Preparation of Disubstituted Phenyl Propargyl Alcohols, their Use in Oxathiolene Oxide Synthesis, and Evaluation of the Oxathiolene Oxide Products as Anticarcinogenic Enzyme Inducers

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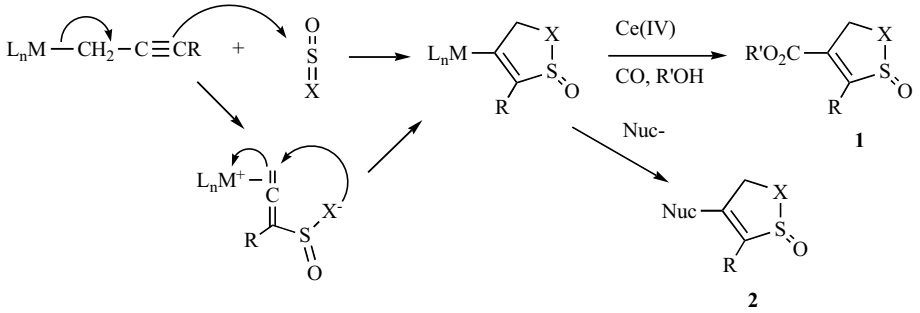
Abstract: A number of alkynols have been prepared by Sonogoshira coupling of propargyl alcohol to disubstituted aromatic halides. Chelation controlled addition of organometallic nucleophiles to these alkynols was then affected followed by the addition of sulfur dioxide. This methodology was used to prepare a number of oxathiolene oxides which have been screened as NQO1 (quinone oxidoreductase) inducers.

Keywords: Alkynol synthesis, cancer chemoprevention, sulfur heterocycle synthesis, NQO1.

INTRODUCTION

We have pursued the synthesis of unusual organosulfur compounds with biomedical science applications for over 15 years [1,2]. Transition metal mediated 3 + 2 cycloaddition reactions have been used to prepare both the oxathiolene oxide (**1**, **2** X = O) and dithiolene oxide (**1**, **2** X = S) core structures (Scheme **1**).



Scheme 1.

We had recognized that these compounds (**1**, **2** X = S or O) were structurally similar to the five-member rings in dithiolethiones, and that the thiolene oxides could participate in both Michael additions and S_N2' reactions with soft nucleophiles. These structural and reactivity characteristics were found in many early chemopreventive agents [3-5] and we became interested in the synthesis of organosulfur compounds that could subsequently be screened for this biological activity.

Chemoprevention of cancer involves the use of chemical agents either to retard or to block carcinogenesis [6,7]. These agents may affect the metabolism of xenobiotic procarcinogens and this metabolism proceeds in two phases. In phase 1, procarcinogens are typically oxidized (cytochrome P-450) or reduced and this change many times increases their chemical reactivity. In phase 2, phase 1 metabolites are typically conjugated to biological nucleophiles or electrophiles, such as glutathione (glutathione S- transferases) or glucoronic acid (UDP-glucuronyl transferases).

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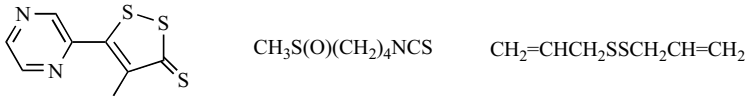


3 **4** **5**

Scheme 2.

Cruciferous vegetables, particularly those of the Brassica genus, contain a number of unusual organosulfur compounds that are excellent phase 2 inducers [8]. During the 1970s and 1980s, the related synthetic organosulfur compound Oltipraz (4-methyl-5-(2-pyrazinyl)-3H-1,2-dithiole-3-thione) (**3**) was being thoroughly investigated as an antischistosomal agent [4,9]. Oltipraz was extremely effective against schistosomiasis and also proved to be an excellent glutathione S-transferase and UDP-glucuronosyl transferase inducer. However, reports of paresthesia and fingertip pain following oltipraz exposure, side effects that were exacerbated by exposure to sunlight, led to the discontinuation of schistosomiasis trials of this compound [4]. The connection between unusual organosulfur compounds and cancer prevention was nevertheless established by the mid-1980s. This work also led to the identification of a number of other naturally occurring sulfur compounds, such as isothiocyanates (**4**) and disulfides (**5**) that function as phase 2 inducers (Scheme **2**) [8,10-17].

Similarities between the oxathiolene oxide nucleus and these organosulfur compounds led us to begin to explore the activity of oxathiolene oxides as candidate chemopreventive agents. Several compounds were prepared using the transition-metal mediated [3 + 2] cycloaddition chemistry described above and then were shown to elevate mRNA levels of glutathione S-transferase (GST), quinone oxidoreductase (NQO1), and ferritin H and L expression in a normal murine liver cell line, BNLCL.2 [18]. Having verified that compounds containing the oxathiolene oxide nucleus could be nontoxic, anticarcinogenic enzyme inducers at both the mRNA and protein levels, we wanted to evaluate this class of compounds in more detail. In 2005, we reported a catalytic rather than stoichiometric transition-metal based synthetic route to the oxathiolene oxides that has proven convenient and general [19]. The NQO1 CD values of the compounds reported in 2005 indicated that oxathiolene oxides containing aromatic substituents which were electron withdrawing were superior. There was also one indication in that work that aromatic rings containing two electron withdrawing groups would be even better as oxathiolene oxide substituents. That preliminary data caused us to set out to synthesize the required propargyl alcohols, convert them into oxathiolene oxides and screen the oxathiolene oxides as NQO1 inducers. The results of that work are reported here.

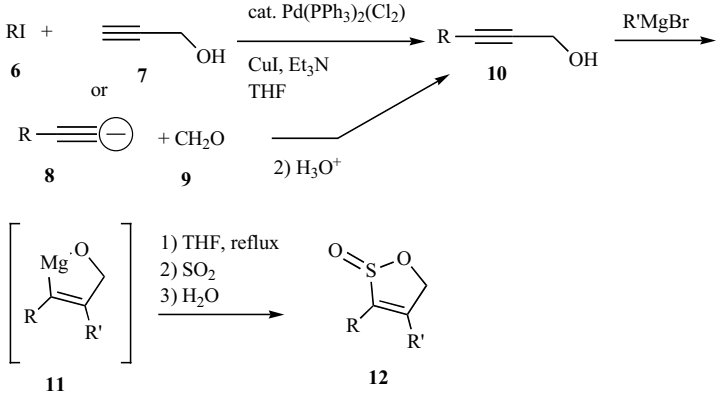
RESULTS AND DISCUSSION

Oxathiolene Oxide Synthesis

Chelation controlled addition of Grignard reagents to alkynols (**10** to **12**) was first reported independently by both Richey and Eisch in 1969 [20,21]. Duboudin *et al*. extended the addition chemistry during the 1970s and 1980s, showing that the intermediate magnesium chelate (**11**) could be trapped by a number of electrophiles including CO_2 and SO_2 (Scheme **3**) [22-24]. Subsequently, Fallis showed that the chelate can be trapped with aldehydes to prepare dienols and trapped with nitriles to make furans [25-27]. Fleming has also recently reported some related chelation-controlled conjugate additions using magnesium chelates [28,29].

