosylate to other groups would influence the rate of the Bergman reaction. The synthesis of **7**–**10** was initiated by conducting consecutive Sonagashira coupling reactions starting with *N*-substituted L-propargyl glycines **19**–**22** and 1,2-diiodobenzene to give **23**–**26**, followed by reaction with propargyl alcohol to give **33**–**36** (Fig. 4). Subsequent ring closing via the Mitsunobu reaction on **33**–**36** provided enediynes **7**–**10** (62–85% yield). Treatment of *N*-nosyl compound **8** with thiophenol provided amine **5**, which furnished **6** upon treatment with acetyl chloride.[10,25]

The Bergman cyclizations of enediynes **4**, and **6**–**10** were compared at 55 °C and the half-lives for conversion are presented in Table 2. Sulfonamides **4** and **7**–**10** were observed to react with a faster rate ($t_{1/2}$ = 4.0–18.5 h) than acetamide **6** ($t_{1/2}$ = 55.4 h). Mesylate **7** had a longer rate of reaction ($t_{1/2}$ = 18.5 h) than the aryl sulfonamides **4** and **8**–**10** ($t_{1/2}$ of 4.0–9.4 h). Therefore, aryl substitution increased the rate of the reaction, and *N*-sulfonyl mesylate **7** reacted ca. 3× faster than *N*-acetyl **6**. The reaction was not influenced by either electron withdrawing (viz., **8**) or electron donating substitution on the aryl ring (viz., **9** and **10**). Since arylsulfonamides promoted the reaction to the greatest degree, it is possible that π–π stacking could stabilize the Bergman diradical intermediates, as documented for through-space radical stabilization.[26] The rate-limiting step of the enediyne cycloaromatization of benzofused enediynes such as **4** has been determined to be hydrogen abstraction by the diradical intermediate,[27] so that stabilization of this intermediate would be expected to promote the reaction.

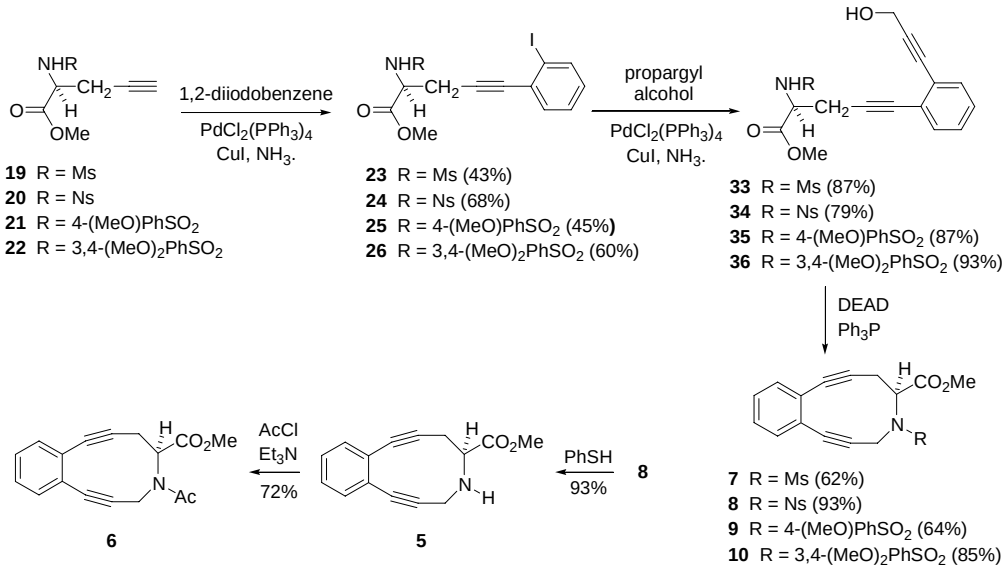
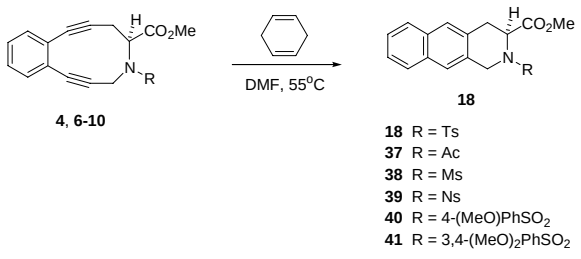


Figure 4. Synthesis of enediynes **5**–**10**.

Table 2. Half life for the Bergman reactions of enediynes **4** and **6**–**10** (55 °C in DMF)



Enediyne	**4**	**6**	**7**	**8**	**9**	**10**
$t_{1/2}$ (h)	9.5	55.4	18.5	7.6	4.0	5.9

The nitrogen atom of sulfonamides can adopt either pyramidal or planar geometry (sp^3 vs sp^2 hybridization), and sulfonamides exhibit the pyramidal form more frequently than do amides.[28] Single-crystal X-ray structures were obtained for acetamide **6** and mesylate **7**. However, in both cases the nitrogens involved adopt the planar sp^2 configuration (Fig. 5). As with enediyne **4**, the methyl group of mesylate **7** is positioned *endo* relative to the enediyne system.

2.2. Twelve membered cyclic enediyne amino acids

We employed a route in which the amide bond was constructed in the last step for the preparation of 12-membered ring enediyne **11** (Fig. 6). *N*-Cbz propargyl glycine **42** was coupled in the Sonogashira reaction with 1,2-diiodobenzene using ammonia as a base at room temperature to give alkyne **43**. Consecutive coupling of **43** with propargyl glycinamide **44** furnished acyclic enediyne **45** (69%). Removal of the Boc group of **45** followed by peptide coupling with HATU/HOAT or DPPA did not afford desired **11**. However, treatment of **45** with thionyl chloride in methanol removed the Boc group and the corresponding methyl ester was formed. Further reaction with trimethylaluminum (2 mol equiv)[29] provided desired product **11** (37%). Trimethylaluminum has recently been reported to convert carbamates to acetamides by substitution of the oxygen substituent of the carbamate with Me;[30] however, no acetamides were isolated upon reaction of **45**.

A single crystal X-ray structure of enediyne **11** was obtained, revealing a reversed turn structure with hydrogen bonding between the carbonyl on the benzyloxycarbonyl group, and NHs on both the *N*-methyl amide terminus and the bridging internal amide (Fig. 7). A β-turn will fall into a particular defined class if three of the four backbone torsional angles do not deviate more than 30 °C and the other not more than 45 °C from ideal values. Evaluation of the torsional angles of **11** indicated that it adopts a Type II β-turn conformation in the solid state.[31] The Type II β-turn comprises ca. 13% of β-turns among structures deposited in the Protein Data Bank.[32]

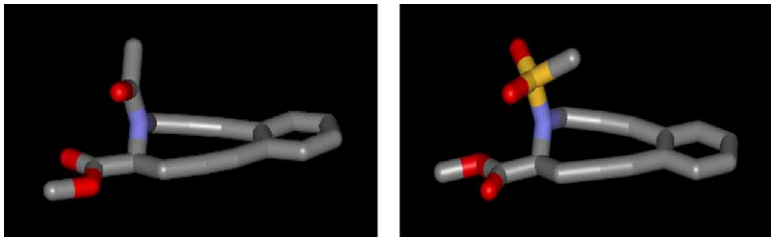


Figure 5. X-ray structures for enediyne acetamide **6** (left) and mesylate **7** (right).

