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Anticancer Prodrug Studies: Diels–Alder Chemistry of 1-Methylthio-1-(*p*-tolylsulfonyl)ethene

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The reactivity of 1-methylthio-1-(*p*-tolylsulfonyl)ethene (**1**) as a dienophile in Diels–Alder chemistry is investigated. Cycloaddition reactions were carried out with a range of pyran-2-ones and isobenzofurans. The initial Diels–Alder adducts have the potential of undergoing fragmentation in chemistry that is relevant to the design of anticancer intercalator prodrugs. The nature of the final products of the reactions provided insights into both the cycloaddition reactions and fragmentation pathways of the adducts. By comparison with a thioether group, the sulfonyl substituent of the dienophile was found to decrease the reactivity and regioselectivity of the cycloaddition chemistry and to facilitate fragmentation of the initial adducts by the elimination of *p*-toluenesulfinic acid.

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Introduction

The targeting and activation of anticancer prodrugs is an active field of cancer chemotherapy research. As part of a program to develop 'prodrugs' of intercalating agents suitable for antibody-directed enzyme prodrug therapy (ADEPT)[1] we have been exploring the chemistry of sulfur-substituted bridged Diels–Alder adducts.[2] The aim of this program is to generate non-planar precursors to aromatic systems that can be fragmented to planar aromatic derivatives under controlled conditions by a carbon–sulfur bond cleavage process (Scheme 1). This controlled change of molecular geometry is potentially applicable to a wide range of activation processes involving recognition of planar aromatic species, including nucleic acids. The investigation of cycloaddition and fragmentation chemistry is aimed at optimizing the synthesis of fragmentable adducts, and hence the development of anticancer prodrugs.

We have demonstrated that 1,1-bis(methylthio)ethene (**2**) is a dienophile of modest reactivity in cycloadditions with pyran-2-ones[3] and provides both non-planar Diels–Alder adducts and aromatic fragmentation products depending on the substitution pattern of the diene. In an effort to produce a more reactive dienophile and adducts of different reactivity we have investigated the Diels–Alder chemistry of an analogous hemi-sulfone, **1** (Fig. 1). Vinyl sulfones have received much attention as useful intermediates in organic synthesis, both as Michael acceptors and in cycloaddition reactions.[4] Sulfonyl substituents have proved to be suitable electron-withdrawing groups for the activation of Diels–Alder reactions and there have been occasional reports of the reaction of vinyl sulfones with electron-rich pyranones and pyridones.[5]

Results and Discussion

1-Methylthio-1-(*p*-toluenesulfonyl)ethene (**1**) was prepared by a variation of the method of Ogura and Fujina.[6] Elimination of hydrogen chloride from 1-chloro-1-methylthio-1-(*p*-toluenesulfonyl)ethane was accomplished more efficiently by heating at 90°C neat rather than refluxing in chloroform. Compound **1** was reacted with a series of pyranones and isobenzofurans to ascertain its potential as a Diels–Alder dienophile.

*Diels-Alder Reactions of **1** with Pyran-2-ones*

1-Methylthio-1-(*p*-tolylsulfonyl)ethene (**1**) was reacted with methyl coumalate (**3**) and methyl 4,6-dimethylcoumalate (**4**). These reactions bore similarities with the corresponding reactions employing 1,1-bis(methylthio)ethene as dienophile. Cycloaddition reactions took place in refluxing toluene but the sulfonyl-substituted alkene **1** required longer reaction times and the yield of products was much lower (less than 10%). The regiochemistry of all the cycloadditions were the same. In the reactions of **1** with these coumalates only aromatized products **5** and **6**, arising from decarboxylation, were isolated. This mirrors the situation when alkene **2** reacts with diene **4** but contrasts the reaction of **2** with **3** where the bridged adduct is the sole product under these conditions (Scheme 2).

The cycloaddition between **1** and a more reactive pyran-2-one, 4-methyl-1-phenylbenzopyran-3-one (**7**) was investigated. In this case the rate of reaction of **1** was comparable to the analogous reaction of **2**. This Diels–Alder reaction occurred in more reasonable yield (38%) but contrasted in two ways with the analogous chemistry observed for **2**: no bridged adduct was obtained, and the high regioselectivity observed when **2** reacts with this diene was not mirrored in the reaction of **1**. The two regioisomers **8** and **9** were obtained in a ratio of 2:5, respectively (Scheme 3).

