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Base catalyzed rearrangement of π-conjugated sulfur and selenium bridged propargylic systems

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Abstract—A series of novel π-conjugated bis-propargylic sulfides, selenides, sulfoxides and sulfones have been prepared. In the presence of amine bases these compounds underwent facile isomerization to the corresponding allenes, followed by a tandem cyclization and aromatization of the latter via a diradical intermediate. While the reactions of sulfones and sulfoxides were almost spontaneous and proceeded in practically quantitative yield, the sulfides and selenides exhibited modest reactivity and required more polar solvents to afford the corresponding thiophenes and selenophenes. Some mechanistic studies and DNA cleaving properties are also presented.

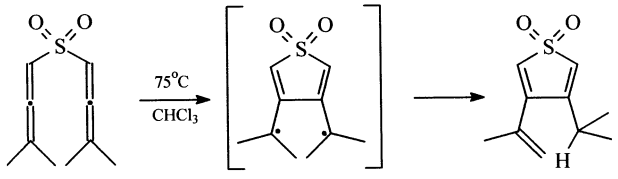
1. Introduction

The renewal of interest in cycloaromatization reactions over the last decade has clearly intensified due to the elegant mode of action of the enediyne natural products.[1] The key to the biological activity of the latter postulated a diradical cycloaromatization which subsequently leads to DNA-cleavage. Due to the complexity and scarcity of the enediyne natural products, synthesis of a variety of enediyne models posed a great challenge for organic chemists.[2] As one such model the cyclization of bis-γ,γ-dimethylallenyl sulfone (**1**)[3] has been used by Nicolaou for the design of a new class of DNA-cleaving molecules.[4] This was based on our previous discovery that sulfone **1** underwent a quantitative cyclization on heating via a 2,2′-bis-allyl diradical intermediate to the thiophene-1,1-dioxide derivative shown in Scheme 1. However, subsequent mechanistic studies by Nicolaou[5] and others[6] have lead to the conclusion that an alternative mechanism, the Maxam–Gilbert mechanism,[7] involving nucleophilic addition of DNA to the diallenic sulfone was responsible for their biological activity. In fact, this conclusion is hardly surprising in view of the relatively high temperature required for the cyclization of **1**.

Based on our previous experience with the cyclization[3,8] and cycloaromatization[9] of π and heteroatom bridged diallenic systems, we became interested in studying the effect of tandem cyclization and aromatization of some novel diallenic systems which, beside their potential biological activity, would also be of considerable mechanistic and synthetic interest. In view of Nicolaou's conclusion mentioned above, we decided to investigate the base catalyzed rearrangement of some novel π-conjugated bis-propargylic sulfones.[10] In addition, we decided to compare the reactivity of such dipropargylic sulfones with the corresponding sulfides, selenides and sulfoxides. Apparently, the last two have never been investigated before.

2. Results and discussion

The required sulfones **2c**, **2g** and **2j** were readily prepared by oxidation of the corresponding sulfides **2a**, **2e** and **2h** with *m*-CPBA or oxone (Scheme 2). Our investigation of base catalyzed tandem isomerization, cyclization and aromatization of π-conjugated bis-propargylic sulfones was initiated with an examination of the behavior of bis-γ-phenylpropargyl sulfone (**2c**). Surprisingly, we have found that reaction of this sulfone with triethylamine in $CHCl_3$ at room temperature results in practically spontaneous and quantitative tandem rearrangement, cyclization and aromatization affording the naphthalene derivative **5c**. In order to test the generality of this reaction, we have examined the reactivity of the other dipropargylic



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Scheme 1. Cyclization of *bis*-γ,γ-dimethylallenyl sulfone.

Keywords: sulfur and selenium compounds; allenes; acetylenes; cyclizations; radicals; rearrangements.

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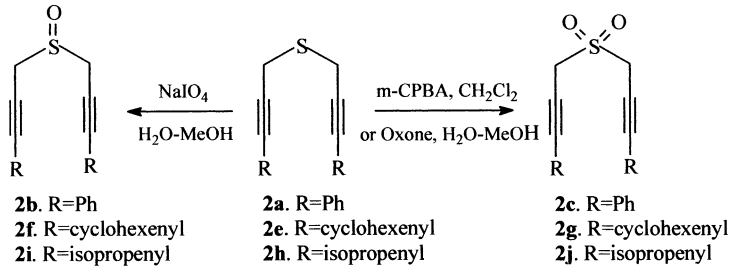
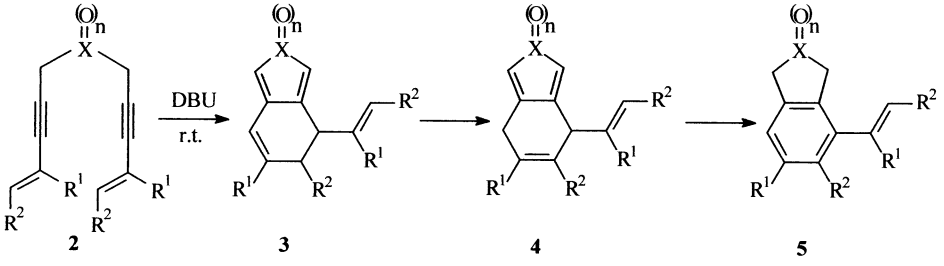


Scheme 2. Preparation of sulfoxides **2b**, **f**, **i** and sulfones **2c**, **g**, **j**.

Table 1. Tandem isomerization, cyclization and aromatization of bridged *bis*-propargylic systems

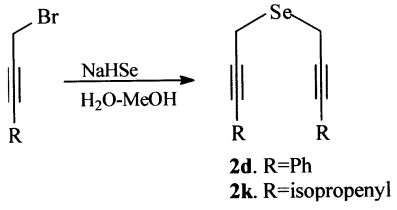


Entry	2	*n*	X	Solvent	Time	Products (yield)
1	**2a**: R^1, R^2=(CH=CH)$_2$	0	S	CH_3CN	24 h	**4a** (25)
2	**2a**			$CHCl_3$	72 h	No reaction
3	**2b**: R^1, R^2=(CH=CH)$_2$	1	S	DMSO-d_6	5 min[a]	**5b**(100)[a]
4	**2b**			$CHCl_3$	1 h	**5b** (100)
5	**2c**: R^1, R^2=(CH=CH)$_2$	2	S	$CHCl_3$	1.5 h[b]	**5c** (100)
6	**2c**			$CDCl_3$[c]	15 min	**5c** (100)[a]
7	**2d**: R^1, R^2=(CH=CH)$_2$	0	Se	DMSO	16 h	**4d** (21)
8	**2e**: R^1, R^2=(CH_2CH_2)$_2$	0	S	DMSO	7 d	No reaction
9	**2f**: R^1, R^2=(CH_2CH_2)$_2$	1	S	CH_3CN	4 h	**5f** (78)
10	**2g**: R^1, R^2=(CH_2CH_2)$_2$	2	S	$CHCl_3$	5 min	**5g** (95)
11	**2h**: R^1=CH_3, R^2=H	0	S	CH_3CN	18 h	**3h** (73)
12	**2i**: R^1=CH_3, R^2=H	1	S	DMSO	10 min	**5i** (100)
13	**2j**: R^1=CH_3, R^2=H	2	S	$CHCl_3$	5 min	**5j** (90)
14	**2k**: R^1=CH_3, R^2=H	0	Se	DMSO	62 h	**3k** (65)

