HETEROCYCLES, Vol. 81, No. 1, 2010, pp. 117 - 143. © The Japan Institute of Heterocyclic Chemistry
Received, 24th September, 2009, Accepted, 26th October, 2009, Published online, 28th October, 2009
DOI: 10.3987/COM-09-11840

EXPLORATION OF BRAVERMAN REACTION CHEMISTRY. SYNTHESIS OF TRICYCLIC DIHYDROTHIOPHENE DIOXIDE DERIVATIVES FROM BISPROPARGYL SULFONES

Ken S. Feldman* and Brandon R. Selfridge

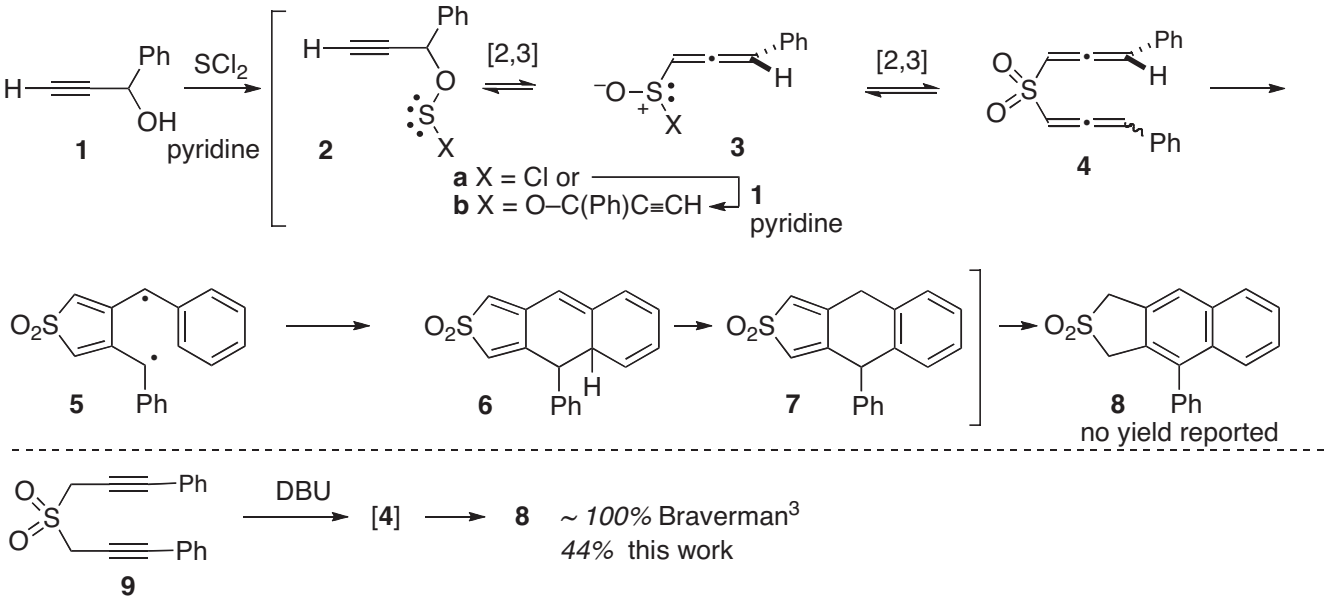
Chemistry Department, The Pennsylvania State University, University Park, Pennsylvania 16802 USA
ksf@chem.psu.edu

Abstract – The base-mediated bicyclization of unsymmetrical bispropargyl sulfones furnishes varying yields of dihydroisobenzothiophene dioxides through a presumed diradical intermediate. Attempts to trap a putative thiophene dioxide intermediate via Diels-Alder reaction with a pendant alkyne were not successful.

INTRODUCTION

The spontaneous thermal cyclization of bisallenyl sulfones to furnish thiophene dioxide derivatives was first reported by Braverman in 1974.[1] Subsequent studies revealed that this transformation likely proceeds through a diyl intermediate followed by several tautomerizations, **4** → **5** → **6** → **7** → **8** (Scheme 1), rather than an intramolecular Diels-Alder reaction of either a bis(3-aryl)allenyl sulfone (i.e., **4** → **6** directly) or a related allenyl, propargyl sulfone.[2-4] The key to successful development of this transformation involved identifying mild methods to access the reactive bisallenyl sulfone, and in 2000/2001 Braverman described a facile procedure based upon simple treatment of the propargyl alcohol **1** with SCl_2; a series of [2,3]-sigmatropic shifts then delivers the bisallenyl sulfone **4**.[2,3] In addition, a base-mediated alternative process that begins with bispropargylic sulfone **9** was introduced in this work, **9** → **8**. The reported yield for this latter process approached quantitative, although there was no report of a yield or description of an experimental procedure for the **1** → **8** reaction.[3] The formation of a thiophene dioxide such as **7**, whether transiently or as an isolable intermediate,[1,4] raised the possibility of linking the Braverman chemistry with the rich Diels-Alder chemistry of thiophene dioxides[5-8] in a multi-step transformation that could forge several new rings from simple precursors. Thus, tethering a dienophile trap to a nascent thiophene dioxide emerging from the Braverman chemistry might test the hypothesis that intramolecular Diels-Alder cycloaddition might compete with proton transfer within an intermediate like **7** and ultimately deliver a pentacyclic product. Probing this hypothesis first would

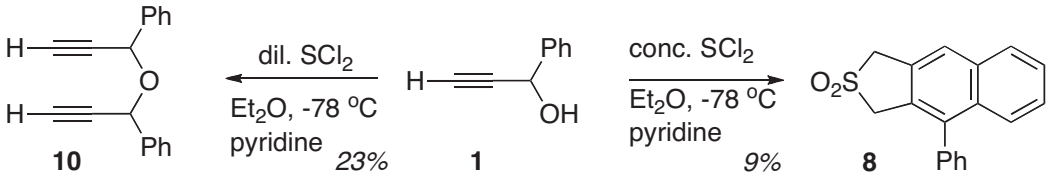
require the development of Braverman chemistry with an unsymmetrical bisallenyl sulfone, a type of substrate heretofore unexamined, in order to introduce both the dienophile and the thiophene dioxide into the same molecule. Our preliminary attempts to access such substrates and execute an unsymmetrical Braverman reaction, as well as a test of the premise that the intermediate thiophene dioxide can be trapped by a pendant dienophile, are described below.



Scheme 1. Braverman's early contributions.[2,3]

RESULTS AND DISCUSSION

Our initial attempts to reproduce the Braverman chemistry with propargyl alcohol **1** led to mixed results. The base-mediated cyclization of the bispropargylic sulfone **9** to furnish tricycle **8** proceeded in moderate yield (44%) in our hands (Scheme 1). However, the more intriguing process starting from two equivalents of the propargyl alcohol **1** and SCl_2 could not be brought to a satisfying endpoint. After much exploration of temperatures, solvents, reagent concentrations, etc., we were able to achieve no better than a 9% yield of the same tricycle **8** that was formed from the DBU-mediated isomerization of **9**. Under alternative conditions where the SCl_2 is metered into the reaction slowly so as to ensure that its concentration is never high, the reaction takes a different course and delivers the symmetrical ether **10** as the only identifiable product. Presumably this ether results from simple S_N2-like substitution of X (X = SCl or SOR) within an intermediate HC≡C–CH(X)Ph. This disappointing turn of events served to focus our attention on the bispropargyl sulfone route.



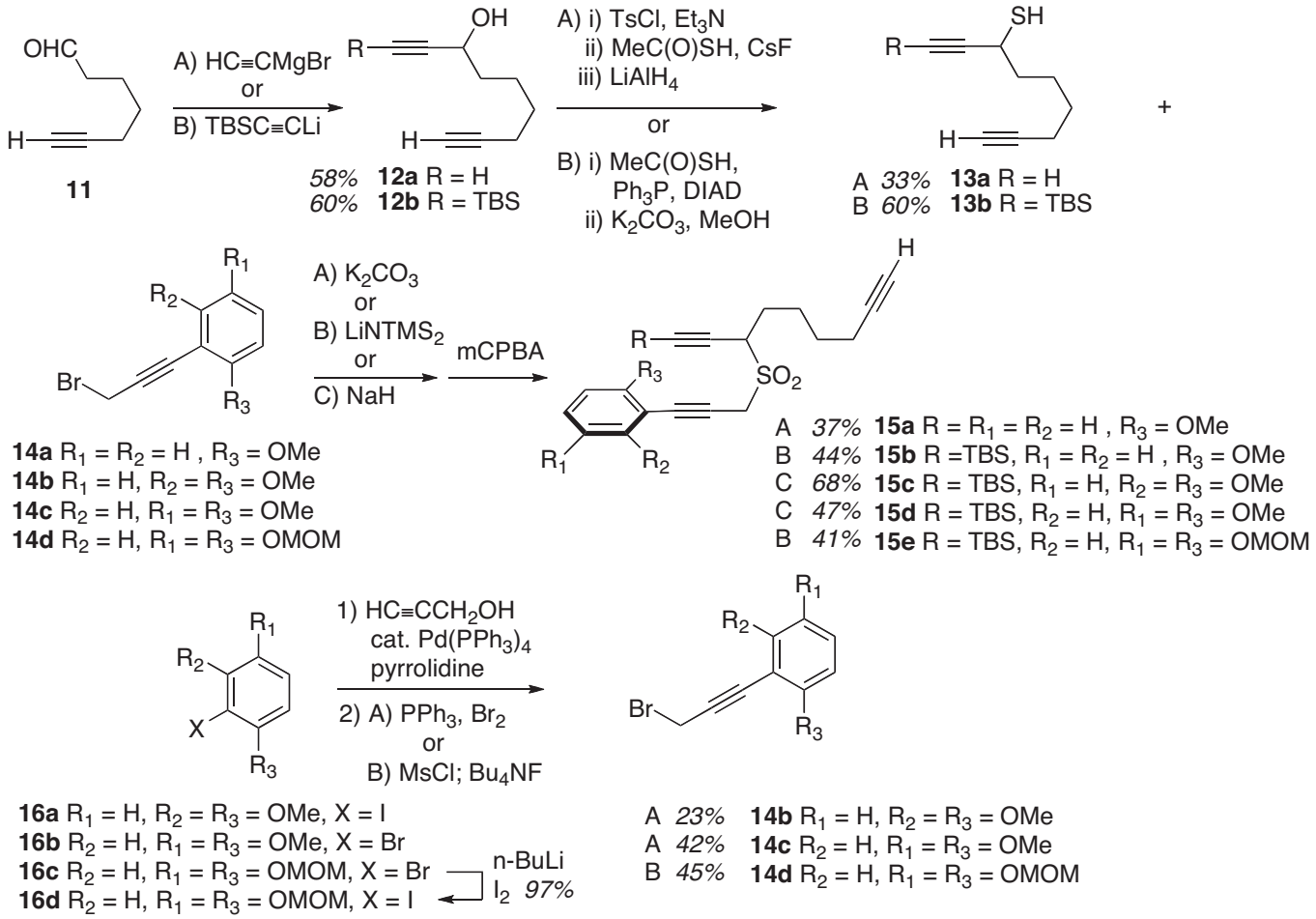
Scheme 2. Attempts to reproduce Braverman chemistry.

SYNTHESIS OF BISPROPARGYL SULFONE SUBSTRATES

The unsymmetrically substituted bispropargyl sulfone substrates **15a**-**15e** were prepared by convergent coupling of the 1,8-nonadiynylmercaptans **13a** and **13b** with the propargyl bromides **14a**-**14d** to furnish a thioether product, which was immediately oxidized to the requisite sulfone, Scheme 3. The inaugural substrate chosen for study was the bispropargylic sulfone **15a**. An alternative convergent coupling plan utilizing the mercaptan equivalent of **14a** and the bromide analogue of **13a** did not provide any sulfide product. The mercaptan of **13a** was introduced via tosylation of the alcohol **12a** followed by S_N2 displacement of the derived tosylate with thioacetic acid and then reductive removal of the acetate fragment (sequence A). In subsequent substrate syntheses, a route employing Mitsunobu chemistry for direct displacement of the alcohol in **12b** with thioacetic acid gave superior yields (sequence B).