In the present report, we were interested in extending our earlier work [19] to include alkynols substituted by a variety of aromatic rings containing two heteroatom substituents and we were interested in the possibility of using a much wider range of organometallic nucleophiles.

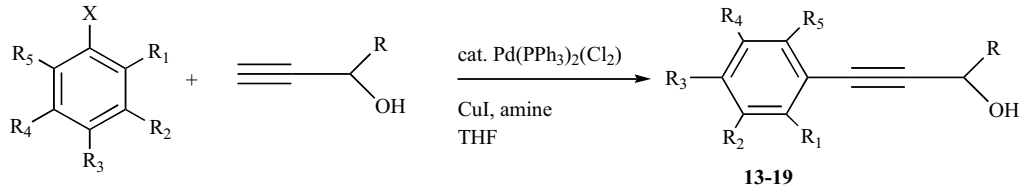
All the alkynols (**13-19**) used in this study were synthesized by Pd catalyzed cross coupling (Sonogashira coupling) [30-32] of propargyl alcohol to an aromatic halide (Table **1**). Isolated yields are generally quite high with the exception of the one case where an aromatic bromide rather than iodide was used (Table **1**, entry 3). All of the aromatic halides used were commercially available with the exception of 2,3-dimethoxyiodobezene. However, this compound (starting material for entry 6, Table **1**) was easily prepared in one step by deprotonation of veratrole followed by treatment with iodine [31].



6 **7** **10** **8** **9** **11** **12**

Scheme 3.

Table 1. Coupling of Phenyl Halides to Propargyl Alcohol



13-19

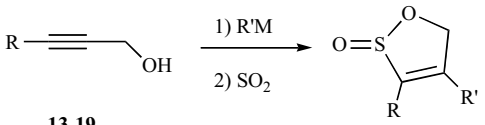
Entry	X	R_1	R_2	R_3	R_4	R_5	R	% yield	Product
1)	I	Cl	Cl	H	H	H	H	73	**13**
2)	I	F	Cl	H	H	H	H	91	**14**
3)	Br	Cl	F	H	H	H	H	14	**15**
4)	I	F	H	F	H	H	H	67	**16**
5)	I	OMe	H	H	H	H	Ph	93	**17**
6)	I	OMe	OMe	H	H	H	H	58	**18**
7)	I	OMe	H	OMe	H	H	H	90	**19**

The yields of cyclization reactions used to prepare oxathiolene oxides are presented in Table **2**. In general these cyclization reactions work much better when the alkynol used is substituted by an aromatic ring containing strong electron withdrawing groups (Table **2**, entries 1-6).

The structure of one of the oxathiolene oxides prepared, 3-[2,3-methoxyphenyl]-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (**26**) was confirmed by X-ray crystallography and the ORTEP of this structure is provided in Fig. (**1**). The bond lengths and angles around the oxathiolene oxide core in this structure are similar to those reported previously [33]. The steric interactions between the vinyl and aromatic substitutents on the oxathiolene oxide ring are seen through the large C(6)-C(1)-C(2) bond angle of 128.2(2)°.

Two additional reactions in this class deserve additional comment. The one secondary propargyl alcohol substrate we prepared (**17**) failed to react with vinyl magnesium bromide even after reflux for 48h. The reaction of alkynol (**19**) with phenyl magnesium bromide produced a surprising result. We isolated no oxathiolene oxide product from this reaction and instead isolated a compound with MS, ^{1}H NMR and ^{13}C NMR data consistent with either structure **30** or **31** (Scheme **4**). We were unsure of which isomer had been formed but suspected isomer **30** since we saw no diastereotopic methylene pair in the ^{1}H NMR. The structure of the isomer formed by this reaction was confirmed by X-ray crystallography and the ORTEP of this molecule (**30**) is provided in Fig. (**2**). Bond distances and angles around the carbonyl and sulfonyl

Table 2. Reactions of Organometallic Nucleophiles with Substituted Propargyl Alcohols Followed by SO_2 Quench



13-19 **20-29**

	Propargyl Alcohol (#)	R'M	%	Product #
1)	**13**	VinylMgBr	51	**20**
2)	**14**	VinylMgBr	32	**21**
3)	**16**	VinylMgBr	29	**22**
4)	**16**	PhenylMgBr	54	**23**
5)	**16**	4-F-PhMgBr	21	**24**
6)	**16**	4-OMe-PhMgBr	25	**25**
7)	**18**	VinylMgBr	25	**26**
8)	**18**	PhMgBr	9	**27**
9)	**18**	4-F-PhMgBr	5	**28**
10)	**19**	VinylMgBr	14	**29**

functional groups are similar to those reported for a related phenylcarbonyl-3-acetoxy-1-(p-tolylsulfonyl)butane in 1999 [34].

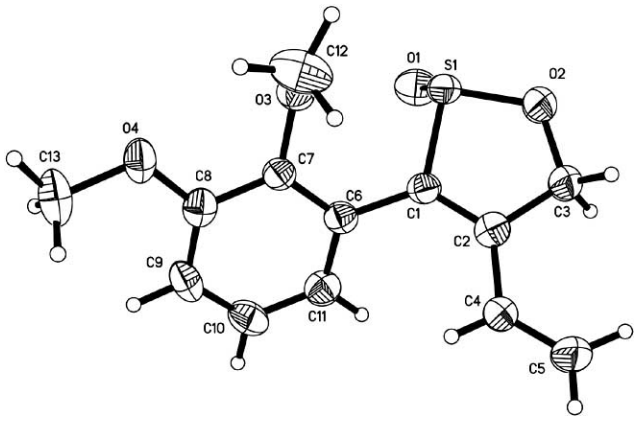
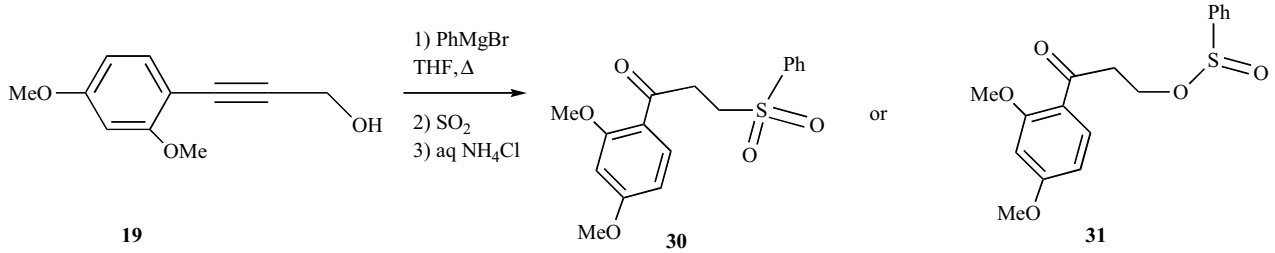


Fig. (1). ORTEP plot of the molecular structure of **26** (50% probability ellipsoids).