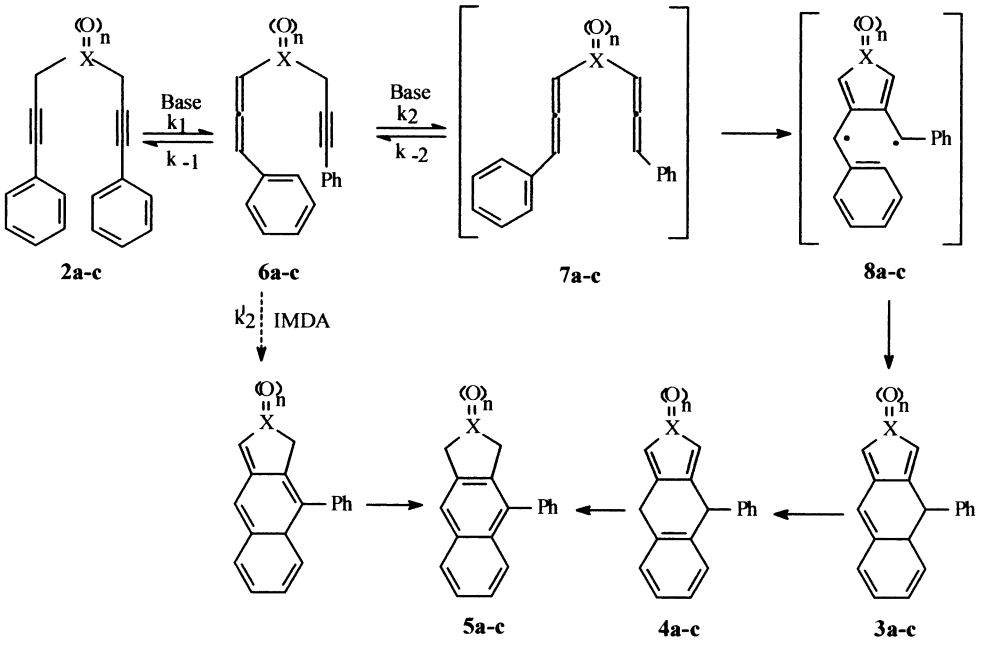
At room temperature using DBU as base.
[a] Determined by ^{1}H NMR.
[b] Reaction with DBU at 0°C.
[c] Using triethylamine as base.

compounds mentioned in Table 1. Examination of the data presented in Table 1 indicates that the formation of products **3**, **4** or **5** as well as the reactivities of **2a**–**k**, are highly dependent on the oxidation number of the sulfur atom and on the nature of both the solvent and the base.

Similarly to the reaction of **2c**, sulfones **2g** and **2j** readily react with DBU in $CHCl_3$ to afford the appropriate naphthalene derivatives **5g** (95%) and **5j** (90%). Of particular interest, sulfoxide analogs **2b**, **2f** and **2i** have been found to undergo cyclization in the same manner but somewhat slower. Interestingly, while the reaction of sulfoxide **2b** was completed within 1 h in $CHCl_3$ affording **5b** quantitatively, the use of DMSO as solvent reduced the reaction time to 5 min. In sharp contrast, the sulfide analogs **2a** and **2h** have been found to be stable to the conditions mentioned above. However, using a more polar solvent such as CH_3CN led to formation of the expected products **4a** (25%) and **3h** (73%) within 24 and 18 h, respectively. Moreover, the cyclization of **2e** could not be achieved under various conditions, even in refluxing chloroform solution. In view of these results we decided to investigate the reactivity of selenides **2d** and **2k**, which have never been examined before. The required selenides **2d** and **2k** were easily prepared by reaction of the appropriate γ-substituted propargyl bromide with sodium hydrogen selenide[11] in aqueous methanol solution, in excellent yield (Scheme 3). We have thus found that the cyclization of selenides **2d** and **2k** was considerably slower than the corresponding sulfur analogs, and required a more polar solvent such as DMSO to obtain the corresponding products **4d** (21%) and **3k** (65%). These results are compatible with the fact that the deprotonation of a carbon



Scheme 3. Preparation of selenides **2d**, **k**.



Scheme 4. Tandem isomerization, cyclization and aromatization of bridged propargylic compounds **2a**–**c**.

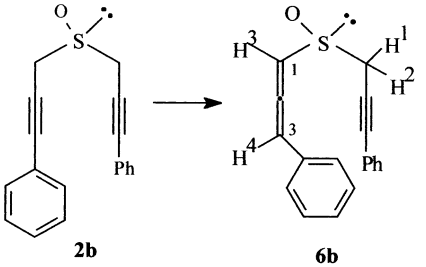
linked to a sulfur atom is easier than that of a carbon linked to selenium.[12]

The generally accepted mechanism for the reaction of dipropargylic sulfides such as **2a** was proposed by Garratt[13] (Scheme 4). The key intermediate, diradical **8a**, is stabilized both because of the formation of an aromatic thiophene ring as well as by the fact that both radical centers are benzylic. Therefore, one might expect that **8b** and **8c**, in which the five-membered ring is nonaromatic, would be less favored and that contrary to our observations the reactions of **2b** and **2c** should actually be slower. In addition, only intermediate **6b** (and not, e.g. **7b**) could be detected. These observations raised the question of whether or not the cyclization of **6b** occurs via the original Garratt mechanism or via an alternative mechanism involving an intramolecular Diels–Alder reaction (IMDA) of the acetylenic triple bond to the conjugated ene–allene, followed by fast aromatization to yield **5b** directly. Such a mechanism was initially suggested by Iwai[14] for the cyclization of **2a** under more drastic conditions, using *t*-BuOK in refluxing *t*-BuOH, which afforded **5a**. However, this mechanism has been rejected by Garratt, who succeeded in isolating intermediate **4a**. In view of these results and in order to ascertain that the unusually facile tandem isomerization, cyclization and aromatization of sulfone **2c** and sulfoxide **2b**, proceed via a bridged diallenyl sulfone **7c** and sulfoxide **7b**, respectively, a brief kinetic study has been performed on sulfoxide **2b**.

The rate of reaction of **2b** could be conveniently monitored by integrating the appropriate ^{1}H NMR signals for **2b**, **6b** and **5b** and by measuring their concentrations as function of time.[15] Intermediate **6b**, which appears at maximum concentration near the beginning of the reaction time, and then gradually decreases, exists as a 6:4 mixture of diastereoisomers due to the chirality of the sulfur atom in sulfoxides as well as the structure chirality of allenes (Table 2).

According to the mechanism involving diallene **7b** (Scheme

Table 2. NMR Data for starting material **2b** and for intermediate **6b**



2b **6b**

Sulfoxide	H1[a]	H2[a]	H3	H4	C-prop.	C1	C3
2b	4.13 (d, *J*=15 Hz)	3.96 (d, *J*=15 Hz)	–	–	41.9	–	–
6b major	4.06 (d, *J*=15.5 Hz)	3.99 (d, *J*=15.5 Hz)	6.75 (d, *J*=6 Hz)	6.64 (d, *J*=6 Hz)	46.2	102.7	101.5
6b minor	4.02 (d, *J*=16 Hz)	3.99 (d, *J*=16 Hz)	6.71 (d, *J*=6 Hz)	6.66 (d, *J*=6 Hz)	46.2	102.8	102.2

[a] ABq system.

