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Synthesis and Biological Activities of Aryl Propargyl Sulfone

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A series of molecules containing monopropargyl sulfone or 1,2-bis-propargyl sulfone were synthesized. The cytotoxicity of these compounds against human carcinoma cells was also examined. This study indicated that the formation of a biradical intermediate is important to the potency of cytotoxicity.

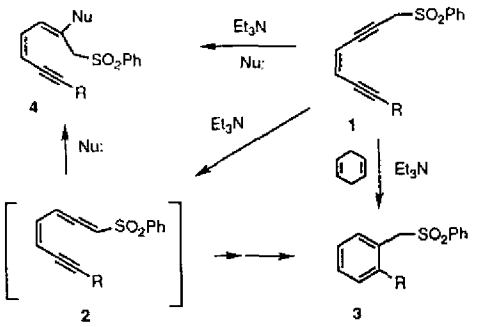
INTRODUCTION

The enediyne antitumor antibiotics, represented by neocarzinostatin,[1] esperamicins,[2] calicheamicins,[3] and dynemicins,[4] have attracted much attention due to their unusual molecular architecture and mode of activation which lead to the formation of benzenoid diradical and the cleavage of DNA. In addition to the synthesis of natural products, considerable efforts have been made toward the development of new simple and stable analogs that mimic natural products' chemistry and biological action.[5] In the previous study, Myers reported the cyclization of allene-eneynes to form α,3-dihydrotoluene.[6] Based on the Myers cyclization, various allene-eneyne containing molecules have been synthesized and tested for the existence of DNA cleaving properties.[7] Molecules containing (Z)-7-sulfonyl-3-hepten-1,5-diyne functionalities were reported to possess DNA cleavage and antitumor activities.[8] Particularly, compounds bearing an aromatic ring at C(3) and C(4) proved to be more active in this series.[8b,8c] Two possible pathways of DNA cleavage activities of these compounds were proposed either by the formation of biradical intermediate or by the alkylation pathway (Scheme I). In order to better understand the mode of the biological actions in this series of compounds caused either by an alkylation process or *via* a biradical intermediate, series compounds containing mono-propargylsulfone or 1,2-bis-propargylsulfone were synthesized and their cytotoxicity against human tumor cell lines is reported.

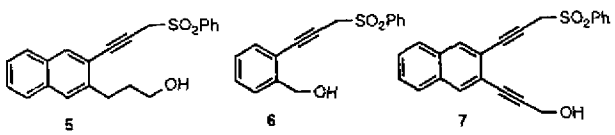
RESULTS AND DISCUSSION

Compounds **5** and **6**, the analogs of **7**,[8b] were designed by removing the acetylene portion at C(1)-C(2). Thus, compounds **5** and **6** could cleave double-stranded DNA only

Scheme I

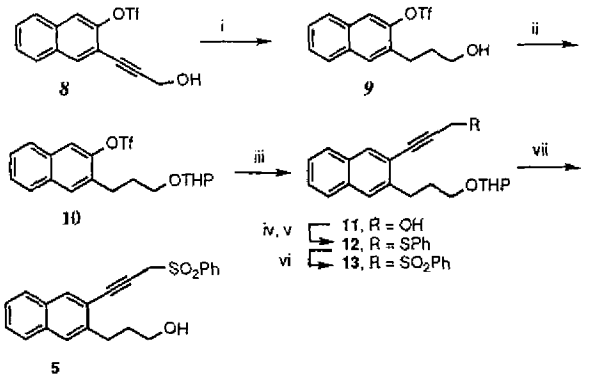


through the alkylation pathway. The synthesis of compound **5** is outlined in Scheme II. Hydrogenation of **8**[8b] using palladium on charcol as catalyst afforded **9** in 31% yield. Protection of the hydroxyl group with 3,4-dihydro-2H-pyrane under acidic condition gave **10** in 41% yield. Palladium catalyzed coupling reaction of triflate **10** with propargyl alcohol gave **11** in 35% yield. Alcohol **11** was converted to sulfide **12** in 24% yield by the reaction of alcohol **11** with methanesulfonyl chloride to give the corresponding mesylate, followed by the reaction of mesylate with thiophenol under alkaline condition. Oxidation of sulfide **12** with mCPBA gave sulfone **13** in 46% yield. Finally, acid-catalyzed deprotection of **13** gave the desired product **5** in 80% yield.