To rationalize the formation of **30**, we need to propose that phenylmagnesium bromide does not add to this alkynol.

Oxathiolene Oxides as NQO1 Inducers

We had already established that the oxathiolene oxide nucleus was a promising phase 2 inducer back in 2003, but the synthetic chemistry used to prepare the initial set of four test compounds was too cumbersome [18]. Hence, the simple synthetic route to these compounds outlined above was initially developed for monosubstituted aromatic substrates in 2005 [19]. In the present work, we wanted to prepare disubstituted aromatic containing oxathiolene oxides and assess the impact of these changes on biological function by measuring NQO1 inducing ability and toxicity [20]. Mouse liver Hepa 1c1c7 cells were used in this study. The Hepa cells were seeded in media first. After 24 hours growth, media was withdrawn and replaced with media that contained dilutions of the test compounds. After 48 hours growth in the media with test compound, NQO1 activity was determined by measuring spectrophotometrically the NADPH-dependent menadiol-mediated reduction of 3-(4,5-demethylthiazo-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to a blue formazan dye. Toxicity of the test compounds was assessed by the crystal violet staining assay, which was performed on 96 well plates that were seeded and treated at the same time as the plates for the NQO1 assay. The concentration required



Scheme 4.

Instead, we presume that **33** and **34** are formed from reactions of organomagnesium species with SO_2 [35] and that these 2 intermediates react to form **35** which is hydrolyzed to **30** (Scheme **5**).

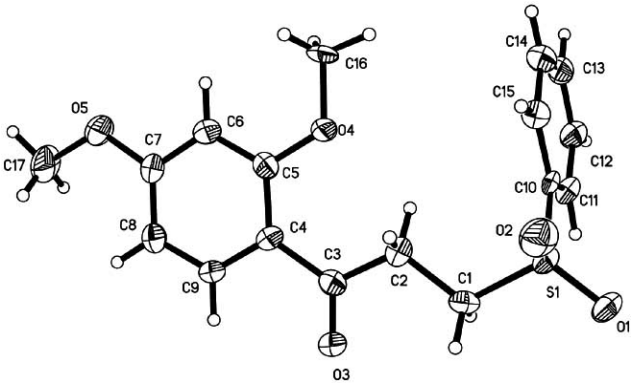
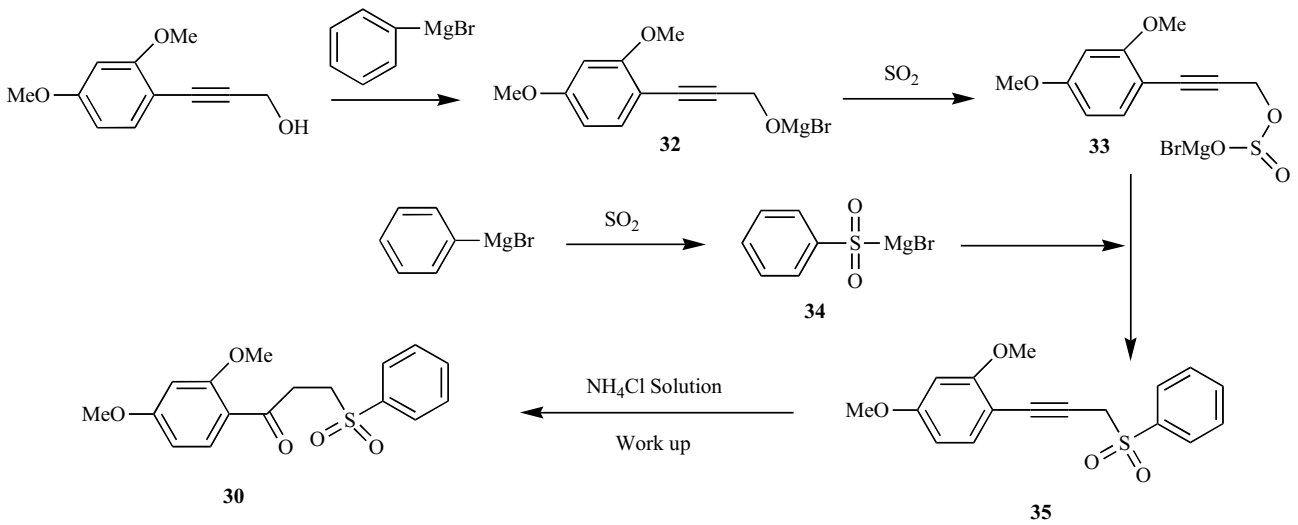


Fig. (2). ORTEP plot of the molecular structure of **30** (50% probability ellipsoids).

for doubling NQO1 activity (CD value) and the concentration at which cells are 50% viable (IC_{50}) were determined using the Calcusyn program (Biosoft).

Unfortunately, none of these disubstituted aromatic compounds proved particularly active as a NQO1 inducer. None of these compounds doubled NQO1 activity at concentrations up to 160μM. They all show some inducing ability but they top out at around a 50% increase in enzyme levels (Table **3** and **4**). They have reduced toxicity relative to the monosubstituted aromatic compounds reported earlier [19] (Table **4**) in that IC_{50}'s proved to be greater than 160μM for all three compounds tested.

In conclusion, we have used Sonogoshira coupling reactions to prepare a large number of disubstituted aromatic substituted alkynols. We found that disubstituted aromatic substrates with two strong electron withdrawing groups participate in the cyclization reaction to make oxathiolene oxides much better than the dialkoxy substituted aromatic substrates. While these new disubstituted aromatic ring containing oxathiolene oxides proved less toxic than their monosubstituted counterparts they are not as effective as the monosubstituted compounds at inducing NQO1.