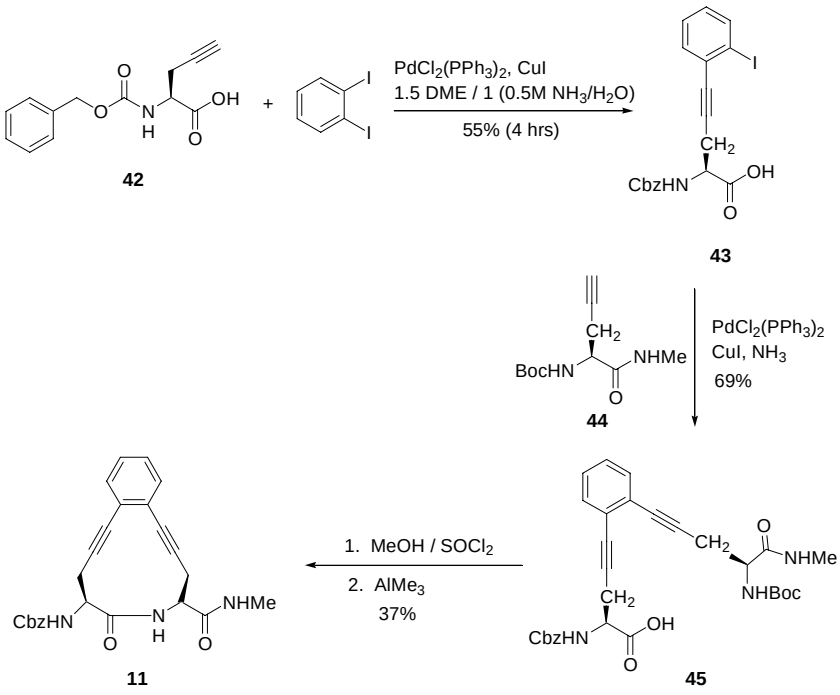
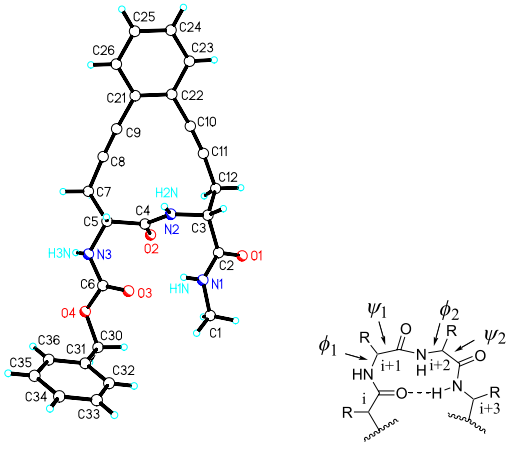


Figure 6. Synthesis of 12-membered ring enediyne **11**.



	Ideal Type II β-Turn	Enediyne **11**
Φ_{i+1}	-60°	-50.4°
Ψ_{i+1}	120°	132.6°
Φ_{i+2}	80°	58°
Ψ_{i+2}	0°	29°

Figure 7. X-ray structure of enediyne **11** revealing a Type II β-turn conformation in the solid state.

The distance between the two reacting alkynyl carbons generally required for spontaneous Bergman cyclization is 2.9–3.3 Å.[7] Accordingly, we were not surprised that **11** was thermally stable either with or without microwave activation because the distance between the two relevant alkynyl carbons of **11** (C11 and C8) in the solid state is 3.86 Å.[33] The photochemical variant of the Bergman reaction has been used for acyclic enediynes that have longer terminal alkyne carbon distances than are required for the thermal reaction.[34] When **11** was irradiated with ultraviolet light in the presence of 1,4-cyclohexadiene in DMF, Bergman product **46** was not observed but *Z*-alkene **47** was obtained (58%, Fig. 8). Although expected product **46** and alkene **47** have the same molecular weight, the presence of only one alkyne in **47** could be seen by the presence of characteristic resonances at 83.1 and 89.6 ppm in the ^{13}C NMR spectrum. The combination of HMBC and COSY allowed for unambiguous assignment of a highly regioselective reduction as shown and no reduction of the other alkyne was observed. The *cis* bond geometry was determined by a strong, positive NOE between the two vinyl protons, along with an 11 Hz coupling constant. Turro and coworkers have observed that photoirradiation of an acyclic 1,2-dialkynylbenzene substrate reduced only one of the olefins to afford a single *Z*-olefin product.[35] Although we do not fully understand the factors leading to the formation of **47** upon irradiation of **11**, we propose that the distance between the alkynes was too long for the Bergman cyclization allowing for the competing addition of a hydrogen radical to the exo face of the alkyne at the β-position providing an aryl-stabilized radical. Computational analysis has suggested that α-alkyl vinylic radicals are generally sp^2-hybridized-radicals, whereas α-phenyl vinylic radicals are the linear sp-hybridized π-radicals.[36] An unpaired electron in the p orbital of sp-hydridized intermediate could suffer attack of an additional hydrogen radical from both sides of the alkene and this process would be expected to be diffusion controlled showing a strong preference for the kinetic *Z*-product.

Since radicals were proposed to be generated in the photoreduction process, we incubated bovine serum

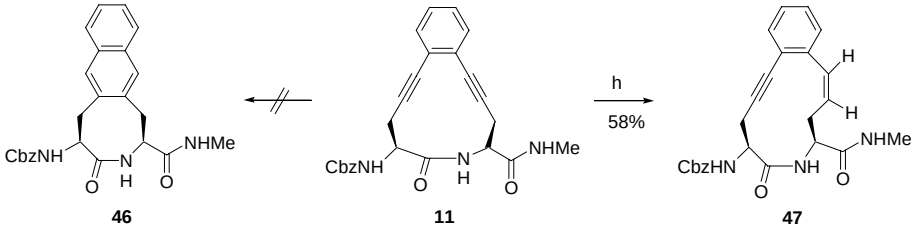


Figure 8. Regioselective photoreduction of enediyne **11.**

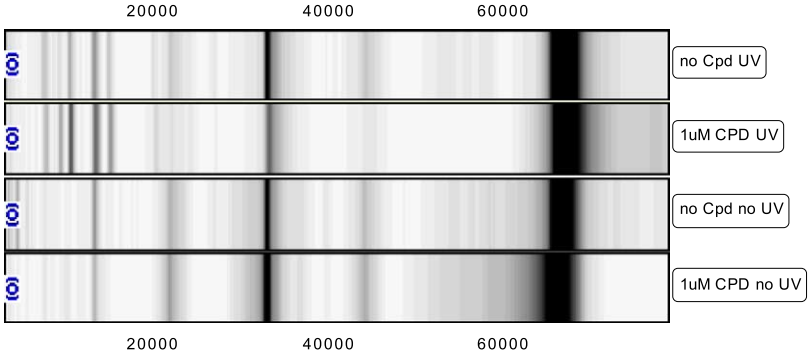


Figure 9. Cleavage of BSA by photoirradiation of enediyne **11** (units in Dalton).

albumin with **11** (at 1.0 μM), irradiated the mixture at ambient temperature for a period of 1 h, and evaluated the reaction mixture by SELDI-MS analysis (Fig. 9). Fragmentation to several protein species of lower mass (e.g., 9703 Da) was observed when **11** was present with UV irradiation, when compared to controls in the absence of **11** or irradiation. Therefore, photoreduction of enediyne **11** could also lead to non-specific protein degradation in addition to formation of *Z*-olefin **47**.

3. Conclusions

We here, report the synthesis of benzofused enediynes, which are incorporated onto a cyclic amino acid scaffold. The synthesis entailed the Sonogashira and Mitsunobu reactions, which appears to be the first time in which a Mitsunobu reaction has been used in the construction of a cyclic enediyne system. *N*-Acyl and sulfonyl substituted variants of **5** were prepared to study the Bergman cyclization to give **18** and **37**–**41**. We found that N-arylsulfonyl substitution promoted the reaction, which may be due to π–π stacking and stabilization of the Bergman diradical intermediate. The Bergman cyclization of **4** was also carried out in high yield using microwave radiation. In addition, **4** cleaved double-stranded DNA upon heating in a dose dependent manner. We then prepared and studied the 12-membered enediyne substrate **11**, which we found to adopt a Type II β-turn conformation in the solid state. It did not undergo the Bergman cyclization possibly because the terminal alkynes are too far apart. Upon irradiation with light, regioselective reduction provided *Z*-olefin **47**. In addition, **11** induced fragmentation of the protein BSA when irradiated, consistent with the formation of radical intermediates under these conditions.

4. Experimental

4.1. General

^{1}H NMR spectra were obtained on either Bruker 500-MHz DRX500 or 300-MHz DPX300 Bruker NMR spectrometers with Me_4Si as an internal standard. Standard conditions (300 MHz, $CDCl_3$ for ^{1}H, and 75 MHz, $CDCl_3$ for ^{13}C) were used unless otherwise noted. Elemental analyses were determined by Robertson Microlit, Madison, NJ, and QTI Quantitative Technologies INC, Whitehouse, NJ. X-ray crystallographic analysis was done by Crystalytics, Lincoln, NE. Mass spectra were generated using a MicroMass Platform LC electrospray mass spectrometer or by chemical ionization on a Hewlett–Packard 5989A mass spectrometer. HRMS was measured by Micromass LCT (ES-TOT). Most reagents and solvents were purchased, and used without further purification. ΦX174 RF I DNA was purchased from New England Biolabs and BSA fraction V protein was purchased from J. T. Baker. Protected propargyl glycine **12**, **19**–**22**, **42**, and **44** were prepared according to general and accepted methods.