The attempt for the preparation of **6** is outlined in Scheme III. The commercially available 2-iodobenzyl alcohol (**14**) was converted to the tetrahydropyranyl ether **15** in 81% yield, and was followed by palladium catalyzed cou-

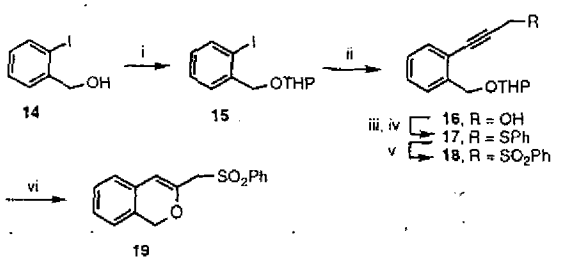
Scheme II



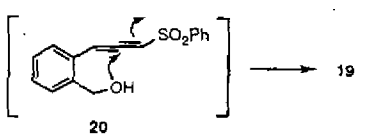
Reagents and conditions: i) H_2, (35 psi) Pd/C, methanol, 31%; ii) 3,4-dihydro-2H-pyrane, p-toluenesulfonic acid, CH_2Cl_2, 7 h, 41%; iii) $HCCCH_2OH$, $Pd(PPh_3)_4$, CuI, $BuNH_2$, Et_2O, 5 h, 35%; iv) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 40 min; v) PhSH, NaOH, THF-H_2O, 2 h, 31%; vi) mCPBA, CH_2Cl_2, 1 h, 46%; vii) camphor sulfonic acid, methanol, 2 h, 80%.

pling reaction with propargyl alcohol to give **16** in 77% yield. Alcohol **16** was then converted to sulfide **17** (51%) using the above described prodedures. Finally, oxidation of **17** with mCPBA gave sulfone **20** in 82% yield. The removal of the protecting group using camphorsulfonic acid in methanol gave compound **19** in 92% yield. The spectra data strongly suggested the indicated structure mainly by the lack of hydroxyl absorption in the IR spectrum and ^1H NMR showed a singlet at 5.81 ppm indicating the existence of benzylic vinyl proton. We believe that the formation of **19** is caused by the isomerization of propargyl sulfone to allenyl sulfone **20**, followed by intramolecular nucleophilic addition by the hydroxyl group.

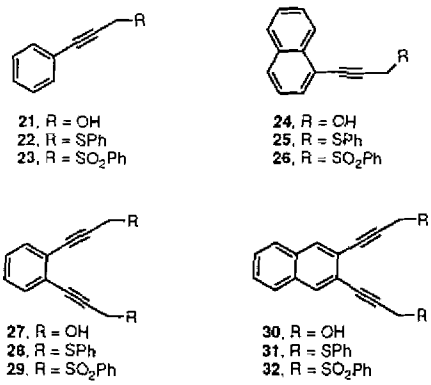
Scheme III



Reagents and conditions: i) 2,3-dihydro-2H-pyrane, p-toluenesulfonic acid, CH_2Cl_2, 81%; ii) $HCCCH_2OH$, $Pd(PPh_3)_4$, CuI, $BuNH_2$, Et_2O, 77%; iii) CH_3SO_2Cl, Et_3N, CH_2Cl_2; iv) PhSH, NaOH, THF-H_2O, 51%; v) mCPBA, CH_2Cl_2, 82%; vi) camphor sulfonic acid, methanol, 92%



Two simple aryl monopropargyl sulfone analogs **23** and **26** were also prepared. The synthesis of these two compounds is straight forward. Starting from iodobenzene and 1-iodonaphthylene and following the standard procedure, alcohols **21** and **24** were obtained in 94% and 95% yield, sulfides **22** and **25** were obtained in 73% and 72% yield and sulfones **23** and **26** were obtained in 79% and 80% yield, respectively. Compounds **29** and **32** were prepared from bis-propargyl alcohols **27** and **30**,[9] respectively. Again, following the standard procedures, alcohols **27** and **30** were converted to bis-sulfides **28** and **31** in 40% and 39% yields, respectively. Oxidation of **28** and **31** gave **29** and **32** in 45% and 43% yields, respectively.



