Preparation of New Anti-Tubulin Ligands through a Dual-Mode, Addition−Elimination Reaction to a Bromo-Substituted α,β-Unsaturated Sulfoxide

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Introduction

The heralded success of the natural product combretastatin A-4 (CA-4)[1] as an antimitotic agent and its prodrug disodium phosphate salt construct (CA-4P) (Figure 1) as a tumor vasculature targeting agent[2] has led to the preparation of a diverse set of anti-tubulin ligands designed to mimic CA-4 (Figure 2).[3] Our recent discovery[11] of a synthetic benzo[*b*]thiophene ligand that demonstrates strong antimitotic activity, coupled with the activity of benzo[*b*]thiophene analogues as selective estrogen receptor modulators (SERMs)[10] and the discovery of diaryl ether analogues of CA-4[12,13] (Figure 3), provided incentive for our current investigation of the preparation of new anti-tubulin ligands **1** and **2** by 1,4 and 1,2 addition−elimination reactions to a bromo-substituted, α,β-unsaturated sulfoxide.

We were intrigued by the idea of replacing the carbonyl group of the benzo[*b*]thiophene antimitotic ligand (Figure 3) with an oxygen atom in order to study the effects of substitution at the 3-position. This oxygen variation also serves as a further evaluation of the apparent require-

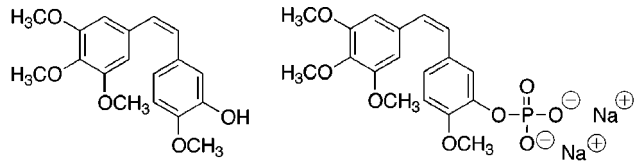

Figure 1. Combretastatin A-4 (CA-4) and the CA-4 Prodrug.

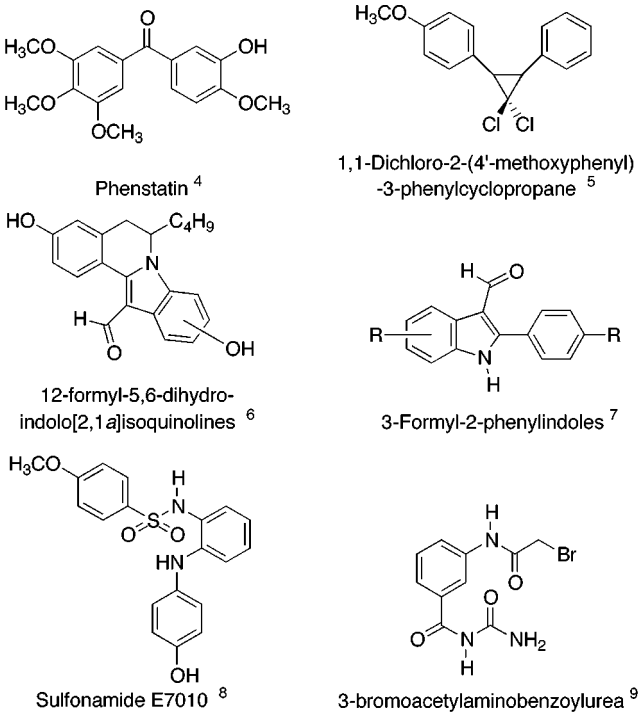

Figure 2. Representative synthetic anti-tubulin polymerization inhibitors.