The propargyl bromides **14b**-**14d** were assembled from the corresponding aryl bromides or iodides **16a**, **16b**, and **16d**, respectively. The conversion of the aryl propargyl alcohol derived by Sonogashira coupling of **16a** into the corresponding bromide **14b** was particularly challenging and accounts for the low yield for this sequence; it appeared that the lability of the bromide **14b** during workup/purification is the likely culprit. The bismethoxymethyl ether bromide **16c** combined with propargyl alcohol under standard Sonogashira conditions to provide the arylated propargyl alcohol in poor yield, and so recourse was made to the corresponding iodide **16d**, prepared by metalation of **16c** followed by I_2 quench of the intermediate lithiate.

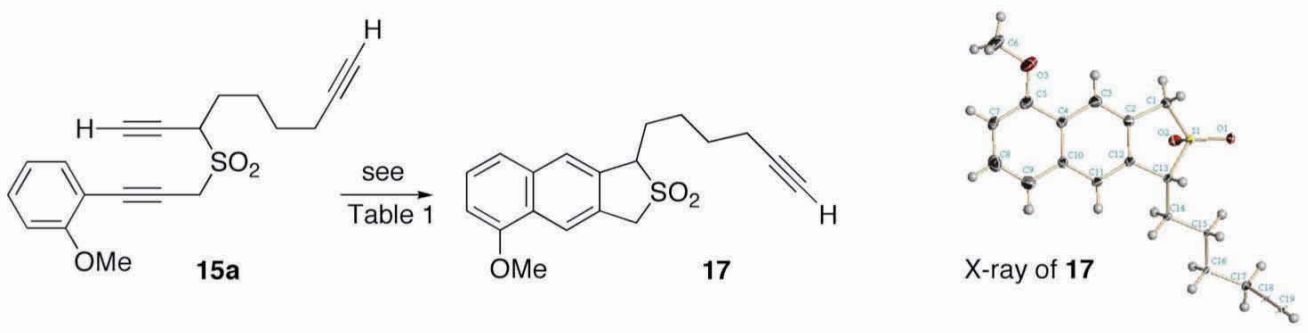
The cyclization substrates **15a**-**15e** all were obtained as spectroscopically pure light yellow oils that displayed no tendency to decompose upon storage at room temperature. No partial isomerization of a propargyl moiety into an allene unit was observed. Characteristic ^{1}H NMR signals at δ 4.2–4.6 indicate the presence of propargylic sulfone substructures, and the geminal coupling of the diastereotopic methylene protons ($J \sim 17$ Hz) confirms this assignment.



Scheme 3. Synthesis of bispropargyl sulfone substrates.

BASE-MEDIATED BICYCLIZATION OF THE BISPROPARGYL SULFONE SUBSTRATES

The base promoted bicyclizations (Braverman reaction) of the bispropargyl sulfones prepared as illustrated in Scheme 3 were explored next. The simple methoxyphenyl-bearing substrate **15a** was chosen to probe the influence of different bases and solvents on the efficiency of the reaction. The pendant alkyne was introduced to assess the possibility that the putative intermediate thiophene dioxide (cf. **7**, Scheme 1) could be intercepted in an IMDA reaction prior to its isomerization into the naphthalene product (cf. **7** → **8**, Scheme 1).



Scheme 4. Cyclization of bispropargyl sulfone **15a**.

Table 1. Optimizing the yield of **17** formation from bicyclization of **15a**.

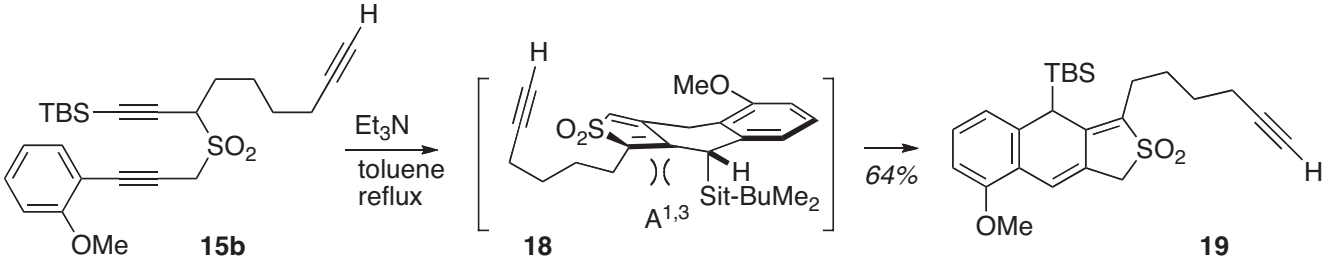
entry	base	solvent	temperature (°C)	yield **17** (%)
1	*t*-BuOK	THF	rt	---[a]
2	*t*-BuOK	THF	110	---[a]
3	*t*-BuOK	*t*-BuOH	rt	---[a]
4	*t*-BuOK	toluene	105	---[a]
5	DBU	$CHCl_3$	0	88
6	DBU	THF	0	13
7	DMAP	THF	rt	7
8	Et_3N	$CHCl_3$	rt	~100
9	Et_3N	toluene	110	~100
10	none	DMF	110	50

[a]In all cases, complex mixtures resulted from which no characterizable compounds could be isolated. No evidence for allene-containing material was detected in the crude product mixtures.

Exposure of bispropargyl sulfone **15a** to a range of bases in a variety of solvents helped delineate the optimum conditions for product formation (Table 1). It is evident that several distinct sets of reaction conditions successfully produced the tricyclic product **17**, whose structure was suggested by key spectral data (H @ δ8.19; triplet for methine proton next to sulfur) and later confirmed by single crystal X-ray analysis.[10] Essentially quantitative yield of **17** could be achieved when the relatively mild base triethylamine was used in either $CHCl_3$ or toluene. The temperature of the reaction medium did not seem to be a critical parameter, at least within the range 25 °C to 110 °C; both temperature extremes led to the same high yield of tricyclic product. However, no set of reaction conditions could be identified where the presumptive thiophene dioxide intermediate could be trapped in a Diels-Alder cycloaddition with the tethered alkyne. In all cases, even when exogenous base was omitted (Table 1, entry 10), Diels-Alder cycloaddition was not competitive with the tautomerizations from a presumed thiophene dioxide/dihydronaphthalene intermediate to the observed naphthalene/dihydrothiophene dioxide product **17**.

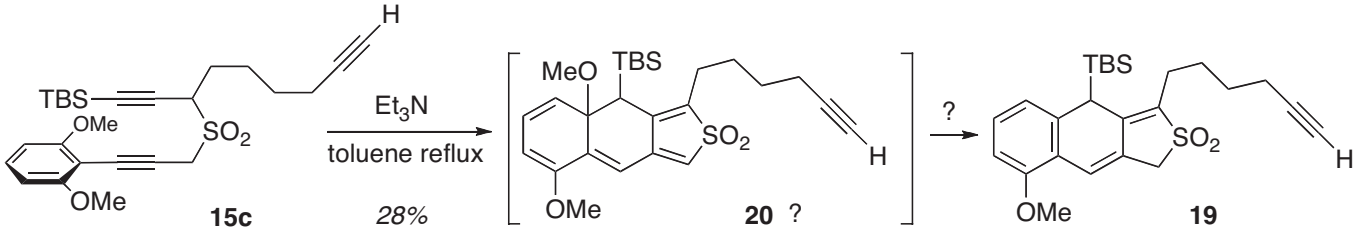
One approach that might circumvent the tautomerization leading to the naphthalene-containing product is to force an otherwise labile methylene proton into the plane of the π-system in order to suppress deprotonation. Scheme 5 describes the Braverman cyclization chemistry of one such substrate, **15b**. Subjection of this silylated bispropargyl sulfone to the optimized conditions from Table 1 led to a good yield of tricyclic material. Thus, at the very least, the terminal silyl group did not complicate the

Braverman cascade sequence. Furthermore, the formation of a partially unisomerized product **19** was in line with the expectations of the tautomerization suppression hypothesis; reaction through an unobserved intermediate thiophene dioxide **18** will engender $A^{1,3}$-type interactions between the alkyl tether and the pseudoequatorial substituent at the benzylic position. This interaction should be less sterically penalizing when the equatorial substituent is a proton, but in that arrangement, poor overlap between the C–H bond and the π-system is likely to suppress deprotonation. However, once again, the putative thiophene dioxide intermediate was not long-lived enough to participate in an IMDA reaction with the attached alkyne; isomerization of the other alkene apparently was just too fast.



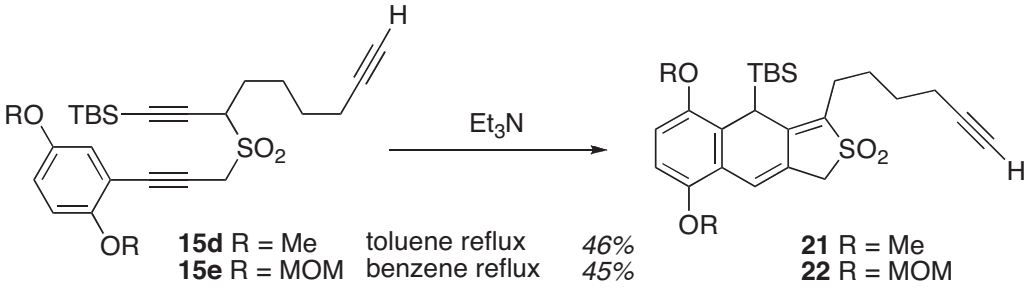
Scheme 5. Base-mediated cyclization of a bispropargyl sulfone bearing an *o*-methoxyphenyl ring and a TBS group; formation of a *dihydro*naphthalene product.

One workaround to this olefin positioning issue might involve raising the oxidation level of a tricyclic species like **19** to generate, at least in situ, an orthonaphthoquinonedimethane-thiophene dioxide species (cf. **24**, Scheme 8). Two distinct approaches to accomplish the introduction of another oxidized substituent into the bispropargyl sulfone cyclization precursor were explored. One manifestation of this plan is illustrated in Scheme 6, where an additional ortho-OMe group serves as this sacrificial oxidation level marker. The idea behind this substrate choice derived from the expectation that an intermediate such as **20** might eliminate the elements of either MeOH or MeOTBS to furnish the extended orthonaphthoquinonedimethane system, a potentially very reactive Diels-Alder partner for the alkyne. However, in one of the more surprising twists of this research, attempted Braverman cyclization of the *o*,*o*'-blocked substrate **15c** furnished a low yield of the familiar tricycle **19**! Clearly, a formal reduction has occurred, but the source of the reducing agent and the mechanism by which putative intermediate **20** is processed further into **19** remains mysterious.



Scheme 6. Base-mediated cyclization of a bispropargyl sulfone bearing an *o*,*o*'-dimethoxyphenyl ring and a TBS group; formation of the dihydronaphthalene product **19** again.

A second attempt to implement the same strategy for oxidation level elevation followed with the protected hydroquinone-containing substrates **15d** and **15e**, Scheme 7. In these instances, the introduction of a higher oxidation level (= orthonaphthoquinonedimethane-thiophene dioxide) was planned for post-cyclization chemistry, given the surprising course of the Braverman reaction with **15c**. These species participated in triethylamine-mediated cyclization without event and furnished the expected dihydro tricycles **21** and **22**, respectively, by analogy with the cyclization of **15b** into **19**.