4.2. Bergman cyclization of 4 in the presence and absence of microwaves

A quantity of 3.9 mg of **4** was dissolved in degassed DMF (10 mL) to give a 1 mM stock solution and 1.8 mg acetophenetidin was dissolved in degassed DMF (100 mL) to give a 0.1 mM stock solution. The

reaction solution was prepared by mixing the enediyne **4** stock solution (1 mM, 2 mL) and the acetophenetidin stock solution (0.1 mM, 2 mL) in degassed DMF (16 mL) to give enediyne **4** at a concentration of 0.1 mM, and acetophenetidin at 0.01 mM concentration. The reaction solution (2 mL) prepared above was added to a 10-mL CEM vial containing a magnetic stir bar and then sealed. After purging with nitrogen and vacuum degassing, 1,4-cyclohexadiene (0.01 mL, 0.1 mmol, 500 mol equiv) was added into the vacuumed system via syringe. The mixture was then submitted to either microwave irradiation (CEM Discovery apparatus setting: 150 W) or an oil bath at the temperature indicated and kept at this temperature for 10 min. The vial was then removed from the appropriate heating sources and frozen immediately on dry ice, and then thawed immediately before analysis. LC/MS–MS was used to follow the formation of **18** with acetophenetidin as an internal standard. The relative conversion of **4** to **18** under these conditions was very similar in the presence or absence of microwaves, with the microwave-assisted reactions proceeding to a slightly higher degree.

4.3. Kinetic studies

Reaction solutions (30 mL) prepared as described above containing **4** or **6**–**10** were added to a 250 mL flask containing a magnetic stir bar and then sealed. After vacuum degassing and refilling with nitrogen, 1,4-cyclohexadiene (0.028 mL, 0.3 mmol, 100 mol equiv) was added. The mixture was then submitted to an oil bath at 55 °C. After defined periods of time, a sample from the reaction mixture (0.8 mL) was taken via syringe and immediately frozen on dry ice, and thawed before analysis. LC/MS–MS was used to follow the reaction with acetophenetidin as an internal standard to detect the amount of product formed and starting material consumed.

4.4. *S*-1-(4-Toluenesulfonyl)-[6,7]-benz-1-azacyclodec-4,8-diyne-2-carboxylic methyl ester (4)

To a solution of **17** (132.7 mg, 0.32 mmol) and PPh_3 (169.0 mg, 0.64 mmol) in THF (35 mL) was added DEAD (40% in toluene, 0.29 mL, 0.64 mmol) slowly at 0 °C. The resulting mixture was stirred at this temperature for 1 h and the solvent was then removed in vacuo. The residue was purified on silica gel (EtOAc/heptane gradient from 1:9 to 5:5) afforded **4** (114.0 mg, 90%) as a white solid: ^{1}H NMR δ 7.86–7.79 (m, 2H), 7.30–7.22 (m, 4H), 7.16–7.10 (m, 2H), 4.78 (d, J = 19.0 Hz, 1H), 4.33 (dd, J = 10.4, 4.0 Hz, 1H), 4.22 (d, J = 19.1, 1H), 3.86 (s, 3H), 3.33 (dd, J = 18.3, 10.2 Hz, 1H), 3.23 (dd, J = 18.7, 4.0 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR δ 170.4, 143.8, 138.2, 129.7 (2C), 129.2, 128.5, 128.4, 128.1, 128.0, 127.9, 127.6 (2C), 95.7, 93.1, 87.6, 84.4, 64.6, 53.3, 42.7, 22.0, 21.7. Anal. Calcd for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87; N, 3.56. Found: C, 66.98; H, 4.85; N, 3.58.

4.5. *S*-1-Methanesulfonyl-[6,7]-benz-1-azacyclodec-4,8-diyne-2-carboxylic methyl ester (7)

According to the procedure described for **4**, compound **33** (293.2 mg, 0.88 mmol) was treated with PPh_3 (459.1 mg, 1.75 mmol) and DEAD (40% in toluene, 0.79 mL, 1.75 mmol) to afford compound **7** (150.4 mg, 62%) as a white solid: ^{1}H NMR δ 7.41–7.25 (m, 4H), 4.78 (d, J = 20.0 Hz, 1H), 4.28 (dd, J = 10.3, 4.5, 1H), 4.19 (d, J = 20.0, 1H), 3.81 (s, 3H), 3.38 (dd, J = 18.7, 10.1 Hz, 1H), 3.29 (dd, J = 18.9, 4.4 Hz, 1H), 3.08 (s, 3H). ^{13}C NMR δ 170.2, 129.1, 129.0, 128.8, 128.3 (2C), 127.9, 95.2, 93.6, 87.9, 84.7, 64.7, 53.4, 43.9, 42.4, 21.4. Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.33; H, 4.57; N, 4.46.

4.6. *S*-1-(2-Nitrobenzenesulfonyl)-[6,7]-benz-1-aza-cyclodec-4,8-diyne-2- carboxylic methyl ester (8)

According to the procedure described for **4**, compound **34** (1.25 g, 2.84 mmol) was treated with PPh_3 (1.49 g, 5.67 mmol) and DEAD (40% in toluene, 2.57 mL, 5.67 mmol) to afford compound **3** (930.0 mg, 77%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 8.24 (d, J = 7.4 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.76 (td, J = 7.7, 0.6 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.43–7.32 (m, 4H), 4.99 (dd, J = 10.9, 3.9 Hz, 1H), 4.72 (d, J = 19.4, 1H), 4.46 (d, J = 19.2, 1H), 3.65 (s, 3H), 3.22 (dd, J = 18.5, 4.0 Hz, 1H), 3.13 (dd, J = 18.7, 10.2 Hz, 1H). ^{13}C NMR δ 169.6, 148.1, 135.1, 132.3, 132.2, 129.9, 129.0, 128.6 (2C), 128.3, 128.1, 127.3, 124.5, 96.4, 94.5, 87.1, 84.0, 64.3, 52.9, 42.6, 21.6. Anal. Calcd for $C_{21}H_{16}N_2O_6S$: C, 59.43; H, 3.80; N, 6.60. Found: C, 59.18; H, 3.61; N, 6.32.

4.7. *S*-[6,7]-Benz-1-azacyclodec-4,8-diyne-2-carboxylic methyl ester (5)

To a solution of **8** (85.0 mg, 0.20 mmol) in DMF (4 mL) were added potassium carbonate (82.9 mg, 0.60 mmol) and thiophenol (0.025 mL, 0.24 mmol). The resulting mixture was stirred at ambient temperature for 2 h and loaded onto a silica gel column. Purification with gradient elution (EtOAc/heptane gradient from 1:9 to 4:6) afforded **5** (44.6 mg, 93%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40–7.30 (m, 4H), 3.73 (dd, J = 18.4, 2.9 Hz, 1H), 3.69–3.65 (m, 1H), 3.65 (s, 3H), 3.54 (dd, J = 18.4, 8.0, 1H), 3.08–2.98 (m, 1H), 2.78 (dd, J = 17.4, 2.2 Hz, 1H), 2.62 (dd, J = 17.3, 11.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 173.0, 128.5, 128.4, 127.8, 127.8 (2C), 127.5, 100.1, 98.3, 84.3, 82.5, 61.7, 51.8, 39.5, 24.2. HRMS (ES) *m*/*z*: calcd for $(M+H)^+$ $C_{15}H_{14}NO_2$, 240.1025; found, 240.1028.