The exclusive generation of aromatic products in these three cycloaddition reactions presumably reflects the ease of elimination of *p*-toluenesulfinic acid from this type of adduct. This elimination would induce decarboxylation because of the

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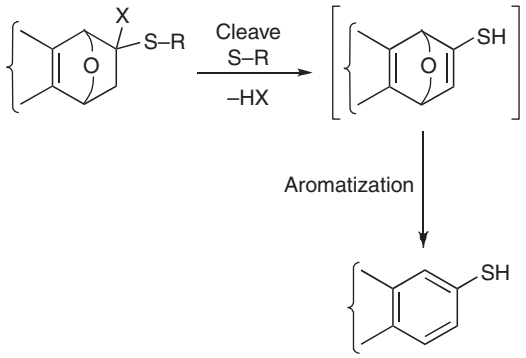


Scheme 1. Schematic illustration of prodrug activation by S–R bond cleavage and spontaneous fragmentation of a bridged Diels–Alder adduct to a planar derivative.

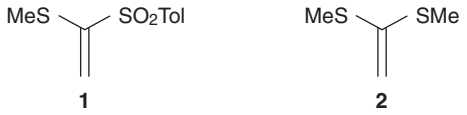


Fig. 1. Structures of compounds **1** and **2**.

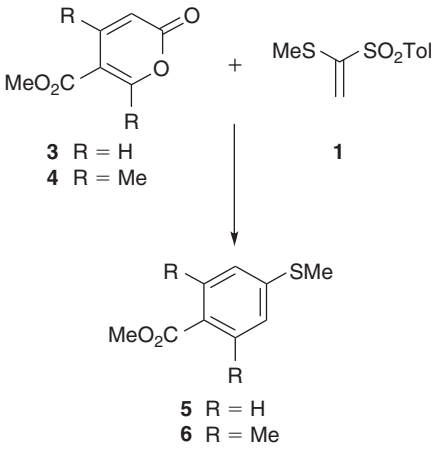
unstable nature of bridged cyclohexadienes. It was hoped that this elimination–fragmentation chemistry could be exploited in prodrug development, provided the system could be modified to allow access to the initial bridged Diels–Alder adduct. The lower reactivity of **1** than **2** in reaction with coumalates is not surprising since it involves the reaction of a less electron-rich dienophile with electron-deficient dienes. For this reason cycloadditions of **1** with a more electron-rich pyranone was evaluated.

Compound **1** was reacted with 1-methylpyrano-[3,4-*b*]indol-3-one (**10**), a polycyclic intercalator precursor. The Diels–Alder reaction was successful and produced two aromatic regioisomers, **11** and **12**, albeit in low yield (Scheme 4). Unfortunately no bridged adducts were observed and so, although **1** appeared to be more reactive with **10** than **2**, this was not further investigated as a synthetic route.

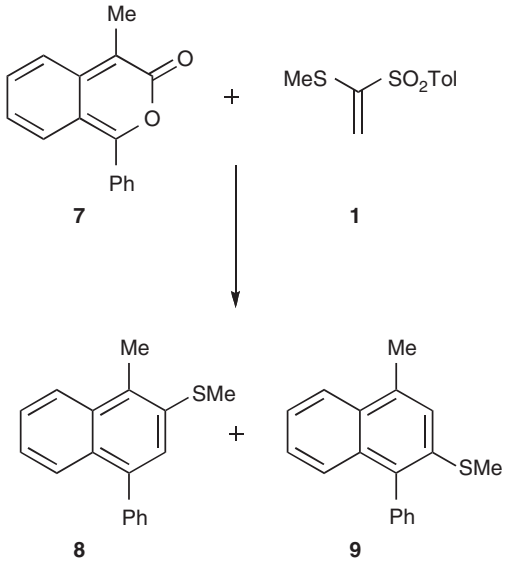
*Diels–Alder Reactions of **1** with Isobenzofurans*

It is clear that **1** is not a synthetically useful dienophile for the formation of bridged Diels–Alder adducts from electron-deficient pyran-2-ones. To complement these studies we investigated the Diels–Alder reactivity of this alkene with two reactive, electron-rich isobenzofuran dienes.

