Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5691–5704

TETRAHEDRON

Synthesis, reactions and DNA damaging abilities of 10-membered enediyne-sulfone and related compounds

Ichiro Suzuki,* Akira Shigenaga, Atsuo Manabe, Hisao Nemoto and Masayuki Shibuya

Faculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi 1-78, Tokushima 770-8505, Japan

Received 3 April 2003; accepted 2 June 2003

Abstract—The synthesis and Myers–Saito type cycloaromatization reactions of 10-membered enediynes containing a sulfone or a sulfoxide moiety are described. These enediynes cycloaromatized smoothly under physiological conditions to generate bioactive α,3-didehydrotoluene biradicals, that showed potent DNA damaging abilities. Further, in the presence of a nucleophile such as amine or sulfide, cycloaromatization did not occur following the radical reaction pathway but ionically induced cycloaromatization took place.

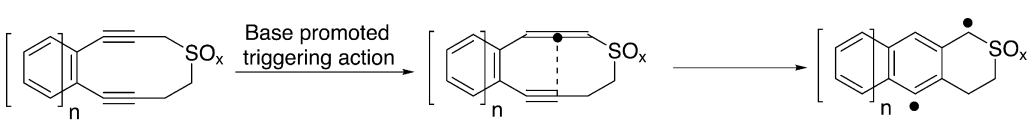
1. Introduction

After the discovery of Neocarzinostatin (NCS) and structurally related compounds endowed with potent antitumor and cytotoxic activities, their remarkable structural features and distinct DNA damaging ability inspired a great deal of effort to evaluate the mechanisms of DNA cleavage and to synthesize naturally occurring enediyne antibiotics.[1] More recently, enediyne antibiotics have been recognized being involved in a wide range of biological events, not only DNA scission but also RNA cleavage, protein agglomeration and apoptosis.[2] As soon as the Saito[3] and Myers groups[4] had elucidated the mechanism of DNA cleavage of NCS, researchers began to effort to design and synthesize enediyne analogues of NCS that afforded enyne–cummlenes or enyne–allenes by triggering reactions and cycloaromatized to generate bioactive α,3-didehydrotoluene biradicals.[5] The most attractive aspect of designing enediyne model compounds is how to regulate the reactivity by simple triggering device.[6] Along the line of these studies, we have developed several enediyne model compounds possessing a characteristic triggering devices acting in biological conditions and we found that 10-membered enediyne models **1**–**4** cycloaromatized under mild basic conditions show potent DNA-cleaving ability.[7] These compounds were stable under neutral conditions and therefore easy to handle, however, under slightly basic conditions facile decomposition took place to form bioactive biradicals. In this article, we report synthesis, reactions and DNA damaging abilities of enediyne model compounds shown in Figure 1.

2. Results and discussions

2.1. Synthesis of enediynes 1–4

Enediynes **1**–**4** were synthesized as shown in Scheme 1. Commercially available (*Z*)-dichloroethylene was used for the starting material of enediynes **1** and **2**. (*Z*)-dichloroethylene was coupled with 3-butyn-1-ol in the presence of Pd catalyst to afford alcohol **6a**, which was reacted with 1-(*tert*-butyldimethylsiloxy)-2-propyne under Sonogashira conditions and **7a** was obtained. Enediyne **7a** was mesylated by the conventional method and the resulting mesylate was treated with KSAc to give **8a**, which was converted to alcohol **9a** by acidic hydrolysis. Alcohol **9a** was treated with MsCl and Et_3N to afford the mesylate, which was cyclized

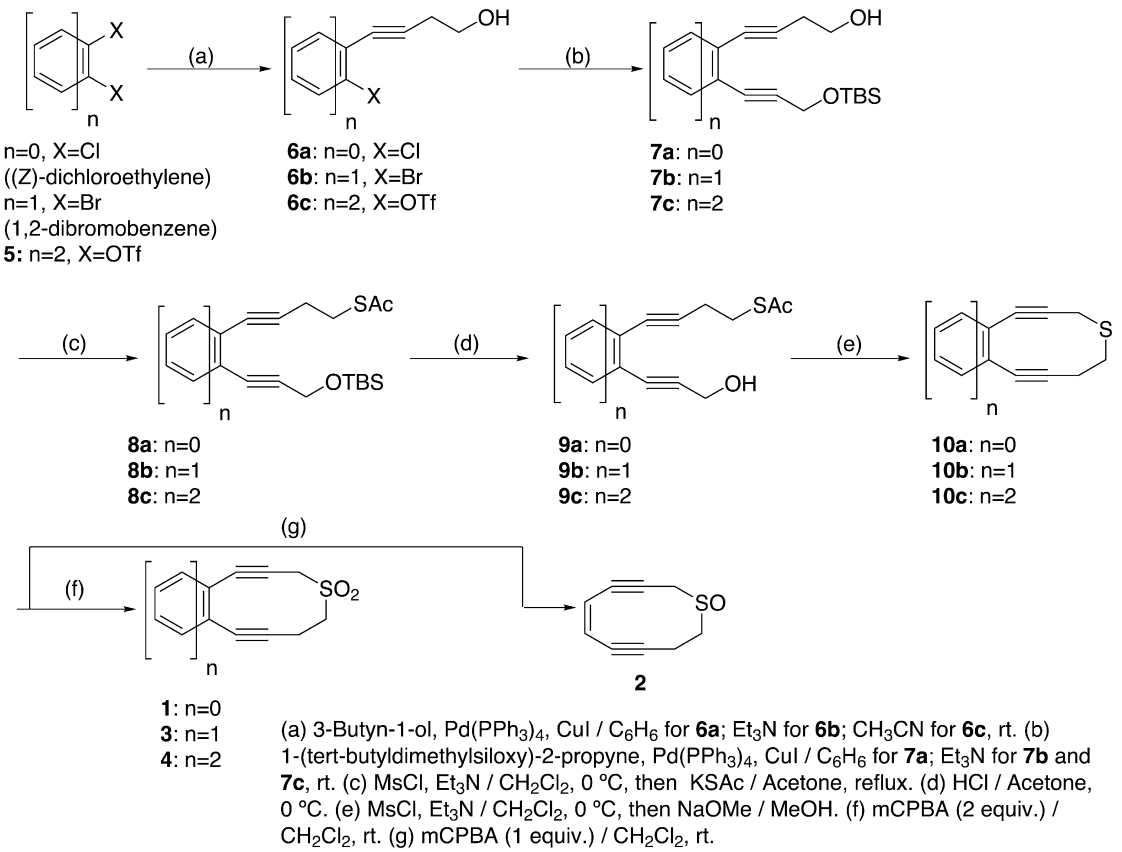


1: n = 0, X = 2; **2**: n = 0, X = 1; **3**: n = 1, X = 2; **4**: n = 2, X = 2.

Figure 1.

Keywords: enediyne; enyne–allene; cycloaromatization; biradical; DNA.
* Corresponding author. Tel.: +81-088-633-9534; fax: +81-088-633-9517; e-mail: isuzuki@ph2.tokushima-u.ac.jp

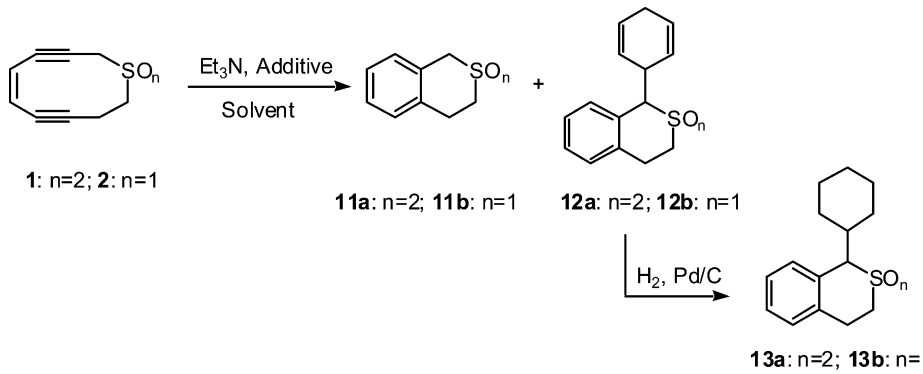
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00903-7



Scheme 1.

at high dilution to give 10-membered sulfide **10a**. The targeting enediyne **1** was obtained from the oxidation of sulfide **10a** using 2 equiv. of mCPBA, and the oxidation of **10a** by an equal amount of mCPBA gave enediyne-sulfoxide **2**. 10-membered enediyne-sulfones **3** and **4** were synthesized from dibromobenzene or ditriflate **5**, respectively, in a manner similar to that used in the synthesis of sulfone **1**.

Table 1. Base promoted cycloaromatization reactions of enediynes **1** and **2**



Entry	Enediyne	Solvent	Additive	Time	Products[a]
1	**1**	Benzene	1,4-CHD	<1 min	**11a** (14%), **12a** (31%)[b]
2	**1**	Benzene	None	<1 min	Complex mixture
3	**1**	Methanol	1,4-CHD	<1 min	**11a** (19%), **12a** (16%)[b]
4	**1**	Methanol	None	<1 min	**11a** (8%)
5	**2**	Benzene	1,4-CHD	24 h	**12b** (23%)[c]
6	**2**	Methanol	1,4-CHD	24 h	Complex mixture

All reactions were carried out with 1.2 equiv. of Et_3N in the presence or absence of 50 equiv. of 1,4-cyclohexadiene (1,4-CHD) at 37°C in a solvent indicated.
[a] Indicated values are isolated yields.
[b] **12a** was obtained as a isomeric and then was converted to **13a** by hydrogenation and the structure was confirmed.
[c] **12b** was obtained as stereoisomeric mixture and then was subjected to hydrogenation to afford sulfoxide **13b**, which was oxidized to sulfone **13a** and the structure was confirmed.