4.8. *S*-1-(2-Acetyl)-[6,7]-benz-1-azacyclodec-4,8-diyne-2-carboxylic methyl ester (6)

To a solution of **5** (120.0 mg, 0.50 mmol) and Et_3N (0.35 mL, 2.51 mmol) in CH_2Cl_2 (20 mL) was added acetyl chloride (0.18 mL, 2.51 mmol) at 0 °C. The resulting mixture was stirred at ambient temperature for overnight. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The residue was purified on silica gel (heptane/EtOAc gradient from 6:4 to 3:7) affording **6** (101.3 mg, 72%) as a white solid: ^{1}H NMR δ 7.40–7.23 (m, 4H), 4.61 (d, J = 19.1 Hz, 1H), 4.22 (d, J = 19.2 Hz, 1H), 4.07 (dd, J = 11.3, 2.8 Hz, 1H), 3.76 (s, 3H), 3.63 (dd, J = 18.3, 11.2 Hz, 1H), 3.14 (dd, J = 18.1, 2.9 Hz, 1H), 2.24 (s,

3H). ^{13}C NMR δ 170.6, 170.0, 129.9, 128.8, 128.7, 128.0, 127.9 (2C), 97.0, 93.3, 88.5, 83.2, 64.4, 53.0, 43.7, 22.2, 20.2. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.42; H, 5.19; N, 4.77.

4.9. *S*-1-(4-Methoxybenzenesulfonyl)-[6,7]-benz-1-azacyclodec-4,8-diyne-2-carboxylic methyl ester (9)

According to the procedure described for **4**, compound **35** (361.8 mg, 0.85 mmol) was treated with PPh_3 (445.9 mg, 1.70 mmol) and DEAD (40% in toluene, 0.77 mL, 1.70 mmol) to afford compound **6** (222.0 mg, 64%) as a white solid: ^{1}H NMR δ 7.91–7.85 (m, 2H), 7.29–7.21 (m, 4H), 6.83–6.76 (m, 2H), 4.75 (d, J = 19.5 Hz, 1H), 4.32 (dd, J = 10.5, 3.9 Hz, 1H), 4.20 (d, J = 19.0 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 3.34 (dd, J = 18.4, 10.5 Hz, 1H), 3.23 (dd, J = 18.2, 3.9 Hz, 1H); ^{13}C NMR δ 170.4, 163.2, 132.7, 129.9 (2C), 129.2, 128.5, 128.4, 128.1, 128.0, 127.9, 114.3, 95.7, 93.3, 87.6, 84.3, 64.6, 55.8, 53.3, 42.6, 22.0. Anal. Calcd for $C_{22}H_{19}NO_5S$: C, 64.53; H, 4.68; N, 3.42. Found: C, 64.39; H, 4.71; N, 3.39.

4.10. *S*-1-(3,4-Dimethoxybenzenesulfonyl)-[6,7]-benz-1-azacyclodec-4,8-diyne-2- carboxylic methyl ester (10)

According to the procedure described for **4**, compound **36** (293.2 mg, 0.88 mmol) was treated with PPh_3 (459.1 mg, 1.75 mmol) and DEAD (40% in toluene, 0.79 mL, 1.75 mmol). The residue was purified on silica gel (CH_2Cl_2) afforded **10** (663.6 mg, 85%) as a white solid: ^{1}H NMR δ 7.59 (dd, J = 8.7, 2.3 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 7.30–7.20 (m, 4H), 6.80 (d, J = 8.8 Hz, 1H), 4.74 (d, J = 19.6 Hz, 1H), 4.35 (dd, J = 9.8, 4.4 Hz, 1H), 4.23 (d, J = 19.4 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.34 (dd, J = 18.8, 9.6 Hz, 1H), 3.26 (dd, J = 18.4, 4.6 Hz, 1H). ^{13}C NMR δ 170.4, 153.0, 149.4, 132.6, 128.8, 128.4, 128.4, 128.0, 127.9, 127.8, 121.9, 110.6, 110.0, 95.9, 93.3, 87.5, 84.3, 64.5, 56.2, 56.1, 53.2, 42.4, 21.8. Anal. Calcd for $C_{23}H_{21}NO_6S$: C, 62.86; H, 4.82; N, 3.19. Found: C, 62.64; H, 4.72; N, 3.02.

4.11. *S*-2-(4-Toluenesulfonylamino)-5-phenylpent-4-ynoic acid methyl ester (13)

To a solution of compound **12** (141.0 mg, 0.50 mmol) in THF (3.3 mL) were added iodobenzene (98%, 0.068 mL, 0.6 mmol), $PdCl_2(PPh_3)_4$ (10.5 mg, 0.015 mmol), and CuI (4.8 mg, 0.025 mmol) at room temperature under nitrogen. A solution of aqueous ammonia (0.5 M, 2 mL, 1.0 mmol) was then added dropwise and the resulting mixture was stirred at ambient temperature for 14 h. The solvent was then removed in vacuo. The residue was dissolved in ethyl acetate (30 mL), washed with saturated NH_4Cl, $NaHCO_3$, and brine sequentially, and then dried over $MgSO_4$. After concentration, purification on silica gel (EtOAc/heptane gradient from 2:8 to 5:5) afforded **13** (143.5 mg, 80%): ^{1}H NMR δ 7.81–7.74 (m, 2H), 7.39–7.26 (m, 7H), 5.49 (d, J = 9.0 Hz, 1H), 4.26–4.15 (m, 1H), 3.65 (s, 3H), 2.95 (dd, J = 17.0, 4.5 Hz, 1H), 2.87 (dd, J = 16.9, 5.3 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR δ 170.7, 144.1, 137.4, 132.1 (2C), 130.1 (2C), 128.6, 122.6 (2C), 127.6 (2C), 123.1, 84.7, 83.1, 54.8, 53.2, 25.4, 21.9. Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.59; H, 5.07; N, 3.69.

4.12. *S*-2-(4-Toluenesulfonylamino)-5-(4-methoxyphenyl)-pent-4-ynoic acid methyl ester (14)

Compound **12** (141.0 mg, 0.5 mmol) was coupled with 1-iodo-4-methoxybenzene (140.4 mg, 0.6 mmol) under the same conditions as described for **13** to furnish compound **14** (106.5 mg, 55%) as white needles: ^{1}H NMR δ 7.81–7.74 (m, 2H), 7.33–7.25 (m, 4H), 6.86–6.78 (m, 2H), 5.48 (d, J = 9.1 Hz, 1H), 4.25–4.13 (m, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 2.92 (dd, J = 17.2, 5.1 Hz, 1H), 2.85 (dd, J = 17.4, 5.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR δ 170.7, 160.0, 144.1, 137.4, 133.5 (2C), 130.1 (2C), 127.6 (2C), 115.2, 114.3 (2C), 84.5, 81.5, 55.7, 54.9, 53.2, 25.4, 21.9. Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 61.88; H, 5.32; N, 3.38.

4.13. *S*-2-(4-Toluenesulfonylamino)-5-(4-trifluoromethylphenyl)pent-4-ynoic acid methyl ester (15)

Compound **12** (141.0 mg, 0.5 mmol) was coupled with 1-iodo-4-trifluoromethylbenzene (0.088 mL, 0.6 mmol) under the same condition as for **13** to afford **15** (163.3 mg, 77%) as a light yellow solid: ^{1}H NMR δ 7.81–7.74 (m, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.59 (d, J = 8.9 Hz, 1H), 4.22 (dt, J = 8.5, 5.5 Hz, 1H), 3.65 (s, 3H), 2.94 (d, J = 5.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR δ 170.6, 144.2, 137.3, 132.4 (2C), 130.4 (q, J = 32.6 Hz), 130.1 (2C), 127.6 (2C), 127.0 (q, J = 1.2 Hz), 125.5 (q, J = 3.9 Hz, 2C), 124.3 (q, J = 272.3 Hz), 86.1, 83.3, 54.7, 53.3, 25.4, 21.9. Anal. Calcd for $C_{20}H_{18}F_3NO_4S$: C, 56.46; H, 4.26; N, 3.29; F, 13.40. Found: C, 56.28; H, 4.03; N, 3.16; F, 13.78.