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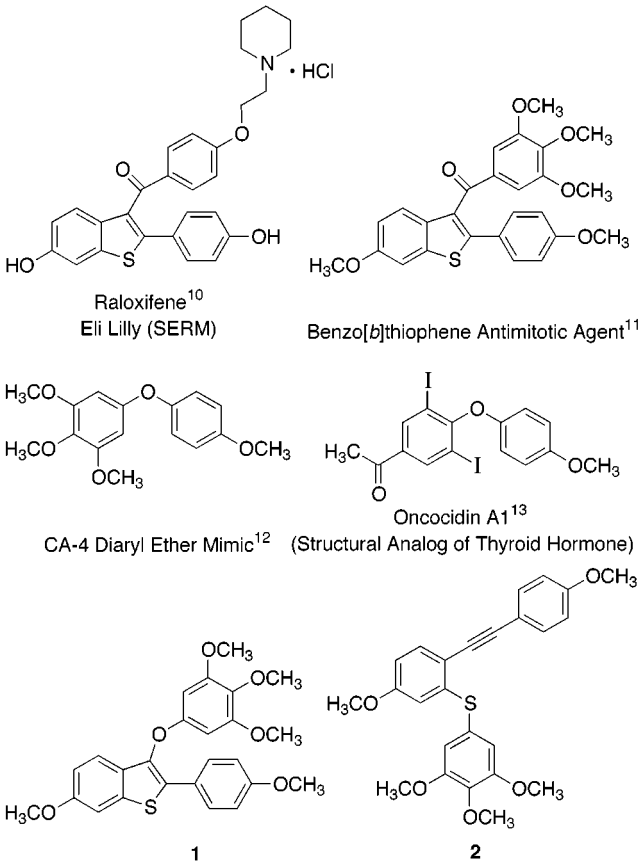
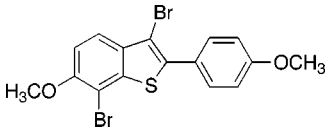


Figure 3. Structural models for the preparation of analogues **1** and **2**.

ment of sp^2 hybridization of bridge atoms between the two aryl rings, which seems important for compounds to display maximal affinity for the colchicine binding site on β-tubulin.

Results and Discussion

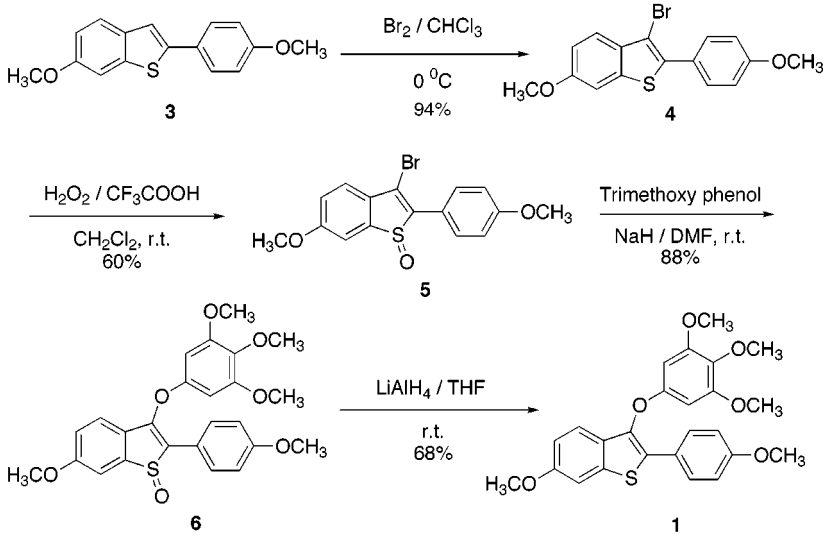
The synthetic strategy shown in Scheme 1 (cf. ref 10) was employed for the preparation of the new aryloxy analogue **1** designed for tubulin binding. Although treatment of thiophene **3** with Br_2 has been reported to yield thiophene **4** in chloroform at 60 °C,[10a] in our hands primarily a dibrominated product (carbon positions 3 and 7) was obtained under these conditions. We therefore