Scheme 5.

Table 3. Biological Activity Data of Oxathiolene Oxides (I)

	NQO1 Fold Induction			
Concentration(μM)	**29**	**22**	**27**	**23**
0	1.00	1.00	1.00	1.00
25	1.46	1.33	1.24	1.56
50	1.58	1.27	1.38	1.59
100	1.10	0.93	1.36	1.54
150	0.29	0.81	0.97	1.37
200	0.24	0.34	1.03	0.59

Table 4. Biological Activity Data of Oxathiolene Oxides (II)

	Concentration(μM)	**0**	**5**	**10**	**20**	**40**	**80**	**160**
26	Fold Induction	1.00	1.16	1.21	1.24	1.41	1.61	1.70
	Toxicity (% of cells still alive)	100.0	92.8	100.0	105.7	105.4	95.0	80.2
24	Fold Induction	1.00	1.10	1.08	1.30	1.44	1.73	0.91
	Toxicity (% of cells still alive)	100.0	94.2	102.3	100.5	95.5	81.0	53.3
25	Fold Induction	1.00	0.92	0.86	0.86	1.04	1.07	0.68
	Toxicity (% of cells still alive)	100.0	93.6	94.2	93.3	82.0	84.1	62.6

EXPERIMENTAL

General Procedures

The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using a Bruker Avance 300 MHz spectrometer operating at 300.13 MHz or a Bruker Avance 500 MHZ spectrometer operating at 500.13 MHz. ^{13}C NMR spectra were obtained using a Bruker Avance 300 MHz spectrometer operating at 75.48 MHz. All spectra were referenced to the residual proton or carbon signals of the respective deuterated solvents. All elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High-resolution mass spectrometry was performed at the UNC-CH Spectrometry Facility in Chapel Hill, NC. All reactions were carried out under an atmosphere of nitrogen.

3-(2,3-Dichlorophenyl)-prop-2-yn-1-ol (13)

A double-neck round bottom flask was flame dried, equipped with a stir bar, and allowed to cool under nitrogen in an ice bath. 1,2-Dichloro-3-iodobenzene (1.030 g, 3.77 mmol), copper (I) iodide (0.029 g, 0.15 mmol), and trans-Dichlorobis(triphenylphosphine) palladium (II) (0.053 g, 0.08 mmol) were then added to the flask. Diisopropylamine (7 mL) was then added to the flask and the solid mass was

allowed to dissolve while stirring under nitrogen. Propargyl alcohol (0.733 g, 13.30 mmol) was then dissolved in THF (7 mL). The solution was then added drop wise by syringe into the flask, the ice bath was removed, and the reaction was allowed to stir for 18h. The mixture was then quenched by the addition of H_2O (30 mL) and extracted with ethyl acetate (2 x 50 mL). The solution was then washed with 1.2 M HCl (25 mL) and saturated NaCl (25 mL) to help facilitate drying. The extract was dried using $MgSO_4$ and the solvent was removed by rotary evaporation and high vacuum. The pure product was obtained following chromatography on SiO_2 (1:2 ethyl acetate/hexane) and the solvent was removed by rotary evaporation followed by high vacuum overnight. The reaction produced a peach flaky solid (0.552 g, 2.75 mmol, 73%). Anal. Calcd for $C_9H_6Cl_2O$: C, 53.77; H, 3.01. Found: C, 53.67; H, 3.03. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.83 (s, OH), 4.56 (s, 2H), 7.26 (s, 1H), 7.27 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$ δ): 51.64, 82.10, 93.22, 124.59, 127.02, 130.44, 131.62, 133.33, 134.34.

3-(3-Chloro-2-fluorophenyl)-prop-2-yn-1-ol (14)

1-Chloro-2-fluoro-3-iodobenzene (0.972 g, 3.79 mmol), copper (I) iodide (0.029 g, 0.15 mmol), and trans-dichlorobis(triphenylphosphine) palladium (II) (0.053 g, 0.08 mmol), diisopropylamine (7 mL) and propargyl alcohol (0.733 g, 13.30 mmol) in THF (7 mL) were allowed to react and worked up as described above. The pure product was obtained following chromatography on SiO_2 (1:2 ethyl acetate/hexane) and the solvent was removed by rotary evaporation followed by high vacuum. The reaction produced an amber crystalline solid (0.639 g, 3.46 mmol, 91%). Anal. Calcd for C_9H_6ClFO: C, 58.56; H, 3.28. Found: C, 58.31; H, 3.75. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.56 (t, J = 5.5Hz, 1H, OH), 4.56 (d, J = 5.5Hz, 2H), 7.22 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$ δ): 52.06, 78.58, 93.95 (d, J = 3.8 Hz), 113.21 (d, J = 15.7 Hz), 121.90 (d, J = 17.3 Hz), 124.76 (d, J = 4.9 Hz), 131.33, 132.21, 158.86 (d, J = 253.8 Hz).

3-(2-Chloro-3-fluorophenyl)-prop-2-yn-1-ol (15)

1-Bromo-2-chloro-3-fluorobenzene (1.645 g, 7.85 mmol), copper (I) iodide (0.060 g, 0.32 mmol), and trans-dichlorobis(triphenylphosphine) palladium (II) (0.266 g, 0.38 mmol), diisopropylamine (5 mL) and propargyl alcohol (1.541 g, 27.49 mmol) in THF (10 mL) were allowed to react and worked up as described above. The pure product was obtained following chromatography on SiO_2 (1:3 ethyl acetate/hexane) and the solvent was removed by rotary evaporation followed by high vacuum. The reaction produced a brown oil (0.198 g, 1.07 mmol, 14%). Anal. Calcd for C_9H_6ClFO: C, 58.56; H, 3.28. Found: C, 57.59; H, 3.43. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.81 (t, J = 6.1Hz, 1H, OH), 4.56 (d, J = 6.1 Hz, 2H), 7.22 (m, 3H). ^{13}C APT NMR (300 MHz, $CDCl_3$ δ): 52.05, 81.85, 93.88, 117.09 (d, J = 21.5 Hz), 127.77 (d, J = 8.3 Hz), 129.16 (d, J = 3.5 Hz), 135.76, 135.66, 158.79 (d, J = 249.0 Hz).