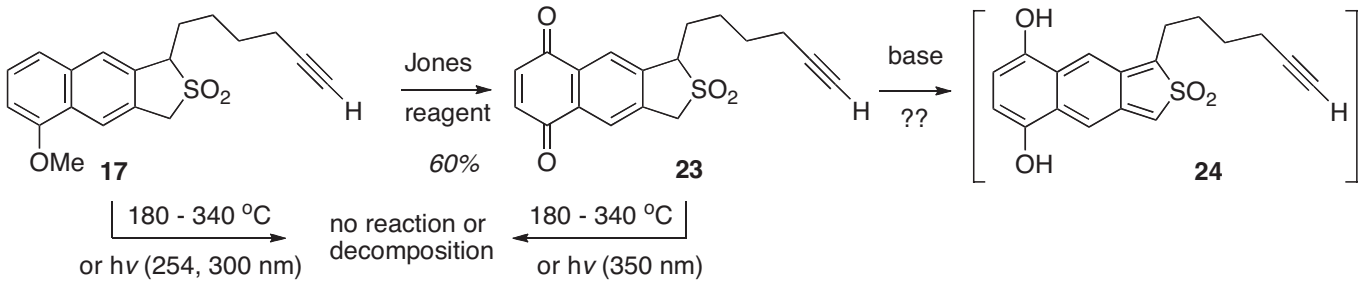


Scheme 7. Base-mediated cyclization of a bispropargyl sulfone bearing either an *o,m*-dimethoxyphenyl ring or an *o,m*-dimethoxymethyeneoxyphenyl ring and a TBS group.

ATTEMPTS TO FORCE THIOPHENE DIOXIDE FORMATION/INTRAMOLECULAR DIELS-ALDER CYCLOADDITION

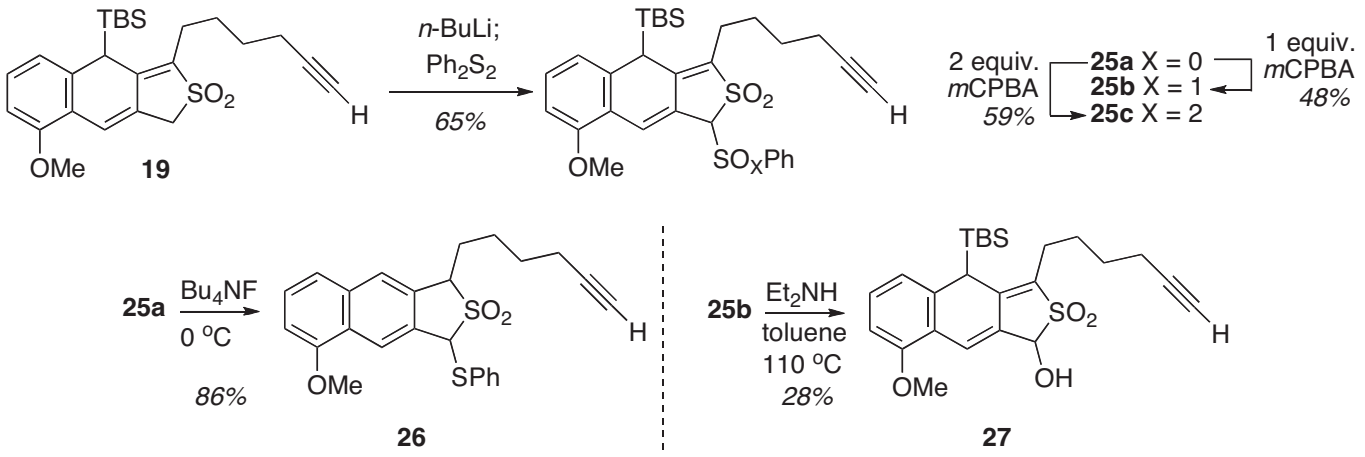
There are some precedents for the formation of orthoquinonedimethane intermediates from either photochemically or thermolytically induced chelatotropic extrusion of SO_2 from dihydroisobenzothiophene dioxides,[11,12] and so heating the sulfone **17** over the temperature range 180 – 340 ºC, as well as irradiation (254 - 300 nm, room temperature), were explored in an attempt to force Diels-Alder cycloaddition of the terminal alkyne (Scheme 8). However, in no instance was anything other than returned starting material or uncharacterizable decomposition products observed. For the naphthalene system **17**, decomposition began at ~ 240 ºC, and irradiated returned only starting material. Oxidation of naphthalene **17** gave the paraquinone **23**, a species that, in principle, offered two different approaches to generating a reactive intermediate (orthonaphthoquinonedimethane or thiophene dioxide) for Diels-Alder cycloaddition. Unfortunately, neither thermolysis nor photolysis of **23** led to anything characterizable. Decomposition set in at ~ 270 ºC, whereas irradiation at 350 nm also destroyed the compound. Furthermore, treatment of **23** with a variety of bases (i.e., pyridine, Et_3N, *i*-Pr_2NEt, pyridine, DBU, KOt-Bu, and *i*-Pr_2NLi) with the intent of effecting an internal redox reaction via proton tautomerization (= formal oxidation of the dihydrothiophene ring to a thiophene dioxide with concomitant reduction of the paraquinone to the hydroquinone or hydroquinone dianion) did not provide any reason to be optimistic. Thus, in the final analysis, the innate thermodynamic preference[13] that favors a naphthalene/dihydrothiophene dioxide structure rather than the dihydronaphthalene/thiophene dioxide

tautomer dominated the chemistry of this system, and no Diels-Alder-capable intermediates with sufficient lifetime to engage in cycloaddition could be accessed.



Scheme 8. Attempts to access orthonaphthoquinonedimethane-type intermediates from tricyclic naphthalene **17**.

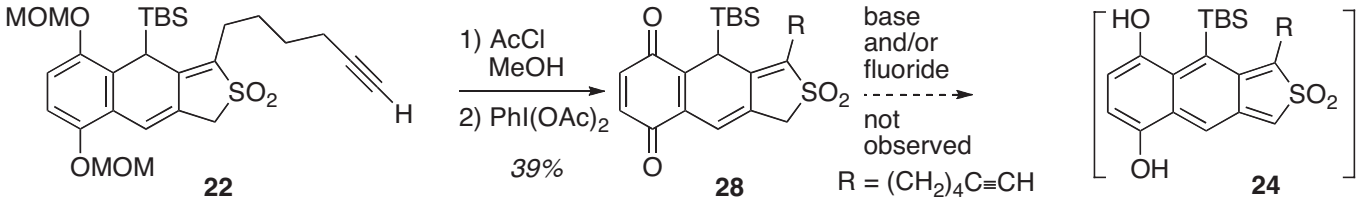
The acquisition of the non-naphthalenic tricycle **19** from Braverman cyclization of the TBS-substituted bispropargyl sulfone **15b** offered the possibility of further manipulation into a thiophene dioxide intermediate without the burden of overcoming the naphthalene moiety's aromatic resonance energy. This strategy for generating the thiophene dioxide moiety from **19** involved oxidation to the aforementioned orthonaphthoquinonedimethane-thiophene dioxide construct, cf. **24**. Efforts towards that end included treating **19** with epoxidizing reagents (H_2O_2/base, *m*CPBA, CF_3CO_3H), but only unconsumed starting material resulted. Direct, benzylic-type oxidation (CrO_3, $KMnO_4$, SeO_2, DDQ) was no more promising, affording either unreacted **19** or decomposition products. Deprotonation of an acidic proton α- to the sulfonyl moiety did afford a tractable anion, and trapping of that anion with Ph_2S_2 produced the α-sulfide **25a** in moderate yield. The corresponding sulfoxide **25b** and sulfone **25c** also were available from the sulfide. Treatment of the α-sulfonyl anion with other electrophiles (Br_2, CN-Br, $BrCCl_3$, TsCl) did not afford any of the oxidized product. Exposure of the sulfide **25a** to a fluoride source did not promote the intended elimination of TBS-SPh, and only the naphthalene-containing product **26** resulted. A similar attempt with the sulfone **25c** led only to decomposition of the starting material without formation of any isolable product. Attempts to effect [2,3]-sigmatropic rearrangement of the allylic sulfoxide within **25b** might have generated a transient thiophene dioxide product, but only the formal direct displacement product, alcohol **27**, was formed. The mechanism of this transformation remains a matter of speculation. Once again, our attempts to access a thiophene dioxide intermediate were thwarted.



Scheme 9. Attempts to isomerize or oxidize **19** to furnish a thiophene dioxide intermediate.

The final attempts at accessing an IMDA-capable thiophene dioxide intermediate from the Braverman cyclization tricycles focused on the hydroquinone derivatives **21** and **22**, Scheme 10. The objective in this instance was to convert the hydroquinone ethers to the paraquinone as per **17** → **23** and in so doing provide a substrate whose tautomerization to a thiophene dioxide product might not be so unfavorable. Unlike the fully aromatic system of **23**, we hoped that the cross-conjugated diene of such an oxidation product (cf. **28**) might be more prone to isomerization and afford access to the desired orthonaphthoquinonedimethane-thiophene dioxide **24**. Unfortunately, the first substrate examined, dimethyl ether **21**, was not a competent oxidation substrate as it decomposed readily under a variety of oxidation conditions. Apparently, the diene of **21** confers an unwanted sensitivity to the system that is not shared by the fully aromatic naphthalene analogue **17**.

The bis MOM ether analogue **22** did not suffer from this disadvantage. In this instance, removal of the MOM protecting groups provided a labile hydroquinone that decomposed upon standing but which could be oxidized immediately after acquisition to generate the requisite paraquinone containing tricycle **28**. Base- and/or fluoride-mediated isomerization of **28** into the corresponding orthonaphthoquinonedimethane-thiophene dioxide **24** was attempted next, under the premise that the normal thermodynamic unfavorability[13] (vide supra) might be mitigated somewhat by the gain in aromatic resonance energy upon concurrent paraquinone → hydroquinone reduction. However, treating this substrate with base and/or fluoride led only to uncharacterizable mixtures with no evidence for thiophene dioxide formation. Thus, in the final analysis, no evidence was forthcoming that supported the notion that introduction of a strategically placed oxygen function into the aromatic ring of the bispropargyl sulfone substrates promoted further oxidation of the remaining rings to generate a thiophene dioxide-containing species.



Scheme 10. Oxidation of the tricyclic Braverman product; attempts to formulate a orthonaphthoquinonedimethane-thiophene dioxide intermediate.

CONCLUSIONS

In summary, we have successfully prepared a range of unsymmetrical bispropargyl sulfones featuring a variety of OR (R = Me or MOM) placements on the aryl ring that caps one propargyl unit and either a proton or a TBS group at the terminus of the other propargyl unit. These species all participated in a Braverman cyclization cascade to furnish tricyclic products with varying efficiency. Depending upon the alkyne substituent (H or TBS), the tricyclic product either isomerized to a naphthalene-containing species (H substituent) or remained as a dihydronaphthalene isomer (TBS substituent). Unfortunately, all efforts to generate and then utilize a thiophene dioxide tautomer in intramolecular Diels-Alder cycloaddition with a pendant alkyne were frustrated by competitive isomerizations that consistently delivered the naphthalene product, presumably a thermodynamic sink. Thus, linking the Braverman sequence with thiophene dioxide Diels-Alder chemistry was not achieved.

EXPERIMENTAL

GENERAL EXPERIMENTAL

Moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under an inert nitrogen atmosphere. Dry ether (Et_2O), toluene, acetonitrile (MeCN), dichloromethane (CH_2Cl_2), methanol (MeOH), tetrahydrofuran (THF) and dimethylformamide (DMF) were purified by passing these solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV visualization and PMA staining. Purification of products via flash chromatography was performed with 40-63 m silica gel and the solvent system indicated. Melting points are uncorrected.