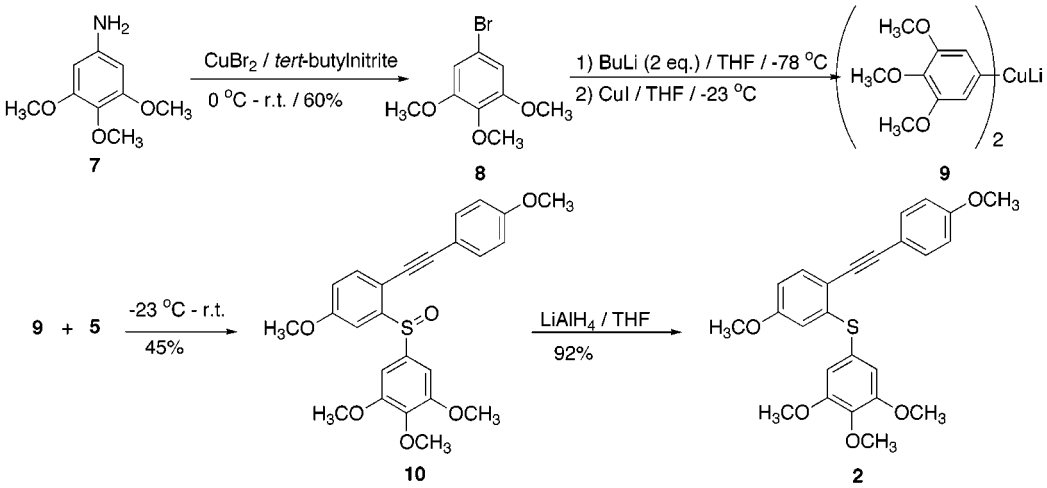
evaluated the reaction both at room temperature and at 0 °C. The reaction was followed by GC, and dibromination was observed even at room temperature. However, at 0 °C, a 90−94% yield of the monobrominated product **4** was obtained. The difference in results could be caused by our scaling down the reaction from 28 g[10a] to 10.5 g. The monobromide **4** was oxidized with hydrogen peroxide in the presence of trifluoroacetic acid to yield sulfoxide **5**.[10a] Use of excess hydrogen peroxide resulted in formation of the corresponding sulfone. The bromosulfoxide **5** upon treatment with 3,4,5-trimethoxyphenoxide, formed from the corresponding phenol with NaH, gave the aryloxy-substituted sulfoxide **6**, which was subsequently reduced with lithium aluminum hydride to afford the desired diaryl ether **1**.

Interestingly, upon treatment with 3,4,5-trimethoxyphenyl cuprate, the bromo-sulfoxide **5** underwent 1,2-addition (rather than the anticipated 1,4 addition−elimination) followed by ring opening and concomitant elimination of bromide to form an alkyne derivative (**10**, Scheme 2). To our knowledge, this is the first observation of this type of 1,2-addition−ring-opening reaction in a bromobenzo[*b*]thiophene sulfoxide. Following treatment with $LiAlH_4$, the corresponding sulfide analogue **2** was obtained in good yield. Although spectroscopic analysis strongly supported the structure assigned as alkyne **10**, we obtained an X-ray crystallographic analysis in order to confirm the structure. Crystals of **10** suitable for X-ray diffraction were obtained from a solution of hexanes/ethyl acetate (60/40). Energy minimization[14] of **10** predicts a very similar structure as a low energy conformer. For the formation of alkyne **10**, we propose a mechanism that involves initial attack of the cuprate at the sulfoxide center to form a tetrahedral intermediate (Figure 4). Collapse of the tetrahedral intermediate forces the five-membered ring of the benzo[*b*]thiophene skeleton to open, allowing the formation of a triple bond upon loss of the

Scheme 1. Synthesis of Diaryl Ether 1 by a 1,4-Addition−Elimination Reaction



Scheme 2. Synthesis of Sulfide 2 by a 1,2-Addition−Elimination Ring-Opening Reaction