The initial investigation utilized a phenyl-substituted isobenzofuran as a model, because of its ease of preparation. When 1-methylthio-3-phenylisobenzofuran (**13**), generated in situ by deprotonation and methylation of 3-phenyl-1,3-dihydroisobenzofuran-1-thione,[2] was reacted with **1**, only one of the four possible isomeric adducts, **14**, was observed (Scheme 5). This compound decomposed rapidly in most solvents making elucidation of its regio- and stereo-chemistry by NMR spectroscopy problematic. The product of this decomposition was shown to be **15** by X-ray crystallography (Fig. 2). The position of the thiomethyl substituent in **15** implies that the two thiomethyl groups of the initial adduct were *meta*-orientated. On steric grounds, and by analogy with the stereoselectivity of cycloaddition between **1** and **17** (see below) the *p*-tolylsulfonyl group is tentatively assumed to be *exo* in adduct **14**.



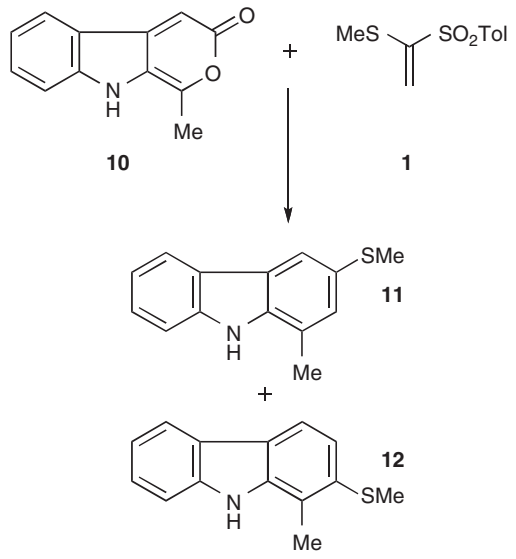
Scheme 2.



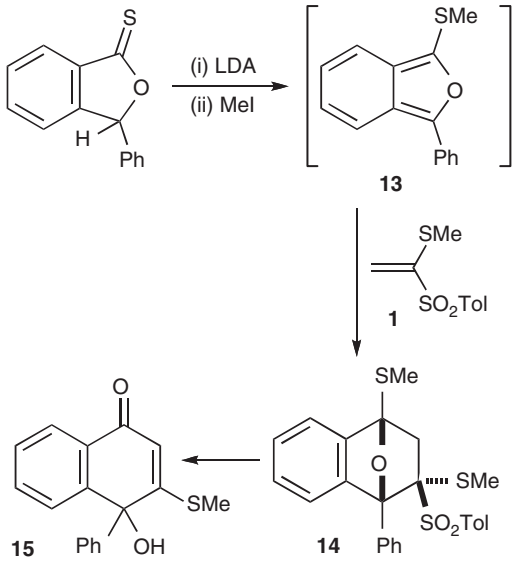
Scheme 3.

The reaction of **13** with **1** was comparatively slow and a major product of the reaction did not involve reaction with the vinyl sulfone. This product was found to be thioester **16**, the structure of which was confirmed by X-ray crystallography (Fig. 3). The formation of this type of compound has been observed before in Diels–Alder reactions of isobenzofurans with poor dienophiles[7] and as the product of prolonged exposure of isobenzofuran solutions to the atmosphere.[8]

For the anticipated prodrugs a hydrogen is preferable to a phenyl group at the bridgehead position to allow subsequent controlled aromatization by elimination chemistry. Consequently, the Diels–Alder reaction of **1**[6] with 1-(methylthio) isobenzofuran (**17**),[2] was investigated to determine whether stable bridged adducts could be prepared by this cycloaddition chemistry. This reaction gave all of the four possible regio- and stereo-isomeric bridged adducts **18a**, **18b**, **19a**, and **19b** in the ratio 12:49:13:26, respectively (as judged by ^{1}H NMR spectroscopy) (Scheme 6). The slight preference for the formation of the isomers **18b** and **19b** can be attributed to steric effects. Three of these isomers were isolated by chromatography in a combined yield of 85%; the other, **18a**, decomposed on the silica. The regio- and stereo-chemistries of the other isomers



Scheme 4.