3-(2, 4-Difluorophenyl)-2-propyn-1-ol (16)

2, 4-Difluoroiodobenzene (2.0 g, 8.34 mmol), $Pd(PPh_3)_2Cl_2$ (117 mg, 0.165 mmol), CuI (63.4 mg, 0.334 mmol) and THF (20 mL) were used along with DIPA (20 mL) and propargyl alcohol (1.64 g, 29.2 mmol). The reaction, work up and purification followed the procedure described above. The reaction produced 3-(2, 4-Difluorophenyl)-2-propyn-1-ol (0.943 g, 5.61 mmol, 67%) as a white solid. Anal. Calcd for $C_9H_6F_2O$: C, 64.29; H, 3.60. Found: C, 63.59; H, 3.44. ^{1}H NMR (300 MHz, $CDCl_3$): 1.90 (s, 1H), 4.52 (s, 2H), 6.83 (m, 2H), 7.42 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 51.56, 78.06, 92.16 (dd, J=1.7, 3.2 Hz), 104.23 (t, J=25.9 Hz), 107.41 (dd, J=4.0, 15.8 Hz), 111.55 (dd, J=3.7, 21.8 Hz), 134.50 (dd, J=2.9, 9.8 Hz), 162.80 (dd, J=11.2, 251.7 Hz), 163.17(dd, J=11.7, 254.3 Hz).

3-(2-Methoxyphenyl)-1-phenylprop-2-yn-1-ol (17)

2-Iodoanisole (1.081 g, 4.62 mmol), copper (I) iodide (0.020 g, 0.11 mmol), and trans-dichlorobis(triphenylphosphine) palladium (II) (0.036 g, .05 mmol), diisopropylamine (5 mL), and 1-phenyl-2-propyn-1-ol (0.555 g, 4.20 mmol) in THF (10 mL) were then allowed to react and worked up as described above. The pure product was obtained following chromatography on SiO_2 (1:3 ethyl acetate/hexane) and the solvent was removed by rotary evaporation followed by high vacuum. The reaction produced a brown oil (1.02 g, 4.28 mmol, 93%). HRMS calc'd for $C_{16}H_{14}O_2$+Na 261.0891; found, 261.0867. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 2.59 (s, 1H, OH), 3.87 (s, 3H), 5.73 (s, 1H), 6.89 (m, 2H), 7.40 (m, 6H), 7.65 (d, J = 6.7 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$ δ): 56.22, 65.70, 83.55, 93.26, 111.11, 112.09, 120.87, 127.36, 128.74, 129.00, 130.51, 134.11, 141.20, 160.65.

3-(2, 3-Dimethoxyphenyl)-2-propyn-1-ol (18)

2, 3-Dimethoxyiodobenzene (1.0 g, 3.79 mmol), $Pd(PPh_3)_2Cl_2$ (53.2 mg, 0.075 mmol), CuI (28.8 mg, 0.152 mmol) and THF (10 mL) were used along with DIPA (10 mL) and propargyl alcohol (0.743 g, 13.3 mmol). The reaction followed the procedure described above. The reaction produced 3-(2, 3-Dimethoxyphenyl)-2-propyn-1-ol (0.301 g, 1.56 mmol, 57.6%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): 1.86 (s, 1H), 3.86 (s, 3H), 3.92 (s, 3H), 4.53 (s, 2H), 6.89 (m, 1H), 6.99 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 51.41, 55.56, 60.65, 81.28, 90.90, 112.75, 116.88, 123.50, 124.77, 150.01, 152.28. HRMS Calcd for [$C_{11}H_{12}O_3$+H^+]: 193.0865. Found: 193.0865.

3-(2, 4-Dimethoxyphenyl)-2-propyn-1-ol (19)

2, 4-Dimethoxyiodobenzene (5.0 g, 18.95 mmol), $Pd(PPh_3)_2Cl_2$ (266mg, 0.375 mmol), CuI (144 mg, 0.760 mmol) and THF (50mL) were used along with DIPA (50mL) and propargyl alcohol (3.72g, 66.5mmol). The reaction followed the procedure described above. The reaction produced 3-(2, 4-Dimethoxyphenyl)-2-propyn-1-ol (3.365g, 17.5 mmol, 92%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): 3.79 (s, 3H), 3.84 (s, 3H), 4.51 (s, 2H), 6.43 (m, 2H), 7.31 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 51.75, 55.38, 55.72, 81.79, 90.00, 98.33, 104.14, 104.79, 134.48, 161.14, 161.24. HRMS Calcd for [$C_{11}H_{12}O_3$+Na^+]: 215.0684. Found: 215.0684.

General Procedure for Addition Reactions between Propyn-1-ols and Grignards

A two neck round bottom flask, equipped with a magnetic stirring bar, was charged with the 3-aryl-2-propyn-1-ol in THF (10-50 mL). The solution was treated with 10

equivalents of the appropriate Grignard reagent. The reaction was heated to reflux for 18 hours. The solution was cooled to room temperature, then to –78°C and sulfur dioxide gas was condensed into the flask over 5 minutes. The brown solution turned to a yellow color as the solution warmed to 25°C over the next hour. The reaction was quenched by stirring the solution with aqueous ammonium chloride (30 mL of a saturated solution) and performing an aqueous ether extraction (3 X 50 mL ether). The extracted ether was washed with water and brine. The ethereal solution was dried using magnesium sulfate and the solvent removed by rotary evaporation. The residue was dissolved in a small amount of chloroform and treated with pentane until a precipitate formed. The precipitate was filtered and the solution was condensed to an oil using rotary evaporation. The product was obtained following chromatography on SiO_2 and removal of the solvent by rotary evaporation and high vacuum.

3-(2',3'-Dichlorophenyl)-4-vinyl-(1,2)-oxathiol-3-en-2-oxide (20)

3-(2,3-Dichlorophenyl)-prop-2-yn-1-ol (**13**) (0.100 g, 0.50 mmol) and vinyl magnesium bromide (5 mL of 1.0 M soln, 5.00 mmol) were allowed to react as described above. The pure product was obtained following chromatography on SiO_2 (1:3 ethyl acetate/hexane). The reaction produced a yellow oily solid (0.070 g, 0.25 mmol, 51%). Anal. Calc'd for $C_{11}H_8Cl_2O_2S$: C, 48.02; H, 2.93. Found: C, 48.00; H, 3.32. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 5.54 (m, 3H), 5.87 (d, J = 14.4 Hz, 1H), 6.27 (dd, J = 18.6 Hz, J = 11.0 Hz, 1H), 7.30 (m, 2H), 7.56 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$ δ): 81.23, 124.21, 126.80, 128.20, 129.77, 131.16, 132.18, 133.09, 134.40, 142.15, 145.04.