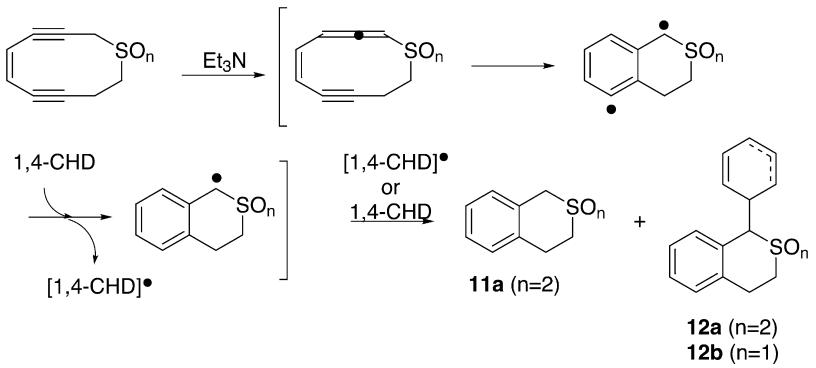
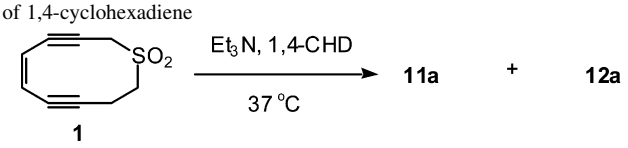


Figure 2.

Table 2. Cycloaromatization reactions of enediyne **1** with various amounts of 1,4-cyclohexadiene



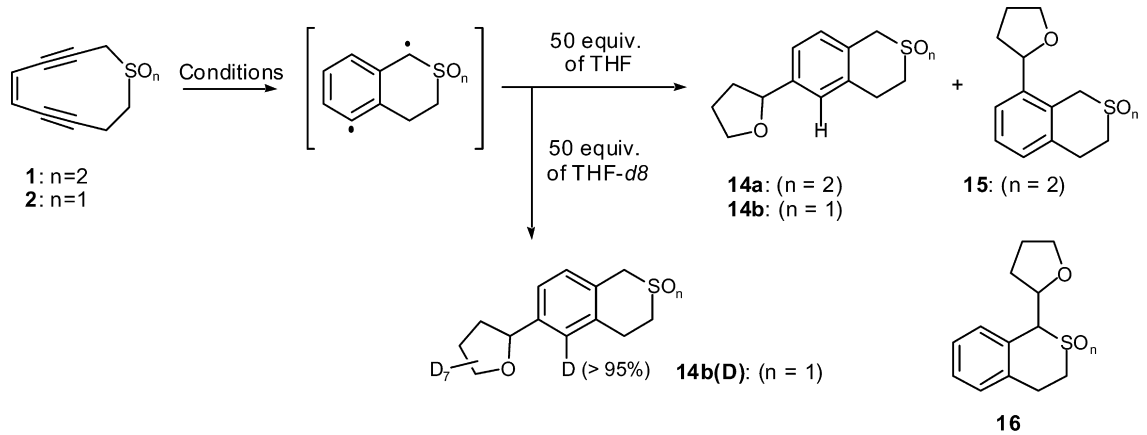
Entry	1,4-CHD (equiv.)	**11a** (%)	**12a** (%)
1	0	8	–
2	1	11	Trace
3	10	13	4
4	20	16	14
5	50	19	16

All experiments were carried out with 1.2 equiv. of Et_3N at 37°C in MeOH in the presence of various amounts of 1,4-cyclohexadiene (1,4-CHD) and all reactions were quenched after 10 min.

2.2. Cycloaromatization reactions of enediynes 1 and 2

First, we examined the cycloaromatization reactions of enediynes **1** and **2** in various conditions. The results are summarized in Table 1. All reactions were carried out with 1.2 equiv. of Et_3N in the presence or absence of 50 equiv. of 1,4-cyclohexadiene (1,4-CHD) in methanol or benzene.[8] In both solvents, enediyne-sulfone **1** cycloaromatized smoothly to give cyclized product **11a** and adduct **12a** as isolable products in the presence of 1,4-CHD or MeOH as a hydrogen donor. Although enediyne-sulfoxide **2** reacted in a similar mode to enediyne-sulfone **1** and afforded **12b**, it needed a prolonged reaction time (1 min vs 24 h). To detect the intermediary enyne–allenes, we monitored the reactions of enediynes **1** and **2** in CD_3OD with Et_3N by using ^1H NMR. For enediyne-sulfone **1**, we could not detect any signals attributed to the enyne–allene because of the facile deprotonation–cyclization reaction, and for enediyne-

Table 3. Cycloaromatization reactions of enediynes **1** and **2** in the presence of THF



Entry	Enediyne	Conditions	Additive[a]	Time	Products[b]
1	**1** (*n*=2)	Et_3N (1.05 equiv.) in C_6H_6	THF	<5 min	**14a** (18%), **15** (5%)
2	**1** (*n*=2)	PB[c]	THF	<5 min	**14a** (14%), **15** (3%)
3	**2** (*n*=1)	Et_3N (1.05 equiv.) in C_6H_6	THF	24 h	**14b** (21%)[d]
4	**2** (*n*=1)	PB[c]	THF	24 h	**14b** (27%)[d]
5	**2** (*n*=1)	PB[c]	THF-*d*8	24 h	**14b(D)** (10%)

All experiments were carried out at 37°C.
[a] 50 equiv. of THF was used.
[b] Indicated values are isolated yields.
[c] PB indicates that the reactions were carried out in the phosphate buffer silution (pH 9.0) containing 20% of acetonitrile.
[d] **14b** was obtained as stereoisomeric mixture and then was oxidized to sulfone **14a** using mCPBA (1 equiv.) to confirm the structure.

sulfoxide **2**, the intermediate could not be detected similarly but gradual deuteration of α-hydrogen was observed. These results indicate that the difference between the efficiency of cycloaromatizations of enediyne **1** and **2** would be attributed to the relatively large pK_a value of the α-hydrogen of enediyne **2** compared to that of **1**.[9]

These results indicate that the cycloaromatization reactions proceeded in the radical reaction pathway as depicted in Figure 2. First, the biradical should abstract a hydrogen from 1,4-cyclohexadiene or any other hydrogen source such as solvent MeOH to afford the benzyl radical, which would couple with cyclohexadienyl radical preferentially rather than abstract a hydrogen due to the low reactivity of the π-radical caused by the stabilization effect of the sulfone moiety.[10]

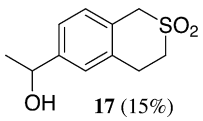
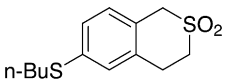
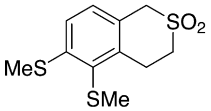
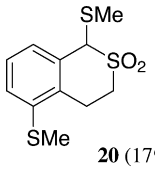
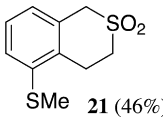
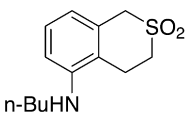
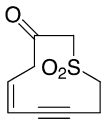
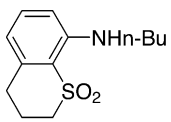
Next, we investigated effects of amount of 1,4-CHD on the reactions and the results are shown in Table 2. Regardless of the amount of 1,4-CHD, the cycloaromatization reactions proceeded smoothly and total yields increased along with the formation of **12a** in proportion to increment of the radical trapping agent.

2.3. Cycloaromatization reactions of enediynes with other trapping agents

To design artificial enediyne antibiotics, better understanding of reactions between biradicals and amino acid, protein, nucleic acid and other biologically important molecules is important.[11] Accordingly, as a preliminary study, we investigated the cycloaromatization reaction of enediynes **1** and **2** in the presence of simple ether, alcohol, thiol, disulfide, sulfide and amine. Table 3 shows the results of cycloaromatizations of enediynes **1** and **2** in the presence of tetrahydrofuran. In benzene and phosphate buffer solution (pH 9.0), in the presence of THF, sulfone **1** cycloaromatized to give adduct **14a** as a major product together with a small amount of **15**, and sulfoxide **2** afforded **14b** similarly. Sulfoxide **14b** was obtained as a stereoisomeric mixture and then was converted to sulfone **14a** by oxidation and the structure was confirmed.

In both cases, the fully hydrogen-trapped product **11a** (or **11b**) was not obtained. From the result of the reaction carried out with THF-*d*8, we confirmed that the phenyl radical part could abstract a hydrogen from THF and would couple with the 2-tetrahydrofuranyl radical.[12] To our expectation, adduct **16** which is a isomer of **14** might be obtained in a similar mode to the reaction of **1** in the presence of 1,4-CHD, however, **16** was not obtained at all but **14** was formed. Similar selectivity was observed in the cycloaromatization reactions with other agents capable of a radical trapping and the results are shown in Table 4. When ethanol or butanethiol was used, adducts **17** or **18** were formed in a similar manner to the formation of **14**. We also examined the cycloaromatization reaction of sulfone **1** in

Table 4. The cycloaromatization reactions of enediyne sulfone **1** with various radical trapping agents

Entry	Trapping agent	Products[a]		
1[b]	EtOH	 **17** (15%)		
2[b]	*n*-BuSH	 **18** (32%)		
3[b]	MeSSMe	 **19** (15%)	 **20** (17%)	
4[b]	MeSMe	 **21** (46%)		
5[c]	*n*-$BuNH_2$	 **22** (21%)	 **23** (14%)	 **24** (4%)

[a] Indicated values are isolated yields.
[b] The reactions were carried out in benzene in the presence of 50 equiv. Of trapping agents with 1.05 equiv. of Et_3N at 37°C and the reactions were quenched after 10 min.
[c] The reaction was carried out in the presence of 50 equiv. of *n*-$BuNH_2$ without Et_3N and was quenched after 10 min.

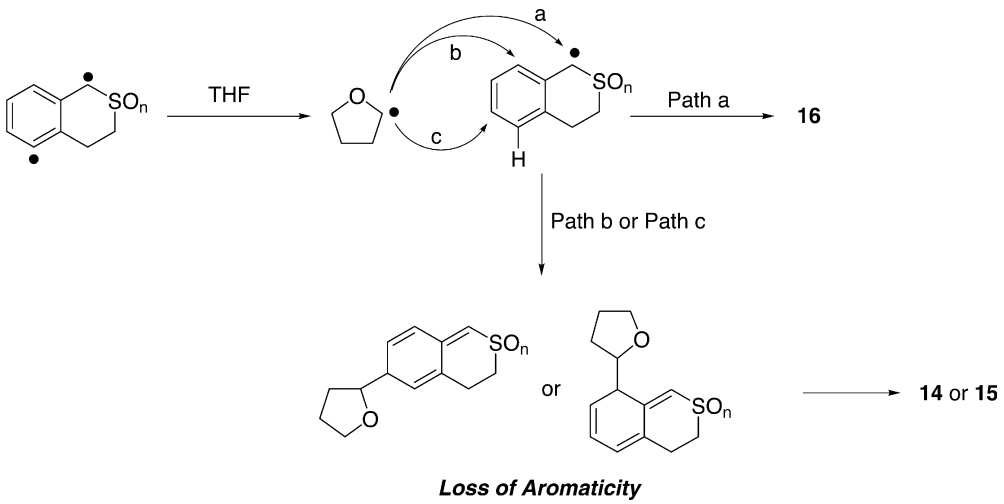


Figure 3.

the presence of dimethyldisulfide and found that, adducts **19** and **20** were obtained in nearly equal amounts. In the case of using disulfide, both radical parts would add to disulfide to form **20** along with **19** which would be formed in a similar manner to the formation of **14**.