4.14. *S*-2-(4-Toluenesulfonylamino)-5-(2-iodophenyl)pent-4-ynoic acid methyl ester (16)

To a solution of compound **12** (783.0 mg, 2.78 mmol) in DME (19.0 mL) were added 1,2-diiodobenzene (0.44 mL, 3.34 mmol), $PdCl_2(PPh_3)_4$ (60.0 mg, 0.085 mmol), and CuI (27.0 mg, 0.14 mmol) at ambient temperature under nitrogen. A solution of aqueous ammonia (0.5 M, 2 mL, 11.0 mmol) was then added dropwise and the resulting mixture was stirred for 4 h. The solvent was then removed in vacuo. The residue was dissolved in ethyl acetate (60 mL), washed with saturated NH_4Cl, $NaHCO_3$, and brine sequentially, and then dried over $MgSO_4$. After concentration, purification on silica gel (EtOAc/heptane gradient from 1:9 to 5:5) afforded **16** (800.8 mg, 60%) as a light yellow liquid: ^{1}H NMR δ 7.83–7.74 (m, 3H), 7.38–7.22 (m, 4H), 6.98 (td, J = 7.5, 1.7 Hz, 1H), 5.75 (d, J = 9.0 Hz, 1H), 4.25 (dt, J = 9.2, 4.8 Hz, 1H), 3.64 (s, 3H), 3.00 (dd, J = 17.0, 4.5 Hz, 1H), 2.92 (dd, J = 17.1, 5.4 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR δ 170.5, 144.1, 138.9, 137.5, 133.3, 130.1 (2C), 129.9, 129.7, 128.2, 127.6 (2C), 101.1, 87.5, 86.5, 54.7, 53.4, 25.4, 21.9. Anal. Calcd for $C_{19}H_{18}INO_4S$: C, 47.22; H, 3.75; N, 2.90. Found: C, 47.41; H, 3.77; N, 2.76.

4.15. *S*-2-(4-Toluenesulfonylamino)-5-[2-(3-hydroxyprop-1-ynyl)phenyl]pent-4-ynoic acid methyl ester (17)

To a solution of **16** (166.0 mg, 0.34 mmol) in DME (2.2 mL) were added propargyl alcohol (0.040 mL, 0.69 mmol), $PdCl_2(PPh_3)_4$ (7.2 mg, 0.01 mmol), and CuI (3.2 mg, 0.017 mmol) at ambient temperature under nitrogen. A solution of aqueous ammonia (0.5 M, 1.36 mL, 0.68 mmol) was then added dropwise and the resulting mixture was stirred at rt for 4 h. The solvent was then removed in vacuo. The residue was dissolved in ethyl acetate (30 mL), washed with saturated NH_4Cl, $NaHCO_3$, and brine sequentially, and then dried over $MgSO_4$. After concentration, purification on silica gel (EtOAc/heptane gradient from 1:9 to 5:5) afforded **17** (132.7 mg, 94%) as a clear liquid: ^{1}H NMR δ 7.74–7.66 (m, 2H), 7.38–7.10 (m, 6H), 6.16 (d, J = 9.2 Hz, 1H), 4.53 (s, 2H), 4.14 (dt, J = 9.1, 4.7 Hz, 1H), 3.56 (s, 3H), 3.22 (br s, 1H), 2.92 (dd, J = 17.0, 4.2 Hz, 1H), 2.84 (dd, J = 16.6, 5.2 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR δ 170.8, 144.1, 137.4, 132.4, 132.2, 130.1 (2C), 128.4, 128.4, 127.5 (2C), 125.8, 125.6, 92.3, 87.1, 84.3, 83.5, 54.6, 53.4, 51.8, 25.5, 21.9. Anal. Calcd for $C_{22}H_{21}NO_5S$: C, 64.22; H, 5.14; N, 3.40. Found: C, 63.96; H, 5.32; N, 3.38.

4.16. *S*-2-(4-Toluenesulfonyl)-1,2,3,4-tetrahydrobenzo[*g*]isoquinoline-3-carboxylic acid methyl ester (18)

A 10-mL CEM vial containing a magnetic stir bar was charged with enediyne **4** (11.8 mg, 0.03 mmol) and DMF (3 mL), and then sealed. After purging with nitrogen and vacuum degassing, 1,4-cyclohexadiene (0.30 mL, 3.1 mmol) was added via syringe. The mixture was then submitted to microwave irradiation (CEM Discovery apparatus setting 120 °C, 150 W), and kept at this temperature for 10 min. The crude reaction mixture was concentrated, and the residue was separated on silica gel (EtOAc/heptane from 15:85 to 45:55) to afford compound **18** (10.0 mg, 84%) as a white solid: ^{1}H NMR δ 7.78–7.70 (m, 4H), 7.58 (s, 1H), 7.54 (s, 1H), 7.48–7.40 (m, 2H), 7.25 (overlapped doublet, J = 8.0 Hz, 2H), 5.01 (t, J = 5.1 Hz, 1H), 4.86 (d, J = 15.0, 1H), 4.69 (d, J = 15.6, 1H), 3.52 (s, 3H), 3.38–3.32 (m, 2H), 2.37 (s, 3H). ^{13}C NMR δ 171.4, 143.9, 136.3, 132.8, 132.7, 130.6, 129.9 (2C), 129.8, 127.8 (2C), 127.8, 127.6, 127.3, 126.3, 126.3, 125.2, 55.0, 52.7, 45.5, 32.8, 21.8. HRMS (ES) *m*/*z*: calcd for $(M+H)^+$ $C_{22}H_{22}NO_4S$, 396.1270; found, 396.1272.

4.17. *S*-2-(Methanesulfonylamino)-5-(2-iodophenyl)pent-4-ynoic acid methyl ester (23)

Compound **19** (335.2 mg, 1.63 mmol) was coupled with 1,2-diiodobenzene (0.43 mL, 3.27 mmol) under similar conditions as described for **16** to afford compound **23** (284 mg, 43%) as a light yellow liquid: ^{1}H NMR δ 7.84 (dd, J = 8.0, 0.8 Hz, 1H), 7.42 (dd, J = 7.7, 1.7 Hz, 1H), 7.31 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 7.03 (ddd, J = 8.0, 8.0, 1.9 Hz 1H), 5.45 (d, J = 9.1 Hz, 1H), 4.47 (dt, J = 9.0, 4.8 Hz, 1H), 3.87 (s, 3H), 3.21–3.02 (m, 2H), 3.09 (s, 3H); ^{13}C NMR δ 171.0, 139.0, 133.2, 130.0, 129.5, 128.2, 101.1, 87.3, 86.8, 54.9, 53.6, 42.6, 25.5. Anal. Calcd for $C_{13}H_{14}INO_4S$: C, 38.34; H, 3.47; N, 3.44. Found: C, 38.46; H, 3.16; N, 3.36.

4.18. *S*-2-(2-Nitrobenzenesulfonylamino)-5-(2-iodophenyl)pent-4-ynoic acid methyl ester (24)

Compound **20** (1.56 g, 5.01 mmol) was coupled with 1,2-diiodobenzene (1.31 mL, 10.03 mmol) under the similar conditions as described for **16** to afford **24** (1.58 g, 61%) as a light yellow liquid: ^{1}H NMR δ 8.17–8.08 (m, 1H), 7.93–7.87 (m, 1H), 7.81 (dd, J = 8.1, 0.8 Hz, 1H), 7.77–7.66 (m, 2H), 7.38 (dd, J = 7.7, 1.7 Hz, 1H), 7.28 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.00 (ddd, J = 8.1, 8.1, 1.8 Hz, 1H), 6.54 (d, J = 9.0 Hz, 1H), 4.53 (dt, J = 9.0, 5.0 Hz, 1H), 3.65 (s, 3H), 3.15 (dd, J = 17.2, 4.6 Hz, 1H), 3.07 (dd, J = 17.2, 5.1 Hz, 1H). ^{13}C NMR δ 169.7, 147.6, 138.6, 134.5, 133.6, 132.9, 132.9, 130.3, 129.5, 129.1, 127.8, 125.6, 100.7, 86.6, 86.4, 55.3, 53.0, 25.0. Anal. Calcd for $C_{18}H_{15}IN_2O_6S$: C, 42.04; H, 2.94; N, 5.45. Found: C, 42.25; H, 2.76; N, 5.37.