3-(3'-chloro-2'-fluorophenyl)-4-vinyl-(1,2)-oxathiol-3-en-2-oxide (21)

3-(3-Chloro-2-fluorophenyl)-prop-2-yn-1-ol (**14**) (0.100 g, 0.54 mmol) and vinyl magnesium chloride (5 mL of a 1.6M soln, 8.00 mmol) were allowed to react as described above. The pure product was obtained following chromatography on SiO_2 (1:3 ethyl acetate/hexane). The reaction produced a yellow oily solid (0.046 g, 0.18 mmol, 32%). Anal. Calc'd for $C_{11}H_8ClFO_2S$: C, 51.07; H, 3.12. Found: C, 51.31; H, 3.75. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 5.49 (m, 3H), 5.82 (d, J = 14.5 Hz, 1H), 6.32 (dd, J = 17.9 Hz, J = 11.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1 H), 7.33 (t, J = 6.9 Hz, 1 H), 7.43 (t, J = 7.5 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$ δ): 81.61, 118.21 (d, J = 15.8 Hz), 122.61 (d, 17.9 Hz), 124.48, 125.51 (d, J = 4.8 Hz), 126.88 (d, J = 1.6 Hz), 130.12 (d, J = 1.7 Hz), 132.61, 140.06 (d, J = 2.0 Hz), 142.74, 155.93 (d, J = 252.3 Hz).

3-(2, 4-Difluorophenyl)-4-vinyl-(1,2)-oxathiol-3-en-2-oxide (22)

3-(2, 4-Difluorophenyl)-2-propyn-1-ol (**16**) (100 mg, 0.595 mmol) in THF (25mL) was treated with vinylmagnesium bromide (5.95 mL of a 1.0 M solution, 5.95 mmol). The reaction was performed using the procedure described above. The reaction yielded 3-(2, 4-Difluorophenyl)-4-vinyl-(1,2)-oxathiol-3-en-2-oxide (0.042g, 0.173mmol, 29%) as a white solid. Anal. Calcd for $C_{11}H_8F_2SO_2$: C, 54.54; H, 3.33. Found: C, 54.99; H, 3.60. ^{1}H NMR (300 MHz, $CDCl_3$): 5.48 (d, J=14.5 Hz, 1H), 5.50 (d, J=17.8 Hz, 1H), 5.59 (d, J=11.0 Hz, 1H), 5.86 (d, J=14.5 Hz, 1H), 6.37 (dd, J=11.0 Hz, J=17.8 Hz, 1H), 6.97 (m, 2H), 7.48 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 81.57, 105.24 (t, J=25.6 Hz), 112.58 (d, J=4.1 Hz), 112.65 (dd, J=3.8 Hz, J=21.7 Hz), 124.13, 126.91, 132.92 (dd, J=4.0 Hz, J=9.9 Hz), 140.05 (d, J=1.9 Hz), 142.23, 160.76 (dd, J=12.1 Hz, J=252.8 Hz), 164.36 (dd, J=11.5 Hz, J=253.0 Hz).

3-(2, 4-Difluorophenyl)-4-phenyl-(1,2)-oxathiol-3-en-2-oxide (23)

3-(2, 4-Difluorophenyl)-2-propyn-1-ol (**16**) (100 mg, 0.595 mmol) and phenylmagnesium bromide (5.95 mL of a 1.0 M solution, 5.95 mmol) were allowed to react as described above. The reaction was performed using the procedure described above. The reaction yielded 3-(2, 4-Difluorophenyl)-4-phenyl-(1,2)-oxathiol-3-en-2-oxide (0.093g, 0.318 mmol, 54%) as a white solid. Anal. Calcd for $C_{15}H_{10}F_2SO_2$: C, 61.64; H, 3.45. Found: C, 61.53; H, 3.57. ^{1}H NMR (300 MHz, $CDCl_3$): 5.57 (d, J=15.1 Hz, 1H), 5.94 (d, J=15.1 Hz, 1H), 6.83 (m, 2H), 7.12 (m, 2H), 7.21 (m, 2H), 7.28 (m, 1H), 7.38 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 83.35, 104.84 (t, J=25.4 Hz), 112.31 (dd, J=3.9 Hz, J=21.4 Hz), 113.01 (dd, J=4.2 Hz, J=15.8 Hz), 127.51, 128.97, 129.62, 130.12, 132.34 (dd, J=4.1 Hz, J=9.8 Hz), 137.28 (d, J=2.2 Hz), 144.22, 160.25 (dd, J=12.4 Hz, J=253.5 Hz), 163.73 (dd, J=12.0 Hz, J=253.1 Hz).

3-(2, 4-Difluorophenyl)-4-(4-fluorophenyl)-(1,2)-oxathiol-3-en-2-oxide (24)

3-(2, 4-Difluorophenyl)-2-propyn-1-ol (**16**) (100 mg, 0.595 mmol) was treated with 4-fluorophenylmagnesium bromide (5.95 mL of a 1.0 M solution, 5.95 mmol). The reaction was performed using the procedure described above. The reaction yielded 3-(2, 4-Difluorophenyl)-4-(4-fluorophenyl)-(1,2)-oxathiol-3-en-2-oxide (0.039g, 0.126mmol, 21%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): 5.63 (d, J=15.1 Hz, 1H), 5.98 (d, J=15.1 Hz, 1H), 6.95 (m, 4H), 7.19 (m, 2H), 7.47 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 83.71, 105.46 (t, J=25.4 Hz), 112.96 (dd, J=4.0 Hz, J=21.5 Hz), 113.29 (dd, J=4.0 Hz, J=15.6 Hz), 116.78 (d, J=21.9 Hz), 126.23 (d, J=3.4 Hz), 130.04 (d, J=8.5 Hz), 132.69 (dd, J=3.9 Hz, J=9.8 Hz), 137.79, 143.55, 160.67 (dd, J=12.7 Hz, J=253.8 Hz), 163.94 (d, J=252.1 Hz), 164.32 (dd, J=11.9 Hz, J=253.4 Hz). HRMS Calcd for $[C_{15}H_9F_3O_2S+H^+]$: 311.0354. Found: 311.0354.