In general, coupling reactions between the benzyl radical and methyl radical proceeded favorably at the α position rather than the *ortho* or *para* positions on the benzyl radical[13] and therefore in the cycloaromatization reactions of enediyne-sulfones **1**, it seems to be quite reasonable to give **12a** in the presence of 1,4-cyclohexadiene. On the other hand, 1-hydroxyethyl radical, 2-tetrahydrofuranyl radical and methylsulfanyl radical mainly coupled with the *para* position of the benzyl radical, although these coupling reactions are considered to be unfavorable processes since they involve the loss of aromaticity (Fig. 3). While it is difficult to determine the reason for this selectivity, it is likely that the reactivity of the counterpart radical of the recombination reaction could play an important role in the determining the reaction course.

Interestingly, in the presence of dimethylsulfide or *n*-$BuNH_2$, a somewhat different mode of reactions took place (Table 4, entries 4 and 5). In the presence of dimethylsulfide, nucleophilic addition of the sulfide to the triple bond would initiate the cycloaromatization reaction to give a sulfonium ion, which had to hydrolyze to arylsulfide **21** by adventitious water (Fig. 4).

When the cycloaromatization reaction was carried out in the presence of *n*-$BuNH_2$, similarly, nucleophilic addition of *n*-$BuNH_2$ occurred to yield ionically cycloaromatized product **22** (Fig. 5, path a) along with **23** and **24** (Fig. 5, path b).[14] The formation of sulfone **24** and ketone **23** should be explained that conjugate addition of *n*-$BuNH_2$ to the 10-membered allenylsulfone followed by intramolecular cyclization afforded sulfone **24**, and hydrolysis of the intermediary enamine yielded ketone **23**.

2.4. Cycloaromatization reactions of aryl-annulated enediynes 3 and 4

We examined cycloaromatization reactions of enediynes **3** and **4**, and the results are depicted in Schemes 2 and 3. Arenediyne **3** cycloaromatized smoothly to give cycloaromatized product **25** accompanied by the adduct **26**, which was subjected to hydrogenation to afford reduced product **27** to confirm the structure. Arenediyne **4** also cyclized to give sulfones **28** and **29**, which was reduced to **30** by hydrogenolysis. Since **28**, **29** and **30** were slightly soluble to common organic solvents and were difficult to isolate, the structures of these compounds were determined using HRMS.

Previously, Nicolaou studied the Masamune–Bergman type cycloaromatization reactions of 10-membered carbocyclic enediynes and reported that the reaction rates of the cyclization of aryl-annulated enediynes became slower with increasing length of the double bond in enediyne systems.[15] Considering the similarity between the Masamune–Bergman type cycloaromatization and Myets–Saito type cycloaromatization, we expected the similar retardation was observed in the cyclization of enediynes **3** and **4**, however the retardation of reactions was not observed at all in Myers–Saito type cycloaromatization

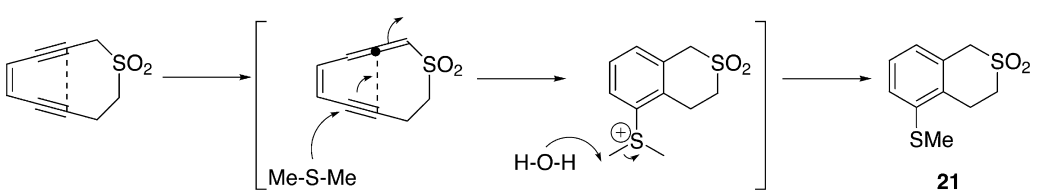


Figure 4.

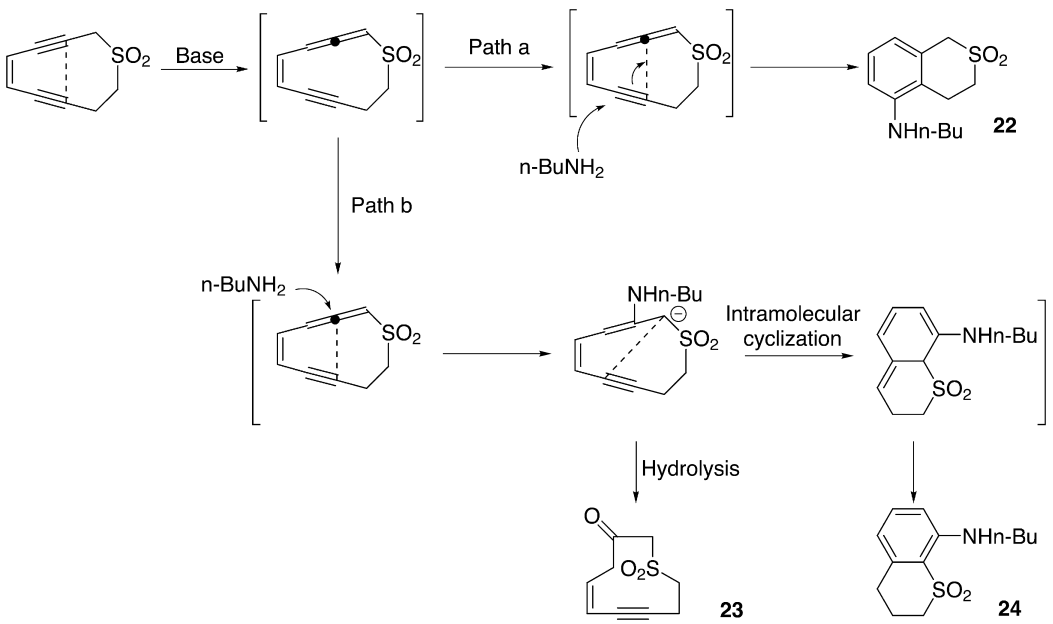
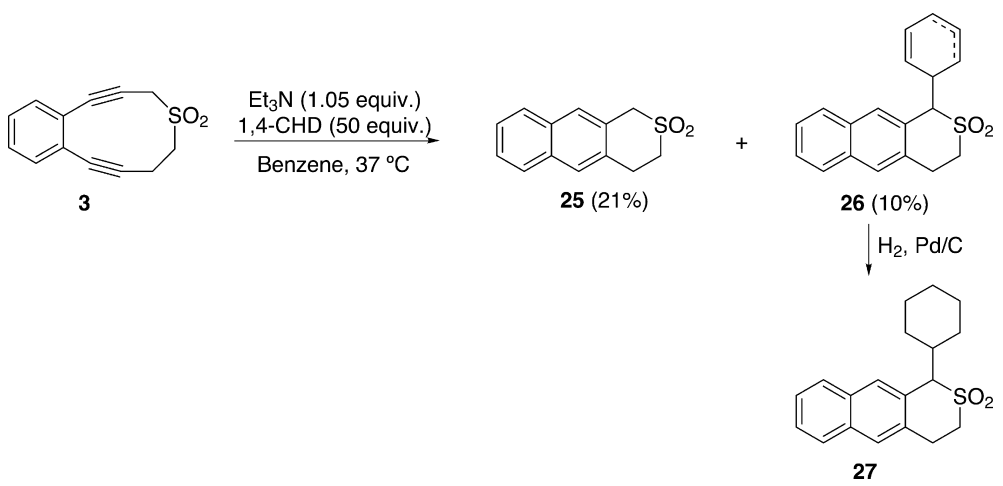
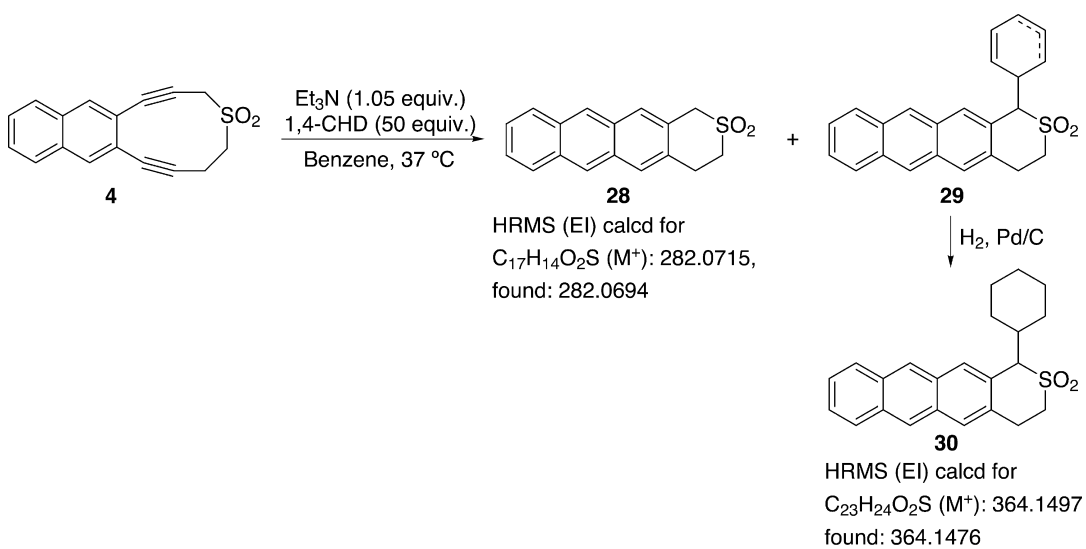


Figure 5.

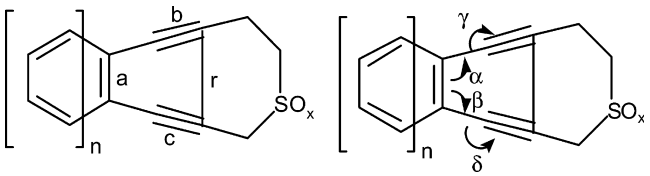


Scheme 2.



Scheme 3.