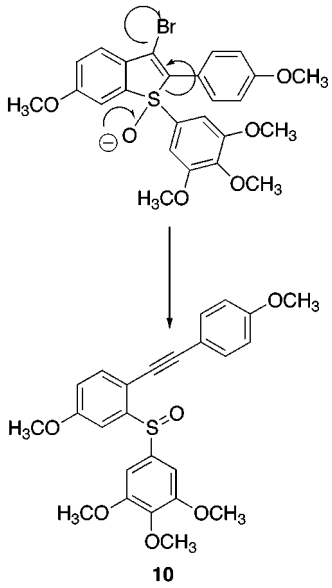


Figure 4. Proposed mechanism for the formation of alkyne **10**.

bromine atom. This dual mode of 1,2 versus 1,4 attack may be rationalized by considering the favorable interaction of the hard nucleophilic oxygen anion with the hard carbon terminus of the α,β-unsaturated sulfoxide compared to the interaction of the relatively soft cuprate nucleophile with the soft sulfoxide moiety.[15]

Biological Evaluation. The four new compounds **1**, **2**, **6**, and **10** were evaluated for their in vitro cytotoxicity against human cancer cell lines (Table 1).[16] Aryloxybenzo[*b*]thiophene **1** displays the most pronouced cytotoxicity of the group. This compound was further evaluated against the NCI 60 cell line panel,[17] in which it demonstrated an average $GI_{50} = 4.90 \times 10^{-7}$ M. For comparison, CA-4 showed an average $GI_{50} = 2.96 \times 10^{-8}$ M against the same NCI cell line panel. Aryl ether ligand **1** was further evaluated for its ability to inhibit tubulin polymerization[18] and was found to have an $IC_{50} = 0.88 \pm 0.1$ (S.D.) μM, which qualifies this ligand as a strong inhibitor. In contemporaneous experiments, CA-4 yielded an IC_{50} value of 1.0 ± 0.05 μM.

Table 1. In Vitro Human Cancer Cell Line Study of Benzo[*b*]thiophene Analogues 1 and 6 and Alkynes 2 and 10[a]

	GI_{50} (μg/mL)[b]					
no.	BXPC-3 pancreas	SK-N-SH neuroblast	SW1736 thyroid	NCI-H460 lung-NSC	FADU pharynx	DU-145 prostate
1	0.23	0.063	0.73	0.31	0.098	0.42
2	0.33	ND[c]	ND	0.38	ND	0.39
6	2.1	1.9	3.7	3.2	3.4	7.3
10	3.7	ND	ND	4.2	ND	4.0

[a] See ref 16. [b] GI_{50} values are reported as concentrations in μg/mL. [c] ND, not determined.

Compound **2** yielded an average GI_{50} value of 7.79×10^{-7} M.[16] When evaluated as a potential inhibitor of tubulin polymerization, compound **2** yielded an IC_{50} value of 3.0 ± 1.0 μM. Finally, compounds **6** and **10** were essentially inactive as inhibitors of tubulin assembly (IC_{50} values > 40 μM).

Conclusions

We have prepared two new anti-tubulin ligands **1** and **2** from a 1,4-addition−elimination reaction and a 1,2-addition−ring-cleavage reaction, respectively, on a bromo-substituted benzo[*b*]thiophene *S*-oxide precursor. This dual mode of reactivity is understandable based on the hard/soft nature of the two nucleophiles compared with the hard/soft environment of the carbon terminus of the α,β-unsaturated sulfoxide versus the sulfur atom of the sulfoxide. The ligands were evaluated for their activity against human cancer cell lines and as inhibitors of tubulin polymerization. The compounds had similar strong cytoxic activity. Aryl ether **1** strongly inhibited tubulin polymerization and has recently been selected for initial in vivo evaluation by the NCI in their hollow fiber assay. Alkynyl sulfide **2** was about 3−4 times less active than **1** as an inhibitor of tubulin polymerization.