3-(2, 4-Difluorophenyl)-4-(4-methoxyphenyl)-(1,2)-oxathiol-3-en-2-oxide (25)

3-(2, 4-Difluorophenyl)-2-propyn-1-ol (**16**) (100 mg, 0.595 mmol) was treated with 4-methoxyphenylmagnesium bromide (5.95 mL of a 1.0 M solution, 5.95 mmol). The reaction was performed using the procedure described above. The reaction yielded 3-(2, 4-Difluorophenyl)-4-(4-methoxyphenyl)-(1,2)-oxathiol-3-en-2-oxide (0.048g, 0.149 mmol, 25%) as a white solid. Anal. Calcd for $C_{16}H_{12}F_2SO_3$: C, 59.62; H, 3.75. Found: C, 59.86; H, 3.90. ^{1}H NMR (300 MHz, $CDCl_3$): 3.79 (s, 3H), 5.63 (d, J=14.9 Hz, 1H), 5.98 (d, J=14.9 Hz, 1H), 6.81 (m, 2H), 6.91 (m, 2H), 7.13 (m, 2H), 7.47 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 55.26, 83.11, 104.89 (t, J=25.5 Hz), 112.35 (dd, J=3.8 Hz, J=21.5 Hz), 113.40 (dd, J=4.0 Hz, J=16.0 Hz), 114.44, 121.75, 129.09, 132.40 (dd, J=4.0 Hz, J=9.8 Hz), 135.23 (d, J=2.0 Hz),

143.68, 160.32 (dd, J=12.7 Hz, J=253.7 Hz), 160.99, 163.71 (dd, J=10.0 Hz, J=251.0 Hz).

3-(2, 3-Dimethoxyphenyl)-4-vinyl-(1,2)-oxathiol-3-en-2-oxide (26)

3-(2, 3-Dimethoxyphenyl)-2-propyn-1-ol (**18**) (100 mg, 0.562 mmol) was treated with vinyl magnesium bromide (5.6 mL of a 1.0 M solution, 5.6 mmol). The reaction was performed using the procedure described above. The reaction yielded 3-(2, 3-Dimethoxyphenyl)-4-vinyl-(1,2)-oxathiol-3-en-2-oxide (0.035g, 0.131mmol, 23%) as a white crystal. Anal. Calcd for $C_{13}H_{14}SO_4$: C, 58.63; H, 5.30. Found: C, 58.25; H, 5.50. ^{1}H NMR (300 MHz, $CDCl_3$): 3.84 (s, 3H), 3.89 (s, 3H), 5.43 (d, J=18.0 Hz, H), 5.44 (d, J=13.7 Hz, 1H), 5.49 (d, J=11.0 Hz, 1H), 5.86 (d, J=14.2 Hz, 1H), 6.48 (dd, J=11.1 Hz, J=17.9 Hz, 1H), 7.01 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 56.32, 61.79, 81.25, 114.50, 122.60, 122.81, 123.86, 124.82, 127.90, 140.11, 144.30, 147.86, 153.36.

3-(2, 3-Dimethoxyphenyl)-4-phenyl-(1,2)-oxathiol-3-en-2-oxide (27)

3-(2, 3-Dimethoxyphenyl)-2-propyn-1-ol (**18**) (100 mg, 0.562 mmol) was treated with phenylmagnesium bromide (5.6 mL of a 1.0 M solution, 5.6 mmol). The reaction was performed using the procedure described above. The reaction yielded 3-(2, 3-Dimethoxyphenyl)-4-phenyl-(1,2)-oxathiol-3-en-2-oxide (0.015g, 0.047mmol, 8%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): 3.74 (s, 3H), 3.81 (s, 3H), 5.47 (d, J=14.7 Hz, 1H), 6.02 (d, J=14.7 Hz, 1H), 6.74 (m, 1H), 6.91 (m, 2H), 7.14 (m, 2H), 7.22 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 55.81, 61.17, 83.08, 113.83, 123.02, 123.31,124.53, 127.76, 128.82, 129.64, 130.42, 141.64, 147.42, 152.88. HRMS Calcd for $[C_{17}H_{16}O_4S+Na^+]$: 339.0667, Found: 339.0667.

3-(2, 4-Dimethoxyphenyl)-4-vinyl-(1, 2)-oxathiol-3-en-2-oxide (29)

3-(2, 4-Dimethoxyphenyl)-2-propyn-1-ol (**19**) (100 mg, 0.562 mmol) in THF (25mL) was treated with vinylmagnesium bromide (5.6 mL of a 1.0 M solution, 5.6 mmol). The reaction was performed using the procedure described above. The reaction yielded 3-(2, 4-Dimethoxyphenyl)-4-vinyl-(1,2)-oxathiol-3-en-2-oxide (0.019g, 0.071 mmol, 13%) as an oil. Anal. Calcd for $C_{13}H_{14}SO_4$: C, 58.63; H, 5.30. Found: C, 58.95; H, 3.76. ^{1}H NMR (300 MHz, $CDCl_3$): 3.83 (s, 3H), 3.84 (s, 3H), 5.38 (d, J=14.0 Hz, 1H), 5.40 (d, J=17.9 Hz, 1H), 5.47 (d, J=11.0 Hz, 1H), 5.82 (d, J=14.0 Hz, 1H), 6.53 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 55.53, 55.66, 80.42, 98.82, 105.13, 109.77, 121.40, 127.62, 133.22, 138.34, 144.68, 158.60, 162.46.

1-(2,4-dimethoxyphenyl)-3-(phenylsulfonyl)propan-1-one (30)

3-(2, 4-Dimethoxyphenyl)-2-propyn-1-ol (**19**) (100 mg, 0.562 mmol) was treated with phenylmagnesium bromide (5.6 mL of a 1.0 M solution, 5.6 mmol). The reaction was performed using the procedure described above. The reaction yielded 1-(2,4-dimethoxyphenyl)-3-(phenylsulfonyl)propan-1-one (0.037g, 0.110mmol, 20%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): 3.43 (t, J=8.0 Hz, 2H), 3.52 (t, J=7.9 Hz, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 6.44 (d, J=2.2 Hz, 1H), 6.51 (dd, J=2.2 Hz, J=8.8 Hz, 1H), 7.57 (t, J=7.8 Hz, 2H), 7.66 (d, J=7.9 Hz, 1H), 7.78 (d, J=8.8 Hz, 1H), 7.94 (d, J=7.8 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$):36.48, 51.57, 55.51, 55.57, 98.19, 105.48, 119.46, 128.06, 129.23, 132.94, 133.69, 139.27, 161.17, 165.11, 194.73. HRMS Calcd for $[C_{17}H_{18}O_5S+H^+]$: 335.0953. Found: 335.0953.

Cell Culture

The murine hepatoma cell line, Hepa 1c1c7 (ATCC, 36) was maintained at 37^{0}C in a humidified atmosphere containing 5% CO_2. Hepa 1c1c7 cells were cultured in α-MEM. The media was supplemented with 10% fetal bovine serum (Gem Cell) and 100-units/ml penicillin G sodium and 100 μg/ml streptomycin sulfate. The cell culture media and penicillin-streptomycin were obtained from Life Technologies.