4.19. *S*-2-(4-Methoxybenzenesulfonylamino)-5-(2-iodophenyl)pent-4-ynoic acid methyl ester (25)

Compound **25** (1.66 g, 5.60 mmol) was prepared using the conditions described in the synthesis of **16** in coupling with 1,2-diiodobenzene (1.46 mL, 11.20 mmol) to afford **25** (1.26 g, 45%) as a white solid: ^{1}H NMR δ 7.88–7.79 (m, 2H), 7.40–7.25 (m, 2H), 7.05–6.92 (m, 3H), 5.63 (d, J = 9.1 Hz, 1H), 4.25 (dt, J = 9.1, 4.8 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 3.02 (dd, J = 16.9, 4.3 Hz, 1H), 2.93 (dd, J = 17.1, 5.3 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR δ 170.5, 163.4, 139.0, 133.2, 132.0, 129.8, 129.8 (2C), 129.7, 128.1, 114.6 (2C), 101.1, 87.4, 86.5, 56.0, 54.6, 53.4, 25.4. Anal. Calcd for $C_{19}H_{18}INO_5S$: C, 45.70; H, 3.63; N, 2.81. Found: C, 45.94; H, 3.71; N, 2.56.

4.20. *S*-2-(3,4-Dimethoxybenzenesulfonylamino)-5-(2-iodophenyl)pent-4-ynoic acid methyl ester (26)

According to the procedure described for compound **16**, compound **22** (500.0 mg, 1.52 mmol) was coupled with 1,2-diiodobenzene (0.40 mL, 3.05 mmol) under the similar conditions to afford compound **26** (0.97 g, 60%) as a white solid: ^{1}H NMR δ 7.83 (d, J = 8.2 Hz, 1H), 7.53 (dd, J = 8.5, 2.1 Hz, 1H), 7.54–7.25(m, 3H), 7.02 (td, J = 7.7, 1.6 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 5.67 (d, J = 8.9 Hz, 1H), 4.25 (dt, J = 9.0, 4.6 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.70 (s, 3H), 3.02 (dd, J = 17.1, 3.9 Hz, 1H), 2.92 (dd, J = 17.3, 5.3 Hz, 1H). ^{13}C NMR δ 170.5, 153.2, 149.6, 139.0, 133.2, 132.0, 129.9, 129.6, 128.2, 121.6, 110.9, 110.1, 101.1, 87.4, 86.6, 56.6, 56.6, 54.6, 53.4, 25.4. Anal. Calcd for $C_{20}H_{20}INO_6S$: C, 45.38; H, 3.81; N, 2.65. Found: C, 45.33; H, 3.76; N, 2.61.

4.21. *S*-2-(Methanesulfonylamino)-5-[2-(3-hydroxyprop-1-ynyl)phenyl]pent-4-ynoic acid methyl ester (33)

Compound **23** (548.4 mg, 1.35 mmol) was coupled under similar conditions as described for **17** using propargyl alcohol (0.16 mL, 2.70 mmol) to afford compound

33 (391.3 mg, 87%) as a light yellow liquid: ^{1}H NMR δ 7.47–7.36 (m, 2H), 7.31–7.22 (m, 2H), 5.95 (d, J = 9.6 Hz, 1H), 4.60 (s, 2H), 4.47 (dt, J = 9.4, 4.6 Hz, 1H), 3.84 (s, 3H), 3.20–3.03 (m, 6H); ^{13}C NMR δ 171.5, 132.4, 132.2, 128.5 (2C), 125.7, 125.4, 92.2, 87.1, 84.3, 83.6, 54.9, 53.7, 51.8, 42.3, 25.8. Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18. Found: C, 57.14; H, 5.36; N, 3.99.

4.22. *S*-2-(2-Nitrobenzenesulfonylamino)-5-[2-(3-hydroxyprop-1-ynyl)phenyl]pent-4-ynoic acid methyl ester (34)

According to the procedure described for **17**, compound **24** (1.87 g, 3.49 mmol) was coupled with propargyl alcohol (0.42 mL, 6.99 mmol) to afford **34** (1.25 g, 79%) as a light yellow liquid: ^{1}H NMR δ 8.18–8.09 (m, 1H), 7.91–7.82 (m, 1H), 7.75–7.65 (m, 2H), 7.46–7.39 (m, 1H), 7.38–7.30 (m, 1H), 7.30–7.20 (m, 2H), 6.68 (d, J = 8.9 Hz, 1H), 4.60–4.47 (m, 3H), 3.66 (s, 3H), 3.14 (dd, J = 17.5, 4.5 Hz, 1H), 3.06 (dd, J = 17.1, 5.0 Hz, 1H), 2.88 (br s, 1H). ^{13}C NMR δ 170.6, 147.9, 134.8, 134.0, 133.2, 132.5, 132.4, 130.8, 128.5, 128.4, 125.8, 125.8, 125.3, 92.3, 86.6, 84.0, 83.6, 55.6, 53.5, 51.9, 25.4. Anal. Calcd for $C_{21}H_{18}N_2O_7S$: C, 57.01; H, 4.10; N, 6.33. Found: C, 56.98; H, 3.90; N, 6.06.

4.23. *S*-2-(4-Methoxybenzenesulfonylamino)-5-[2-(3-hydroxyprop-1-ynyl)phenyl]pent-4-ynoic acid methyl ester (35)

According to the procedure described for **17**, compound **25** (190.0 mg, 0.38 mmol) was coupled with propargyl alcohol (0.044 mL, 0.76 mmol) to afford **35** (140.8 mg, 87%) as a white solid: ^{1}H NMR δ 7.88–7.81 (m, 2H), 7.48–7.39 (m, 1H), 7.38–7.31 (m, 1H), 7.30–7.20 (m, 2H), 6.96–6.89 (m, 2H), 6.18 (d, J = 9.4 Hz, 1H), 4.62 (s, 2H), 4.22 (dt, J = 9.2, 4.4 Hz, 1H), 3.84 (s, 3H), 3.67 (s, 3H), 3.25 (s, 1H), 3.01 (dd, J = 17.3, 4.1 Hz, 1H), 2.93 (dd, J = 17.1, 5.1 Hz, 1H). ^{13}C NMR δ 170.8, 163.4, 132.5, 132.2, 131.9, 129.7 (2C), 128.4, 128.4, 125.8, 125.6, 114.6 (2C), 92.3, 87.1, 84.3, 83.5, 56.0, 54.5, 53.4, 51.8, 25.5. Anal. Calcd for $C_{22}H_{21}NO_6S$: C, 61.81; H, 4.95; N, 3.28. Found: C, 61.63; H, 5.15; N, 3.19.

4.24. *S*-2-(3,4-Dimethoxybenzenesulfonylamino)-5-[2-(3-hydroxyprop-1-ynyl)-phenyl]pent-4-ynoic acid methyl ester (36)

According to the procedure described for **17**, compound **26** (945.0 mg, 1.78 mmol) was coupled with propargyl alcohol (0.21 mL, 3.57 mmol) to afford **36** (810.0 mg, 93%) as a white solid: ^{1}H NMR δ 7.53–7.46 (m, 1H), 7.41–7.35 (m, 2H), 7.34–7.27 (m, 1H), 7.26–7.17 (m, 2H), 6.87–6.82 (m, 1H), 6.40–6.30 (m, 1H), 4.60 (s, 2H), 4.21 (dt, J = 9.2, 4.5 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.64 (s, 3H), 3.37 (br s, 1H), 2.97 (dd, J = 16.9, 4.1 Hz, 1H), 2.88 (dd, J = 17.0, 5.0 Hz, 1H). ^{13}C NMR δ 170.8, 153.1, 149.5, 132.4, 132.1, 132.0, 128.4, 128.3, 125.7, 125.5, 121.5, 110.8, 110.0, 92.3, 87.2, 84.2, 83.4, 56.5, 56.5, 54.6, 53.4, 51.8, 25.4. Anal. Calcd for $C_{23}H_{23}NO_7S$: C, 60.38; H, 5.07; N, 3.06. Found: C, 60.30; H, 4.79; N, 2.79.

4.25. *S*-2-Acetyl-1,2,3,4-tetrahydrobenzo[*g*]isoquinoline-3-carboxylic acid methyl ester (37)

According to the procedure described for **18**, compound **6** (10.5 mg, 0.037 mmol) was treated with 1,4-cyclohexadiene (0.30 mL, 3.2 mmol) and subjected to microwave irradiation for 60 min at 200 °C. The crude reaction mixture was concentrated, and the residue was separated on silica gel (EtOAc/heptane gradient from 20:80 to 70:30) to afford **37** (8.4 mg, 79%) as a sticky clear oil: ^{1}H NMR (500 MHz, mixture of rotamers) δ 7.82–7.74 (m, 2H), 7.69–7.61 (m, 2H), 7.50–7.42 (m, 2H), 5.36 (t, J = 5.5 Hz, 1H), 5.10–4.74 (m, 2H), 3.63 & 3.61 (s, 3H in total), 3.48–3.23 (m, 2H), 2.29 & 2.15 (s, 3H in total). HRMS (ES) m/z: calcd for $(M+H)^+$ $C_{17}H_{18}NO_3$, 284.1287; found, 284.1291.