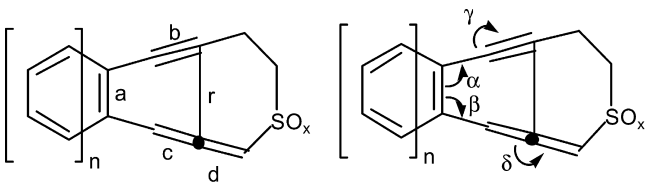
Table 5. Calculated geometries of arenediynes **1**–**4**



Entry	Enediyne	*a* (Å)	*b* (Å)	*c* (Å)	*r* (Å)	*α* (deg.)	*β* (deg.)	*γ* (deg.)?	*δ* (deg.)
1	**1** (*n*=0, *x*=2)	1.33	1.18	1.18	3.43	119	119	167	170
2	**2** (*n*=0, *x*=1	33	1.18	1.18	3.49	119	119	168	170
3	**3** (*n*=1, *x*=2)	1.41	1.18	1.18	3.42	117	117	168	171
4	**4** (*n*=2, *x*=2)	1.43	1.18	1.18	3.42	117	117	169	171

All calculations were performed using the theoretical level of RHF/6-31G(d).

Table 6. Calculated geometries of arenyne–allenes **I**–**IV**



Entry	Enediyne	*a* (Å)	*b* (Å)	*c* (Å)	*d* (Å)	*r* (Å)	*α* (deg.)	*β* (deg.)?	*γ* (deg.)	*δ* (Å)
1	**I** (*n*=0, *x*=2)	1.33	1.18	1.29	1.29	3.28	119	119	167	170
2	**II** (*n*=0, *x*=1)	1.33	1.18	1.30	1.29	3.28	119	119	168	170
3	**III** (*n*=1, *x*=2)	1.41	1.18	1.30	1.29	3.16	117	117	168	171
4	**IV** (*n*=2, *x*=2)	1.44	1.18	1.30	1.29	3.10	117	117	169	171

All calculations were performed using the theoretical level of RHF/6-31G(d).

of these enediynes.[16] In order to understand better the structure–reactivity relationship in arenediyne cycloaromatizations, ab initio calculations were performed on **1**–**4** and their arenyne–allene forms **I**–**IV**. Geometries were optimized at the theoretical level of RHF/6-31G(d) and the results are summarized in Tables 5 and 6.

The geometrical changes observed in enediynes **1**–**4** were very similar to those reported for carbocyclic enediynes. However, in their arenyne–allene forms **I**–**IV**, a considerable shortening was observed in the distance *r* of arenyne–allenes **III** and **IV** compared to arenyne–allenes **I** and **II**. The other factor which alters significantly in **I**–**IV** is bond length *a*, which becomes longer on annulation of aryl systems such as benzene and naphthalene, and this change observed in arenyne–allene **III** and **IV**, may have a retarding effect on cycloaromatization. Although the increment of bond length *a* from **I** to **III** (or **IV**) might lower the cyclization efficiency, the shortening of *r* accelerates the reaction, and this acceleration should overcome the retarding effect caused by the decrease in bond order.

2.5. Studies on DNA damaging abilities of the synthetic enediynes

We also examined the DNA cleaving abilities of our synthetic enediynes **1**–**4**. DNA strand cleavage by the enediynes was estimated on agarose gels by conversion of covalently closed circular DNA (Form I) to open circular DNA (Form II) and the results are summarized in Table 7.

Enediynes **1**, **3**, and **4** were completely consumed within 1 h, although it took more than 12 h for enediyne **2**. All enediynes **1**–**4** showed potent DNA damaging abilities in slightly basic phosphate buffer solutions (containing 20% of acetonitrile). Mechanistically, the σ-radical part of the biradical instead of the resonace-stabilized π-radical part would be responsible for this DNA scission, although the alkylation pathway cannot be ruled out.[17]

Time dependency of DNA %cleavage in enediynes **1** and **2** is shown in Figure 6. Although the extent of DNA cleavage by sulfone **1** reached a maximum in 60 min, sulfoxide **2** showed a gradual increase in cleavage over 4 h and finally reached a similar level to sulfone **1**. This difference between sulfone **1** and sulfoxide **2** is considered to reflect the slower cycloaromatization reaction rate of sulfoxide **2**.

Table 7. DNA cleaving abilities of enediynes **1**–**4**

Entry	Enediyne	DNA cleavage[a] (%)
1	**1**	79±5
2	**2**	79±5
3	**3**	72±7
4	**4**	89±6

Col E1 DNA (12.5 μg/mL) was incubated for 12 h at 37°C with enediynes **1**–**4** (150 μM) in pH 7.8 phosphate buffers, and analyzed by electrophoresis (1% agarose gel, ethidium bromide staining).

[a] Indicated values are mean value±SD of three runs. A Control reaction mixture without the addition of any drug was incubated and the mean value of three runs was used as the background to be subtracted from the obtained values.

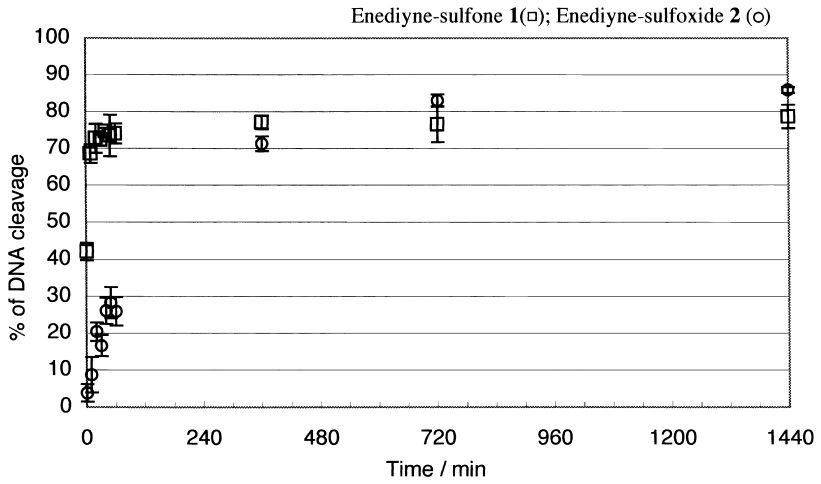


Figure 6. (a) Col E1 DNA (12.5 μg/mL) was incubated for 1 h at 37°C with enediyne **1** and **2** (150 μM) in PH 7.8 phosphate buffers, and analyzed by electropholysis(1% agarose gel, ethidium bromide staining). Results presented are mean value±SD of three runs. A control reaction mixture without the addition of any drug was incubated and the mean value of three runs was used as the backgroung to be subtracted from the obtained values.

3. Conclusion

We synthesized several 10-membered cyclic enediynes bearing a sulfone or a sulfoxide moiety and demonstrated that these enediynes cycloaromatized smoothly under physiological conditions to afford α,3-didehydrotoluene biradicals, which showed potent DNA damaging abilities. The reactivity of these biradicals was also investigated to show that the σ-radical part of these biradicals could abstract hydrogen, but the π-radical part would mainly undergo recombination reactions rather than hydrogen abstraction. The origin of the regiochemistry of these recombination reactions still remains unclear, however it seems to depend on the reactivity of the counterpart radical of the reactions. These findings hold considerable promise for the design of the artificial enediyne antibiotics and understanding of the biological behavior of these compounds.

4. Experimental

4.1. General

^{1}H NMR spectra were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using JEOL JNM-AL400 (400 MHz), JEOL JNM-AL300 (300 MHz) spectrometers, unless otherwise noted. ^{13}C NMR spectra were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) using JEOL JNM-AL400 (100 MHz) and JEOL JNM-AL300 (75 MHz) spectrometers. IR spectra were recorded on JASCO FT/IR-420 and Perkin–Elmer 1720 FT-IR spectrometer. Mass Spectra were obtained on a JEOL JMS-DX303 and JMS-SX102A. Melting points were obtained on YAMATO-MODEL20 melting point apparatus and were uncorrected. Column chromatography was performed on silicagel, KANTO KAGAKU N-60. Thin-layer chromatography was performed on precoated plates (0.25 mm, silicagel Merck Kieselgel 60 F254). All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. Reaction mixtures were stirred magnetically.

4.1.1. 1-Thia-5-cyclodecen-3,7-diyne 1,1-dioxide (1). Sulfide **10a** (1.00 g, 6.75 mmol) was dissolved in CH_2Cl_2 (6.0 mL) and the solution was cooled to 0°C. To this solution was added mCPBA (70 wt%, 3.4 g, 14.8 mmol) and the mixture was allowed to warm to room temperature and stirred for additional 30 min. The mixture was poured into saturated aqueous solution of $NaHCO_3$ and extracted twice with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, $CHCl_3$) to give 975 mg of desired sulfone **1** (5.41 mmol, 80%) as a colorless solid: mp 117°C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (1H, d, J=10.0 Hz), 5.92 (1H, d, J=10.0 Hz), 4.15 (2H, s), 3.64 (2H, deformed t, J=5.5 Hz), 2.98 (2H, deformed t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.7 (CH), 121.8 (CH), 99.9 (C), 88.2 (C), 86.2 (C), 83.3 (C), 58.1 (CH_2), 49.9 (CH_2), 16.0 (CH_2); IR ($CHCl_3$) 2952, 2240, 2218, 1329, 1126 cm^{-1}; HRMS (EI) calcd for $C_9H_8O_2S$ (M^+): 180.0245, found: 180.0230; Anal. calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47. Found: C, 59.66; H, 4.38.

4.1.2. 1-Thia-5-cyclodecen-3,7-diyne 1-oxide (2). Sulfide 10a (700 mg, 4.72 mmol) was dissolved in CH_2Cl_2 (14.0 mL) and the solution was cooled to 0°C. To this solution was added mCPBA (70 wt%, 1.364 g, 5.53 mmol) and the mixture was stirred for 30 min at 0°C. The mixture was poured into saturated aqueous solution of $NaHCO_3$ and extracted twice with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, $CHCl_3$) and 614 mg of desired sulfoxide **2** (3.74 mmol, 79%) was obtained as a light brown solid: mp 107°C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (2H, s), 3.96 (2H, s), 3.86 (1H, ddd, J=14.0, 13.0 and 2.0 Hz), 3.20–2.90 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.1 (CH), 122.1 (CH), 100.4 (C), 88.8 (C), 87.0 (C), 84.7 (C), 60.9 (CH_2), 45.9 (CH_2), 17.5 (CH_2); IR (neat) 3427, 2910, 2195, 1040 cm^{-1}; HRMS (EI) calcd for C_9H_8OS (M^+): 164.0296, found: 164.0270.