Table 3. Rate constants for the rearrangement of *bis*-γ-phenylpropargyl sulfoxide

[Sulfoxide **2b**][a] (M)	[DBU][a] (M)	10^3k_1 (s^{-1})	10^3k_2 (s^{-1})	[Sulfoxide **6b**]$^b_{max}$
0.20	0.06	0.65	2.0	0.21
0.20	0.20	1.70	5.0	0.24
0.20	0.60	3.50	10.0	0.21

[a] In the communication which preceded this paper[10] these concentrations were reported incorrectly.
[b] Molar fraction.

4), we would expect that both prototropic steps defined by k_1/k_{-1} and k_2/k_{-2} would be sensitive to the base concentration. In contrast, according to the alternative mechanism, involving IMDA of **6b**, only the first step (k_1/k_{-1}) would be affected since k'_2 is not dependent on base concentration. Increasing the base concentration should then increase the maximal concentration of **6b**, while in the case of the diallene mechanism the maximal concentration of **6b** would not change. Therefore, we decided to determine the maximal concentration of **6b** in order to distinguish between the two mechanistic alternatives by reacting 0.1 mmol of **2b** with 5, 15 and 45 μL of DBU in 0.5 mL of $CDCl_3$. We thus found that the maximal concentrations of **6b** in these three experiments were roughly similar; the concentration of the two diastereoisomeric intermediates

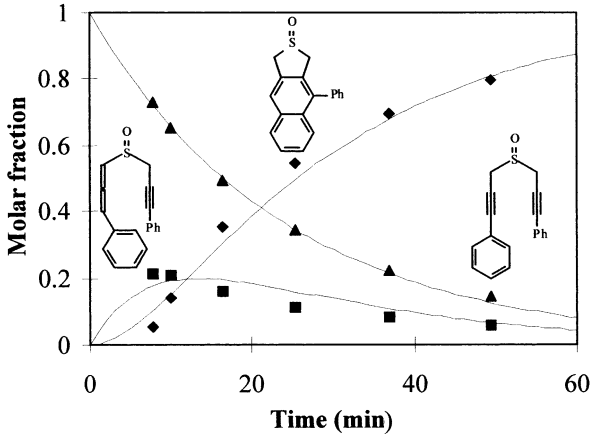
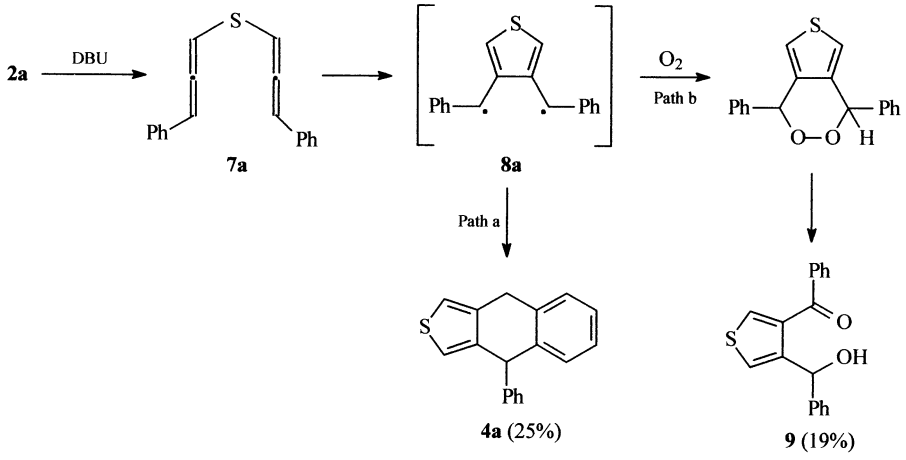


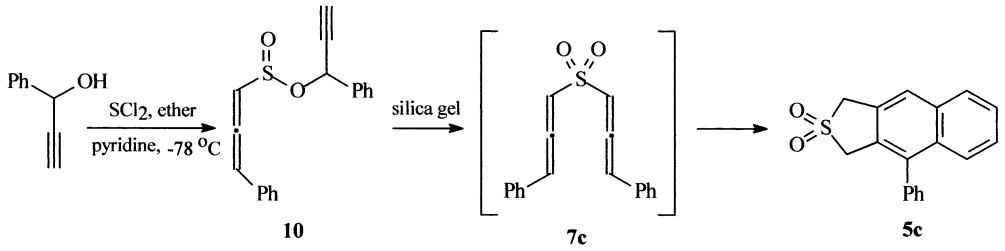
Figure 1. Fitting results for the reaction of **2b** (0.02 mmol) with 5 μL of DBU (0.006 mmol).

gradually decreases over the reaction time (Table 3). Moreover, the rate constants k_1 and k_2, which were obtained by fitting the experimental points to calculated curves (one example is illustrated in Fig. 1), show the same dependence on base concentration. The data presented in Table 3 indicate that the isomerization of bis-propargyl sulfoxide **2b** to propargyl allene **6b** is the rate determining step and it is about three times slower than the second isomerization from **6b** to diallene **7b**. This conclusion may explain the unexpected difference in the rate of reaction of dipropargyl sulfide **2a**, relative to the corresponding sulfoxide and sulfone, since the first step is dependent on the relative acidity of the α-hydrogens of these three systems and is slowest in the case of sulfide **2a**. The effects of solvent polarity on the reaction rates are also consistent with this mechanism. Thus, the rate of conversion for **2b** in $CDCl_3$ is slower than the rate in DMSO-d_6, where the reaction is complete within 5 min, using 1 equiv. of DBU at room temperature. With all three systems investigated the cyclization step is proceeding at high rate, regardless of the nature of the bridging functionality, or of the nature of the diradical intermediate **8a–c**. Therefore, only intermediate **6b** can be detected. One should add, that in view of the relative instability of thiophene monoxides in general,[16] the facile and quantitative tandem cyclization and aromatization of **2b** is rather remarkable.

Interestingly, while in all cases studied, compounds **2b–k** have led to a single product, **3**,**4** or **5**, the reaction of sulfide **2a** afforded a mixture of **4a** (25%) and **9** (19%) as shown in Scheme 5. The latter product was not reported by Garratt[13] and Ollis,[17] who used *t*-BuOK as base in the cyclization of the bis-propargylic sulfides. The formation of hydroxyketone **9** could arise from the reaction of molecular oxygen



Scheme 5. Suggested mechanism for the formation of **9** from the reaction of sulfide **2a** with DBU.