Experimental Section

General Methods. Proton (^{1}H) and carbon (^{13}C) NMR were obtained at 300 and 75 MHz or 90 MHz, respectively, in the

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solvent indicated. Chemical shifts are expressed in ppm (δ). Elemental analyses were carried out by Atlantic Microlab Inc. (Norcross, GA) and are within ±0.4% of the theoretical values unless otherwise indicated. All reagents and solvents were obtained from commercial sources and used without further purification unless indicated. Lithium cuprate reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried at 120 °C. Tetrahydrofuran (THF) was distilled from potassium, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride (CaH_2) immediately prior to use. Silica gel for flash chromatography was purchased from Merck EM Science (300−450 mesh), and compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm).

Inhibition of Tubulin Polymerization. The tubulin polymerization assays were performed as described previously,[18] except that Beckman DU7400/7500 spectrophotometers equipped with "high performance" temperature controllers were used. Unlike the manual control possible with the previously used Gilford spectrophotometers, the polymerization assays required use of programs provided by MDB Analytical Associates, South Plainfield, NJ, since the Beckman instruments are microprocessor controlled. The Beckman instruments were unable to maintain 0 °C, and the lower temperature in the assays fluctuated between 2 and 4 °C. Temperature changes were, however, more rapid than in the Gilford instruments with the jump from the lower temperature to 30 °C taking about 20 s and the reverse jump about 100 s.

2-(4′-Methoxyphenyl)-3-bromo-6-methoxybenzo[*b*]-thiophene (4). A solution of bromine (6.20 g, 38.8 mmol) in $CHCl_3$ (50 mL) was added dropwise to a solution of 6-methoxy-2-(4′-methoxyphenyl)benzo[*b*]thiophene **3**[10b] (10.5 g, 38.8 mmol) in $CHCl_3$ (300 mL) at room temperature. After the addition was complete, the reaction was stirred at room temperature for 0.5 h, and GC was employed to monitor the reaction progress (GC conditions: 200° C to 270 °C, 10 °C/min). The reaction mixture was concentrated in vacuo to provide 2-(4′-methoxyphenyl)-3-bromo-6-methoxybenzo[*b*]thiophene **4** (12.7 g, 36.4 mmol, 94%): mp 83−85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H), 3.40 (s, 3H), 7.00 (m, 2H), 7.07 (dd, J = 8.9, 2.3 Hz, 1H), 7.65−7.75 (m, 4H).

2-(4′-Methoxyphenyl)-3-bromo-6-methoxybenzo[*b*]-thiophene *S*-Oxide (5). To a solution of 3-bromo-2-(4′-methoxyphenyl)-6-methoxybenzo[*b*]thiophene **4** (7.00 g, 20.0 mmol) in anhydrous CH_2Cl_2 (50 mL) was added trifluoroacetic acid (50 mL). After 5 min of stirring, H_2O_2 (2.30 mL, 20.0 mmol, 30% aqueous solution) was added. The resulting mixture was stirred at room temperature for 2 h. Solid sodium bisulfite (1.00 g) was added to the dark solution followed by H_2O (15 mL). The mixture was partitioned between CH_2Cl_2 and a saturated $NaHCO_3$ solution (150 mL each). The layers were separated, and the organic layer was extracted sequentially with saturated $NaHCO_3$ and saturated NaCl solutions. The organic layer was dried by anhydrous sodium sulfate and concentrated in vacuo to a solid that was triturated with EtOAc. The crude product was obtained after filtration as a yellow solid, which was recrystallized from EtOAc to afford sulfoxide **5** (5.50 g, 15.1 mmol, 75%): mp 170−173 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87(s, 3H), 3.91 (s, 3H), 7.03 (d, J = 8.9 Hz, 2H), 7.12 (dd, J = 8.5, 2.3 Hz, 1H), 7.48−7.56 (m, 2H), 7.78 (d, J = 8.8 Hz, 2H).