Scheme 5. LDA: lithium diisopropylamide.

were determined by analysis of ^{1}H NMR chemical shifts, coupling constants, and nuclear Overhauser effects (the effect of irradiating each of the three methyl singlet resonances was evaluated).

Isomer **18b** underwent elimination of *p*-toluenesulfinic acid and bridge opening within a few hours in chloroform to give a naphthol **20**. This product slowly oxidized in air to give the known naphthaquinone **21** (Fig. 4). This chemistry is analogous to the aromatization anticipated for prodrug activation. The adducts with an *ortho* regiochemistry (**19a** and **19b**) are of greater stability and so bridged adducts of this class are of potential as prodrug precursors to intercalators.

Conclusion

1-Methylthio-1-(*p*-tolylsulfonyl)ethene (**1**) shows modified reactivity as a dienophile compared with the bis-thioether analogue. With a lower electron density it is of limited utility as a dienophile with electron-deficient pyranones. Cycloaddition

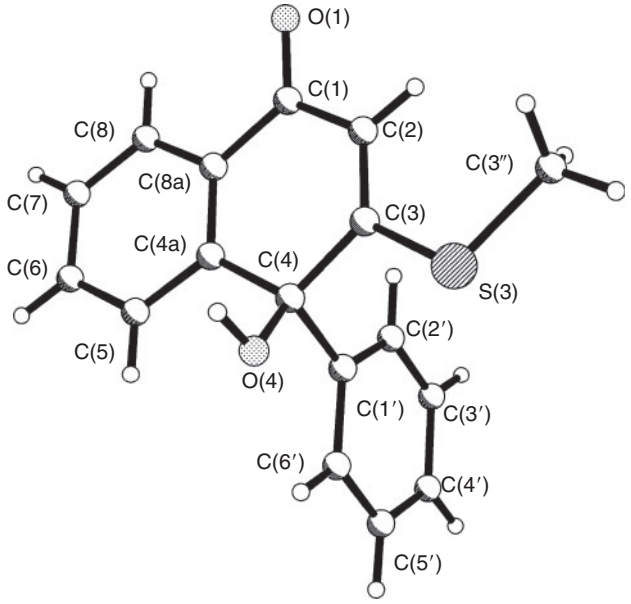


Fig. 2. The X-ray crystal structure of **15**.

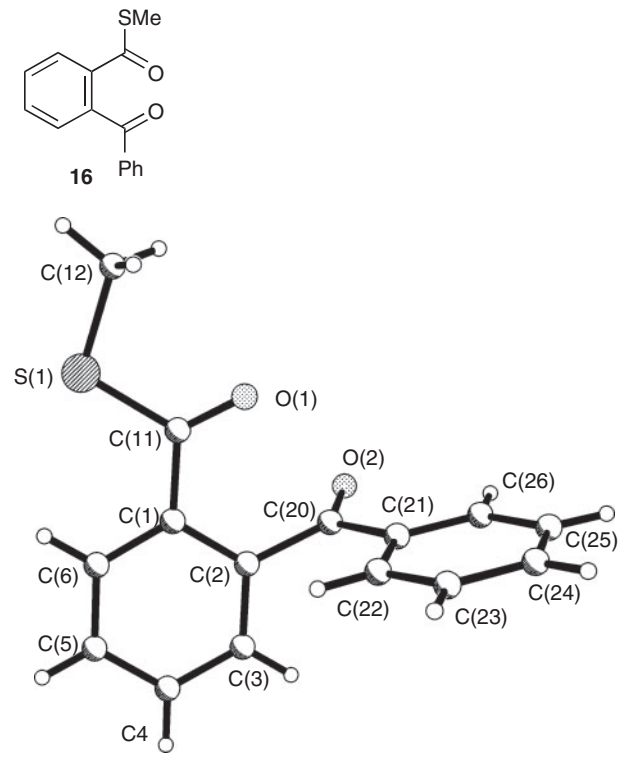
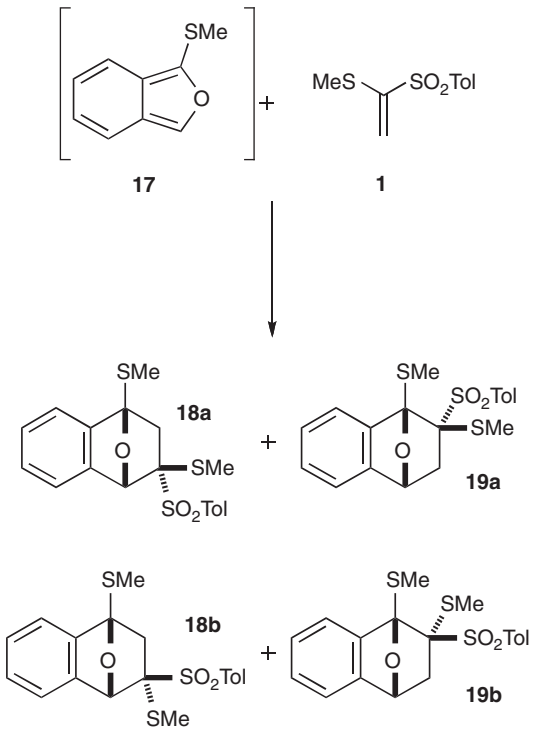