Scheme 6. The formation and cyclization of α-phenylpropargyl-γ-phenylallene sulfinate (**10**).

with diradical intermediate **8a**, followed by a disproportionation process (Scheme 5). Sondheimer[18] and Garratt[19] have shown that such diradical intermediates formed by cyclization of bridged diallenes could be trapped by molecular oxygen to afford the appropriate peroxides. In order to confirm this mechanism, we have performed the reaction of **2a** with DBU in dry CH_3CN under an oxygen atmosphere. Under these conditions, the **4a**:**9** ratio (determined by ^1H NMR) changes from 58:42 to 38:62. One may wonder why the other sulfides, sulfoxides and sulfones do not give the appropriate hydroxy ketone product, especially since reaction of the selenide analog **2d** under the same conditions yielded only the cyclization product **4d** (21%). We assume that the reduced stability of thiophene monoxide (and dioxide) diradical may explain their preference of the cyclization pathway rather than reaction with oxygen. The relative stability of **8a** may be explained by the 'dibenzylic-like' radical system and comparison between thiophene diradical **8a** with the selenophene diradical analog is consistent with the reduced aromaticity of selenophene vs. thiophene[20] as well as the lack of α-radical stabilization by the selenium atom.[21]

Further mechanistic evidence of bis-allene formation in the cyclization of bis-γ-phenylpropargyl sulfone (**2c**) is provided by the double [2,3]-sigmatropic rearrangement of bis-α-phenylpropargyl sulfoxylate to bis-γ-phenylallenyl sulfone (**7c**). Bis-α-phenylpropargyl sulfoxylate was prepared by the reaction of α-phenylpropargyl alcohol with SCl_2, and subsequently underwent spontaneous [2,3]-sigmatropic rearrangement to α-phenylpropargyl γ-phenylallenesulfinate (**10**) (Scheme 6). Surprisingly, we have found that during attempted isolation and purification of the latter by column chromatography, a spontaneous tandem rearrangement, cyclization and aromatization was observed, affording naphthalene derivative **5c**. The product was identical to the one described above in all respects. Moreover, in order to ascertain that the unusually facile cyclization of sulfone **2c** proceeds by the mechanism presented above, a brief kinetic study has been performed on this reactive compound. In view of the high reactivity of sulfone **2c**, we had to select a weak enough base for the reaction to be slowed down to a measurable rate. Thus, with 0.5 equiv. of triethylamine in $CDCl_3$, only intermediate **6c** could be detected by NMR and the reaction rates are $k_1=7.0\times10^{-4}\ s^{-1}$ and $k_2=2.3\times10^{-3}\ s^{-1}$. This behavior is therefore similar to that of sulfoxide **2b**.

3. DNA-Cleaving activity

The DNA cleaving properties of bis-propargylic sulfide **2a**, sulfoxides **2b**,**i** and sulfones **2c**,**j** were assayed using double-stranded supercoiled ΦX174 form I DNA in 10% DMSO–tris-HCl at pH 8.5. Despite our expectation for DNA cleavage by both pairs of sulfones **2c**,**j** and sulfoxides **2b**,**i** due to their facile base catalyzed diradical cyclization, we were surprised to find that only sulfone **2c** exhibited such biological activity. Thus, incubation of bis-γ-phenylpropargyl sulfone (**2c**) with ΦX174 form I DNA aerobically at 37°C led to cleaved DNA as shown by gel electrophoresis analysis (Fig. 2). The lack of activity of bis-propargylic sulfoxides **2b**,**i** may be partly explained by the relatively slow acetylene–allene isomerization comparable to the corresponding sulfones. A different another interpretation is required to explain the unexpected lack activity of sulfone **2j**. Due to the short life of the diradical intermediate formed by the tandem isomerization and cyclization of **2j**, one may expect this intermediate will undergo faster coupling than that of the more stable diradical **8c**.

4. Conclusion

The whole body of evidence in this paper establishes unambiguously that the pathway for cyclization of

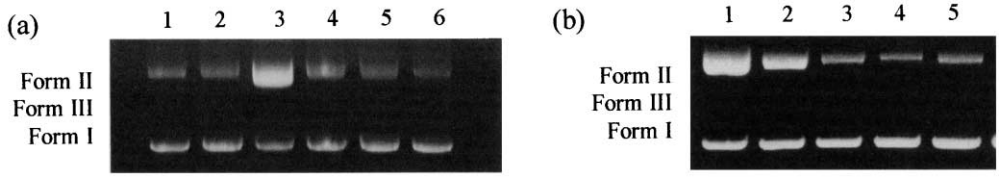


Figure 2. DNA Cleavage by sulfone **2c**. ΦX 174 form I DNA (50 μM per base pair) was incubated for 24 h at 37°C with compounds **2a**–**c**,**i**,**j** in 10% DMSO in tris-HCl buffer (pH 8.5, 50 mM) and analyzed by electrophoresis (1% agarose gel, ethidium bromide stain). (a) lanes 1–5 correspond to DNA and sulfide **2a**, sulfoxide **2b**, sulfone **2c**, sulfoxide **2i** and sulfone **2j** at 1000 μM respectively, and lane 6 to DNA alone; (b) lanes 1–3 correspond to DNA and sulfone **2c** at 1000, 500 and 100 μM respectively, lane 4 to DNA and naphtalenic product **5c** at 1000 μM and lane 5 to DNA alone. Forms I, II and III correspond to supercoiled, relaxed and linear DNA, respectively.

bis-propargylic systems goes through base-catalyzed isomerizations to bis-allenic species, which then cyclize through a diradical intermediate. The latter can be stabilized by adjacent π systems, in which case the cyclization is quite fast; the diallene can never be detected by NMR. Diradical **8c**, which is formed the fastest and is efficiently stabilized, is also the one with best DNA-cleaving properties.

5. Experimental

5.1. General

Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 60 SXB FTIR. ^{1}H- and ^{13}C NMR were recorded on Bruker AC-200, DPX-300 or DMX-600 spectrometers in either $CDCl_3$ or other deuterated solvents, using TMS as internal standard. Chemical shifts are reported in δ units, and coupling constants in Hertz. High-resolution mass spectra were obtained on a VG-Fison Autospec instrument. Other mass spectra were obtained on a Finningan GC/Ms 4021, with either electronic (EI) or chemical ionization (CI). Column chromatography was performed with Merck silica gel 60 (230–400 mesh), and TLC was run on precoated Merck silica gel plates 60 F254 (2.00 mm). Tetrahydrofuran was distilled from Na, diethyl ether was dried over Na wires. Other commercially available chemicals were used without further purification.

5.1.1. Bis-3-(cyclohex-1-enyl)-2-propynyl sulfide (2e). A solution of $Na_2S{\cdot}9H_2O$ (1.60 g, 6.6 mmol) in water (30 mL) was slowly added to a magnetically stirred solution of 1-bromo-3-(cyclohex-1-enyl)-2-propyne[22,23] (1.56 g, 7.84 mmol) in methanol (40 mL) at 0°C. After 2 h the turbid solution was warmed to room temperature and stirred for further 2 h before 50 mL of ether was added. The organic layer was separated, washed with water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 1.10 g (4.0 mmol) of pure yellow oil; yield 100%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 (2H, bs, C═C*H*), 3.53 (4H, s, SCH_2), 2.10–2.07 (8H, m, CH_2CH═CCH_2), 1.63–1.55 (8H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 134.7 (CH), 120.2 (C), 84.9 (C), 81.6 (C), 29.5 (CH_2), 25.4 (CH_2), 22.1 (CH_2), 21.3 (CH_2), 19.9 (CH_2); IR (neat): 1434, 1229, 917 cm^{-1}; MS(CI): *m/e* 271 (MH^+, 100%), 237 (48.5%), 151(11.5%), 119(73%); HRMS (Elemental composition) calc. ($C_{18}H_{23}S$) 271.1520, obs. 271.1526.