2-(4′-Methoxyphenyl)-3-(3′,4′,5′-trimethoxyphenoxy)-6-methoxybenzo[*b*]thiophene *S*-Oxide (6). To a well-stirred solution of 3,4,5-trimethoxyphenol (0.514 g, 2.79 mmol) in DMF (10 mL) was added NaH (0.103 g, 4.29 mmol). After the solution was stirred at room temperature for 15 min, 3-bromo-2-(4′-methoxyphenyl)-6-methoxybenzo[*b*]thiophene *S*-oxide **5** (1.25 g, 3.42 mmol) was added. After 2 h, the reaction mixture was partitioned between an ethanol−ethyl acetate (10:90) mixture and water. The aqueous phase was extracted three times with an ethanol/ethyl acetate (10%) solution. The organic layer was washed with water (five times), followed by brine, and dried over $MgSO_4$. Evaporation of the solvent gave a dark colored oil. Trituration of the residue with an ether/hexane mixture resulted in sulfoxide **6** as a yellow fluffy solid (1.15 g, 2.46 mmol, 88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, J = 8.9 Hz, 2H), 7.34 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 6.99 (dd, J = 8.6, 2.4 Hz, 1H), 6.86 (d, J = 8.9, 2H), 6.29 (s, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.75 (s, 6H). Anal. Calcd for $C_{25}H_{24}O_7S$: C, 64.09; H, 5.16; S, 6.84. Found: C, 63.89; H, 5.21; S, 6.69.

2-(4′-Methoxyphenyl)-3-(3′,4′,5′-trimethoxyphenoxy)-6-methoxybenzo[*b*]thiophene (1). To an ice-cooled, well-stirred solution of 3-(3′,4′,5′-trimethoxyphenoxy)-2-(4′-methoxyphenyl)-6-methoxybenzo[*b*]thiophene *S*-oxide **6** (0.900 g, 1.92 mmol) in THF (20 mL) was added lithium aluminum hydride (0.077 g, 2.03 mmol). After 3 h, the reaction was terminated with water followed by an extraction/washing sequence with ethyl acetate, brine, and drying over $MgSO_4$. Removal of the solvent followed by purification by flash chromatography (80:20 hexanes/EtOAc) resulted in benzo[*b*]thiophene **1** (0.585 g, 1.29 mmol, 67%) as a colorless solid: mp 129−131 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 6.90 (dd, J = 8.8, 2.3 Hz, 1H), 6.21 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.71 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 159.2, 157.9, 154.1, 153.8, 139.0, 136.7, 133.1, 128.7, 128.0, 126.8, 124.9, 122.1, 114.3, 114.3, 105.3, 93.2, 61.0, 56.1, 55.6, 55.3; HRMS (EI) M^+ calcd for $C_{25}H_{24}O_6S$ 452.1248, found 452.1294. Anal. Calcd for $C_{25}H_{24}O_6S$: C, 66.36; H, 5.35; S, 7.08. Found: C, 66.06; H, 5.42; S, 7.08.

1-Bromo-3,4,5-trimethoxybenzene (8).[19] 3,4,5-Trimethoxyaniline (7.33 g, 40.0 mmol) and *tert*-butylnitrite (6.88 g, 90% technical grade, 60.0 mmol) were added to a solution of cupric bromide (10.7 g, 48.0 mmol) in acetonitrile (160 mL) under dry nitrogen. After the mixture was stirred for 10 min at 0 °C, the temperature was raised to room temperature for 2 h. HCl (50 mL, 10%) was added, and the mixture was partitioned between CH_2Cl_2 and a saturated NaCl solution (150 mL each). The organic layer was washed once with a saturated NaCl solution, dried with anhydrous sodium sulfate, and concentrated in vacuo to obtain a solid that was purified by trituration with hexane. Bromide **8** was obtained after filtration as a colorless solid (5.90 g, 23.9 mmol, 60%): mp 78−79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 3.86 (s, 6H), 6.75 (s, 2H).