Compounds **5**, **19**, **23**, **26**, **29** and **32** were evaluated *in vitro* against four tumor cell lines (Colo 205, HA22T, SK-BR-3 and Molt-4). For each compound, dose-response curves for each cell line were measured with five different drug concentrations and the concentration causing 50% cell growth inhibition (IC_{50}) compared with the control was calculated.[10] The results are summarized in Table 1. Compound **19** lacking propargyl sulfone moiety exhibited no cytotoxicity at all. Compared to compound **7**, the monopropargyl sulfone analogue **5** showed about ten times lower inhibition activity and the bis-propargyl sulfone analogs **29** and **32** bearing enediyne moiety showed about equal activity against the growth of leukemia (Molt-4), colon (colo 205), epidermoid (HA22T) and melanoma (SK-BR-3) cancer cell lines.

In conclusion, propargyl sulfone moiety is essential for cytotoxicity against human tumor cell lines. Particu-

Table 1. Inhibition of *in vitro* Human Tumor Cell Growth by **15**, **22** and **25** (IC_{50}, μg/mL)[a]

Compound	Colo 205	HepG2	HA22T	SK-BP-3	Molt-4
15	5.63	5.40	---	7.18	0.78
22	57.32	---	65.91	70.00	9.45
25	8.44	---	4.62	5.39	1.96

[a] Relative potency of growth inhibition of cancer cell line was graded by concentration required for 50% inhibition.

larly, molecules that contain (Z)-7-sulfonyl-3-hepten-1,5-diyne functionalities, such as compounds **29** and **32**, show higher potency of cytotoxicity.

EXPERIMENTAL SECTION

Melting points were determined on a Yanaco MP apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Varian XL-200E or Varian Unity Plus 400 spectrometer. All chemical shifts are reported in ppm using tetramethylsilane as internal standard. Elemental analyses were performed on a Hereus CHNO rapid analyser. Low resolution mass spectra were recorded on a JOEL SX-102A and high resolution spectra were recorded on a JOEL JMX-HX 110 spectrometer.

3-(3-Hydroxypropyl)-2-trifluoromethanesulfonyloxynaphthylene (9)

The solution of **8** (2.94 g, 8.9 mmol) in methanol (20 mL) containg Pd/C (1.42 g) was stirred under hydrogen pressure (35 psi) for 6 h. The solid was then filtered off and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexane as eluent) to give **9** (0.94 g, 32%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81-7.73 (m, 4H), 7.62-7.31 (m, 2H), 3.68 (t, 2H, J = 6.4 Hz), 2.85 (t, 2H, J = 7.2 Hz), 2.00-1.89 (m, 2H), 1.77 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.3, 133.6, 132.0, 130.0, 127.9, 127.5, 127.3, 127.2, 126.4, 125.9, 125.1, 62.1, 34.0, 32.1; MS (EI) m/z 334 (M^+, 65), 141 (100); HRMS calcd for $C_{14}H_{13}F_3O_4S$ 334.0487, found 334.0476.

3-(3-(2-Tetrahydropyranyl)oxypropyl)-2-(trifluoromethanesulfonyloxy)naphthylene (10)

2,3-Dihydro-2H-pyrane (0.25 g, 3.0 mmol) was added to a stirred solution of **9** (0.94 g, 2.8 mmol) in CH_2Cl_2 (10 mL), followed by the addition of p-toluene sulfonic acid (0.71 g, 2.8 mmol). The resulting solution was stirred for 7 h, quenched with saturated aqueous Na_2CO_3 solution and extracted with ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by flash column chromatography to give **10** (0.48 g, 41%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84-7.75 (m, 4H), 7.57-7.50 (m, 2H), 4.61 (t, 1H, J = 3.2 Hz), 3.92-3.79 (m, 2H), 3.56-3.42 (m, 2H), 3.02-2.94 (m, 2H), 2.11-1.97 (m, 2H), 1.88-1.53 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.5, 133.6, 132.0, 127.8, 127.6, 127.3, 126.4, 125.8, 125.0, 98.9, 66.8, 62.3, 32.6, 31.2, 30.8, 25.5, 19.7. MS (EI) m/z 418 (M^+, 0.2), 270 (58), 168 (100); HRMS calcd for $C_{19}H_{21}F_3O_5S$ 418.1062, found 418.1065.