5.1.2. Bis-3-isopropenyl-2-propynyl sulfide (2h). The title compound was prepared according to the above procedure as a yellow oil; yield 97%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29–5.28 (2H, m, C═CH_2), 5.22 (2H, quintet, *J*=1.5 Hz, C═CH_2), 3.55 (4H, s, SCH_2), 1.88 (6H, dd, *J*=1.5, 1 Hz, CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 126.4 (C), 121.9 (CH_2), 84.5 (C), 83.5 (C), 23.4 (CH_3), 19.9 (CH_2); IR (neat): 1613, 1456, 897 cm^{-1}; MS (CI): *m/e* 191 (MH^+, 100%), 111 (35.4%); HRMS (Elemental composition) calc. ($C_{12}H_{15}S$) 191.0894, obs. 191.0897.

5.1.3. Bis-3-phenyl-2-propynyl selenide (2d). A solution of sodium borohydride (0.41 g, 10.7 mmol) in water (10 mL), was added to a well stirred selenium suspension (0.42 g, 5.4 mmol) in water (10 mL). After 10 min the clear colorless solution of NaHSe was cooled to 0°C, and a solution of 1-bromo-3-phenyl-2-propyne, (1.50 g, 7.7 mmol) in methanol (15 mL) was added. The yellow solution was stirred for 1.5 h and then left at room temperature for another 14 h. The product was extracted with dichloromethane, washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave the pure selenide as a yellow oil (1.19 g, 100% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.40 (4H, m, Ph), 7.3–7.27 (6H, m, Ph), 3.69 (4H, s, SeCH_2; $^2J_{Se-H}$= 14 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 131.7, 128.2, 128.1 (Ph), 123.1 (C), 85.7 (C), 83.6 (C), 9.4 (CH_2); IR (neat): 1489, 1441, 1175, 755, 690 cm^{-1}; MS (CI): *m/e* 307, 308, 309, 311, 313 (MH^+, 1:1:3:7:1, 24%), 243 (100%), 232 (13.7%); HRMS (Elemental composition) calc. ($C_{18}H_{15}{}^{80}Se$) 311.0338, obs. 311.0363.

5.1.4. Bis-3-isopropenyl-2-propynyl selenide (2k). The title compound was prepared according to the procedure described for the preparation of **2d** as a yellow oil; yield 95%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.27–5.26 (2H, m, C═CH_2), 5.20 (2H, quintet, *J*=1.5 Hz, C═CH_2), 3.53 (4H, s, SeCH_2; $^2J_{Se-H}$=14 Hz), 1.88 (6H, dd, *J*=1.5, 1 Hz, ═CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 126.5 (C), 121.7 (CH_2), 84.67 (C), 84.66 (C), 23.4 (CH_3), 9.2 (CH_2); IR (neat): 2221, 1660, 1611, 1451, 1294, 897, 733 cm^{-1}; MS (CI): *m/e* 234, 235, 236, 238, 240 (M^+, 1:1:3:7:1, 46.3%), 158 (61%), 131 (100%); HRMS (Elemental composition) calc. ($C_{12}H_{14}{}^{80}Se$) 238.0260, obs. 238.0245.

5.1.5. Bis-3-phenyl-2-propynyl sulfoxide (2b). To a magnetically stirred solution of $NaIO_4$ (5.1 g, 23.7 mmol) in water (40 mL) was added a solution of bis-3-phenyl-2-propynyl sulfide[14] (5 g, 19 mmol) in methanol (30 mL) at 0°C. The mixture was warmed to room temperature and stirred for two weeks. It was then diluted with chloroform, washed with water, satd. NaCl and then dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave a mixture of more than two products which were separated by column chromatography (silica gel). Elution with ethyl acetate–hexane 1:1 gave 2.36 g (8.5 mmol) of a white solid (44%) which was recrystallized from dichloromethane–hexane. Mp 99–100°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.46 (4H, m, Ph), 7.35–7.32 (6H, m, Ph), 4.15 and 3.96 (ABq system, each: 2H, d, *J*=15 Hz, S(O)CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 131.5, 128.7, 128.4, 121.5 (Ph), 87.7 (C), 77.2 (C), 41.9 (CH_2); IR (neat): 1066, 1442, 1490 cm^{-1}; MS (CI): *m/e* 279 (MH^+, 43%), 147 (71%), 115 (100%); HRMS (Elemental composition), calc. ($C_{18}H_{15}OS$) 279.0843, obs. 279.0840.

5.1.6. Bis-3-(cyclohex-1-enyl)-2-propynyl sulfoxide (2f). The title compound was prepared by the procedure described for the preparation of **2b** and obtained in 18% yield as a viscous oil, after separation by column chromatography (silica gel, elution with ethyl acetate–hexane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.18–6.15 (2H, m, C═C*H*), 3.94 and 3.76 (ABq system, each: 2H, d, *J*=16 Hz, S(O)CH_2), 2.13–2.08 (8H, m, CH_2CH═CCH_2), 1.64–1.26 (8H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 136.5

(CH), 119.7 (C), 90.0 (C), 74.1 (C), 42.0 (CH_2), 28.9 (CH_2), 25.5 (CH_2), 22.1 (CH_2), 21.2 (CH_2); IR (neat): 1066, 1431 cm^{-1}; MS (CI): *m/e* 287 (MH^+,78.8%), 279 (100%), 119 (64%); HRMS (Elemental composition), calc. ($C_{18}H_{23}OS$) 287.1469, obs. 287.1464.

5.1.7. Bis-3-isopropenyl-2-propynyl sulfoxide (2i). The title compound was prepared by the procedure described for the preparation of **2b** and obtained in 69% yield as a viscous oil, after separation by column chromatography (silica gel, ethyl acetate–hexane 1:1); ^1H NMR (300 MHz, $CDCl_3$): δ 5.37 (2H, bs, C=CH_2), 5.31 (2H, dq, J=1.5, 1 Hz, C=CH_2), 3.95 and 3.78 (ABq system, each: 2H, d, J=16 Hz, S(O)CH_2), 1.9 (6H, dd, J=1.5, 1 Hz, =CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 125.7 (C), 123.4 (CH_2), 89.3 (C), 76.0 (C), 42.0 (CH_2), 23.1 (CH_3); IR (neat): 1614, 1456, 1061 cm^{-1}; MS (CI): *m/e* 207 (MH^+, 64%), 159 (59%), 147 (100%); HRMS (Elemental composition), calc. ($C_{12}H_{15}OS$) 207.0843, obs. 207.0855.

5.1.8. Bis-3-phenyl-2-propynyl sulfone (2c). To a magnetically stirred solution of bis-3-phenyl-2-propynyl sulfoxide (1.00 g, 3.6 mmol), in methanol (20 mL) at 0°C was added a solution of 49.5% $KHSO_5$ in water (20 mL). The resulting cloudy slurry was stirred for 4 days at room temperature, diluted with water and extracted with chloroform. The organic layer was washed with water, satd. NaCl and then dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a mixture of sulfoxide and sulfone, which was separated by column chromatography (silica gel, ethyl acetate–hexane 1:1). The sulfone product (0.45 g, 42% yield) was recrystallized from dichloromethane–hexane as colorless crystals. Mp 114–115°C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.47 (4H, m, Ph), 7.35–7.32 (6H, m, Ph), 4.31 (4H, s, SO_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 131.9, 129.2, 128.3, 121.3 (Ph), 87.9 (C), 75.9 (C), 44.5 (CH_2); IR (neat): 1326, 1135 cm^{-1}; MS (CI): *m/e* 295 (MH^+, 22.7%), 230 (54.3%), 115 (100%); HRMS (Elemental composition), calc. ($C_{18}H_{15}O_2S$) 295.0793, obs. 295.0780.