4.26. *S*-2-Methanesulfonyl-1,2,3,4-tetrahydro-benzo[*g*]-isoquinoline-3-carboxylic acid methyl ester (38)

According to the procedure described for **18**, compound **7** (9.5 mg, 0.03 mmol) was treated with 1,4-cyclohexadiene (0.28 mL, 3.0 mmol) and subjected to microwave irradiation for 20 min. The crude reaction mixture was concentrated, and the residue was separated on silica gel (EtOAc/heptane gradient from 15:85 to 50:50) to afford **38** (7.8 mg, 82%) as a white solid: ^{1}H NMR δ 7.84–7.75 (m, 2H), 7.68 (s, 1H), 7.64 (s, 1H), 7.52–7.43 (m, 2H), 5.02 (t, J = 5.0 Hz, 1H), 4.96 (d, J = 15.2 Hz, 1H), 4.74 (d, J = 15.8 Hz, 1H), 3.67 (s, 3H), 3.48 (d, J = 4.8 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR δ 171.8, 132.9, 132.8, 130.3, 129.8, 127.8, 127.7, 127.5, 126.5, 126.4, 125.2, 55.4, 53.0, 45.2, 38.8, 33.0. Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.02; H, 5.60; N, 4.16.

4.27. *S*-2-(2-Nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-benzo[*g*]isoquinoline-3-carboxylic acid methyl ester (39)

According to the procedure described for **18**, compound **8** (13.7 mg, 0.03 mmol) was treated with 1,4-cyclohexadiene (0.28 mL, 3.0 mmol). The crude reaction mixture was concentrated, and the residue was separated on silica gel (EtOAc/heptane gradient from 15:85 to 45:55) to afford **39** (13.5 mg, 98%) as a white solid: ^{1}H NMR δ 8.12–8.04 (m, 1H), 7.71–7.53 (m, 6H), 7.51 (s, 1H), 7.40–7.30 (m, 2H), 5.09 (t, J = 4.7 Hz, 1H), 4.86 (d, J = 15.8 Hz, 1H), 4.80 (d, J = 16.3 Hz, 1H), 3.45 (s, 3H), 3.45–3.41 (m, 2H). ^{13}C NMR δ 170.7, 148.0, 133.7, 132.5, 132.4, 132.3, 131.7, 131.1, 129.2, 128.9, 127.3, 127.3, 127.2, 126.1, 126.0, 124.8, 124.3, 55.0, 52.5, 45.1, 32.3. HRMS (ES) m/z: calcd for $(M+H)^+$ $C_{21}H_{19}N_2O_6S$: 427.0964, found 427.0967.

4.28. *S*-2-(4-Methoxybenzenesulfonyl)-1,2,3,4-tetrahydro-benzo[*g*]isoquinoline-3-carboxylic acid methyl ester (40)

According to the procedure described for **18**, compound **9** (12.3 mg, 0.03 mmol) was treated with 1,4-cyclohexadiene (0.28 mL, 3.0 mmol). The crude reaction mixture was concentrated, and the residue was separated on silica gel (EtOAc/heptane gradient from 15:85 to 45:55) to afford compound **40** (11.9 mg, 96%) as a white solid: ^{1}H

NMR δ 7.73–7.67 (m, 2H), 7.67–7.61 (m, 2H), 7.48 (s, 1H), 7.44 (s, 1H), 7.38–7.31 (m, 2H), 6.85–6.78 (m, 2H), 4.89 (t, J = 5.3 Hz, 1H), 4.76 (d, J = 15.5 Hz, 1H), 4.58 (d, J = 15.3 Hz, 1H), 3.72 (s, 3H), 3.44 (s, 3H), 3.26 (d, J = 5.3 Hz, 2H). ^{13}C NMR δ 171.1, 163.0, 132.4, 132.3, 130.5, 130.3, 129.5 (2C), 129.5, 127.4, 127.2, 126.8, 125.9, 125.9, 124.8, 114.0 (2C), 55.5, 54.6, 52.4, 45.1, 32.4. Anal. Calcd for $C_{22}H_{21}NO_5S$: C, 64.22; H, 5.14; N, 3.40. Found: C, 64.03; H, 5.46; N, 3.03.

4.29. *S*-2-(3,4-Dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydro-benzo[*g*]isoquinoline-3-carboxylic acid methyl ester (41)

According to the procedure described for **18**, compound **10** (13.4 mg, 0.03 mmol) was treated with 1,4-cyclohexadiene (0.28 mL, 3.0 mmol). The crude reaction mixture was concentrated, and the residue was separated on silica gel (EtOAc/heptane gradient from 15:85 to 45:55) to afford **41** (13.4 mg, 100%) as a white solid: ^{1}H NMR δ 7.79–7.70 (m, 2H), 7.58 (s, 1H), 7.55 (s, 1H), 7.49 (dd, J = 8.8, 2.3 Hz, 1H), 7.47–7.40 (m, 2H), 7.31 (d, J = 2.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.97 (t, J = 5.3 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.68 (d, J = 16.2 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.56 (s, 3H), 3.35 (d, J = 5.1 Hz, 2H). ^{13}C NMR δ 171.2, 152.7, 149.0, 132.5, 132.3, 130.5, 130.4, 129.5, 127.3, 127.2, 126.8, 126.0, 126.0, 124.7, 121.5, 110.4, 109.9, 56.1, 56.1, 54.7, 52.4, 45.2, 32.3. Anal. Calcd for $C_{23}H_{23}NO_6S$: C, 62.57; H, 5.25; N, 3.17. Found: C, 62.52; H, 5.57; N, 2.83.

4.30. *S*-2-Benzyloxycarbonylamino-5-(2-iodophenyl)pent-4-ynoic acid (43)

According to the procedure described for **16**, compound **42** (1.21 g, 4.89 mmol) was coupled with 1,2-diiodobenzene (0.77 mL, 5.86 mmol). Purification of the product on silica gel (EtOAc/AcOH gradient from 100:0 to 200:1) afforded **43** (1.21 g, 55%) as a light yellow liquid: ^{1}H NMR δ 10.88 (br s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.45–7.30 (m, 6H), 7.26 (t, J = 7.7 Hz, 1H), 6.97 (td, J = 7.5, 1.3 Hz, 1H), 5.91 (d, J = 8.4 Hz, 1H), 5.23–5.12 (m, 2H), 4.73 (dt, J = 8.4, 4.7 Hz, 1H), 3.21–3.02 (m, 2H). ^{13}C NMR (100 MHz) δ 175.6, 156.4, 139.0, 136.4, 133.2, 129.8, 129.7, 129.0 (2C), 128.6, 128.5 (2C), 128.1, 101.3, 87.9, 86.5, 67.7, 52.8, 24.0. Anal. Calcd for $C_{19}H_{16}INO_4$: C, 50.80; H, 3.59; N, 3.12. Found: C, 50.94; H, 3.58; N, 2.87.

4.31. *S*,*S*-2-Benzyloxycarbonylamino-5-[2-(4-*tert*-butoxycarbonylamino-4-(methylcarbamoyl)-but-1-ynyl)phenyl]pent-4-ynoic acid (45)

According to the procedure described for compound **17**, compound **43** (188.9 mg, 0.42 mmol) was treated with **44** (190.2 mg, 0.84 mmol), $PdCl_2(PPh_3)_2$ (8.8 mg, 0.013 mmol), CuI (4.0 mg, 0.021 mmol), and NH_3 (0.5 M, 2.5 mL). Purification on HPLC (MeCN/H_2O gradient from 40:60 to 60:40) afforded compound **45** (0.16 gm, 69%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, 65 °C, mixture of rotamers) δ 7.71–7.62 (m, 1H), 7.41–7.22 (m, 9H), 6.70–6.40 (br s, 1H), 5.07 (s, 2H), 4.30 (td, J = 8.3, 5.4 Hz, 1H), 4.22–4.13 (m, 1H), 3.02 (d, J = 6.28 Hz, 0.2H), 2.98 (dd, J = 17.1, 5.5 Hz, 1H), 2.90 (dd, J = 16.7, 8.2 Hz, 1H), 2.85 (dd, J = 16.9, 5.6 Hz, 1H), 2.75 (dd, J = 17.0, 7.9 Hz, 1H), 2.71 (d, J = 4.8 Hz, 0.3H), 2.62 (d, J = 4.9 Hz, 2.7H), 1.37 (s, 9H). HRMS (ES) m/z: calcd for $(M+H)^+$ $C_{30}H_{34}N_3O_7$, 548.2397; found, 548.2384.