3-(3-(2-Tetrahydropyranyl)oxypropyl)-2-(3-hydroxypropynyl)naphthylene (11)

A solution of propargyl alcohol (0.087 mL, 1.5 mmol) and $nBuNH_2$ (0.34 g, 4.7 mmol) in ether (5 mL) was added to a stirred solution of **10** (0.48 g, 1.14 mmol) in ether (15 mL) containing CuI (0.05 g, 0.26 mmol) and $Pd(PPh_3)_4$ (0.066 g, 0.06 mmol). The resulting brown suspension was stirred for 5 h and worked-up as usual to give **11** (0.13 g, 35%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.75-7.70 (m, 2H), 7.63 (s, 1H), 4.63 (t, 1H, J = 3.0 Hz), 4.55 (s, 2H), 3.98-3.72 (m, 2H), 3.60-3.46 (m, 2H), 3.07-2.95 (m, 2H), 2.72 (bs, 1H), 2.13-2.00 (m, 2H), 1.83-1.50 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.4, 133.1, 132.1, 131.5, 127.3, 127.1, 126.9, 126.7, 125.7, 120.7, 99.1, 91.3, 84.4, 67.3, 62.6, 51.5, 31.6, 30.6, 25.4, 19.7.

3-(3-(2-Tetrahydropyranyl)oxypropyl)-2-(3-phenylthiopropynyl)naphthylene (12)

Methanesulfonyl chloride (0.04 mL, 0.5 mmol) was added to a solution of **11** (0.13 g, 0.4 mmol) in CH_2Cl_2 (2 mL), followed by the addition of Et_3N (0.08 mL, 0.6 mmol). The resulting reaction mixture was stirred for 30 min, quenched with 10% aqueous hydrogen chloride solution and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and were then concentrated. The residue was redesolved in THF (0.5 mL) and added to the solution of thiophenol (0.08 mL, 0.8 mmol) in aqueous THF (2 mL) containing NaOH (0.03 g, 0.8 mmol). The resulting solution was stirred for 3 h and quenched with 10% aqueous NaOH solution. The reaction mixture was extracted with ethyl acetate. The orgaic extracts were dried over $MgSO_4$ and were then concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexane as eluent) to give **12** (0.04 g, 24%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.74-7.70 (m, 2H), 7.61 (s, 1H), 7.55-7.25 (m, 7H), 4.59 (t, 1H, J = 3.0 Hz), 3.94 (s, 2H), 3.90-3.70 (m, 2H), 3.55-3.32 (m, 2H), 2.90 (dd, 2H, J = 8.8, 6.5 Hz), 2.02-1.50 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.3, 135.3, 133.1, 132.4, 131.5, 130.1, 129.0, 127.23, 127.18, 126.9, 126.8, 126.6, 125.6, 121.0, 98.9, 88.6, 82.4, 66.9, 62.3, 31.2, 30.8, 30.2, 25.5, 23.8, 19.7; MS (EI) m/z 416 (M^+, 12), 307 (33), 205 (100); HRMS calcd for $C_{27}H_{28}O_2S$ 416.1811, found 416.1816.

3-(3-(2-Tetrahydropyranyl)oxypropyl)-2-(3-phenylsulfonylpropynyl)naphthylene (13)

mCPBA (0.04 g, 0.25 mmol) was added to a solution

of **12** (0.04 g, 0.096 mmol) in CH_2Cl_2. The reaction mixture was stirred at 25 °C for 30 min, quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and were then concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexane as eluent) to give **29** (0.02 g, 46%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, J = 7.1 Hz), 7.86 (s, 1H), 7.74-7.68 (m, 3H), 7.62-7.57 (m, 3H), 7.49-7.41 (m, 2H), 4.57 (t, 1H, J = 2.6 Hz), 4.29 (s, 2H), 3.90-3.85 (m, 1H), 3.78-3.72 (m, 1H), 3.51-3.48 (m, 1H), 3.41-3.35 (m, 1H), 2.88-2.83 (m, 2H), 1.95-1.50 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 138.0, 134.2, 133.4, 133.2, 131.3, 129.2, 128.9, 127.4, 127.3, 127.1, 127.0, 125.9, 119.7, 99.0, 86.7, 79.9, 66.9, 62.5, 49.7, 31.1, 30.8, 30.3, 25.5, 19.8; MS (EI) *m/z* 448 (M^+, 3), 205 (100); HRMS calcd for $C_{27}H_{28}O_4S$ 448.1709, found 448.1688.