5.1.9. Bis-3-(cyclohex-1-enyl)-2-propynyl sulfone (2g). A solution of 70% *m*-chloroperoxybenzoic acid (1.18 g, 4.8 mmol) in dichloromethane (20 mL) was added to a solution of **2e** (0.53 g, 1.96 mmol) in dichloromethane (20 mL) at 0°C. After the addition, the mixture was warmed to room temperature and further stirred for 18 h. Then, the organic layer was washed with 5% aqueous solutions of KI (50 mL), $K_2S_2O_3$ (20 mL), $NaHCO_3$ (2×30 mL) and water (3×50 mL). The solution was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford a white solid, which was purified by column chromatography (silica gel, ethyl acetate–hexane 1:2) and recrystallized from dichloromethane–hexane as colorless crystals (0.13 g, 22% yield). Mp 94–95°C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.20 (2H, quintet, J=2 Hz, C=CH), 4.13 (4H, s, SO_2CH_2), 2.13–2.10 (8H, m, CH_2CH=CCH_2), 1.63–160 (8H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 137.3 (CH), 119.4 (C), 89.6 (C), 73.1 (C), 44.2 (CH_2), 28.7 (CH_2), 25.6 (CH_2), 22.0 (CH_2), 21.2 (CH_2); IR (neat): 1434, 1332, 1127 cm^{-1}; MS (CI): *m/e* 303 (MH^+, 46.9%), 239 (15.8%), 119 (100%); HRMS (Elemental composition) calc. ($C_{18}H_{23}O_2S$) 303.1419, obs. 303.1415.

5.1.10. Bis-3-isopropenyl-2-propynyl sulfone (2j). The title compound was obtained by the reaction of **2h** with *m*-chloroperoxybenzoic acid according to the above procedure, purified by column chromatography (silica gel, ethyl acetate–hexane 1:2) and recrystallized from dichloromethane–hexane as colorless crystals in 92% yield. Mp 38–39°C; ^1H NMR (300 MHz, $CDCl_3$): δ 5.42 (2H, bs, C=CH_2), 5.35 (2H, dq, J=1.5, 1 Hz, C=CH_2), 4.16 (4H, s, SO_2CH_2), 1.91 (6H, dd, J=1.5, 1 Hz, =CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 125.4 (C), 124.1 (CH_2), 89.0 (C), 74.7 (C), 44.2 (CH_2), 22.8 (CH_3); IR (neat): 1614, 1332, 1129 cm^{-1}; MS (EI): *m/e* 222 (M^+, 62.8%), 158 (26.4%), 143 (100%); HRMS (Elemental composition) calc. ($C_{12}H_{14}O_2S$) 222.0714, obs. 222.0700.

5.2. General procedure for tandem isomerization, cyclization and aromatization

This procedure refers to all of the sulfur/selenium bridged bis-propargylic systems, while the exact conditions and reaction times are as shown in Table 1. All thiophene, selenophene, sulfoxide and sulfone products were purified by column chromatography.

To a solution of the appropriate bis-propargylic system (1 mmol) in 30 mL of solvent were added 1.5 equiv. of DBU. After stirring at room temperature for the appropriate time the reaction was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The solid products were recrystallized from dichloromethane–hexane to give the pure products. The data for all products are listed below.

5.2.1. 3-Hydroxyphenylmethyl-4-benzoylthiophene (9). The title compound was obtained as a mixture with **4a**[12a] and separated by column chromatography (silica gel, ethyl acetate–hexane 2:8), as viscous oil in 19% yield; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (1H, d, J=3.2 Hz, SCH), 7.78–7.76 (2H, m, Ph), 7.62–7.57 (1H, m, Ph), 7.50–7.42 (m, 4H), 7.36–7.30 (2H, m, Ph), 7.27–7.24 (1H, m, Ph), 6.99 (1H, dd, J=3.2, 0.6 Hz, SCH), 6.02 (1H, s, CHOH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 193.0 (C), 147.0 (C), 142.1 (C), 139.0 (C), 138.6 (C), 138.4 (CH), 132.9 (CH), 129.8 (CH), 128.4 (CH), 128.2 (CH), 127.3 (CH), 126.5 (CH), 125.9 (CH), 70.7 (CH); IR (neat): 1633, 1451, 1254, 1179, 1024 cm^{-1}; MS (EI): *m/e* 294 (M^+, 46.4%), 277 (100%); HRMS (Elemental composition) calc. ($C_{18}H_{14}O_2S$) 294.0714, obs. 294.0700.

5.2.2. 4-Isopropenyl-6-methyl-4,5-dihydrobenzo[*c*]thiophene (3h). The title compound was obtained in 73% yield after separation by column chromatography (silica gel, chloroform–hexane 1:8) as a yellowish viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.80–6.75 (2H, m, SCH), 6.26 (1H, s, C=CH), 4.88 (1H, dq, J=1.5, 1 Hz, C=CH_2), 4.84 (1H, bs, C=CH_2), 3.59 (1H, dd, J=10.5, 7 Hz, CH_2CH), 2.36 and 2.22 (2H, ABX system, J_{AB}=16.5 Hz, J_{AX}=10.5 Hz, J_{BX}=7 Hz, CH_2CH; long range couplings are also visible), 1.88 (3H, s, C^6CH_3), 1.77–1.76 (3H, m, =CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 146.4 (C), 138.0 (C), 137.7 (C), 136.4 (C), 119.2 (CH), 118.2 (CH), 116.5 (CH), 112.4 (CH_2), 44.3 (CH), 34.9 (CH_2), 23.4 (CH_3), 19.2

(CH_3); IR (neat): 1645, 1437, 1347, 893, 847, 786 cm^{-1}; MS (CI): *m/e* 191 (MH^+, 100%), 149 (37%); HRMS (Elemental composition) calc. ($C_{12}H_{15}S$) 191.0894, obs. 191.0897.

5.2.3. 4-Isopropenyl-6-methyl-1′,3′-dihydrobenzo[*c*]-thiophene-2′-oxide (5i). The title compound was obtained in 100% yield as a viscous yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (1H, s, Ar*H*), 7.03 (1H, s, Ar*H*), 5.26 (1H, quintet, J=1.5 Hz, C=CH_2), 4.93–4.92 (1H, m, C=CH_2), 4.27 and 4.26 (ABq system, each: 1H, d, J=16 Hz, S(O)CH_2), 4.14 and 4.11 (ABq system, each: 1H, d, J=16 Hz, S(O)CH_2), 2.35 (3H, s, C^6CH_3), 2.08 (3H, dd, J=1.5, 0.6 Hz, =CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 143.5 (C), 141.9 (C), 138.4 (C), 135.6 (C), 128.9 (C), 127.9 (CH), 125.7 (CH), 115.8 (CH_2), 59.0 (CH_2), 58.4 (CH_2), 23.6 (CH_3), 21.1 (CH_3); IR (neat): 1612, 1443, 1039 cm^{-1}; MS (CI): *m/e* 207 (MH^+, 100%), 191 (37.5%), 157 (47%); HRMS (Elemental composition) calc. ($C_{12}H_{15}OS$) 207.0843, obs. 207.0827.