4.1.3. 8-Thia-benzocyclodec-5,11-diyne 8,8-dioxide (3). Obtained in 79% as a yellow oil: ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.40–7.20 (4H, m), 4.20 (2H, s), 3.68 (2H, deformed t, J=5.6 Hz), 3.02 (2H, deformed t, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.1 (C), 127.8 (CH), 126.8 (C), 95.3 (C), 88.3 (C), 83.2 (C), 82.5 (C), 57.9 (CH_2), 49.8 (CH_2), 15.9 (CH_2); IR (neat) 2994, 2904, 2220, 1290, 1135 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{10}O_2S$ (M^+): 230.0402, found: 230.0403.

4.1.4. 9-Thia-naphtho[2,3-*f*]cyclodec-6,12-diyne 9,9-dioxide (4). Obtained in 82% as a colorless powder: mp >300°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.82 (1H, s), 7.80–7.75 (2H, m), 7.53–7.49 (2H, m), 4.24 (2H, s), 3.72 (2H, deformed t, J=5.6 Hz), 3.07 (2H, deformed t, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1 (C), 131.7 (C), 128.5 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 123.6 (C), 122.9 (C), 97.1 (C), 86.4 (C), 85.9 (C), 82.0 (C), 56.8 (CH_2), 48.6 (CH_2), 15.4 (CH_2); IR (KBr) 2948, 2905, 2219, 1407, 1288 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{12}O_2S$ (M^+): 280.0558, found: 280.0558.

4.1.5. (*Z*)-6-Chloro-5-hexen-3-yn-1-ol (6a). To a stirred solution of (*Z*)-dichloroethylene (12.0 mL, 0.16 mol) in degassed benzene (100 mL) were added sequentially *n*-butylamine (39.0 mL, 0.40 mol), 3-butyn-1-ol (6.0 mL, 79.3 mmol), $Pd(PPh_3)_4$ (4.60 g, 3.98 mmol) and CuI (2.30 g, 12.0 mmol). The resulting mixture was stirred for 12 h at room temperature and the reaction was quenched with saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/AcOEt=87:13) and 10.36 g of the desired alcohol **6a** (79.3 mmol, 100%) was obtained as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (1H, d, J=7.8 Hz), 5.87 (1H, dt, J=7.8 and 2.0 Hz), 3.79 (2H, t, J=6.0 Hz), 2.67 (2H, dt, J=2.0 and 6.0 Hz), 1.98–1.86 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.9 (CH), 112.1 (CH), 95.3 (C), 76.5 (C), 60.9 (CH_2), 24.1 (CH_2); IR (neat) 3365, 2216, 1591, 1334 cm^{-1}; HRMS (EI) calcd for C_6H_7OCl (M^+): 130.0185, found: 130.0186.

4.1.6. 4-(2-Bromo-phenyl)-3-butyn-1-ol (6b). To a stirred solution of 1,2-dibromobenzene (2.41 mL, 20.0 mmol) in triethylamine (20.0 mL) were added $Pd(PPh_3)_4$ (462 mg, 0.4 mmol), CuI (114 mg, 0.60 mmol) and 3-butyn-1-ol (1.67 mL, 22.0 mmol) sequentially and the mixture was stirred for 10 h at 70°C. After removal of solvent under reduced pressure, the residue was dissolved in AcOEt. The organic layer was washed with saturated aqueous solution of NH_4Cl, brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/AcOEt=66:34) to give 3.184 g of alcohol **6b** (14.1 mmol, 71%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, d, J=8.1 Hz), 7.46 (1H, dd, J=8.1 and 1.2 Hz), 7.26 (1H, t, J=8.1 Hz), 7.17 (1H, td, J=8.1 and 1.2 Hz), 3.87 (2H, t J=6.0 Hz), 2.76 (2H, t, J=6.0 Hz), 2.00 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0 (CH), 132.1 (CH), 129.0 (CH), 126.9 (CH), 125.4 (C), 125.1 (C), 91.6 (C), 81.2 (C), 60.9 (CH_2), 24.0 (CH_2); IR (neat) 3348, 2885, 2233, 1469, 1043 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9BrO$ (M^+): 223.9837, found: 223.9850.

4.1.7. 2-Trifluoromethanesulfonyloxy-3-(4-hydroxy-1-butynyl)naphthalene (6c). To a stirred solution of ditriflate **5**[11] (24.46 g, 57.6 mmol) in acetonitrile (300 mL) were added 3-butyn-1-ol (3.92 mL, 51.84 mmol), $Pd(PPh_3)_4$ (3.06 g, 2.64 mmol), CuI (3.06 g, 10.36 mmol) and triethylamine (15.3 mL, 109.4 mmol) sequentially and the mixture was stirred for 12 h at ambient temperature. The mixture was poured into saturated aqueous solution of NH_4Cl and extracted twice with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/AcOEt=66:34) to give 15.1 g of **6c** (43.0 mmol, 85%) as a colorless powder: mp 134–136°C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, s), 7.85–7.75 (2H, m), 7.69 (1H, s), 7.60–7.50 (2H, m), 3.89 (2H, t, J=6.0 Hz), 2.78 (2H, t, J=6.0 Hz), 2.17 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (C), 134.0 (CH), 132.3 (C), 131.8 (C), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 119.3 (CH), 116.3 (C), 94.2 (C), 76.1 (C), 60.8 (CH_2), 24.2 (CH_2); IR (KBr) 3356, 2896, 2232, 1496, 1428, 1226 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{11}F_3O_4S$ (M^+): 344.0330, found: 344.0331; Anal. calcd for $C_{15}H_{11}F_3O_4S$: C, 52.33; H, 3.22. Found: C, 52.32; H, 3.32.

4.1.8. (*Z*)-9-(*tert*-Butyldimethylsiloxy)-5-nonen-3,7-diyn-1-ol (7a). To a stirred solution of alcohol **6a** (10.36 g, 79.3 mmol) in degassed benzene (100 mL) were added sequentially *n*-butylamine (12.0 mL, 122 mmol), 1-(*tert*-butyldimethylsiloxy)-2-propyne (27.02 g, 158.6 mmol), CuI (6.04 g, 31.7 mmol) and $Pd(PPh_3)_4$ (9.16 g, 7.93 mmol). The resulting mixture was stirred for 12 h at room temperature and the reaction was quenched with saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, Benzene/AcOEt=95:5) to give 12.66 g of alcohol **7a** (47.9 mmol, 91%) was obtained as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, dt, J=10.5 and 1.5 Hz), 5.79 (1H, dt, J=10.5 and 1.5 Hz), 4.51 (2H, d, J=1.5 Hz), 3.77 (2H, t, J=6.0 Hz), 2.66 (2H, dt, J=6.0 and 1.5 Hz), 1.82 (1H, brs), 0.92 (9H, s), 0.16 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.7 (CH), 118.9 (CH), 95.1 (C), 94.7 (C), 82.2 (C), 80.1 (C), 60.9 (CH_2), 52.3 (CH_2), 25.8 (CH_3), 24.2 (CH_2), 18.3 (C), −5.2 (CH_3); IR (neat) 3376, 2964, 2857, 2217, 1471, 1369 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{24}O_2Si$ (M^+): 264.1546, found: 264.1557.

4.1.9. 1-[3-(*tert*-Butyldimethylsilyloxy)-1-propynyl]-2-(4-hydroxy-1-butynyl)benzene (7b). Obtained in 79% as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (2H, m), 7.17–7.11 (2H, m), 4.50 (2H, s), 3.72 (2H, t, J=6.0 Hz), 2.62 (2H, t, J=6.0 Hz), 2.19 (1H, brs), 0.84 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9 (CH), 131.5 (CH), 127.9 (CH), 127.5 (CH), 125.7 (C), 125.4 (C), 91.4 (C), 90.8 (C), 83.7 (C), 81.4 (C), 60.9 (CH_2), 52.3 (CH_2), 25.9 (CH_3), 24.2 (CH_2), 18.4 (C), −5.0 (CH_3); IR (neat) 3407, 2929, 2857, 2234, 1481, 1364 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{26}O_2Si$ (M^+): 314.1702, found: 337.1573 ($[M+Na]^+$).

4.1.10. 2-[3-(*tert*-Butyldimethylsiloxy)-1-propynyl]-3-(4-hydroxy-1-butynyl)naphthalene (7c). Obtained in 89% as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, s),

7.91 (1H, s), 7.80–7.70 (2H, m), 7.50–7.40 (2H, m), 4.64 (2H, s), 3.86 (2H, t, J=6.0 Hz), 2.77 (2H, t, J=6.0 Hz), 2.08 (2H, brs), 0.96 (9H, s), 0.20 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3 (C), 132.0 (CH), 131.3 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 124.1 (C), 122.3 (CH), 122.1 (CH), 91.0 (C), 90.4 (C), 83.9 (C), 81.5 (C), 61.0 (CH_2), 52.4 (CH_2), 25.9 (CH_3), 24.2 (CH_2), 18.4 (C), −4.9 (CH_3); IR (neat) 3418, 2929, 2231, 1461, 1368 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{28}O_2Si$ (M^+): 364.1859, found: 364.1827.

4.1.11. *S*-Acetyl 9-(*tert*-butyldimethylsiloxy)-5-nonen-3,7-diynylthiol (8a). A solution of alcohol **7a** (12.66 g, 47.9 mmol) in CH_2Cl_2 (340 mL) was treated with triethylamine (10.0 mL, 71.9 mmol) and methanesulfonyl chloride (4.8 mL, 62.3 mmol) at 0°C. The mixture was stirred for 15 min at 0°C and poured into water. The resulting mixture was extracted twice with CH_2Cl_2 and the combined organic layer was washed with brine, dried over $MgSO_4$, concentrated in vacuo. The crude mesylate was obtained as a brown oil and was used without further purification. To a solution of the crude mesylate in acetone (460 mL) was added potassium thioacetate (10.941 g, 95.8 mmol) and the solution was refluxed for 2 h. The solvent was removed in vacuo and water was added. The mixture was extracted three times with AcOEt and the combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane/AcOEt=91:9) to give 10.37 g of *S*-acetate **8a** (32.2 mmol, 67%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, dd, J=10.5 and 1.0 Hz), 5.77 (1H, dd, J=10.5 and 1.0 Hz), 4.53 (2H, d, J=1.0 Hz), 3.07 (2H, t, J=7.2 Hz), 2.67 (2H, dt, J=7.2 and 1.0 Hz), 2.36 (3H, s), 0.92 (9H, s), 0.16 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C), 119.6 (CH), 118.7 (CH), 95.7 (C), 95.2 (C), 82.1 (C), 79.2 (C), 52.3 (CH_2), 30.6 (CH_3), 28.3 (CH_2), 25.8 (CH_3), 20.9 (CH_2), 18.3 (C), −5.1 (CH_3); IR (neat) 2954, 2360, 2216, 1695 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{26}O_2SSi$ (M^+): 322.1423, found: 322.1402.