4-Phenyl-1,3-dihydro-naphtho[2,3-*c*]thiophene 2,2-Dioxide (8). A stirring solution of alkyne **1** (50 mg, 0.39 mmol) in 5 mL of Et_2O was treated with pyridine (35 μL, 0.44 mmol). After 1 h, the reaction mixture was cooled to -78 °C and freshly distilled SCl_2 (13 μL, 0.94 mmol) was added dropwise. After 1 h at -78 °C, saturated aqueous $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned

between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 25% Et_2O/hexanes → 50% Et_2O/hexanes as eluent) gave tetracycle **8** (4.9 mg, 9%) as a light yellow oil. Spectral data matched those reported by Braverman.[3]

1,1'-(Oxydi-2-propyn-1-ylidene)bis-benzene (10). A stirring solution of alkyne **1** (0.100 g, 0.774 mmol) in 10 mL of Et_2O was treated with pyridine (70 μL, 0.87 mmol). After 1 h, the reaction mixture was cooled to -78 °C and a solution of freshly distilled SCl_2 (26 μL, 0.39 mmol) in 330 μL of CH_2Cl_2 was added to the reaction solution. After 1 h at -78 °C, saturated aqueous $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10% Et_2O/hexanes → Et_2O as eluent) gave bis-propargylic ether **10** (21.7 mg, 23%) as a colorless oil. Spectral data matched those reported by Bustelo.[14]

Nona-1,8-diyne-3-ol (12a). To a stirring solution of hept-6-ynal[15] (**11**) (1.01 g, 9.14 mmol) in 75 mL of THF at 0 °C was added a solution of ethynylmagnesium bromide in THF (0.5M, 21.9 mL, 11.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and then saturated NH_4Cl (100 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic fractions were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford nona-1,8-diyn-3-ol (**12a**) (0.717 g, 58%) as a colorless oil. A yield of 90% was obtained on a 32 mg scale. IR (thin film) 3950, 3500, 2115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (qd, J = 6.1, 2.0 Hz, 1H), 2.49 (br s, 1H), 2.43 (d, J = 2.1 Hz, 1H), 2.19-2.13 (m, 2H), 1.91 (t, J = 2.6, 1H), 1.71-1.64 (m, 2H), 1.57-1.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.8, 84.2, 72.9, 68.4, 65.8, 61.9, 36.9, 27.9, 24.1, 18.2; GC-MS (EI) m/z (relative intensity) 136.2 (5%, M^+).

1-(*tert*-Butyldimethylsilanyl)nona-1,8-diyne-3-ol (12b). To a stirring solution of TBS acetylene (6.32 g, 44.9 mmol) in 80 mL of THF at 0 °C was added *n*-BuLi (2.5 M in hexanes, 18 mL, 45 mmol) dropwise. The reaction mixture was stirred for 10 min at 0 °C and then a solution of hept-6-ynal (4.95 g, 44.9 mmol) in 20 mL of THF was added. The reaction mixture was stirred at room temperature for 2 d, and then saturated NH_4Cl (100 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic fractions were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 10% Et_2O/hexanes as eluent) afforded 1-(tert-butyldimethylsilanyl)nona-1,8-diyn-3-ol (**12b**) (4.78 g, 43%) as a colorless oil. A yield of 60% was obtained on a 1.41 g scale. IR (thin film) 3400, 3307, 2175 cm^{-1}; ^1H

NMR (360 MHz, $CDCl_3$) δ 4.36 (t, *J* = 5.1 Hz, 1H), 2.21-2.16 (m, 2H), 1.97 (brs, 1H), 1.93 (t, *J* = 2.1 Hz, 1H), 1.71-1.70 (m, 2H), 1.60-1.54 (m, 4H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 107.3, 87.7, 84.2, 68.4, 62.6, 37.3, 28.1, 26.0, 24.3, 18.3, 16.4, -4.7; LRMS (ESI) *m/z* (relative intensity) 251.3 (70%, M + H^+).

Nona-1,8-diyne-3-thiol (13a). To a stirring solution of nona-1,8-diyn-3-ol (**12a**) (0.668 g, 4.88 mmol) in 1.55 mL at 0 °C was added *p*-toluenesulfonyl chloride (0.998 g, 5.23 mmol). The reaction mixture was stirred for 3 h and then H_2O (25 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with 1M HCl (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of the oil by SiO_2 flash column chromatography (5 % EtOAc/hexanes as eluent) gave toluene-4-sulfonic acid 1-ethynyl-hept-6-ynyl ester (0.988 g, 70%) as a yellow oil. IR (thin film) 3292, 2123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.00 (td, *J* = 6.5, 2.1 Hz, 1H), 2.39 (s, 3H), 2.38 (s, 1H), 2.11 (td, *J* = 6.6, 2.6 Hz, 2H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.83-1.73 (m, 2H), 1.56-1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 133.5, 129.6, 127.9, 83.7, 79.4, 76.2, 70.7, 68.6, 34.9, 27.4, 23.5, 21.5, 18.0; LRMS (ESI) *m/z* (relative intensity) 308.1 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{16}H_{22}NO_3S]^+$, 308.1320, found 308.1316.

To a stirring solution of CsF (0.44 g, 2.9 mmol) in 10 mL of DMF was added thioacetic acid (274 μL, 3.89 mmol). The reaction mixture was stirred for 20 min, and then a solution of toluene-4-sulfonic acid 1-ethynyl-hept-6-ynyl ester (0.832 g, 2.87 mmol) in 5 mL of DMF was added. The reaction mixture was stirred for 20 h at 50 °C and then H_2O (10 mL) were added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic fractions were sequentially washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude yellow oil. Purification of the oil by SiO_2 flash column chromatography (10% Et_2O/hexanes as eluent) afforded thioacetic acid *S*-(1-ethynyl-hept-6-ynyl) ester (0.433 g, 78%) as a yellow oil. IR (thin film) 3294, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (td, *J* = 6.8, 2.5 Hz, 1H), 2.31 (s, 3H), 2.26 (d, *J* = 2.6 Hz, 1H), 2.20-2.13 (m, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.77-1.70 (m, 2H), 1.62-1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 84.0, 82.2, 71.6, 68.5, 34.9, 33.3, 30.2, 27.7, 26.0, 18.2; GC-MS (EI) *m/z* (relative intensity) 194.0 (5%, M^+).

To a stirring solution of $LiAlH_4$ (49.1 mg, 1.29 mmol) in 10 mL of Et_2O at 0 °C was added a solution of thioacetic acid *S*-(1-ethynyl-hept-6-ynyl) ester (346 mg, 1.78 mmol) in 5 mL of Et_2O. The reaction mixture was warmed to room temperature, stirred for 14 h, and poured into ice-cold H_2O. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 20

mL). The combined organic fractions were sequentially washed with 1M H_3PO_4 (60 mL) and then brine (60 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude yellow oil. Purification of this oil by passing through a thin pad of SiO_2 (33% Et_2O/hexanes as eluent) gave thiol **13a** (125 mg, 46%) as a yellow oil. A yield of 60% was obtained on a 2.12 g scale. IR (thin film) 3293 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53-3.51 (m, 1H), 3.26 (s, 1H), 2.17-2.14 (m, 3H), 1.93 (d, *J* = 2.4 Hz, 1H), 1.76-1.73 (m, 2H), 1.59-1.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.0, 84.0, 71.4, 68.5, 38.5, 28.3, 27.6, 26.1, 18.2; GC-MS (EI) *m*/*z* (relative intensity) 152.0 (100%, M^+).

1-(*tert*-Butyldimethylsilanyl)nona-1,8-diyne-3-thiol (13b). To a stirring solution of PPh_3 (4.28 g, 19.5 mmol) and 1-(*tert*-butyldimethylsilanyl)nona-1,8-diyn-3-ol (**12b**) (4.44 g, 17.7 mmol) in 60 mL of THF at 0 °C was added DIAD (3.04 mL, 19.5 mmol) dropwise. The reaction mixture was stirred for 10 min at 0 °C and then treated with thiolacetic acid (1.06 mL, 19.5 mmol). After 2 h at 0 °C, the reaction mixture was concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% Et_2O/hexanes as eluent) afforded thioacetic acid S-{1-[(*tert*-butyldimethylsilanyl)ethynyl]hept-6-ynyl} ester (3.84 g, 70%) as a yellow oil. IR (thin film) 3295, 2150, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29 (t, *J* = 6.8 Hz, 1H), 2.32 (s, 3H), 2.19 (td, *J* = 6.7, 2.6 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.77-1.74 (m, 2H), 1.62-1.56 (m, 4H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 104.2, 86.7, 84.1, 68.4, 35.5, 34.4, 30.2, 27.8, 26.0 (2), 18.2, 16.5, -4.7; LRMS (ESI) *m*/*z* (relative intensity) 309.2 (100%, M + H^+).

To a stirring suspension of K_2CO_3 (1.89 g, 12.4 mmol) in 130 mL of MeOH was added thioacetic acid *S*-{1-[(tert-butyldimethylsilanyl)ethynyl]hept-6-ynyl} ester (3.84 g, 12.4 mmol) in 20 mL of MeOH. The reaction mixture was stirred for 3 h at room temperature at which time 1M H_3PO_4 (200 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic fractions were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give thiol **13b** (2.84 g, 86%) as a yellow oil. A yield of 98% was obtained on a 4.91 g scale. IR (thin film) 3295, 2150 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.60 (app q, *J* = 6.5 Hz, 1H), 2.20 (td, *J* = 6.8, 2.5 Hz, 2H), 2.13 (d, *J* = 6.5 Hz, 1H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.79-1.77 (m, 2H), 1.64-1.56 (m, 4H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 107.4, 86.0, 84.1, 68.5, 38.9, 29.4, 27.9, 26.1, 26.05, 18.3, 16.6, -4.7; LRMS (ESI) *m*/*z* (relative intensity) 267.2 (30%, M + H^+).

1-(3-Bromo-prop-1-ynyl)-2-methoxybenzene (14a). To a stirring solution of 2-iodoanisole (13.9 mL, 107 mmol) in 350 mL of THF was sequentially added propargyl alcohol (21.6 mL, 371 mmol), $Pd(PPh_3)_2Cl_2$ (1.09 g, 1.40 mmol), Et_3N (40.5 mL, 291 mmol), and CuI (1.08 g, 5.67 mmol). After 14 h, the reaction mixture was poured into H_2O (400 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 250 mL). The combined organic

fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (50% EtOAc/hexanes as eluent) gave 3-(2-methoxy-phenyl)-prop-2-yn-1-ol (17.3 g, 100%) as a light yellow solid. Spectral data matched those reported by Franks.[16]

A stirring solution of PPh_3 (28.1 g, 107 mmol) in 350 mL of CH_2Cl_2 was cooled to 0 ºC and Br_2 (5.47 mL, 107 mmol) was added dropwise to the reaction mixture. A solution of 3-(2-methoxyphenyl)-prop-2-yn-1-ol (17.3 g, 107 mmol) in 100 mL of CH_2Cl_2 was added dropwise to the reaction mixture and solution was stirred for an additional 4 h at 0 ºC. The reaction mixture was warmed to room temperature and concentrated in vacuo to give a light yellow oil. Purification of the oil by SiO_2 flash column chromatography (10% benzene/hexanes) gave bromide **14a** (18.9 g, 79%) as a colorless oil whose spectral data matched those reported by Dai.[9]

2-(3-Bromo-prop-1-ynyl)-1,3-dimethoxybenzene (14b). To a stirring solution of 1-iodo-2,6-dimethoxybenzene (15.0 g, 56.8 mmol) in 120 mL of pyrrolidine was added propargyl alcohol (3.31 mL, 114 mmol) and $Pd(PPh_3)_4$ (3.33 g, 2.84 mmol). The reaction mixture was heated at 45 °C for 3 d and then saturated aqueous NH_4Cl (120 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 12:7:1 Et_2O/hexanes/CH_2Cl_2 → 8:1:1 Et_2O/hexanes/CH_2Cl_2) afforded 3-(2,6-dimethoxy-phenyl)-prop-2-yn-1-ol (9.39 g, 86%) as a white solid. mp 92-94 °C; IR (thin film) 3378, 2214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 8.4 Hz, 1H), 6.50 (d, J = 8.4 Hz, 2H), 4.56 (d, J = 5.1 Hz, 2H), 3.84 (s, 6H), 2.26 (t, J = 5.4 Hz, 1H) ; ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.4, 129.8, 103.3, 100.6, 96.0, 77.6, 55.9, 51.8; LRMS (ESI) *m/z* (relative intensity) 193.2 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{11}H_{13}O_3]^+$, 193.0865, found 193.0867.