3-(3-Hydroxypropyl)-2-(3-phenylsulfonylpropynyl)-naphthylene (5)

Camphorsulfonic acid (0.011 g, 0.05 mmol) was added to a stirred solution of **13** (0.018 g, 0.04 mmol) in methanol (1 mL). The resulting solution was stirred for 10 min and was then concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexane as eluent) to give **5** (0.012 g, 80%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H), 7.87 (s, 1H), 7.77-7.42 (m, 8H), 4.29 (s, 2H), 3.71 (t, 2H, J = 6.2 Hz), 2.95 (dd, 2H, J = 8.0, 5.6 Hz), 1.98-1.87 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6, 138.1, 134.3, 133.5, 133.1, 131.4, 129.3, 128.8, 127.4, 127.2, 126.0, 119.6, 86.8, 79.6, 62.3, 49.7, 34.0, 31.1; MS (EI) *m/z* 364 (M^+, 8), 179 (100); HRMS calcd for $C_{22}H_{20}O_3S$ 364.1134, found 364.1124.

2-Tetrahydropyranyloxymethyl-1-iodobenzene (15)

2,3-Dihydro-2H-pyrane (3.78 g, 45 mmol) was added to a stirred solution of **14** (10.0 g, 43 mmol) in CH_2Cl_2 (80 mL), followed by the addition of *p*-toluene sulfonic acid (1.07 g, 4.27 mmol). The resulting solution was stirred for 7 h and quenched with saturated aqueous Na_2CO_3 solution and extracted with ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by flash column chromatography to give **15** (11.0 g, 81%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 7.7, 1.1 Hz), 7.48 (dd, 1H, J = 7.7, 1.8 Hz), 7.34 (td, 1H, J = 7.4, 1.1 Hz), 6.94 (td, 1H, J = 8.0, 1.1 Hz), 4.80-4.72 (m, 2H), 4.48 (d, 1H, J = 13.1 Hz), 3.99-3.87 (m, 1H), 3.62-3.53 (m, 1H), 1.92-1.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 139.0, 128.9, 128.6, 128.0, 98.3, 97.6, 72.8, 62.0, 30.4, 25.3, 19.2.

2-Tetrahydropyranyloxymethyl-1-(3-hydroxypropynyl)-benzene (16)

Starting from **15** (2.0 g, 6.2 mmol) and following the same procedure as for the preparation of **11** gave **16** (1.16 g, 77%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50-7.19 (m, 4H), 4.91 (d, 1H, J = 12.5 Hz), 4.78 (t, 1H, J = 3.0 Hz), 4.69 (d, 1H, J = 12.5 Hz), 4.56 (s, 2H), 4.01-3.89 (m, 1H), 3.63-3.54 (m, 1H), 2.67 (bs, 1H), 1.92-1.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 131.8, 128.6, 128.1, 127.3, 121.6, 98.1, 92.0, 83.5, 67.2, 62.3, 51.5, 30.6, 25.4, 19.3; MS (EI) *m/z* 217 (100); HRMS calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1256.

2-Tetrahydropyranyloxymethyl-1-(3-phenylthio-propynyl)benzene (17)

Starting from **16** (1.16 g, 4.7 mmol) and following the same procedure as for the preparation of **12** gave **17** (0.81 g, 51%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.15 (m, 9H), 4.81 (d, 1H, J = 12.9 Hz), 4.70 (t, 1H, J = 3.3 Hz), 4.57 (d, 1H, J = 12.9 Hz), 3.96-3.90 (m, 1H), 3.88 (s, 2H), 3.59-3.51 (m, 1H), 1.90-1.51 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.5, 135.2, 132.2, 130.2, 128.9, 128.3, 127.2, 126.9, 126.8, 121.3, 98.4, 89.7, 81.2, 67.2, 62.1, 30.5, 25.5, 23.7, 19.4; MS (EI) *m/z* 338 (M^+, 0.6), 236 (100); HRMS calcd for $C_{21}H_{22}O_2S$ 338.1342, found 338.1311.