4.1.12. 1-[3-(*tert*-Butyldimethylsiloxy)-1-propynyl]-2-(*S*-acetyl-4-mercapto-1-butynyl) benzene (8b). Obtained in 61% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.35 (2H, m), 7.30–7.20 (2H, m), 4.61 (2H, s), 3.14 (2H, t, J=7.0 Hz), 2.74 (2H, t, J=7.0 Hz), 2.36 (3H, s), 0.94 (9H, s), 0.18 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2 (C), 132.0 (CH), 131.9 (CH), 127.8 (CH), 127.5 (CH), 125.7 (C), 125.2 (C), 91.6 (C), 91.5 (C), 83.4 (C), 80.5 (C), 52.4 (CH_2), 30.7 (CH_3), 28.5 (CH_2), 25.9 (CH_3), 20.8 (CH_2), 18.4 (C), −4.9 (CH_3); IR (neat) 2929, 2856, 2230, 1695, 1481, 1361 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{28}O_2SSi$ (M^+): 372.1579, found: 395.1508 ([M+Na]$^+$).

4.1.13. 2-[3-(*tert*-Butyldimethylsiloxy)-1-propynyl]-3-(*S*-acetyl-4-mercapto-1-butynyl) naphthalene (8c). Obtained in 84% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, s), 7.91 (1H, s), 7.78–7.67 (2H, m), 7.50–7.40 (2H, m), 3.18 (2H, t, J=7.2 Hz), 2.78 (2H, t, J=7.2 Hz), 2.37 (3H, s), 0.96 (9H, s), 0.20 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2 (C), 132.2 (C), 132.0 (CH), 131.9 (C), 131.7 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 122.3 (C), 122.0 (C), 91.2 (C), 91.0 (C), 83.6 (C), 80.6 (C), 52.5 (CH_2), 30.7 (CH_3), 28.6 (CH_2), 25.9 (CH_3), 20.9 (CH_2), 18.4 (C), −4.9 (CH_3); IR (neat) 3460, 2929, 2856, 2234, 1698, 1488, 1461 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{30}O_2SSi$ (M^+): 422.1736, found: 445.1719 ([M+Na]$^+$).

4.1.14. *S*-Acetyl 9-hydroxy-5-nonen-3,7-diynylthiol (9a). A solution of **8a** (10.373 g, 32.2 mmol) in acetone (225 mL) was cooled in an ice bath and was treated with aqueous HCl (1 M, 48.3 mL). The mixture was allowed to warm to room temperature and was stirred for additional 1 h. The resulting mixture was poured into water and extracted twice with AcOEt. The combined organic layer was washed with saturated aqueous solution of $NaHCO_3$, brine and dried over $MgSO_4$. The organic phase was concentrated in vacuo to give a crude product, which was purified by column chromatography (SiO_2, hexane/AcOEt=2:1) to give 6.34 g of alcohol **9a** (30.5 mmol, 95%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (2H, s), 4.48 (2H, s), 3.10 (2H, t, J=7.0 Hz), 2.70 (2H, t, J=7.0 Hz), 2.36 (3H, s), 2.25 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6 (C), 120.2 (CH), 118.5 (CH), 96.0 (C), 94.6 (C), 82.9 (C), 79.1 (C), 51.7 (CH_2), 30.6 (CH_3), 28.2 (CH_2), 20.9 (CH_2); IR (neat) 3416, 2936, 2213, 1691 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{12}O_2S$ (M^+): 208.0558, found: 208.0552.

4.1.15. 1-(3-Hydroxy-1-propynyl)-2-(*S*-acetyl-4-mercapto-1-butynyl) benzene (9b). Obtained in 87% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.35 (2H, m), 7.26–7.20 (2H, m), 4.57 (2H, s), 3.17 (2H, t, J=7.0 Hz), 2.75 (2H, t, J=7.0 Hz), 2.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4 (C), 132.5 (CH), 132.4 (CH), 128.7 (CH), 128.2 (CH), 126.4 (C), 125.7 (C), 92.4 (C), 91.7 (C), 84.8 (C), 81.1 (C), 52.3 (CH_2), 31.2 (CH_3), 29.0 (CH_2), 21.3 (CH_2); IR (neat) 3416, 2920, 2233, 1693, 1481, 1443 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}O_2S$ (M^+): 258.0715, found: 258.0719.

4.1.16. 2-(3-Hydroxy-1-propynyl)-3-(*S*-acetyl-4-mercapto-1-butynyl) naphthalene (9c). Obtained in 81% as a colorless powder: mp 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, s), 7.90 (1H, s), 7.75–7.70 (2H, m), 7.49–7.44 (2H, m), 4.61 (2H, s), 3.20 (2H, t, J=7.2 Hz), 2.79 (2H, t, J=7.2 Hz), 2.37 (3H, s), 2.04 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7 (C), 132.3 (C), 132.0 (C), 131.9 (CH), 131.6 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 122.2 (C), 121.7 (C), 91.3 (C), 90.7 (C), 84.4 (C), 80.6 (C), 51.8 (CH_2), 30.7 (CH_3), 28.5 (CH_2), 20.8 (CH_2); IR (KBr) 3344, 2934, 2864, 2232, 1680 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{16}O_2S$ (M^+): 308.0871, found: 308.0856; Anal. calcd for $C_{19}H_{16}O_2S$: C, 74.00; H, 5.23. Found: C, 73.69; H, 5.31.

4.1.17. 1-Thia-5-cyclodecene-3,7-diyne (10a). To a stirred solution of the alcohol **9a** (6.34 g, 30.4 mmol) in CH_2Cl_2 (150 mL) were added sequentially triethylamine (6.4 mL, 45.6 mmol) and methanesulfonyl chloride (3.1 mL, 39.5 mmol). The mixture was stirred for 30 min at 0°C and poured into water. The mixture was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude mesylate was obtained as a brown oil and was used without further purification. To a stirred solution of NaOMe (6.22 g, 109.4 mmol) in MeOH (3.04 L) was added a

solution of the crude mesylate in MeOH (100 mL) and the solution was stirred for 12 h at room temperature. The mixture was evaporated in vacuo and the residue was dissolved in AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, benzene/hexane=33:67) to give 1.369 g of enediyne-sulfide **10a** (9.24 mmol, 30.4%) as a yellow needle: mp 59–61°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (1H, d, J=9.5 Hz), 5.83 (1H, d, J=9.5 Hz), 3.46 (2H, s), 3.16 (2H, deformed t, J=5.2 Hz), 2.64 (2H, deformed t, J=5.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 124.1 (CH), 122.5 (CH), 101.4 (C), 99.1 (C), 83.9 (C), 82.2 (C), 34.8 (CH_2), 23.7 (CH_2), 22.9 (CH_2); IR ($CHCl_3$) 3014, 2928, 2190, 1659, 1414 cm^{-1}; HRMS (EI) calcd for C_9H_8S (M^+): 148.0347, found: 148.0347; Anal. calcd for C_9H_8S: C, 72.93; H, 5.44. Found: C, 72.67; H, 5.34.

4.1.18. 8-Thia-benzocyclodec-5,11-diyne (10b). Obtained in 78% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (2H, s), 7.25–7.21 (2H, m), 3.52 (2H, s), 3.17 (2H, deformed t, J=5.2 Hz), 2.72 (2H, deformed t, J=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.2 (C), 128.4 (CH), 128.3 (CH and C), 127.8 (CH), 127.4 (CH), 97.1 (C), 95.2 (C), 83.9 (C), 82.2 (C), 34.8 (CH_2), 23.9 (CH_2), 22.9 (CH_2); IR (neat) 2992, 2928, 1544, 1445, 1037 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{10}S$ (M^+): 198.0503, found: 198.0518.

4.1.19. 9-Thia-naphtho[2,3-*f*]cyclodec-6,12-diyne (10c). Obtained in 91% as a colorless powder: mp 249°C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.80 (1H, s), 7.76–7.70 (2H, m), 7.48–7.43 (2H, m), 3.56 (2H, s), 3.18 (2H, deformed t, J=5.2 Hz), 2.77 (2H, deformed t, J=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3 (C), 132.0 (C), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 126.9 (CH), 126.8 (CH), 125.3 (C), 124.6 (C), 95.17 (C), 94.9 (C), 83.9 (C), 82.1 (C), 34.8 (CH_2), 24.0 (CH_2), 23.0 (CH_2); IR (KBr) 2926, 2815, 2213, 1121 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{12}S$ (M^+): 248.0660, found: 248.0677; Anal. calcd for $C_{13}H_{10}S$: C, 82.22; H, 4.87. Found: C, 81.88; H, 4.99.

4.2. General procedure of cycloaromatization reactions

To a solution of sulfone **1** (40 mg, 0.22 mmol) in degassed benzene (7.80 mL) was added 1,4-cyclohexadiene (1.05 mL, 11.1 mmol) and the mixture was warmed to 37°C. To this solution was added triethylamine (0.039 mL, 0.26 mmol) and the mixture was stirred for 5 min. The resulting mixture was poured into water and extracted twice with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/AcOEt=67:33) to give 5.6 mg of **11a** as a colorless solid (0.031 mmol, 14%) and 17.8 mg of **12a** as a colorless solid in a form of isomeric mixture (0.068 mmol, 31%). Adduct **12a** (40 mg, 0.15 mmol) was dissolved in MeOH (2.0 mL) and was subjected to hydrogenation over 4 mg of Pd/C (10%) for 24 h at ambient temperature. After filtration, the resulting mixture was concentrated in vacuo and the residue was purified by column chromatography (SiO_2, hexane/AcOEt=66:34) to give 31 mg of **13a** (0.12 mmol, 80%) as a colorless powder.