Fig. 3. The X-ray crystal structure of **16**.

reactions with isobenzofurans proved more successful and allowed the preparation and study of bridged Diels–Alder adducts. The sulfonyl group labilized some of the initial adducts and provided insights into the fragmentation chemistry required for prodrug activation and structural features that are important in producing stable bridged adducts.

Experimental

All solvents and reagents were dried rigorously before use and all reactions were carried out under dry nitrogen. Radial



Scheme 6.

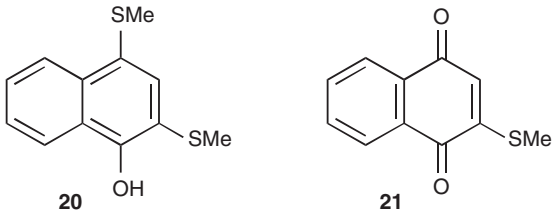


Fig. 4. Structures of compounds **20** and **21**.

chromatography was performed using a 1 mm silica plate. The plate was washed and reactivated using methanol. Melting points (mp) were determined on a Reichert Hotstage microscope and are uncorrected. Infrared spectra were scanned on a Shimadzu FTIR-8201PC or a Perkin-Elmer 1600-FTIR spectrophotometer. The sample was presented as a $CDCl_3$ solution in a 0.1 or 1.0 mm NaCl solution cell. Positions of selected absorptions (ν_{max}) are recorded in wavenumbers (cm^{-1}) and relative intensities denoted as weak (w), medium (m), or strong (s). ^1H NMR spectra were determined on a Varian Unity 300 MHz Fourier transform spectrophotometer. Peaks are quoted in ppm relative to tetramethylsilane (TMS) and the $CHCl_3$ signal referenced to 7.24 ppm. Coupling constants (J) are quoted in hertz (Hz). ^{13}C NMR spectra were measured at 75 MHz on a Varian Unity 300 MHz or a Varian XL 300 MHz Fourier transform spectrophotometer. Peaks are quoted in ppm relative to TMS and the $CDCl_3$ signal referenced to 77.0 ppm. Electron ionization mass spectra (m/z) were determined on a Kratos MS80RFA operating at 4 kV and electron impact at 70 eV. Elemental microanalyses of crystalline samples were performed at the Chemistry Department, University of Otago, New Zealand.