2-Tetrahydropyranyloxymethyl-1-(3-phenylsulfonyl-propynyl)benzene (18)

Starting from **17** (0.25 g, 0.7 mmol) and following the same procedure as for the preparation of **13** gave **18** (0.21 g, 82%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, 2H, J = 7.1 Hz), 7.69-7.48 (m, 4H), 7.39-7.16 (m, 3H), 4.77 (d, 1H, J = 13.1 Hz), 4.70 (t, 1H, J = 3.3 Hz), 4.53 (d, 1H, J = 13.1 Hz), 4.24 (s, 2H), 3.93-3.84 (m, 1H), 3.59-3.50 (m, 1H), 1.89-1.51 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.8, 137.8, 134.1, 133.7, 132.3, 129.8, 129.1, 128.9, 128.7, 127.2, 127.0, 119.8, 98.3, 85.3, 81.1, 66.8, 62.0, 49.4, 30.4, 25.3, 19.3; MS (EI) *m/z* 369 (M^+-H, 0.2), 269 (19), 128 (100); HRMS calcd for $C_{21}H_{22}O_4S$ 370.1240, found 370.1229.

Benzopyrane (19)

Starting from **18** (0.13 g, 0.35 mmol) and following the same procedure as for the preparation of **5** gave **19** (0.92 g, 92%) as a white solid. mp 131.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, 2H, J = 8.4 Hz), 7.66 (t, 1H, J = 7.5 Hz), 7.55 (t, 2H, J = 7.3 Hz), 7.18 (quintet, 2H, J = 7.3 Hz), 6.94 (d, 2H, J = 6.8 Hz), 6.91 (d, 1H, J = 7.0 Hz), 5.81 (s, 1H),

4.85 (s, 2H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 138.6, 133.9, 130.2, 129.0, 128.7, 128.3, 127.4, 127.3, 123.8, 123.5, 108.7, 69.0, 61.5; Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.92. Found: C, 66.95; H, 5.19.

3-Phenyl-2-propyn-1-ol (21)

Propargyl alcohol (2.1 g, 10 mmol), $nBuNH_2$ (3.0 g, 41 mmol), CuI (0.36 g, 0.19 mmol) and $Pd(PPh_3)_4$ (0.23 g, 0.19 mmol) were sequentially added to a stirred solution of iodobenzene (2.04 g, 10 mmol) in ether (100 mL). The resulting suspension was degased and stirred for 6 h at 25 °C. The reaction mixture was quenched with 10% aqueous hydrogen chloride solution and extracted with ethyl acetae. The combined organic extracts were dried over $MgSO_4$ and were then concentrated. The residue was purified by flash column chromatography to give **21** (1.24 g, 9.4 mmol) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H), 7.31-7.27 (m, 3H), 4.75 (bs, 1H), 4.49 (s, 2H); MS (EI) *m/z* 132 (M^+, 67), 131 (100); HRMS calcd for C_9H_8O 132.0575, found 132.0580.

1-Phenyl-3-phenylthio-1-propyne (22)

Starting from **21** (1.0 g, 7.6 mmol) and following the same procedure as for the preparation of **12** gave **22** (1.25 g, 73%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57-7.21 (m, 10H), 3.85 (s, 2H); MS (EI) *m/z* 224 (M^+, 7), 115 (89), 109 (100).

1-Phenyl-3-phenylsulfonyl-1-propyne (23)

Starting from **22** (0.5 g, 2.2 mmol) and following the same procedure as for the preparation of **13** gave **23** (0.45 g, 79%) as a white solid. mp 137 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (dd, 2H, *J* = 7.0, 1.5 Hz), 7.74-7.26 (m, 8H), 4.19 (s, 2H). Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72. Found: C, 70.25; H, 4.71.