Determination of NQO1 Activity in Hepa 1c1c7 Cells

NQO1 activity was measured as previously described [36] with minor modifications. Briefly, Hepa 1c1c7 cells were seeded in 96 well plates at a density of $1x10^4$ cells/ml in 200 μl. After 24 hours of growth, media was withdrawn and replaced with media that contained dilutions of the test compounds. Treatments for each individual experiment were performed in octuplicates. After growing Hepa 1c1c7 cells in the presence of test compounds for 48 hours, NQO1 activity was determined by measuring spectrophotometrically the NADPH-dependent menadiol-mediated reduction of 3-(4, 5-dimethylthiazo-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) to a blue formazan dye [36]. Toxicity of the test compounds was assessed by the crystal violet staining assay (40), which was performed on 96 well plates that were seeded and treated at the same time as the plates for the NQO1 assay. The concentration required for doubling NQO1 activity (CD value) and the concentration at which cells are 50% viable (IC_{50}) were determined using the Calcusyn program (Biosoft). Calculations of NQO1 fold induction are based on NQO1 specific activity, which was calculated as described [36].

Crystal Structure Determination for Compound 26 [35]

Tan plate-shaped crystals of $C_{13}H_{14}O_4S$ are, at 193(2) K, orthorhombic, space group $P2_12_12_1 - D_2^4$ (No. 19) with a = 7.2394(8) Å, b = 8.1159(9) Å, c = 21.638(2) Å,

V = 1271.3(2) Å^3 and Z = 4 formula units {d_{calcd} = 1.391 g/cm^3; μ_a(MoK$\bar{\alpha}$) = 0.258 mm^{-1}}. A full hemisphere of diffracted intensities (1868 20-second frames with an ω scan width of 0.30°) was measured using graphite-monochromated MoK$\bar{\alpha}$ radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA.

Lattice constants were determined with the Bruker SAINT software package using peak centers for 2166 reflections having 7.54°≤ 2θ ≤ 41.57°. A total of 10375 integrated reflection intensities having 2θ((MoK$\bar{\alpha}$)≤ 52.78° were produced using the Bruker program SAINT; 2592 of these were unique and gave R_{int} = 0.059 with a coverage which was

99.5% complete. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.12 software package.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. Hydrogen atoms H3A, H3B, H4, H5A and H5B were located in a difference Fourier map and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. The remaining hydrogen atoms were included in the structural model as fixed atoms (using idealized sp^2- or sp^3-hybridized geometry and C-H bond lengths of 0.95 - 0.98 Å) "riding" on their respective carbon atoms. The isotropic thermal parameters for these hydrogen atoms were fixed at a value 1.2(non-methyl) or 1.5(methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded. A total of 186 parameters were refined using no restraints and 2592 data. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.047 for 2113 independent "observed" reflections having 2θ(MoK$\bar{\alpha}$)< 52.78° and I>2σ(I); R_1(unweighted, based on F) = 0.060 and wR_2(weighted, based on F^2) = 0.090 for all 2592 independent reflections having 2θ(MoK$\bar{\alpha}$)< 52.78°. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.381 and -0.234 $e^-/Å^3$, respectively. The structure was refined as a racemic twin with twin ratio 51%/49% .

Crystal Structure Determination for Compound 30 [36]

Colorless plate-shaped crystals of $C_{17}H_{18}O_5S$ are, at 193(2) K, monoclinic, space group $P2_1/c$ - C_{2h}^5 (No. 14) with a = 7.077(5) Å, b = 10.218(8) Å, c = 22.181(16) Å, β = 99.067(10)° , V = 1584(2) $Å^3$ and Z = 4 formula units {d_{calcd} = 1.402 g/cm^3; μ_a(MoK$\bar{\alpha}$) = 0.228 mm^{-1}}. A full hemisphere of diffracted intensities (1868 30-second frames with an ω scan width of 0.30°) was measured using graphite-monochromated MoK$\bar{\alpha}$ radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA.

Lattice constants were determined with the Bruker SAINT software package using peak centers for 1050 reflections having 8.20°≤ 2θ ≤ 41.82°. A total of 9843 integrated reflection intensities having 2θ((MoK$\bar{\alpha}$)≤ 46.50° were produced using the Bruker program SAINT(3); 2340 of these were unique and gave R_{int} = 0.090 with a coverage which was 99.4% complete. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.12 software package.

The crystal initially appeared to utilize the C-centered orthorhombic space group $C222_1$ - D_2^5 (No. 20) with **a** = 7.077 Å, **b** = 43.808 Å and **c** = 10.218 Å . Merging the intensity data according to orthorhombic D_{2h}-mmm Laue symmetry gave R_{sym} = 0.108. When the structure could not be solved in this orthorhombic space group, the symmetry was reduced to monoclinic $P2_1$ - C_2^2 (No. 4) with **c** as the unique axis. The structure was solved in this space group to give an asymmetric unit that contained two crystallographically-independent molecules. When properly translated and transformed in the unit cell, these two molecules were seen to be rigorously related by the symmetry operations of space group $P2_1/c$ when the C-centered orthorhombic unit cell was transformed to the corresponding primitive monoclinic cell. The data frames were reintegrated based on the primitive monoclinic unit cell and final lattice constants were obtained. However, the structural model containing one independent $C_{17}H_{18}O_5S$ molecule in space group $P2_1/c$ would not refine below R_1 = 0.25. Incorporation of 2-domain (56/44) pseudomerohedral twinning by a twofold rotation about the orthorhombic **a** axis, reduced R_1 to 0.06.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The hydrogen atoms were included in the structural model as fixed atoms (using idealized sp^2- or sp^3-hybridized geometry and C-H bond lengths of 0.95 – 0.99 Å) "riding" on their respective carbon atoms. The isotropic thermal parameters for these hydrogen atoms were fixed at a value 1.2(non-methyl) or 1.5(methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded. A total of 211 parameters were refined using no restraints and 2340 data. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.064 for 1750 independent "observed" reflections having 2θ(MoK$\bar{\alpha}$)< 46.50° and I>2σ(I); R_1(unweighted, based on F) = 0.091 and wR_2(weighted, based on F^2) = 0.168 for all 2340 independent reflections having 2θ(MoK$\bar{\alpha}$)< 46.50°. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.271 and -0.520 $e^-/Å^3$, respectively. The structure was refined as a pseudomerohedral twin with twin law 1 0 0 0 -1 0 -1 0 -1 and BASF parameter 0.440.

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