To a stirring solution of PPh_3 (12.8 g, 48.9 mmol) in 125 mL of CH_2Cl_2 at 0 °C was added Br_2 (2.51 mL, 48.9 mmol). The reaction mixture was held at this temperature for 30 min and then a solution of 3-(2,6-dimethoxy-phenyl)-prop-2-yn-1-ol (9.39 g, 48.9 mmol) in 75 mL CH_2Cl_2 was added to the reaction solution. After an additional 2 h at 0 °C the reaction mixture was concentrated in vacuo to give an off-white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 17:2:1 hexanes/ Et_2O/CH_2Cl_2 → 3:6:1 hexanes/ Et_2O/CH_2Cl_2) afforded bromide **14b** (2.77 g, 23%) as an off-white solid. A yield of 31% was obtained on a 75 mg scale. mp 90-92 °C; IR (thin film) 2205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (app t, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 4.26 (s, 2H), 3.78 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.5, 130.2, 103.1, 99.9, 92.1, 79.4, 55.7, 16.2; LRMS (ESI) *m/z* (relative intensity) 255.1 (100%, M + H^+).

2-(3-Bromo-prop-1-ynyl)-1,4-dimethoxybenzene (14c). To a stirring solution of 1-bromo-2,5-dimethoxybenzene (17.0 g, 78.1 mmol) in 250 mL of pyrrolidine was added propargyl alcohol (9.17 mL, 156 mmol) and $Pd(PPh_3)_4$ (4.76 g, 3.91 mmol). The reaction mixture was heated at reflux for 14 h, cooled to room temperature, and then saturated aqueous NH_4Cl (120 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 20% EtOAc/hexanes → 30% EtOAc/hexanes) afforded 3-(2,5-dimethoxyphenyl)-prop-2-yn-1-ol (6.70 g, 45%) as an orange solid. Spectral data matched those reported by Franks.[16]

To a stirring solution of PPh_3 (8.29 g, 31.6 mmol) in 80 mL of CH_2Cl_2 at 0 °C was added Br_2 (1.63 mL, 31.7 mmol). After 30 min, a solution of 3-(2,5-dimethoxyphenyl)-prop-2-yn-1-ol (6.06 g, 31.5 mmol) in 40 mL CH_2Cl_2 was added to the reaction mixture. After an additional 5 h, the reaction solution was concentrated in vacuo to give an off-white solid. Purification of this solid by SiO_2 flash column chromatography (10% EtOAc/hexanes as eluent) afforded bromide **14c** (7.47 g, 93%) as an off-white solid. mp 47-48 °C; IR (thin film) 2205 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.91 (d, J = 2.9 Hz, 1H), 6.84-6.73 (m, 2H), 4.18 (s, 2H), 3.78 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 154.6, 152.9, 118.2, 116.2, 111.8, 111.5, 88.0, 83.0, 56.2, 55.6, 15.6; LRMS (ESI) *m/z* (relative intensity) 255.1 (80%, $M + H^+$).

2-(3-Bromoprop-1-ynyl)-1,4-bis-methoxymethoxybenzene (14d). To a stirring suspension of 60% NaH (2.8 g, 53 mmol) in 100 mL of DMF at 0 °C was added a solution of bromohydroquinone (5.00 g, 26.5 mmol) in 50 mL DMF. After 10 min, chloromethyl methyl ether (4.4 mL, 53 mmol) was added and the mixture was warmed to room temperature and stirred for an additional 14 h. To the reaction mixture was added H_2O (300 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organic fractions were washed with H_2O (3 x 300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-bromo-1,4-bis-methoxymethoxy-benzene (**16d**) (7.34 g, 100%) as a colorless oil. IR (thin film) 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 2.9 Hz, 1H), 7.09 (dd, J = 9.0, 0.8 Hz, 1H), 6.95 (ddd, J = 9.0, 2.9, 0.8 Hz, 1H), 5.18 (d, J = 1.0 Hz, 2H), 5.11 (d, J = 1.0 Hz, 2H), 3.53 (d, J = 1.0 Hz, 3H), 3.48 (d, J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 148.8, 121.3, 117.4, 116.3, 113.2, 95.7, 94.9, 56.2, 55.8.

To a stirring suspension of NaH (0.174 g, 7.25 mmol) in 150 mL of THF was added a solution of 2-bromo-1,4-bis-methoxymethoxybenzene (**16d**) (7.07 g, 25.5 mmol) in 20 mL of THF. After 30 min, the reaction mixture was cooled to -84 °C and *n*-BuLi (2.5 M in hexanes, 12.3 mL, 30.6 mmol) was added dropwise via syringe. The reaction solution was held at this temperature for 10 min after which a

solution of I_2 (13.0 g, 51.0 mmol) in 45 mL was added. The reaction mixture was allowed to warm to room temperature and aqueous $Na_2S_2O_3$ was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-iodo-1,4-bis-methoxymethoxybenzene (8.01 g, 97%) as a light brown oil. IR (thin film) 1478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.08-6.92 (m, 2H), 5.14 (s, 2H), 5.07 (s, 2H), 3.49 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 152.6, 151.3, 127.2, 117.3, 115.8, 95.6, 95.0, 87.3, 56.3, 55.9. LRMS (ESI) *m/z* (relative intensity) 294.1 (10%, $M + NH_4^+$).

To a stirring solution of 2-iodo-1,4-bis-methoxymethoxybenzene (3.27 g, 10.1 mmol) in 100 mL of pyrrolidine was added propargyl alcohol (1.20 mL, 19.7 mmol) and $Pd(PPh_3)_4$ (0.563 g, 0.505 mmol). The reaction mixture was heated at reflux for 16 h, and then allowed to cool to room temperature. Saturated aqueous NH_4Cl (100 mL) was added. The resulting solution was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (60% Et_2O/hexanes as eluent) afforded 3-(2,5-bis-methoxymethoxy-phenyl)-prop-2-yn-1-ol (1.22 g, 48%) as a light brown oil. A yield of 66% was obtained on a 23 mg scale. IR (thin film) 3425 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.05-7.04 (m, 1H), 6.98 (dd, J = 9.0, 2.2 Hz, 1H), 6.91-6.88 (m, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 4.45 (d, J = 1.8 Hz, 2H), 3.45 (s, 3H), 3.40 (s, 3H), 1.16 (t, J = 1.8 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 152.8, 151.6, 121.0, 118.2, 116.8, 114.0, 95.6, 94.9, 91.7, 81.3, 56.1, 55.8, 51.4; LRMS (ESI) *m/z* (relative intensity) 253.2 (100%, $M + H^+$).

To a stirring solution of 3-(2,5-bis-methoxymethoxyphenyl)prop-2-yn-1-ol (1.22 g, 4.83 mmol) and Et_3N (2.0 mL, 14 mmol) in 20 mL of Et_2O at 0 °C was added MsCl (416 μL, 5.40 mmol). After 1 h, saturated aqueous $NaHCO_3$ (30 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (25 mL) followed by EtOAc (25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the mesylate. To the crude mesylate was added 20 mL of $CHCl_3$ and NBu_4Br (2.46 g, 7.63 mmol). The resulting solution was refluxed 30 min and concentrated in vacuo. EtOAc (20 mL) was added to the crude mixture, washed with H_2O (20 mL) followed by brine (20 mL). The organic fraction was dried with Na_2SO_4 and concentrated in vacuo to give bromide **14d** (1.48 g, 97%) as a tacky orange solid. This material was used without further purification. IR (thin film) 2226 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.06 (d, J = 2.9 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.92 (dd, J = 9.0, 2.9 Hz, 1H), 5.13 (s, 2H), 5.05 (s, 2H), 4.15 (s, 2H), 3.47 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.0, 151.6, 120.9, 118.7,

116.9, 113.5, 95.6, 94.8, 87.9, 82.8, 56.1, 55.7, 15.3; LRMS (ESI) *m/z* (relative intensity) 315.0 (90%, M + H^+).

1-Methoxy-2-[3-(nona-1,8-diyne-3-sulfonyl)prop-1-ynyl]benzene (15a). To a stirring suspension of K_2CO_3 (0.254 g, 1.84 mmol) in 7 ml of MeCN was added a solution of thiol **13a** (0.432 g, 2.83 mmol) in 3 mL of MeCN. The reaction mixture was stirred for 10 min and then bromide **14a** (404 μL, 2.83 mmol) was added. The reaction mixture was heated at 60 °C for 14 h, cooled to room temperature, and then 1M phosphoric acid (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give the sulfide as a yellow oil, which was carried on without further purification. IR (thin film) 3284, 2214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.26 (td, *J* = 7.9, 1.7 Hz, 1H), 6.87 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.92-3.86 (m, 1H), 3.85 (s, 3H), 3.81 (d, *J* = 16.8 Hz, 1H), 3.62 (d, *J* = 16.8 Hz, 1H), 2.39 (d, *J* = 2.4 Hz, 1H), 2.19 (td, *J* = 6.9, 2.6 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.82 (t, *J* = 7.0 Hz, 2H), 1.69-1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 133.3, 129.6, 120.2, 111.9, 110.4, 89.3, 83.9, 82.8, 79.5, 72.1, 68.4, 55.5, 34.0, 33.7, 27.7, 26.2, 20.1, 18.1; LRMS (ESI) *m/z* (relative intensity) 297.1 (60%, M + H^+).

A stirring suspension of crude sulfide from above and Na_2CO_3 (1.07 g, 10.1 mmol) in 65 ml of CH_2Cl_2 was treated with 70% *m*CPBA (0.917 g, 5.04 mmol). The reaction mixture was heated at reflux for 12 h, cooled to room temperature, and then saturated aqueous $NaHCO_3$ (70 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were sequentially washed with 1M H_3PO_4 (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (5% Et_2O/hexanes, then CH_2Cl_2 as eluent) gave sulfone **15a** (0.343 g, 37% over 2 steps) as a light yellow oil. IR (thin film) 3272, 2359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 1H), 7.31 (tdd, *J* = 8.0, 1.7, 1.0 Hz, 1H), 6.88 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.55 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.44-4.39 (m, 1H), 4.13 (d, *J* = 17.0 Hz, 1H), 3.84 (s, 3H), 2.60 (d, *J* = 2.5 Hz, 1H), 2.20 (td, *J* = 6.1, 2.0 Hz, 2H), 2.13-2.07 (m, 1H), 2.01-1.92 (m, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.85-1.79 (m, 1H), 1.60-1.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 133.5, 130.6 (2), 120.4, 110.6, 84.5, 83.7, 79.9, 75.8, 68.7 (2), 55.7, 44.3, 44.2, 27.7, 25.8, 25.7, 18.1; LRMS (ESI) *m/z* (relative intensity) 346.2 (50%, M + NH_4^+). HRMS (ESI) *m/z* calcd for $[C_{19}H_{24}NO_3S]^+$, 346.1477, found 346.1474.