3-(1-Naphthyl)-2-propyn-1-ol (24)

Starting from 1-iodonaphthylene (2.47 g, 10 mmol) following the same procedure as for the preparation of **21** gave **24** (1.73 g, 95%) as a white solid. mp 49.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32-8.30 (m, 1H), 7.76-7.71 (m, 2H), 7.62-7.60 (m, 1H), 7.51-7.40 (m, 2H), 7.32-7.28 (m, 1H), 4.61 (s, 2H), 3.25 (bs, 1H); MS (EI) *m/z* 182 (M^+, 66), 152 (100); Anal. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.35; H, 5.63.

1-(3-Phenylthiopropynyl)naphthylene (25)

Starting from **24** (1.5 g, 8.2 mmol) following the same procedure as for the preparation of **12** gave **25** (1.62 g, 72%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.04 (m, 1H), 7.77-7.72 (m, 2H), 7.57-7.53 (m, 3H), 7.45-7.42 (m, 2H), 7.35-7.29 (m, 3H), 7.26-7.24 (m, 1H), 3.96 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.0, 133.3, 133.0, 130.6, 130.3, 128.9, 128.6, 128.1, 126.9, 126.2, 126.1, 125.0, 120.5, 90.1, 81.6, 23.9; MS (EI) *m/z* 274 (M^+, 47), 165 (100); HRMS calcd for $C_{19}H_{14}S$ 274.0817, found 274.0803.

1-(3-Phenylsulfonylpropynyl)naphthylene (26)

Starting from **25** (0.7 g, 2.7 mmol) and following the same procedure as for the preparation of **13** gave **26** (0.66 g, 80%) as a white solid. mp 101.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 8.03-8.00 (m, 1H), 7.85-7.83 (m, 2H), 7.72-7.68 (m, 1H), 7.60-7.56 (m, 3H), 7.52-7.49 (m, 2H), 7.42-7.26 (m, 1H), 4.37 (s, 2H); Anal. Calcd for $C_{19}H_{14}SO_2$: C, 74.53; H, 4.61. Found: C, 74.22; H, 4.76.

1,2-Bis-(3-hydroxy-1-propynyl)benzene (27)

36% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 2H, *J* = 5.6, 3.3 Hz), 7.26 (dd, 2H, *J* = 5.6, 3.3 Hz), 4.55 (s, 4H), 2.50 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 128.2, 125.4, 91.7, 84.6, 51.8. MS (EI) *m/z* 186 (M^+, 22), 139 (100); HRMS calcd for $C_{12}H_{10}O_2$ 186.0681, found 186.0680.

1,2-Bis-(3-phenylthiopropynyl)benzene (28)

Starting from **27** (0.32 g, 1.73 mmol) and following the same procedure as for the preparation of **12** gave **28** (0.26 g, 40%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.48 (m, 4H), 7.33-7.19 (m, 10H), 3.80 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.5, 131.9, 130.0, 128.9, 127.8, 126.7, 125.6, 89.3, 82.1, 23.7; MS (EI) *m/z* 370 (M^+, 2), 260 (100); HRMS calcd for $C_{24}H_{18}S_2$ 370.0851, found 370.0847.

1,2-Bis-(3-phenylsulfonylpropynyl)benzene (29)

Starting from **28** (0.15 g, 0.4 mmol) and following the same procedure as for the preparation of **13** gave **29** (78 mg, 45%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.08-7.96 (m, 4H), 7.72-7.52 (m, 6H), 7.50-7.25 (m, 4H), 4.22 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0, 134.1, 131.9, 129.1, 128.9, 128.7, 124.8, 85.5, 81.2, 49.5; MS (EI) *m/z* 434 (M^+, 9), 293 (59), 152 (100); HRMS calcd for $C_{24}H_{18}O_2S_4$ 434.0647, found 434.0627.

2,3-Bis-(3-hydroxy-1-propynyl)naphthalene (30)

52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.75 (dd, 2H, *J* = 6.2, 3.3 Hz), 7.49 (dd, 2H, *J* = 6.2, 3.3 Hz), 4.59 (s, 4H), 1.84 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 127.6, 127.4, 121.8, 91.3, 84.7, 51.8; MS (EI) *m/z* 236 (M^+, 51), 139 (100); HRMS calcd for $C_{16}H_{12}O_2$ 236.0837, found 236.0842.