5.2.4. 4-(Cyclohex-1-enyl)-1′,3′,5,6,7,8-hexahydronaphtho[2,3-*c*]thiophene-2′-oxide (5f). The title compound was obtained in 78% yield after separation by column chromatography (silica gel, first with chloroform then ethyl acetate–methanol 12:1) as an orange viscous oil. These data refer to two stable rotamers which are easily distinguishable by the appearance of two olefinic triplets of triplets, resulting from the orientation of the cyclohexenyl double bond with respect to the sulfinyl oxygen. ^1H NMR (300 MHz, $CDCl_3$): δ 6.96 (1H, s, C^1H), 5.56 and 5.47 (each 0.5H, 2 tt, J=7, 1.5 Hz, C=C*H*), 4.26, 4.10; 4.26, 4.09, 4.20 and 3.93; (3 ABq systems, each: 0.5H, d, J=16 Hz, S(O)CH_2), 4.11 (2×0.5H, s, S(O)CH_2), 2.77–2.50 (4H, m, CH_2C=CCH_2), 2.18–1.80 (4H, m, CH_2CH=CCH_2), 1.77–1.25 (8H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.4 (C), 142.3 (C), 137.8 (C), 136.8 (C), 136.0 (C), 134.9 (C), 131.34 (C), 131.29 (C), 130.4 (C), 130.1 (C), 126.5 (CH), 126.2 (CH), 125.1 (CH), 59.2 (CH_2), 59.1 (CH_2), 58.3 (CH_2), 57.9 (CH_2), 29.9 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 23.2 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 22.1 (CH_2); IR (neat): 1637, 1448, 1044 cm^{-1}; MS (CI): *m/e* 287 (MH^+, 20%), 271 (100%), 237 (54.8%); HRMS (Elemental composition) calc. ($C_{18}H_{23}OS$) 287.1470, obs. 287.1492.

5.2.5. 4-Phenyl-1′,3′-dihydronaphtho[2,3-*c*]thiophene-2′-oxide (5b). The title compound was obtained in 100% yield as an orange viscous oil, which was recrystallized from dichloromethane–hexane as yellowish crystals: mp 161°C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87–7.85 (2H, m, C^1H, C^8H), 7.6–7.26 (m, 8H, Ph, C^5H, C^6H, C^7H), 4.45 and 4.36 (ABq system, each: 1H, d, J=15 Hz, S(O)CH_2), 4.17 and 4.02 (ABq system, each: 1H, d, J=16 Hz, S(O)CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 138.2 (C), 137.7 (C), 133.5 (C), 132.8 (C), 132.1 (C), 131.9 (C), 129.8 (CH), 129.4 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 126.3 (CH), 126.1 (CH), 126.0 (CH), 125.2 (CH), 58.9 (CH_2), 58.4 (CH_2); IR (neat): 1492, 1444, 1041 cm^{-1}; MS (CI): *m/e* 230 (65%), 279 (MH^+, 100%), 230 (64.7%), 202 (5.5%), 169 (6%); HRMS (Elemental composition), calc. ($C_{18}H_{15}OS$) 279.0843, obs., 279.0840.

5.2.6. 4-Phenyl-1′,3′-dihydronaphtho[2,3-*c*]thiophene-2′,2′-dioxide (5c). The title compound was obtained as a pure yellowish solid product in 100% yield before it was recrystallized from dichloromethane–hexane mp 187–188°C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88–7.83 (2H, m, C^1H, C^8H), 7.55–7.45 (6H, m), 7.31–7.28 (2H, m), 4.59 (2H, s, SO_2CH_2), 4.24 (2H, s, SO_2CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 138.1 (C), 137.5 (C), 133.2 (C), 132.1 (C), 129.5 (CH), 129.0 (CH), 128.6 (C), 128.3 (CH), 127.9 (CH), 126.9 (CH), 126.8 (CH), 126.3 (CH), 124.9 (CH), 57.2 (CH_2), 56.5 (CH_2); IR (neat): 1317, 1133 cm^{-1}; MS (CI): *m/e* 295 (MH^+, 100%), 230 (41%); HRMS (Elemental composition), calc. ($C_{18}H_{15}O_2S$) 295.0790, obs. 295.0730.

5.2.7. 4-(Cyclohex-1-enyl)-1′,3′,5,6,7,8,-hexahydronaphtho[2,3-*c*]thiophene-2′,2′-dioxide (5g). The title compound was obtained in 95% yield and recrystallized from dichloromethane–hexane as colorless prisms. Mp 208–209°C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (1H, s, C^1H), 5.52–5.50 (1H, m, C=C*H*), 4.32 (2H, s, SO_2CH_2), 4.28 and 4.13 (ABq system, each: 1H, d, J=16 Hz, S(O)CH_2), 2.78–2.76 (m, 2H, C=CCH_2), 2.74 and 2.52 (ABq system, each: 1H, dm, J=16 Hz, C=CCH_2), 2.15–1.89 (4H, m, CH_2CH=CCH_2), 1.78–1.67 (8H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 141.8 (C), 138.2 (C), 136.2 (C), 135.5 (C), 127.7 (C), 126.8 (CH), 126.7 (C), 124.6 (CH), 57.4 (CH_2), 56.2 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 25.2 (CH_2), 23.0 (CH_2), 22.8 (CH_2), 22.6 (CH_2), 22.0 (CH_2); IR (neat): 1445, 1316, 1133, 1096 cm^{-1}; MS (CI): *m/e* 303 (MH^+, 57.5%), 237 (100%); HRMS (Elemental composition), calc. ($C_{18}H_{23}O_2S$) 303.1419, obs. 303.1415.

5.2.8. 4-Isopropenyl-6-methyl-1′,3′-dihydrobenzo[*c*]-thiophene-2′,2′-dioxide (5j). The title compound was obtained in 90% yield and recrystallized from dichloromethane–hexane as colorless prisms. Mp 139–140°C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (1H, s, Ar*H*), 7.03 (1H, s, Ar*H*), 5.26 (1H, quintet, J=1.5 Hz, C=CH_2), 4.90 (1H, bs, C=CH_2), 4.34 (2H, s, SO_2CH_2), 4.33 (2H, s, SO_2CH_2), 2.36 (3H, s, C^6CH_3), 2.05 (3H, dd, J=1.5, 1 Hz, =CCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 143.3 (C), 141.7 (C), 138.7 (C), 131.6 (C), 128.4 (CH), 125.6 (C), 125.2 (CH), 116.2 (CH_2), 57.1 (CH_2), 56.4 (CH_2), 23.5 (CH_3), 21.3 (CH_3); IR (neat): 1637, 1603, 1448, 1377, 1302, 1087 cm^{-1}; MS (EI): *m/e* 222 (M^+, 29%), 158 (93.5%), 143 (100%); HRMS (Elemental composition), calc. ($C_{12}H_{14}O_2S$) 222.0714, obs. 222.0716.