***tert*-Butyl-{3-[3-(2-methoxyphenyl)-prop-2-yne-1-sulfonyl]nona-1,8-diynyl}dimethylsilane (15b).** To a stirring solution of solid LHMDS (3.39 g, 20.3 mmol) in 120 mL of THF at 0 °C was added a solution of thiol **13b** (5.14 g, 19.3 mmol) in 120 mL of THF. The reaction mixture was stirred for 5 min

at 0 °C and treated with bromide **14a** (2.9 mL, 19 mmol). After 14 h, the reaction mixture was warmed to room temperature and H_2O (120 mL) was added. The resulting mixture was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic fractions were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give tert-butyl-{3-[3-(2-methoxyphenyl)prop-2-ynylsulfanyl]nona-1,8-diynyl}dimethylsilane as a yellow oil that was used without further purification. IR (thin film) 3295, 2150 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.26 (td, *J* = 7.9, 1.8 Hz, 1H), 6.90-6.83 (m, 2H), 3.91 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 16.9 Hz, 1H), 3.65 (d, *J* = 16.6 Hz, 1H), 2.19 (td, *J* = 6.5, 2.5 Hz, 2H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.83 (q, *J* = 7.0 Hz, 2H), 1.75-1.66 (m, 2H), 1.58 (q, *J* = 7.2 Hz, 2H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.0, 133.5, 129.4, 120.2, 112.1, 110.4, 105.1, 89.1, 86.9, 84.0, 79.4, 68.3, 56.0, 35.1, 34.0, 27.8, 26.1, 26.0, 20.2, 18.2, 16.4, -4.6; LRMS (ESI) *m/z* (relative intensity) 433.0 (100%, M + Na^+). HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{25}H_{38}NOSSi]^+$, 428.2443, found 428.2427.

To a stirring solution of tert-butyl-{3-[3-(2-methoxyphenyl)-prop-2-ynylsulfanyl]nona-1,8-diynyl}dimethylsilane (7.15 g, 17.3 mmol) in 500 mL of CH_2Cl_2 was added 70-75% *m*CPBA (8.57 g, 34.6 mmol). The reaction mixture was stirred for 1.5 h and then treated with Et_3N (5.2 mL, 37 mmol) followed by H_2O (500 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 400 mL). The organic fractions were washed with brine (800 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (8:1:1 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded linear sulfone **15b** (3.74 g, 44% over 2 steps) as a yellow oil. IR (thin film) 3284, 2355, 1326, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.33 (td, *J* = 3.9, 1.7 Hz, 1H), 6.93-6.85 (m, 2H), 4.55 (d, *J* = 16.9 Hz, 1H), 4.42 (dd, *J* = 10.5, 4.3 Hz, 1H), 4.13 (d, *J* = 16.9 Hz, 1H), 3.85 (s, 3H), 2.22 (td, *J* = 6.7, 2.6 Hz, 2H), 2.17-2.00 (m, 1H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.88-1.75 (m, 1H), 1.74-1.58 (m, 4H), 0.94 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 133.5, 130.5, 120.3, 110.8, 110.6, 97.4, 93.0, 84.3, 83.7, 79.9, 68.6, 55.7, 54.7, 44.1, 27.7, 26.0, 25.9, 25.8, 18.1, 16.6, -5.0; LRMS (ESI) *m/z* (relative intensity) 460.3 (90%, M + NH_4^+). HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{25}H_{38}NO_3SSi]^+$, 460.2342, found 460.2342.

***tert*-Butyl-{3-[3-(2,6-dimethoxyphenyl)prop-2-yne-1-sulfonyl]nona-1,8-diynyl}dimethylsilane (15c).** To a stirring solution of NaH (75 mg, 1.9 mmol) in 14 mL of THF at 0 °C was added a solution of thiol **13b** (0.50 g, 1.9 mmol) in 3 mL of THF. The reaction mixture was held at this temperature for 15 min and then bromide **14b** (0.479 g, 1.88 mmol) in 3 mL of CH_2Cl_2 was added to the reaction solution. After an additional 30 min at 0 °C, H_2O (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic

fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (5% Et_2O/hexanes) afforded *tert*-butyl-{3-[3-(2,6-dimethoxyphenyl)prop-2-ynylsulfanyl]nona-1,8-diynyl}dimethylsilane (0.657 g, 80%) as a yellow oil. IR (thin film) 3295, 2155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (app t, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 2H), 4.01 (t, *J* = 6.9 Hz, 1H), 3.85-3.79 (m, 1H), 3.83 (s, 6H), 3.66 (d, *J* = 16.8 Hz, 1H), 2.16 (td, *J* = 6.9, 2.6 Hz, 2H), 1.89 (t, *J* = 2.6 Hz, 1H), 1.82-1.77 (m, 2H), 1.73-1.52 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 129.4, 105.4, 103.3, 101.3, 93.5, 86.6, 84.1, 75.7, 68.3, 55.9, 34.9, 33.9, 27.9, 26.4, 26.0, 20.6, 18.2, 16.5, -4.6; LRMS (ESI) *m/z* (relative intensity) 441.1 (100%, M + H^+).

To a stirring solution of *tert*-butyl-{3-[3-(2,6-dimethoxyphenyl)prop-2-ynylsulfanyl]nona-1,8-diynyl}dimethylsilane (0.108 g, 0.243 mmol) in 10 mL of CH_2Cl_2 at room temperature was added 70-75% *m*CPBA (0.123 g, 0.498 mmol). The reaction mixture was stirred for 3 h and then saturated aqueous $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 18:1:1 hexanes/Et_2O/CH_2Cl_2 → 4:5:1 hexanes/Et_2O/ CH_2Cl_2) afforded sulfone **15c** (98 mg, 85%) as a yellow oil. IR (thin film) 3284, 1326, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (app t, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 2H), 4.61 (dd, *J* = 10.5, 4.1 Hz, 1H), 4.57 (d, *J* = 17.0 Hz, 1H), 4.15 (d, *J* = 16.9 Hz, 1H), 3.86 (s, 6H), 2.24 (td, *J* = 6.7, 2.6 Hz, 2H), 2.08-2.05 (m, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.95-1.82 (m, 1H), 1.75-1.60 (m, 4H), 0.97 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 131.3, 104.0, 98.3, 97.6, 93.2, 84.9, 84.4, 81.4, 69.0, 56.6, 54.8, 45.1, 28.4. 26.6, 26.5, 26.3, 18.6, 17.1, -4.6; LRMS (ESI) *m/z* (relative intensity) 490.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{26}H_{40}NO_4SiS]^+$, 490.2447, found 490.2453.

***tert*-Butyl-{3-[3-(2,5-dimethoxyphenyl)-prop-2-yne-1-sulfonyl]nona-1,8-diynyl}dimethylsilane (15d).** To a stirring solution of NaH (0.118 g, 2.96 mmol) in 30 mL of THF at 0 °C was added a solution of thiol **13b** (0.789 g, 2.96 mmol) in 10 mL of THF. After 15 min, a solution of bromide **14c** (0.755 g, 2.96 mmol) in 5 mL of CH_2Cl_2 was added to the reaction solution. After an additional 30 min at 0 °C, H_2O (50 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give *tert*-butyl-{3-[3-(2,5-dimethoxyphenyl)-prop-2-ynylsulfanyl]nona-1,8-diynyl}dimethylsilane as a yellow oil. This material was used without further purification. IR (thin film) 3284 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.8 Hz, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 6.77 (s, 1H), 3.87 (t, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 19.3 Hz, 1H), 3.72 (s, 3H), 3.62 (d, *J* = 16.7 Hz, 1H), 2.17 (td, *J* = 6.9, 2.6 Hz, 2H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.81-1.77 (m, 2H),

1.70-1.66 (m, 2H), 1.64-1.53 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 153.1, 118.3, 115.4, 112.7, 111.9, 105.0, 89.3, 87.1, 84.1, 79.4, 68.4, 56.3, 55.7, 35.3, 34.1, 27.9, 26.4, 26.1, 20.2, 18.2, 16.5, -4.6; LRMS (ESI) *m/z* (relative intensity) 441.3 (100%, M + H^+).

To a stirring solution of the crude *tert*-butyl-{3-[3-(2,5-dimethoxyphenyl)-prop-2-ynylsulfanyl]nona-1,8-diynyl}dimethylsilane in 45 mL of CH_2Cl_2 at room temperature was added 70-75% *m*CPBA (1.61 g, 5.92 mmol). The reaction mixture was stirred for 1 h and then Et_3N (883 μL, 6.34 mmol) followed by saturated aqueous $NaHCO_3$ (50 mL) were added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give an orange oil. Purification of this oil by SiO_2 flash column chromatography (10% EtOAc/hexanes as eluent) afforded linear sulfone **15d** (0.657 g, 47% over 2 steps) as an orange oil. IR (thin film) 3284, 1326, 1126 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.9 Hz, 1H), 6.85 (d, *J* = 3.2 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 4.51 (d, *J* = 16.6 Hz, 1H), 4.39 (dd, *J* = 10.4, 4.3 Hz, 1H), 4.10 (d, *J* = 16.9 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.19 (td, *J* = 6.7, 2.7 Hz, 2H), 2.13-2.03 (m, 1H), 1.90 (t, *J* = 2.5 Hz, 1H), 1.86-1.72 (m, 1H), 1.64-1.50 (m, 4H), 0.92 s, 9H), 0.11 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.1, 153.0, 118.1, 116.4, 111.9, 111.2, 97.4, 92.9, 84.1, 83.6, 79.9, 68.6, 56.2, 55.7, 54.8, 44.0, 27.6, 25.9 (2), 25.8, 18.0, 16.5, -5.1; LRMS (ESI) *m/z* (relative intensity) 490.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{26}H_{40}NO_4SiS]^+$, 490.2447, found 490.2438.

{3-[3-(2,5-Bis-methoxymethoxyphenyl)-prop-2-yne-1-sulfonyl]nona-1,8-diynyl}*tert*-butyldimethylsilane (15e). To a stirring solution of LHMDS (0.742 g, 4.19 mmol) in 30 mL of THF at 0 °C was added a solution of thiol **13b** (1.12 g, 4.19 mmol) in 15 mL of THF. After 15 min, a solution of bromide **14d** (1.32 g, 4.19 mmol) in 10 mL of THF was added to the reaction solution and after an additional 14 h at 0 °C, H_2O (60 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (95:4:1 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded {3-[3-(2,5-bis-methoxymethoxyphenyl)-prop-2-ynylsulfanyl]nona-1,8-diynyl}tert-butyldimethylsilane (1.33 g, 63%) as a yellow oil. A yield of 68% was obtained on a 0.389 g scale. IR (thin film) 3295, 2155 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.05 (d, *J* = 2.9 Hz, 1H), 6.99 (d, *J* = 9.0, 1H), 6.91 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 3.87 (t, *J* = 7.0 Hz, 1H), 3.76 (d, *J* = 16.9 Hz, 1H), 3.60 (d, *J* = 16.6 Hz, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 2.18 (td, *J* = 6.8, 2.5 Hz, 2H), 1.91 (t, *J* = 2.7 Hz, 1H), 1.82-1.76 (m, 2H), 1.70-1.60 (m, 2H), 1.60-1.53 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.0, 151.8, 121.0, 117.9, 117.1, 114.7, 105.0, 95.7, 95.0, 89.2, 87.1, 84.1, 79.2, 68.4, 56.2, 55.9, 35.2, 34.0, 27.9, 26.4, 26.1, 20.2, 18.2, 16.5, -4.6; LRMS (ESI) *m/z* (relative intensity) 518.3 (100%, M + NH_4^+).