2,3-Bis-(3-phenylthiopropynyl)naphthalene (31)

Starting from **30** (0.15 g, 0.64 mmol) and following the same procedure as for the preparation of **12** gave **31** (0.10 g, 39%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.73-7.69 (m, 2H), 7.55-7.43 (m, 6H), 7.36-7.23 (m, 6H), 3.84 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.6, 132.2, 131.9, 130.0, 128.9, 127.5, 127.1, 126.7, 122.1, 88.8, 82.3, 23.8; MS (EI) *m/z* 420 (M^+, 2), 421 (M^++1, 27), 310 (100); HRMS calcd for $C_{28}H_{20}S_2$ 420.1008, found 420.1007.

2,3-Bis-(3-phenylsulfonylpropynyl)naphthalene (32)

Starting from **22** (0.10 g, 0.24 mmol) and following the same procedure as for the preparation of **13** gave **32** (50 mg, 45%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05-8.03 (m, 4H), 7.87 (s, 2H), 7.76-7.65 (m, 4H), 7.58-7.51 (m, 6H), 4.26 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 134.1, 132.4, 132.3, 129.1, 129.0, 127.8, 127.7, 120.9, 85.7, 80.7, 49.6.

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REFERENCES

1. (a) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Fuvihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. (b) Hasuda, K.; Kobayashi, H.; Kuroiwa, T.; Aoki, K.; Taniguchi, S.; Baba, T. *Jpn. J. Cancer Res.* **1989**, *80*, 283. (c) Maeda, H.; Ueda, M.; Morinaga, T.; Matsumoto, T. *J. Med. Chem.* **1985**, *28*, 455. (d) Kohgo, Y.; Kondo, H.; Kato, J.; Sasaki, K.; Tsushima, N.; Nishisato, T.; Hirayama, M.; Fujikawa, K. *Jpn. J. Cancer Res.* **1990**, *81*, 91.
2. (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Okuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishman, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.
3. (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S,; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. (c) Wallace, R. E.; Hinman, L. H.; Hamann, P.; Upeslacis, J.; Durr, F. E. *Proc. Amer. Assoc. Cancer Res.* **1990**, *31*, 285.
4. Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449.
5. (a) For a recent review of enediyne chemistry see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497. (c) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172.
6. (a) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130. (b) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (c) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369.
7. (a) Toshima, K.; Kazumi, O.; Ohashi, A.; Nakamura, T.; Nakata, M.; Tatsuta, K.; Matsumura, S. *J. Am. Chem. Soc.* **1995**, *117*, 4822. (b) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825. (c) Saito, I.; Nagata, R.; Yamanaka, H.; Okazaki, E. *Tetrahedron Lett.* **1989**, *30*, 4995. (d) Saito, I.; Nagata, R.; Yamanaka, H.; Murahashi, E. *Tetrahedron Lett.* **1990**, *31*, 2907. (e) Shibuya, M.; Sakai, Y.; Bando, Y.; Shishido, K. *Tetrahedron Lett.* **1992**, *33*, 957. (f) Morokuma, K.; Koga, N. *J. Am. Chem. Soc.* **1991**, *113*, 1907. (g) Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688.
8. (a) Wu, M.-J.; Lin, C.-F.; Wu, J.-S.; Chen, H.-T. *Tetrahedron Lett.* **1994**, *35*, 1879. (b) Wu, M.-J.; Lin, C.-F.; Ong, C.-W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 675. (c) Wu, M.-J.; Lin, C.-F.; Chen, H.-T.; Duh, T.-H.; Wang, S.-S.; Hsu, S.-C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2183. (d) Dai, W.-M.; Fong, K. C.; Danjo, H.; Nishimoto, S.-i. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 779. (e) Lin, C.-F.; Wu, M.-J. *J. Org. Chem.* **1997**, *62*, 4546.
9. Compound **27** and **30** were obtained as byproducts from the palladium catalyzed coupling reaction of 1,2-diiodobenzene and 1,2-bis-trifluoromethanesulfonyloxybenzene with propargyl alcohol in 36% and 52% yield, respectively.
10. Carmichael, J.; Graff, D. E.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936.