4.32. *S*,*S*-(8-Methylcarbamoyl-10-oxo-7,8,9,10,11,12-hexahydro-9-azabenzocyclododec-5,13-diyn-11-yl)-carbamic acid benzyl ester (11)

To a stirred solution of **45** (186.0 mg, 0.34 mmol) in methanol was added thionyl chloride (0.1 mL) at 0 °C. The mixture was stirred at ambient temperature for overnight and then concentrated. The residue was dissolved in satd Na_2CO_3 (10 mL) and extracted with CH_2Cl_2 (20 mL) three times. The combined organic phase was dried over $MgSO_4$ and concentrated. Trimethylaluminum (0.29 mL, 0.58 mmol, 2.0 M in hexane) was added dropwise to the resulting free amine in CH_2Cl_2 (34 mL) at 0 °C. The mixture was then stirred under reflux for 24 h. The reaction was quenched by slow addition of aqueous HCl (0.5 M, 10 mL) at 0 °C. The aqueous solution was extracted with CH_2Cl_2 (34 mL) three times. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was separated by reverse phase HPLC (gradient in CH_3CN/H_2O from 40:60 to 80:20) to give **11** (54 mg, 37%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.51 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 4.9 Hz, 1H), 7.72–7.63 (m, 1H), 7.48–7.26 (m, 9H), 5.13 (d, J = 12.5 Hz, 1H), 5.04 (d, J = 12.3 Hz, 1H), 4.36 (q, J = 7.8 Hz, 1H), 4.25–4.14 (m, 1H), 3.03 (dd, J = 17.5, 4.2 Hz, 1H), 2.98 (d, J = 7.8 Hz, 2H), 2.79 (dd, J = 17.1, 6.0 Hz, 1H), 2.58 (d, J = 4.4 Hz, 3H). ^{13}C NMR (100 MHz) δ 169.9, 169.8, 156.5, 136.5, 131.1, 130.5, 128.4 (2C), 128.1, 128.0, 127.9, 127.8 (2C), 126.0, 125.6, 91.7, 89.7, 81.7, 81.4, 66.0, 54.9, 51.9, 25.7, 22.7, 21.5. Anal. Calcd for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78. Found: C, 69.68; H, 5.15; N, 9.68.

4.33. *S*,*S*-(8-Methylcarbamoyl-10-oxo-7,8,9,10,11,12-hexahydro-9-aza- benzocyclododec-13-yn-5-*cis*-ene-11-yl)carbamic acid benzyl ester (47)

Photolysis experiments were carried out with a Rayonette photochemical reactor with a carousel unit equipped with eight 3000 Å lamps (RMR-600). A solution of **11** (12.0 mg, 0.028 mmol) and 1,4-cyclohexadiene (0.26 mL) in degassed DMF (2.8 mL) in a quartz reaction vessel (15 mL) was irradiated for 6 h. The crude reaction mixture was concentrated, and the residue was separated on a reverse phase HPLC (MeCN/H_2O gradient from 10:90 to 90:10) to afford **47** (7.0 mg, 58%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6, 75 °C) δ 7.64–7.52 (br, 2H), 7.44–7.39 (m, 2H), 7.38–7.34 (m, 4H), 7.34–7.28 (m, 2H), 7.28–7.23 (m, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.42 (d, J = 11.2 Hz, 1H), 5.73 (dd, J = 10.1, 5.0 Hz, 1H), 5.71 (dd, J = 11.2, 5.1 Hz, 1H), 5.07 (s, 2H), 4.56 (td, J = 9.3, 2.5 Hz, 1H), 4.17 (dt, J = 6.7, 4.3 Hz, 1H), 2.94 (dd, J = 17.0, 4.6 Hz, 1H), 2.65 (dd, J = 16.9, 4.1 Hz, 1H),

2.59 (d, $J = 4.6$ Hz, 3H), 2.39–2.31 (m, 1H), 2.13–2.01 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 75 °C) δ 170.4, 168.6, 155.4, 140.5, 136.3, 130.7, 129.8 (2C), 128.0, 127.8 (3C), 127.4, 127.3, 127.1, 126.2, 121.6, 89.6, 83.1, 65.5, 55.1, 51.1, 32.8, 25.0, 22.9. HRMS (ES) *m/z*: calcd for $(M+H)^+$ $C_{25}H_{26}N_3O_4$, 432.1923; found, 432.1928.

4.34. *S*,*S*-16,18-Dioxo-15,17-diaza-tricyclo[13.2.1.0^{5,10}]-octadeca-5(10),6,8-triene-3,11-diyne-14-carboxylic acid methylamide (48)

A 10-mL CEM vial containing a magnetic stir bar was charged with enediyne **11** (4.0 mg, 0.0093 mmol) and DMF (2 mL), and then sealed. After purging with nitrogen and vacuum degassing, 1,4-cyclohexadiene (0.10 mL) was added into the system via syringe, and the mixture was stirred at 120 °C in an oil bath for 2 days. The crude reaction mixture was concentrated, and the residue was separated on silica gel (EtOAc/methanol gradient from 100:0 to 90:10) to afford **48** (2.1 mg, 70%) as a white solid: ^{1}H NMR δ 7.45–7.34 (m, 2H), 7.32–7.23 (m, 2H), 6.78–6.68 (m, 1H), 6.41 (br s, 1H), 4.95 (dd, $J = 12.3$, 5.2 Hz, 1H), 4.46 (br s, 1H), 3.78 (dd, $J = 17.2$, 12.9 Hz, 1H), 3.22 (dd, $J = 17.2$, 4.9 Hz, 1H), 3.14 (dd, $J = 17.7$, 2.5 Hz, 1H), 2.84 (d, $J = 4.6$ Hz, 3H), 2.76 (dd, $J = 17.9$, 4.1 Hz, 1H). ^{13}C NMR δ 173.1, 168.7, 157.9, 131.9, 131.8, 128.7, 128.5, 126.3, 125.8, 89.2, 86.8, 83.2, 82.5, 56.8, 53.8, 27.2, 22.8, 20.5. The structure assignment for **48** was based upon extensive 2-D NMR analysis. For example, an HMBC study revealed a three-bond correlation between the 2-carbonyl on the hydantoin ring with both of the amino acid α-hydrogens. HRMS (ES) *m/z*: calcd for $(M+H)^+$ $C_{18}H_{16}N_3O_3$: 322.1192, found: 322.1188.

4.35. DNA nicking study with enediyne 4

The compound was dissolved in 100% DMSO and diluted to the concentrations listed in Figure 3. The ϕX174 RF I DNA (1 μg) was incubated with various of the compound solutions at the room temperature for 24 h and then separated on a 1% agarose gel containing ethidium bromide. The DNA bands were visualized using a UV transluminator, and the image was obtained by a digital gel doc camera (8400 FluorChem, CA) and processed using Adobe Photo Deluxe 1.1.

4.36. BSA cleavage experiment with enediyne 11

Enediyne **11** (100 μM, 10 μL) was mixed with BSA (10% in H_2O, 5 μL) and DMSO (50% in H_2O, 85 μL). The mixture was irradiated by UV at ambient temperature for 1 h and then submitted for SELDI-MS analysis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2005.07.016.

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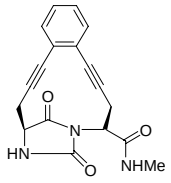

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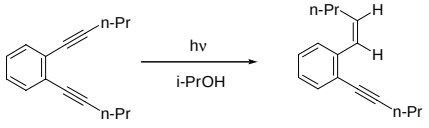

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