To a stirring solution of {3-[3-(2,5-bismethoxymethoxyphenyl)-prop-2-ynylsulfanyl]nona-1,8-diynyl}tert-butyldimethylsilane (0.830 g, 1.66 mmol) in 50 mL of CH_2Cl_2 was added *m*CPBA (0.857 g, 3.49 mmol). After 90 min, additional *m*CPBA (82 mg, 0.33 mmol) was added to the reaction mixture. After 30 min, saturated aqueous $NaHCO_3$ (50 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic fractions were washed with 1M phosphoric acid (50 mL). The aqueous fraction was back-extracted with CH_2Cl_2 (50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 15% Et_2O/hexanes as eluent) afforded linear sulfone **15d** (0.528 g, 60%). IR (thin film) 3284, 1331, 1149 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.03 (d, *J* = 2.5 Hz, 1H), 6.98-6.90 (m, 2H), 5.10 (s, 2H), 5.02 (s, 2H), 4.48 (d, *J* = 16.9 Hz, 1H), 4.35 (dd, *J* = 10.4, 4.1 Hz, 1H), 4.10 (d, *J* = 16.9 Hz, 1H), 3.42 (s, 3H), 3.37 (s, 3H), 2.16-2.13 (m, 2H), 2.09-1.92 (m, 2H), 1.90 (t, *J* = 2.5 Hz, 1H), 1.82-1.69 (m, 1H), 1.62-1.47 (m, 3H), 0.86 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.2, 151.4, 120.6, 118.7, 116.5, 112.8, 97.3, 95.2, 94.6, 92.8, 83.7, 83.5, 79.9, 68.7, 55.9, 55.6, 54.7, 43.7, 27.5, 25.7 x 2, 25.6, 17.8, 16.3, -5.2; LRMS (ESI) *m*/*z* (relative intensity) 550.0 (100%, M + NH_4^+).

1-Hex-5-ynyl-5-methoxy-1,3-dihydro-naphtho[2,3-*c*]thiophene 2,2-Dioxide (17). A stirring solution of sulfone **15a** (209 mg, 0.635 mmol) in 20 mL of $CHCl_3$ was treated with Et_3N (136 μL, 0.953 mmol). The reaction mixture was stirred for 3 d and concentrated in vacuo to give tricycle **17** (209 mg, 100%) as a yellow solid. mp 141-143 ºC; IR (thin film) 3284, 1308, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.68 (s, 1H), 7.44-7.39 (m, 2H), 6.84 (d, *J* = 6.8 Hz, 1H), 4.43 (s, 2H), 4.29 (t, *J* = 7.1 Hz, 1H), 3.99 (s, 3H), 2.27 (td, *J* = 7.0, 2.1 Hz, 2H), 2.25-2.04 (m, 2H), 1.98 (t, *J* = 2.2 Hz, 1H), 1.88-1.76 (m, 2H), 1.75-1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 134.3, 134.0, 127.05, 127.02, 125.1, 124.1, 120.0, 119.8, 104.6, 83.9, 68.7, 64.9, 55.6, 55.2, 29.0, 28.2, 25.6, 18.1; LRMS (ESI) *m*/*z* (relative intensity) 346.1 (100%, M + NH_4^+).

***tert*-Butyl-(3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-*c*]thiophen-4-yl)dim ethylsilane (19).** To a refluxing solution of linear sulfone **15b** (0.125 g, 0.282 mmol) in 10 mL of toluene was added Et_3N (59 μL, 0.42 mmol). The reaction mixture was held at reflux for 14 h and then cooled to room temperature and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient 10% Et_2O/hexanes → 20% Et_2O/hexanes as eluent) afforded tricycle **19** (80 mg, 64%) as a yellow oil. IR (thin film) 3300, 1290, 1120 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.10 (app t, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 4.01-3.82 (m, 3H), 3.82 (s, 3H), 2.58-2.50 (m, 1H), 2.45-2.36 (m, 1H), 2.21 (td, *J* = 7.0, 2.7 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.86-1.79 (m, 2H), 1.62-1.58 (m, 2H), 0.91 (s, 9H), 0.00 (s, 3H), -0.35 (s, 3H); ^{13}C

NMR (90 MHz, $CDCl_3$) δ 155.4, 146.6, 137.9, 131.8, 128.5, 125.8, 120.2, 120.1, 119.6, 107.8, 84.0, 68.6, 55.5, 53.3, 34.6, 28.1, 27.3, 26.8, 23.5, 18.4, 18.0, -4.5, -6.2; LRMS (ESI) *m/z* (relative intensity) 443.3 (100%, M + H^+). HRMS (ESI) *m/z* calcd for $[C_{25}H_{38}NO_3SSi]^+$, 460.2342, found 460.2350.

Conversion of Dimethoxy Sulfone 15c to Tricycle 19. To a refluxing solution of linear sulfone **15c** (66 mg, 0.14 mmol) in 5 mL of toluene was added Et_3N (29 μL, 0.21 mmol). The reaction mixture was heated at reflux for 14 h, cooled to room temperature and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 30% Et_2O/hexanes as eluent) afforded tricycle **19** (17 mg, 28%) as a yellow oil.

***tert*-Butyl-(3-hex-5-ynyl-5,8-dimethoxy-2,2-dioxo-2,4-dihydro-1*H*-2α^6-naphtho[2,3-*c*]thiophen-4-yl) dimethylsilane (21).** To a solution of sulfone **15d** (0.206 g, 0.434 mmol) in 10 mL of toluene at 110 °C was added Et_3N (90 μL, 0.65 mmol). The reaction mixture was held at reflux for 14 h, cooled to room temperature and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% Et_2O/hexanes as eluent) afforded *tert*-butyl-(3-hex-5-ynyl-5,8-dimethoxy-2,2-dioxo-2,4-dihydro-1*H*-2α^6-naphtho[2,3-c]thiophen-4-yl)dimethylsilane (**21**) (95 mg, 46%) as a tacky yellow solid. IR (thin film) 3284, 1284, 1114 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 6.57 (d, *J* = 9.0 Hz, 1H), 4.25 (s, 1H), 3.95 (d, *J* = 15.1 Hz, 1H), 3.86 (d, *J* = 15.5 Hz, 1H), 3.74 (s, 6H), 2.53-2.44 (m, 2H), 2.16 (td, *J* = 5.6, 2.2 Hz, 2H), 1.91-1.87 (m, 1H), 1.86-1.73 (m, 2H), 1.59-1.53 (m, 2H), 0.84 (s, 9H), -0.04 (s, 3H), -0.38 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 149.7, 148.5, 147.1, 132.1, 126.6, 125.7, 120.9, 120.0, 109.9, 107.5, 83.9, 68.5, 55.8, 54.8, 53.3, 28.0, 27.8, 27.0, 26.7, 23.7, 18.3, 17.9, -4.3, -5.7; LRMS (ESI) *m/z* (relative intensity) 473.2 (100%, M + H^+).

***tert*-Butyl-(3-hex-5-ynyl-5,8-bis-methoxymethoxy-2,2-dioxo-2,4-dihydro-1*H*-2α^6-naphtho[2,3-*c*]thio phen-4-yl)dimethylsilane (22).** A solution of sulfone **15e** (0.528 g, 0.991 mmol) in 10 mL of benzene was heated to reflux and then treated with Et_3N (242 μL, 1.49 mmol). The reaction mixture was held at this temperature for 3 d, cooled to room temperature, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10% Et_2O/hexanes → 40% Et_2O/hexanes as eluent) afforded tricycle **22** (0.237 g, 45 %) as yellow oil. IR (thin film) 3284, 1284, 1114 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.89 (d, *J* = 9.4 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 5.16-5.02 (m, 4H), 4.23 (s, 1H), 3.95 (d, *J* = 15.1 Hz, 1H), 3.86 (d, *J* = 15.1 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.53-2.40 (m, 2H), 2.12 (td, *J* = 5.6, 2.2 Hz, 2H), 1.87 (s, 1H), 1.80-1.74 (m, 2H), 1.56-1.50 (m, 2H), 0.83 (s, 9H), -0.05 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.0, 147.3, 146.6, 132.3, 126.3, 121.7, 119.9, 119.8, 114.6, 111.9, 95.1, 95.0, 83.7, 68.4, 56.1, 55.8, 53.2, 27.8, 26.89, 26.87, 26.6, 23.5, 18.1, 17.7, -4.5, -5.7; LRMS (ESI) *m/z* (relative intensity) 533.3 (100%, M + H^+).

1-Hex-5-ynyl-2,2-dioxo-2,3-dihydro-1*H*-2α^6-naphtho[2,3-c]thiophene-5,8-dione (23). A stirring solution of sulfone **17** (0.209 g, 0.635 mmol) in 15 ml of acetone was treated with Jones reagent (695 μL,

2.54 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 14 h after which time additional Jones reagent (695 μL, 2.54 mmol) was added. The reaction mixture was stirred for 1 h at room temperature and then isopropanol (15 mL) and H_2O (15 mL) were added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this yellow oil by SiO_2 flash column chromatography (15:4:1 hexanes/Et_2O/CH_2Cl_2, then 13:5:2 hexanes/Et_2O/CH_2Cl_2 as eluent) gave quinone **23** (126 mg, 60%) as a yellow oil. IR (thin film) 3272, 1666, 1314, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (app d, *J* = 5.1 Hz, 2H), 7.01 (s, 2H), 7.68 (s, 1H), 4.41 (app s, 2H), 4.29 (dd, *J* = 8.4, 6.0 Hz, 1H), 2.25 (td, *J* = 6.8, 2.6 Hz, 2H), 2.19-2.11 (m, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.84-1.76 (m, 2H), 1.67 (q, *J* = 4.4 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 183.9, 183.8, 142.4, 138.7 (2), 136.6, 132.0, 131.8, 124.2, 123.5, 83.6, 69.0, 65.3, 55.3, 28.7, 28.0, 25.6, 18.1; LRMS (ESI) *m/z* (relative intensity) 351.2 (100%, M + Na^+).

***tert*-Butyl-(3-hex-5-ynyl-8-methoxy-2,2-dioxo-1-phenylsulfanyl-2,4-dihydro-1*H*-2α^6-naphtho[2,3-*c*] thiophen-4-yl)dimethylsilane (25a).** To a stirring solution of tricycle **19** (0.24 g, 0.55 mmol) in 7 mL of THF at -78 °C was added *n*-BuLi (2.5M in hexanes, 220 μL, 0.55 mmol) dropwise. The reaction mixture was held at this temperature for 15 min and then diphenyl disulfide (1.2 g, 5.5 mmol) was added and the solution was warmed to 0 °C over 30 min. The mixture was held at this temperature for 4 h and then H_2O (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (95:5:2 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded thiophenyl adduct **25a** (0.197 g, 65%) as a yellow oil. IR (thin film) 3284, 1297, 1108 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 9.4, 1.8 Hz, 2H), 7.37-7.29 (m, 3H), 7.22 (s, 1H), 7.12 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.06 (d, *J* = 1.1 Hz, 1H), 3.92 (s, 1H), 3.83 (s, 3H), 2.58-2.50 (m, 1H), 2.43-2.37 (m, 1H), 2.21 (td, *J* = 7.0, 2.7 Hz, 2H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.87-1.81 (m, 2H), 1.64-1.54 (m, 2H), 0.94 (s, 9H), 0.08 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.8, 145.3, 138.3, 133.0, 131.9, 130.4, 129.3, 129.2, 128.2, 127.5, 123.9, 120.3, 119.8, 107.9, 84.0, 68.7, 67.7, 56.3, 34.8, 28.2, 27.7, 26.8, 24.1, 18.5, 18.0, -4.0, -6.2; LRMS (ESI) *m/z* (relative intensity) 568.3 (100%, M + NH_4^+). HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{31}H_{42}NO_3S_2Si]^+$, 568.2375, found 568.2397.