5.2.9. 4-Isopropenyl-6-methyl-4,5-dihydrobenzo[*c*]-selenophene (3k). The title compound was obtained in 65% yield after separation by column chromatography (silica gel, ethyl acetate–hexane 5:95) as a yellowish viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (2H, m, SeC*H*), 6.23 (1H, s, C=C*H*), 4.90 (1H, dq, J=1.5, 1 Hz, C=CH_2), 4.84–4.83 (1H, m, C=CH_2), 3.52 (1H, dd, J=10.5, 7 Hz, CH_2C*H*), 2.35 and 2.31 (2H, ABX system, J_{AB}=16.5 Hz, J_{AX}=10.5 Hz, J_{BX}=7 Hz, CH_2CH; long range couplings are also visible), 1.88 (3H, s, C^6CH_3), 1.77 (3H, dd, J=1.5, 1 Hz, =CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 146.3 (C), 140.4 (C), 140.2 (C), 136.4 (C), 123.3 (CH), 120.9 (CH), 120.0 (CH), 112.6 (CH_2), 46.3 (CH), 34.9 (CH_2), 23.3 (CH_3), 19.3 (CH_3); IR

(neat): 1644, 1434, 893, 847, 776 cm^{-1}; MS (EI): *m/e* 234, 235,236, 238, 240 (M^+, 1:1:3:7:1, 100%), 193, 194, 195, 197, 199 (1:1:3:7:1, 47%); HRMS (Elemental composition) calc. ($C_{12}H_{14}{}^{80}Se$) 238.0260, obs. 238.0256.

5.2.10. 4-Phenyl-1,4-dihydronaphtho[2,3-*c*]selenophene (4d). The title compound was obtained in 21% yield after separation by column chromatography (silica gel, ethyl acetate–hexane 5:95) as a yellow viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (1H, dtd, J=2.5, 1.5, 1 Hz, SeC*H*), 7.58 (1H, ddt, J=2.5, 1, 0.5 Hz, SeC*H*), 7.30–7.12 (9H, m, Ph, C^5H, C^6H, C^7H, C^8H), 5.21 (1H, s, Ph–C*H*), 3.90 (2H, s, $=CCH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 144.1 (C), 142.8 (C), 140.2 (C), 139.7 (C), 136.7 (C), 128.5 (CH), 128.4 (CH), 128.1 (CH), 126.6 (CH), 126.5 (CH), 126.4 (CH), 124.7 (CH), 122.8 (CH), 50.1 (CH), 34.0 (CH_2); MS (CI): *m/e* 307, 308, 309, 311, 313 (MH^+, 1:1:3:7:1 100%), 229, 230, 231, 233, 235 (1:1:3:7:1, 72.7%); HRMS (Elemental composition) calc. ($C_{18}H_{15}{}^{80}Se$) 311.0338, obs. 311.0327.

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References

1. Selected reviews: (a) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*, Stang, P. J., Diedrich, F., Eds.; VCH: Weinheim, 1995 Chapter 7. (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D. *Tetrahedron* **1996**, *52*, 6453 Tetrahedron Report No. 399. (c) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (d) Maier, M. E. *Synlett* **1995**, 13.
(e) Magnuse, P. *Tetrahedron* **1994**, *50*, 1397. (f) Nicolaou, K. C.; Dau, W. M.; Tsay, S. C.; Estevez, V. A. *Science* **1992**, *256*, 1172.
2. Nicolaou, K. C.; Pitsinos, E. N.; Theodorakis, E. A.; Wrasidio, W. *Chem. Biol.* **1994**, *1*, 57.
3. Braverman, S.; Segev, D. *J. Am. Chem. Soc.* **1974**, *96*, 1245.
4. Nicolaou, K. C.; Skokolas, F.; Malogres, P.; Zucuarello, G.; Schweger, E. J.; Toshima, K.; Wenderborn, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1272.
5. Nicolaou, K. C.; Wenderborn, S.; Maligres, P.; Isshiki, K.; Zein, N.; Ellestad, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 418.
6. (a) Kerwin, S. M. *Tetrahedron Lett.* **1994**, *35*, 1023. (b) McPhee, M. M.; Kerwin, S. M. *J. Org. Chem.* **1996**, *61*, 9385. (c) Sakai, Y.; Bando, Y.; Shishido, K.; Shibuya, M. *Tetrahedron Lett.* **1992**, *33*, 957. (d) Toshima, K.; Ohta, K.; Ohtsuka, A.; Matsumura, S.; Nakata, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1406. (e) Xie, G.; Morgan, A. R.; Lown, J. W. *Biorg. Med. Chem. Lett.* **1993**, *3*, 1565.
7. Maxam, A. M.; Gilbert, W. *Method Enzymol.* **1980**, *65*, 499.
8. (a) Braverman, S.; Reisman, D. *J. Am. Chem. Soc.* **1977**, *99*, 605. (b) Braverman, S.; Duar, Y. *J. Am. Chem. Soc.* **1983**, *105*, 1061. (c) Braverman, S.; Cohen, D.; Reisman, D.; Basch, H. *J. Am. Chem. Soc.* **1980**, *102*, 6556. (d) Braverman, S.; Freund, M. *Tetrahedron* **1990**, *46*, 5759.
9. (a) Braverman, S.; Duar, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5830. (b) Braverman, S.; Duar, Y. *Tetrahedron Lett.* **1978**, 1493. (c) Braverman, S.; Duar, Y.; Segev, D. *Tetrahedron Lett.* **1976**, 3181.
10. Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *Tetrahedron Lett.* **2000**, *41*, 2675.
11. Klayman, D. L.; Scott, G. T. *J. Am. Chem. Soc.* **1973**, *95*, 197.
12. Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1977**, *42*, 326.
13. (a) Garratt, P. J.; Neoh, S. B. *J. Org. Chem.* **1979**, *44*, 2667. (b) Garratt, P. J.; Neoh, S. B. *J. Am. Chem. Soc.* **1975**, *97*, 3255. (c) Cheng, Y. S. P.; Garratt, P. J.; Neoh, S. B.; Rumjamebe, V. M. *Isr. J. Chem.* **1985**, *26*, 101.
14. Iwai, I.; Ide, J. *J. Chem. Pharm. Bull. Jpn* **1964**, *12*, 1094.
15. Goldschmidt, Z.; Genizi, E.; Gottlieb, H. E. *J. Organomet. Chem.* **1999**, *81*, 587.
16. Kellog, R. M. *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Cheesman, G. W. H., Eds.; Pergamon: Oxford, 1984; Vol. 4, pp. 713–740.
17. (a) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315. (b) Bartlett, A. J.; Laird, T.; Ollis, W. D. *Chem. Commun.* **1974**, 496.
18. (a) Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, 3181. (b) Bell, T. W.; Bowes, C. M.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 3299.
19. Cheng, Y. S. P.; Dominguez, E.; Garratt, P. J.; Neoh, S. B. *Tetrahedron Lett.* **1978**, 691.
20. Fringualli, F.; Marino, G.; Taticchi, A. *J. Chem. Soc., Perkin Trans. 2* **1974**, 322.
21. Budzikiewicz, H.; Pesch, R. *Org. Mass. Spectrom.* **1974**, *9*, 861.
22. Hurley, A. L.; Walker, M. E.; Day, C. S. *J. Organomet. Chem.* **2000**, *598*, 150.
23. Doutheau, A.; Gorg, J.; Diab, J. *Tetrahedron* **1985**, *41*, 329.