X-Ray crystallographic data was collected as follows: The unit cell parameters were obtained by least-squares refinement of the setting angles of reflections from a Siemens P4 diffractometer. A unique dataset was measured (ω scans). The unique reflections obtained were used in the full-matrix least-squares refinement (*SHELXL-93*).[9] The intensities of three standard reflections were measured every 97 reflections throughout the data collection to check for decay. The structure was solved by direct methods (*SHELXS-86*).[10] Hydrogen atoms were fixed in idealized positions. All non-hydrogen atom parameters were refined using anisotropic atomic displacement parameters. Neutral scattering factors and anomalous dispersion corrections for non-hydrogen atoms were taken from Ibers and Hamilton.[11]

*1-Methylthio-1-(*p*-tolylsulfonyl)ethene (**1**)*

1-Chloro-1-(methylthio)ethyl *p*-tolyl sulfone[6] (6.34 g, 23.9 mmol) was heated neat at 90°C for 5 h. The resulting crude product was purified by vacuum distillation (155°C/0.5 mmHg). Ether (7 mL) was added to the distillate and the solution kept in a freezer overnight. The resulting white platelets of the *title compound* **1**, were isolated by vacuum filtration (1.1 g, 20%); mp 82–85°C Anal. Calc. for $C_{10}H_{12}O_2S_2$: C 52.6, H 5.30, S 28.1, $M^{+\bullet}$ 228.0279. Found: C 52.4, H 5.4, S 27.8, $M^{+\bullet}$ 228.0277. δ_H ($CDCl_3$) 2.27 (s, 3H), 2.41 (s, 3H), 5.64 (d, J 1.9, 1H), 6.53 (d, J 1.9, 1H), 7.31 (d, J 7.8, 2H), 7.80 (d, J 7.8, 2H). δ_C ($CDCl_3$) 17.04, 21.61, 121.24, 128.44, 129.65, 135.76, 144.80, 150.06. ν_{max} 1917w, 1597m, 1319s, 1157s. m/z 228 (M), 139, 91, 73 (100%).

*Methyl 4-(Methylthio)benzoate (**5**)*

Methyl-2-oxo-2*H*-pyrano-5-carboxylate (46 mg, 0.30 mmol, 1.0 equiv.) and **1** (137 mg, 0.60 mmol, 2.0 equiv.) were dissolved in toluene (12 mL). The solution was refluxed under nitrogen for 5.5 days and then concentrated under vacuum. Purification by radial chromatography gave the *title compound* **5** (4 mg, 7%), identical to a previously prepared sample.[12]

*Methyl 2,6-Dimethyl-4-(methylthio)benzoate (**6**)*

Methyl 4,6-dimethyl-2-oxo-2*H*-pyrano-5-carboxylate (55 mg, 0.30 mmol, 1.0 equiv.) and **1** (137 mg, 0.60 mmol, 2.0 equiv.) were refluxed in toluene (12 mL) under nitrogen for 9 days and then concentrated under vacuum. Purification by radial chromatography gave the *title compound* **6** (0.6 mg, 1%), identical to a previously prepared sample.[3]

*1-Methyl-2-methylthio-4-phenylnaphthalene (**8**) and 1-Methyl-3-methylthio-4-phenylnaphthalene (**9**)*

2-Benzoylphenylpropanoic acid (41 mg, 0.16 mmol, 1.0 equiv.) was dissolved in conc. H_2SO_4 (0.16 mL) with gentle warming to give an orange solution. Water (20 mL) was added to produce a deep red precipitate which was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum to ~10 mL. Toluene (15 mL) was added and the solution again concentrated to ~10 mL. This process was repeated to remove any remaining ethyl acetate. The final volume was 12 mL. Compound **1** (110 mg, 0.48 mmol, 3.0 equiv.) was added and the red solution was refluxed under nitrogen for 20 h. By this stage the solution was pale yellow in colour and so was concentrated under vacuum and separated into its components by radial chromatography. Elution with 90% petroleum ether/10% ethyl acetate gave *title compound* **8** (5 mg, 12%) identical to a previously prepared sample.[12] Further elution gave *title compound* **9** (11 mg, 26%) as a pale yellow oil (Found: $M^{+\bullet}$ 264.0971.

$C_{18}H_{16}S$ requires: 264.0973). δ_H ($CDCl_3$) 2.45 (s, SCH_3), 2.77 (s, Ar-CH_3), 7.35 (s, 1H), 7.31–7.56 (m, 8H), 7.99 (d, *J* 8.3, 1H). δ_C ($CDCl_3$) 16.29, 19.68, 123.94, 124.05, 124.82, 126.13, 126.24, 127.57, 128.42, 130.38, 130.63, 132.92, 134.04, 134.49, 135.63, 138.72. ν_{max} cm^{-1} 3062m, 2982m, 2926m, 1717w, 1601m, 1587s, 1556m, 1508m, 1443s. *m/z* 264 (M, 100%), 249 (M – CH_3), 234 (M – 2 × CH_3), 215 (M – SCH_5), 202 (M – CH_3 – SCH_3).