4.2.1. 1,3,4-Trihydro-2-thia-naphthalene 2,2-dioxide (11a). Obtained as a colorless powder: mp 169°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.10 (5H, m), 4.28 (2H, s), 3.38 (2H, t, J=6.0 Hz), 3.28 (2H, t, J=6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.1 (C), 129.7 (CH), 128.7 (CH), 128.5 (CH), 128.3 (C), 127.4 (CH), 54.9 (CH_2), 49.8 (CH_2), 29.0 (CH_2); IR (KBr) 2959, 2918, 1316, 1285, 1114 cm^{-1}; HRMS (EI) calcd for $C_9H_{10}O_2S$ (M^+): 182.0402, found: 182.0418; Anal. calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.01; H, 5.55.

4.2.2. 3,4-Dihydro-1-cyclohexyl-2-thia-naphthalene 2,2-dioxide (13a). Obtained in 80% as a colorless powder: mp 106°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.08 (4H, m), 3.87 (1H, d, J=5.5 Hz), 3.47–3.32 (2H, m), 3.32–3.12 (2H, m), 2.35–2.20 (1H, m), 2.20–2.10 (1H, m), 1.83–1.49 (4H, m), 1.45–0.80 (6H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.2 (C), 132.1 (C), 131.0 (CH), 128.8 (CH), 128.2 (CH), 126.9 (CH), 70.6 (CH), 49.2 (CH_2), 40.2 (CH), 33.3 (CH_2), 30.6 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 25.8 (CH_2); IR ($CHCl_3$) 2933, 2856, 1311, 1291, 1119 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_2S$ (M^+): 264.1184, found: 264.1165; Anal. calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.62. Found: C, 67.94; H, 7.59.

4.2.3. 3,4-Dihydro-1-cyclohexyl-2-thia-naphthalene 2-oxide (13b). Obtained in 72% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.10 (4H, m), 3.76 (1H, d, J=8.0 Hz), 3.40–3.24 (1H, m), 3.24–3.10 (1H, m), 3.07–2.87 (2H, m), 1.98 (1H, d, J=11.5 Hz), 1.83–1.49 (4H, m), 1.38–1.10 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.2 (C), 131.8 (CH), 130.4 (C), 129.0 (CH), 127.7 (CH), 126.7 (CH), 68.5 (CH), 43.8 (CH_2), 40.6 (CH), 31.9 (CH_2), 31.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 22.6 (CH_2); IR ($CHCl_3$) 2997, 2932, 2855, 1223, 1029 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{20}OS$ (M^+): 248.1235, found: 249.1325 ([M+H]$^+$).

4.2.4. 1,3,4-Trihydro-6-(2-tetrahydrofuranyl)-2-thia-naphthalene 2,2-dioxide (14a). Obtained as a colorless powder: mp 131°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (1H, s), 7.22 (1H, d, J=8.0 Hz), 7.10 (1H, d, J=8.0 Hz), 4.87 (1H, t, J=7.0 Hz), 4.27 (2H, s), 4.09 (1H, dt, J=8.0 and 7.0 Hz), 3.94 (1H, dt, J=8.0 and 7.0 Hz), 3.38 (2H, t, J=6.5 Hz), 3.28 (2H, t, J=6.5 Hz), 2.33 (1H, dq, J=11.5 and 7.0 Hz), 2.01 (2H, tdd, J=8.0, 7.0 and 6.5 Hz), 1.75 (1H, dq, J=11.5 and 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.3 (C), 133.2 (C), 129.8 (CH), 127.1 (C), 125.9 (CH), 124.9 (CH), 80.0 (CH), 68.8 (CH_2), 54.9 (CH_2), 49.9 (CH_2), 34.6 (CH_2), 29.2 (CH_2), 26.0 (CH_2); IR ($CHCl_3$) 3019, 2873, 1323, 1121, 1062 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}O_3S$ (M^+): 252.0820, found: 252.0838.

4.2.5. 1,3,4-Trihydro-8-(2-tetrahydrofuranyl)-2-thia-naphthalene 2,2-dioxide (15). Obtained as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (1H, d, J=7.5 Hz), 7.30 (1H, t, J=7.5 Hz), 7.16 (1H, d, J=7.5 Hz), 4.95 (1H, t, J=7.5 Hz), 4.38 (1H, d, J=16.0 Hz), 4.29 (1H, d, J=16.0 Hz), 4.13 (1H, dt, J=8.0 and 7.0 Hz), 3.94 (1H, dt, J=8.0 and 7.0 Hz), 3.40 - 3.18 (4H, m), 2.36 (1H, dq, J=6.5 and 12.0 Hz), 2.04 (2H, tdd, J=6.5, 7.0 and 8.0 Hz), 1.82 (1H, dq, J=12.0 and 7.5 Hz); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 134.4 (C), 129.9 (C), 128.9 (C), 128.5 (CH), 127.7 (CH), 125.0 (CH), 78.1 (CH), 68.7 (CH_2), 51.8 (CH_2), 50.0 (CH_2), 33.3 (CH_2), 29.3 (CH_2), 25.8 (CH_2); IR ($CHCl_3$) 1320, 1215, 1122 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}O_3S$ (M^+): 252.0820, found: 252.0838.

4.2.6. 1,3,4-Trihydro-6-(1-hydroxyethyl)-2-thia-naphthalene 2,2-dioxide (17). Obtained in 15% as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.22 (2H, m), 7.13 (1H, d, J=8.5 Hz), 4.91 (1H, q, J=6.5 Hz), 4.28 (2H, s), 3.53 (1H, brs), 3.40 (2H, t, J=6.5 Hz), 3.29 (2H, t, J=6.5 Hz), 1.49 (3H, d, J=6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.5 (C), 133.4 (C), 130.0 (CH), 127.5 (C), 125.8 (CH), 124.7 (CH), 69.8 (CH), 54.8 (CH_2), 49.8 (CH_2), 29.2 (CH_2), 25.4 (CH_3); IR ($CHCl_3$) 3688, 1323, 1122 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}O_3S$ (M^+): 226.0664, found: 226.0672.

4.2.7. 1,3,4-Trihydro-6-Butylsulfanyl-2-thia-naphthalene 2,2-dioxide (18). Obtained in 32% as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20 (1H, dd, J=8.0 and 2.0 Hz), 7.16 (1H, d, J=2.0 Hz), 7.05 (1H, d, J=8.0 Hz), 4.24 (2H, s), 3.35 (2H, t, J=6.0 Hz), 3.28 (2H, t, J=6.0 Hz), 2.93 (2H, t, J=7.3 Hz), 1.70–1.59 (2H, m), 1.51–1.40 (2H, m), 0.93 (3H, t, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3 (C), 133.8 (C), 130.2 (CH), 128.4 (CH), 127.2 (CH), 125.5 (C), 54.7 (CH_2), 49.7 (CH_2), 32.8 (CH_2), 31.0 (CH), 29.0 (CH_2), 21.9 (CH_2), 13.6 (CH_3); IR ($CHCl_3$) 2961, 2932, 1323, 1124 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{18}O_2S_2$ (M^+): 270.0748, found: 270.0767.

4.2.8. 1,3,4-Trihydro-5,6-bis(methylsulfanyl)-2-thia-naphthalene 2,2-dioxide (19). Obtained in 15% as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.14 (1H, d, J=8.0 Hz), 7.04 (1H, d, J=8.0 Hz), 4.22 (2H, s), 3.79 (2H, t, J=6.5 Hz), 3.27 (2H, t, J=6.5 Hz), 2.44 (3H, s), 2.30 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6 (C), 138.9 (C), 132.0 (C), 130.7 (CH), 125.2 (C), 122.5 (CH), 55.1 (CH_2), 50.4 (CH_2), 27.3 (CH_2), 18.5 (CH_3), 15.8 (CH_3); IR ($CHCl_3$) 3003, 2924, 1322, 1120 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}O_2S_3$ (M^+): 274.0156, found: 274.0148; Anal. calcd for $C_{11}H_{14}O_2S_3$: C, 48.14; H, 5.14. Found: C, 48.50; H, 4.99.

4.2.9. 1,3,4-Trihydro-1,5-bis(methylsulfanyl)-2-thia-naphthalene 2,2-dioxide (20). Obtained in 17% as a colorless powder: mp 85–86°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29 (1H, d, J=8.0 Hz), 7.18 (1H, t, J=8.0 Hz), 7.16 (1H, d, J=8.0 Hz), 4.74 (1H, d, J=2.5 Hz), 4.03 (1H, ddd, J=14.2, 11.0 and 6.0 Hz), 3.43 (1H, ddd, J=17.5, 6.0 and 4.0 Hz), 3.29 (1H, ddd, J=17.5, 11.0 and 6.0 Hz), 3.14 (1H, dddd, J=14.2, 6.0, 4.0 and 2.5 Hz), 2.52 (3H, s), 2.48 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8 (C), 131.6 (C), 129.5 (C), 128.2 (CH), 127.5 (CH), 125.0 (CH), 65.7 (CH), 42.0 (CH_2), 26.6 (CH_2), 18.2 (CH_3), 15.6 (CH_3); IR ($CHCl_3$) 3006, 2926, 1325, 1116 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}O_2S_3$ (M^+): 274.0156, found: 274.0148.

4.2.10. 1,3,4-Trihydro-5-methylsulfanyl-2-thia-naphthalene 2,2-dioxide (21). Obtained in 46% as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26 (1H, t, J=7.5 Hz), 7.21 (1H, d, J=7.5 Hz), 6.93 (1H, d, J=7.5 Hz), 4.26 (2H, s), 3.43 (2H, t, J=6.5 Hz), 3.29 (2H, t, J=6.5 Hz), 2.49 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5 (C), 130.8 (C), 129.2 (C), 127.7 (CH), 126.5 (CH), 125.5 (CH), 54.5 (CH_2), 48.9 (CH_2), 26.2 (CH_2), 16.0 (CH_3); IR ($CHCl_3$) 1322 and 1120 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{12}O_2S_2$ (M^+): 228.0279, found: 228.0285; Anal. calcd for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30. Found: C, 52.39; H, 5.24.

4.2.11. 1,3,4-Trihydro-5-butylamino-2-thia-naphthalene 2,2-dioxide (22). Obtained in 21% as a colorless powder: mp 173°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.16 (1H, t, J=7.5 Hz), 6.64 (1H, d, J=7.5 Hz), 6.47 (1H, d, J=7.5 Hz), 4.24 (2H, s), 3.47 (1H, brs), 3.29 (2H, t, J=6.2 Hz), 3.14 (2H, t, J=7.0 Hz), 3.09 (2H, t, J=6.2 Hz), 1.66 (2H, m), 1.45 (2H, m), 0.96 (3H, t, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9 (C), 128.8 (C), 128.3 (CH), 118.6 (CH), 118.5 (CH), 110.2 (CH), 53.8 (CH_2), 47.5 (CH_2), 43.8 (CH_2), 31.4 (CH_2), 24.0 (CH_2), 20.3 (CH_2), 13.9 (CH_3); IR ($CHCl_3$) 1469, 1323, 1297, 1120 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{19}O_2S$ (M^+): 253.1136, found: 253.1136.