(1-Benzenesulfinyl-3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2α^6-naphtho[2,3-*c*]thiophen-4-yl)-*tert*-butyldimethylsilane (25b). To a stirring solution of phenyl sulfide **25a** (0.173 g, 0.314 mmol) in 25 mL of CH_2Cl_2 was added 70-75% *m*CPBA (75 mg, 0.31 mmol). The reaction mixture was stirred for 2 h at room temperature and then saturated aqueous $NaHCO_3$ (25 mL) was added. The resulting

solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (17:3:1 hexanes/EtOAc/CH_2Cl_2 as eluent) afforded sulfoxide **25b** (79 mg, 44%) as a yellow oil. A yield of 48% was obtained on a 427 mg scale. IR (thin film) 3295, 1291, 1149 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.94 (d, *J* = 4.0 Hz, 2H), 7.64-7.56 (m, 3H), 7.16 (app t, *J* = 7.9, 1H), 6.95 (s, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 4.60 (s, 1H), 3.97 (s, 1H), 3.81 (s, 3H), 2.56-2.52 (m, 1H), 2.48-2.39 (m, 1H), 2.27-2.19 (m, 2H), 2.00-1.95 (m, 1H), 1.91-1.73 (m, 2H), 1.67-1.55 (m, 2H), 1.01 (s, 9H), 0.22 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 156.1, 146.9, 142.9, 138.3, 131.9, 130.3, 129.39, 129.38, 126.4, 125.4, 121.3, 120.1, 119.7, 107.5, 83.8, 80.7, 68.7, 56.2, 34.8, 28.0, 27.7, 26.6, 23.6, 18.4, 17.9, -6.7; LRMS (ESI) *m/z* (relative intensity) 567.3 (100%, M + H^+).

(1-Benzenesulfonyl-3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2α^6-naphtho[2,3-*c*]thiophen-4-yl)-*tert*-butyldimethylsilane (25c). To a stirring solution of thiophene **25a** (72 mg, 0.13 mmol) in 5 mL of CH_2Cl_2 at room temperature was added 70-75% *m*CPBA (86 mg, 0.34 mmol). The reaction mixture was stirred for 30 min at room temperature and saturated aqueous $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 20% Et_2O/hexanes as eluent) afforded sulfone **25c** (45 mg, 59%) as a yellow oil. IR (thin film) 3284, 1303, 1108 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.2 Hz, 2H), 7.70-7.66 (m, 1H), 7.60-7.55 (m, 2H), 7.45 (s, 1H), 7.14 (app t, *J* = 7.9 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 5.07 (s, 1H), 3.96 (s, 1H), 3.83 (s, 3H), 2.47-2.43 (m, 1H), 2.36-2.34 (m, 1H), 2.17 (td, *J* = 7.0, 2.5 Hz, 2H), 1.92 (t, *J* = 2.5 Hz, 1H), 1.82-1.64 (m, 2H), 1.63-1.53 (m, 2H), 0.93 (s, 9H), 0.07 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 156.2, 147.0, 138.3, 138.2, 134.6, 130.4, 130.0, 129.7, 129.0, 127.4, 120.1, 120.0, 119.9, 108.1, 83.8, 78.3, 68.7, 55.5, 35.5, 28.0, 27.8, 27.4, 26.6, 23.8, 18.6, 17.9, -5.5, -7.0; LRMS (ESI) *m/z* (relative intensity) 600.2 (100%, M + NH_4^+). HRMS (ESI) *m/z* calcd for $[C_{31}H_{42}NO_5S_2Si]^+$, 600.2274, found 600.2277.

1-Hex-5-ynyl-5-methoxy-3-phenylsulfanyl-1,3-dihydro-naphtho[2,3-*c*]thiophene 2,2-Dioxide (26). To a stirring solution of **25a** (17 mg, 0.031 mmol) in 1 mL of THF at 0 °C was added Bu_4NF (1.0 M in THF, 33 μL, 0.032 mmol). The reaction mixture was stirred for 20 min at 0 °C and then H_2O (5 mL) were added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give a 1:1 mixture of diastereomers of thiophenyl adduct **26** (12 mg, 86%) as a yellow oil. IR (thin film) 3284, 1314, 1102 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$, mixture of diastereomers) δ 8.52 (s, 1H), 8.46 (s, 1H), 7.76-7.59 (m, 6H), 7.44-7.30 (m, 10H), 6.85 (d, *J* = 7.3 Hz, 2H), 5.56 (s, 1H), 5.50 (s, 1H), 4.29 (t, *J* = 7.2 Hz, 1H), 4.17 (t, *J* = 7.1 Hz, 1H), 4.02 (s, 6H), 2.29-2.20 (m, 6H), 2.20-2.01 (m, 2H), 1.97-1.94 (m, 2H), 1.91-1.81 (m, 4H), 1.73-1.62 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$, mixture of diastereomers) δ 155.4 (2), 134.52, 134.48, 133.9, 133.1, 132.9 (2), 132.5, 131.2, 129.3 (2), 129.2 (2), 128.95, 128.93, 128.65, 128.62, 127.7 (2), 125.30, 125.26, 124.01, 123.8, 121.7, 121.5, 119.86, 119.84, 83.96, 83.93, 71.7, 70.6, 68.7 (2), 63.9, 62.2, 55.6 (2), 29.7, 28.16, 28.13, 26.1, 25.8, 25.6, 18.1 (2); LRMS (ESI) *m/z* (relative intensity) 454.2 (100%, M + NH_4^+). HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{25}H_{28}NO_3S_2]^+$, 454.155, found 454.1510.

4-(*tert*-Butyl-dimethyl-silanyl)-3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-*c*]thiophen-1-ol (27). To a stirring solution of sulfoxide **25b** (0.213 g, 0.376 mmol) in 5 mL of toluene was added Et_2NH (389 μL, 3.76 mmol). The reaction mixture was then heated at 65 °C for 36 h and then warmed to 110 °C for an additional 12 h. The reaction solution was cooled to room temperature and H_2O (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5-15% Et_2O/hexanes, then 30% EtOAc/hexanes as eluent) afforded a 3:1 mixture of diastereomers of alcohol **27** (49 mg, 28%) as a yellow oil. IR (thin film) 3389, 3295, 1269, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 7.24-7.07 (m, 2H), 6.65-6.60 (m, 2H), 5.35 (s, 1H), 3.93-3.78 (m, 1H), 3.78 (s, 3H), 2.60-2.44 (m, 1H), 2.44-2.30 (m, 1H), 2.26-2.10 (m, 2H), 1.89 (s, 1H), 1.86-1.69 (m, 2H), 1.69-1.48 (m, 2H), 0.86 (s, 9H), -0.05 (s, 3H), -0.37 (s, 3H), OH not observed; ^{13}C NMR (90 MHz, $CDCl_3$, major isomer) δ 155.9, 146.1, 138.5, 129.8, 129.1, 127.8, 121.0, 119.9, 119.6, 107.9, 84.4, 83.9, 68.6, 55.9, 34.8, 28.0, 27.2, 26.7, 23.7, 18.3, 17.9, -4.6, -6.2; LRMS (ESI) *m/z* (relative intensity) 476.3 (90%, M + NH_4^+).

4-(*tert*-Butyldimethylsilanyl)-3-hex-5-ynyl-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-*c*]thiophene-5,8-dione (28). A stirring solution of MOM-protected hydroquinone **22** (47 mg, 0.088 mmol) in 1 mL of MeOH was treated with acetyl chloride (25.2 μL, 0.352 mmol). After 3 h, H_2O (10 mL) was added to the reaction solution. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 4-(*tert*-butyldimethylsilanyl)-3-hex-5-ynyl-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-*c*]thiophene-5,8-diol as a colorless oil. This material was used without further purification.

To a stirring solution of this crude dihydroquinone in 1.5 mL of CH_2Cl_2 was added iodobenzene diacetate (31 mg, 0.097 mmol). After 15 min, the reaction mixture was concentrated in vacuo to give a pink oil. Purification of this oil by flash column chromatography (Florasil, 20% EtOAc/hexanes as eluent) afforded

4-(*tert*-butyldimethylsilanyl)-3-hex-5-ynyl-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-*c*]thiophene-5,8-dione **(28)** (33 mg, 39% over 2 steps) as a pink oil. IR (thin film) 3284, 1643 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 10.1 Hz, 1H), 6.89 (d, *J* = 10.0 Hz, 1H), 6.71 (s, 1H), 4.22 (s, 1H), 3.97-3.96 (m, 2H), 2.55-2.44 (m, 2H), 2.22 (td, *J* = 6.9, 2.6 Hz, 2H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.90-1.79 (m, 2H), 1.63-1.56 (m, 2H), 0.92 (s, 9H), 0.05 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 183.4, 143.9, 140.7, 136.7, 136.4, 135.6, 134.8, 132.1, 117.1, 83.7, 69.0, 52.9, 29.3, 28.0, 27.1, 26.5, 24.2, 18.0, 1.0, -4.0, -5.0; LRMS (ESI) *m*/*z* (relative intensity) 443.2 (100%, M + H$^+$).

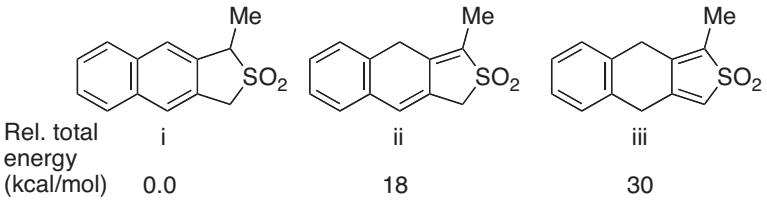
ACKNOWLEDGEMENTS

Financial support from the National Institutes of Health, General Medical Sciences Division under the auspices of GM-37681 is gratefully acknowledged. The X-ray crystallography facility of the Huck Institutes for the Life Sciences is supported through CHE-0131112 from the National Science Foundation.

REFERENCES AND NOTES

1. S. Braverman and D. Segev, *J. Am. Chem. Soc.,* 1974, **96**, 1245.
2. S. Braverman, Y. Zafrani, and H. E. Gottlieb, *Tetrahedron Lett.,* 2000, **41**, 2675.
3. S. Braverman, Y. Zafrani, and H. E. Gottlieb, *Tetrahedron,* 2001, **57**, 9177.
4. Y. Zafrani, H. E. Gottlieb, M. Sprecher, and S. Braverman, *J. Org. Chem.,* 2005, **70**, 10166.
5. W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.,* 1954, **76**, 1940.
6. J. Nakayama, R. Hasemi, K. Yoshimura, Y. Sugihara, S. Yamaoka, and N. Nakamura, *J. Org. Chem.*, 1998, **63**, 4912.
7. J. Nakayama, M. Kuroda, and M. Hoshino, *Heterocycles,* 1986, **24**, 1233.
8. D. Bailey and V. E. Williams, *Tetrahedron Lett.,* 2004, **45**, 2511.
9. W. Dai, J. L. Petersen, and K. K. Wang, *Org. Lett.,* 2006, **8**, 4665.
10. Cambridge Crystallographic Data Centre deposition number: CCDC 713998. Crystallographic data (excluding structure factors) for **17** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. M. P. Cava, R. H. Schlessinger, and J. P. Van Meter, *J. Am. Chem. Soc.,* 1964, **86**, 3173.
12. L. A. Levy and V. P. Sashikumar, *J. Org. Chem.,* 1985, **50**, 1760.

13. Density functional calculations on the model systems i-iii with the B3LYP 631G* functional on Spartan '04:



14. E. Bustelo and P. H. Dixneuf, *Adv. Syn. Catal.,* 2007, **349**, 933.
15. H. Hopf and A. Krüger, *Chem. Eur. J.,* 2001, **7**, 4378.
16. M. A. Franks, E. A. Schrader, E. C. Pietsch, D. R. Pennella, S. V. Torti, and M. E. Welker, *Bioorg. Med. Chem.,* 2005, **13**, 2221.