1,2-Bis(4′-methoxyphenyl)-2′-(3′′,4′′,5′′-trimethoxyphenylthioether)ethyne *S*-Oxide (10). A solution of 3,4,5-trimethoxyphenylbromide **8** (2.47 g, 10.0 mmol) in ether (20 mL) was added to a solution of *n*-butyllithium (8 mL, 2.5 M in hexane solution, 20 mmol) in dry ether (100 mL) under dry nitrogen at −78 °C. The solution was stirred for 1 h in order to form 3,4,5-trimethoxyphenyllithum. This solution was added slowly to a solution of copper iodide (0.952 g, 5.00 mmol) in dry ether (50 mL) at −23 °C. The mixture was stirred for 1 h to complete formation of the cuprate reagent. Thiophene *S*-oxide **5** (0.913 g, 2.50 mmol) was added to the cuprate solution at −23 °C, and stirring was continued for 12 h (−23 °C to rt). HCl (20 mL, 10%) was added, and the mixture was partitioned between CH_2Cl_2 and a saturated NaCl solution. The organic layer was washed with water, dried over anhydrous sodium sulfate, and after filtration, the organic layer was concentrated in vacuo to provide alkyne **10** as a yellow oil (1.20 g). Purification by column chromatography afforded 1,2-bis(4′-methoxyphenyl)-2′-(3′′,4′′,5′′-trimethoxyphenylthioether)ethyne *S*-oxide (**10**, 0.50 g, 1.11 mmol, 44%) as a colorless solid: mp 128−129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 6H), 3.81 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 6.90−6.96 (m, 3H), 7.07 (s, 2H), 7.43−7.48 (m, 3H), 7.57 (d, J = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.4, 55.8, 56.1, 60.8, 96.2, 101.9, 107.5, 112.6, 114.2, 114.6, 117.4, 132.9, 133.9, 140.1, 148.8, 153.7, 160.0, 160.5; HRMS (EI) M^+ calcd for $C_{25}H_{24}O_6S$ 452.1248, found 452.1294. Anal. Calcd for $C_{25}H_{24}O_6S$: C, 66.36; H, 5.35; S, 7.08. Found: C, 66.20; H, 5.24; S, 7.14.

1,2-Bis(4′-methoxyphenyl)-2′-(3′′,4′′,5′′-trimethoxyphenylthioether)ethyne (2). Lithium aluminum hydride (0.038 g, 1.00 mmol) was added to the solution of 1,2-bis-(4′-methoxyphenyl)-2′-(3′′,4′′,5′′-trimethoxyphenylthioether)ethyne *S*-oxide (**10**, 0.45 g, 1.0 mmol) in anhydrous THF (20 mL) under dry nitrogen at 0 °C. After being stirred at 0 °C for 1 h, HCl (10 mL, 10%) was added, and the mixture was partitioned between CH_2Cl_2 and a saturated NaCl solution. The organic layer was washed with water and dried with anhydrous sodium sulfate. The reside

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(0.500 g) was purified by column chromatography to afford sulfide **2** (0.400 g, 0.917 mmol, 92%) as a colorless solid: mp 117−118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.47 (d, J = 2.5 Hz, 1H), 6.67 (dd, J = 8.5, 2.5 Hz, 1H), 6.81 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.7, 56.6, 61.4, 85.8, 94.9, 111.2, 111.9, 113.3, 114.3, 127.1, 133.3, 133.8, 143.2, 154.2, 160.1; HRMS (EI) M^+ calcd for $C_{25}H_{24}O_5S$ 436.1258, found 436.1344. Anal. Calcd for $C_{25}H_{24}O_5S$: C, 68.79; H, 5.54; S, 7.34. Found: C, 68.76; H, 5.61; S, 7.28.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **1**, **2**, **6**, and **10**. An ORTEP diagram and tables of crystallographic data for alkyne **10**. This information is available free of charge via the Internet at http://pubs.acs.org.

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