4.2.12. 1-Thia-cyclodec-3-on-5-en-7-yne 1,1-dioxide (23). Obtained in 14% as a colorless powder: mp 109°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.95 (1H, dt, J=5.4 and 11.0 Hz), 5.62 (1H, dt, J=2.0 and 11.0 Hz), 4.45 (2H, s), 3.52 (2H, deformed t J=5.4 Hz), 3.37 (2H, dd, J=6.0 and 2.0 Hz), 2.88 (2H, t, J=6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1 (C), 135.6 (CH), 111.3 (CH), 93.6 (C), 83.7 (C), 66.6 (CH_2), 50.9 (CH_2), 44.6 (CH_2), 15.3 (CH_2); IR ($CHCl_3$) 3000, 2926, 1725, 1323, 1121 cm^{-1}; HRMS (EI) calcd for $C_9H_{10}O_3S$ (M^+): 198.0351, found: 198.0350; Anal. calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.18; H, 5.04.

4.2.13. 2,3,4-Trihydro-8-butylamino-1-thia-naphthalene 1,1-dioxide (24). Obtained in 4% as a colorless powder: mp 169°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22 (1H, t, J=8.0 Hz), 6.64 (1H, d, J=8.0 Hz), 6.46 (1H, d, J=8.0 Hz), 6.05 (1H, brs), 3.37 (2H, deformed t, J=6.5 Hz), 3.17 (2H, t, J=7.0 Hz), 2.95 (2H, t, J=6.5 Hz), 2.44–2.38 (2H, m), 1.69 (2H, m), 1.46 (2H, m), 0.96 (3H, t, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.6 (C), 138.0 (C), 133.0 (CH), 120.0 (C), 116.7 (CH), 110.6 (CH), 53.1 (CH_2), 43.5 (CH_2), 30.9 (CH_2), 29.3 (CH_2), 20.7 (CH_2), 20.2 (CH_2), 13.8 (CH_3); IR ($CHCl_3$) 1469, 1280, 1107 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{19}O_2S$ (M^+): 253.1136, found: 253.1124.

4.2.14. 1,3,4-Trihydro-2-thia-anthracene-2,2 dioxide (25). Obtained in 21% as a yellow powder: mp 289°C (decomp.); ^1H NMR($CDCl_3$, 400 MHz) δ 7.78–7.67 (2H, m), 7.63 (1H, s), 7.61 (1H, s), 7.43–7.39 (2H, m), 4.35 (2H, s), 3.79 (2H, deformed t, J=6.4 Hz), 3.28 (2H, deformed t, J=6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.2 (C), 132.4 (C), 131.5 (C), 129.1 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 127.0 (CH), 126.9 (C), 126.5 (CH), 56.2 (CH_2), 52.0 (CH_2), 29.1 (CH_2); IR (KBr) 2934, 1390 and 1119 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{12}O_2S$ (M^+): 232.0558, found: 232.0565.

4.2.15. 1,3,4-Trihydro-1-cyclohexyl-2-thia-anthracene 2,2-dioxide (27). Obtained in 75% as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83–7.78 (2H, m), 7.67 (1H, s), 7.64 (1H, s), 7.52–7.47 (2H, m), 4.06 (1H, d, J=6.4 Hz), 3.64–3.47 (2H, m), 3.39–3.18 (2H, m), 2.50–2.20 (2H, m),

1.90–0.70 (11H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.9 (C), 132.0 (C), 131.5 (C), 130.4 (CH), 130.2 (C), 127.6 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 72.2 (CH), 51.8 (CH_2), 39.2 (CH), 33.9 (CH_2), 30.7 (CH_2), 28.4 (CH_2), 26.4 (CH_2), 26.4 (CH_2), 25.8 (CH_2); IR (neat) 2928, 2853, 1297, 1108 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}O_2S$ (M^+): 314.1340, found: 314.1313.

4.3. Computational methods

The molecular structures of all stationary points have been determined using ab initio techniques, at the restricted Hartree–Fock (RHF) self-consistent filed (SCF) level of theory. The calculations were performed with the GAUSSIAN-98[18] package of programs. Optimized geometries were obtained using 6-31G(d)[19] basis set.

4.4. DNA-cleavage assay

In a typical experiment, 0.25 μg Col E1 DNA (WAKO Pure Chemical Industries, Ltd) in 20 μL phosphate buffer (pH 9.0) containing drugs (0.15 mM) was incubated in Eppendorf tube at 37°C for 1 h. Immediately, 15 μL samples were loaded into 1% agarose gel. The running buffer was 20 mM TAE, pH 7.8. Electrophoresis was at 50 V for 8 h. After electrophoresis, gel was stained for 1 h in ethidium bromide (1 μg/mL) and de-stained for 5 min in water. Relative amounts of DNA in form I, Form II and Form III were determined by densitometry.

Acknowledgements

This work was supported by a research grant from Faculty of Pharmaceutical Sciences, The University of Tokushima and Grant-in-Aid for Scientific research (No. 13771334) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

1. (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387–1416. (b) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191–198. (c) Nicolaou, K. C.; Dai, W. M.; Tsay, S. C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172–1178. (d) Gleiter, R.; Kratz, D. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 842–845. (e) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103–2117.
2. (a) Xi, Z.; Goldberg, I. *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Eds.; Pergamon: Oxford, 1999; Vol. 7, pp 392–553. (b) Zein, N.; Solomon, W.; Casazza, A. M.; Kadow, J. F.; Krishnan, B. S.; Tun, M. M.; Vyas, D. M.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1351–1356. (c) Jones, G. B.; Plourde, G. W.; Wright, J. M. *Org. Lett.* **2000**, *2*, 811–813. (d) Jones, G. B.; Wright, J. M.; Hynd, G.; Wyatt, J. K.; Yancisin, M.; Brown, M. A. *Org. Lett.* **2000**, *2*, 1863–1866.
3. (a) Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907–2910. (b) Saito, I.; Yamaguchi, K.; Nagata, R.; Murahashi, E. *Tetrahedron Lett.* **1990**, *31*, 7469–7472. (c) Sugiyama, H.; Yamashita, K.; Nishi, M.; Saito, I. *Tetrahedron Lett.* **1992**, *33*, 515–518. (d) Sugiyama, H.; Fujiwara, T.; Kawabata, H.; Yoda, N.; Hirayama, N.; Saito, I. *J. Am. Chem. Soc.* **1992**, *114*, 5573–5578. (e) Sugiyama, H.; Yamashita, K.; Fujiwara, T.; Saito, I. *Tetrahedron* **1994**, *50*, 1311–1325.
4. (a) Myers, A. G.; Arvedson, S. P.; Lee, W. *J. Am. Chem. Soc.* **1996**, *118*, 4725–4726. (b) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369–9386. (c) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057–8059.
5. (a) Grissom, J. W.; Gunawardena, G. U.; Huang, D. *Tetrahedron* **1996**, *52*, 6453–6518. (b) Maier, M. E. *Synlett* **1995**, 13–26. (c) Hirama, M.; Fujiware, K.; Shigematsu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120–4122. (d) Kawata, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 4591–4598.
6. (a) Suzuki, I.; Tsuchiya, Y.; Shigenaga, A.; Nemoto, H.; Shibuya, M. *Tetrahedron Lett.* **2002**, *43*, 6779–6781. (b) Suzuki, I.; Shigenaga, A.; Nemoto, H.; Shibuya, M. *Heterocycles* **2001**, *54*, 571–576. (c) Suzuki, I.; Wakayama, M.; Shigenaga, A.; Nemoto, H.; Shibuya, M. *Tetrahedron Lett.* **2000**, *41*, 10019–10023.
7. (a) Sakai, Y.; Bando, Y.; Shishido, K.; Shibuya, M. *Tetrahedron Lett.* **1992**, *33*, 957–960. (b) Sakai, Y.; Nishiwaki, E.; Shishido, K.; Shibuya, M.; Kido, M. *Tetrahedron Lett.* **1991**, *32*, 4363–4366.
8. When the cycloaromatization reaction of enediyne **1** was carried out with 0.1 equiv. of Et_3N, the starting enediyne was recovered along with trace amounts of the cycloaromatized products.
9. Valter, E. *Chem. Listy* **1986**, *80*, 918–934.
10. (a) Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688. (b) Hirama, M.; Tokuda, M.; Fujiwara, K. *Synlett* **1991**, 651–653.
11. (a) Braslau, R.; Anderson, M. O. *Tetrahedron Lett.* **1998**, *39*, 4227–4230. (b) Hirama, M.; Akiyama, K.; Tanaka, T.; Noda, T.; Iida, K.; Sato, I.; Hanaishi, R.; Fukuda-Ishisaka, S.; Ishiguro, M.; Otani, T.; Leet, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 720–721.
12. We could not detect the fully deuterium-trapped product, probably because of the facile exchange from deuterium to hydrogen on the benzylic position in the presence of Et_3N.
13. Huang, X. L.; Dannenberg, *J. Org. Chem.* **1991**, *56*, 6367–6371.
14. (a) Wu, M. J.; Lee, C. Y.; Lin, C. F. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4077–4079. (b) Wu, M. J.; Chang, L. J.; Wei, L. M.; Lin, C. F. *Tetrahedron* **1999**, *55*, 13193–13200. (c) Wu, M. J.; Lin, C. F.; Chen, S. H. *Org. Lett.* **1999**, *1*, 767–768.
15. Nicolaou, K. C.; Dai, W. M.; Hong, Y. P.; Tsay, S. C.; Baldridge, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 7944–7953.
16. Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907–1911.
17. (a) Hirama, M.; Gomibuchi, T.; Fujiwara, K. *J. Am. Chem. Soc.* **1991**, *113*, 9851–9853. (b) Nicolaou, K. C.; Wendeborn, S.; Maligres, P.; Isshiki, K.; Zein, N.; Ellestad, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 418.
18. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, R. E.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford,

S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Pople, J. A. Gaussian 98, revision A.5; Gaussian, Inc.: Pittsburgh, PA, 1998.

19. (a) Gordon, M. S. *Chem. Phys. Lett.* **1980**, *76*, 163–168. (b) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657–2664.