*1-Methyl-3-methylthiocarbazole (**11**) and 1-Methyl-2-methylthiocarbazole (**12**)*

1-Methylpyrano[3,4-*b*]indol-3-one (58 mg, 0.29 mmol, 1.0 equiv.) and **1** (132 mg, 0.58 mmol, 2.0 equiv.) were dissolved in bromobenzene (14 mL). The solution was heated at 120°C under nitrogen. The reaction was monitored by ^{1}H NMR spectroscopy. After 4 h there was no remaining diene. The reaction mixture was concentrated under vacuum and was separated into its components by radial chromatography. Elution with 80% petroleum ether/20% ethyl acetate gave *title compound* **11** (0.7 mg, 1%) identical to a previously prepared product. Further elution gave *title compound* **12** which recrystallized from methanol (2 mg, 3%) as white platelets (Found: $M^{+\bullet}$ 227.0766. $C_{14}H_{13}NS$ requires: 227.0769). mp 158–160°C. δ_H ($CDCl_3$) 2.52 (s, 3H), 2.59 (s, 3H), 7.19 (d, *J* 7.9, 2H), 7.35–7.44 (m, 2H), 7.87 (d, *J* 8.3, 1H), 7.91 (br s, 1H), 8.00 (d, *J* 8.3, 1H). *m/z* 227 (M, 100%), 212 (M – CH_3), 180 (M – SCH_3), 167 (M – C_2H_4S).

S-*Methyl 2-(Benzoyl)thiobenzoate (**16**) and 1,9-Bis (methylthio)-11-oxa-8-phenyl-9-(*p*-tolylsulfonyl)tricyclo [6.2.1.0^{2,7}]undeca-2,4,6-triene (**14**)*

n-Butyl lithium (0.27 mL of a 1.6 mol L^{-1} solution in hexanes, 0.43 mmol, 1.25 equiv.) was added dropwise to a stirred solution of diisopropylamine (58 μL, 0.41 mmol, 1.2 equiv.) in tetrahydrofuran (3.5 mL) under dry nitrogen in an ice-salt bath. The solution was stirred for 35 min at this temperature and then cooled further in an acetone/dry ice bath. A solution of 3-phenyl-1,3-dihydroisobenzofuran-1-thione[2] (78 mg, 0.34 mmol, 1.0 equiv.) in tetrahydrofuran (3.5 mL) was added dropwise. The bright red solution was stirred under nitrogen at −78°C for 1 h. Iodomethane (28 μL, 0.45 mmol, 1.3 equiv.) was added dropwise and the resulting mixture allowed to warm to room temperature over 2 h. A solution of **1** (157 mg, 0.69 mmol, 2.0 equiv.) in tetrahydrofuran (0.7 mL) was added. The reaction solution was left stirring overnight under nitrogen at room temperature. The solution was then concentrated under vacuum to remove excess tetrahydrofuran. The residue was partitioned between water (6 mL) and ethyl acetate (6 mL). The aqueous layer was further extracted with ethyl acetate (2 × 6 mL). The combined organic layers where dried ($MgSO_4$), filtered, and concentrated under vacuum. Purification by radial chromatography, eluting with 90% petroleum ether/10% ethyl acetate, gave S-*Methyl 2-(benzoyl)thiobenzoate* (**16**), which was recrystallised from petroleum ether (30 mg, 41%) as white needles, mp 60–61.5°C. δ_H ($CDCl_3$) 2.29 (s, 3H), 7.41 (t, *J* 7.3, 3H), 7.50–7.62 (m, 3H), 7.75 (dd, *J* 7.4, 1.4, 2H), 7.99 (dd, *J* 7.4, 1.9, 1H). δ_C ($CDCl_3$) 11.95, 128.10, 128.33, 129.39, 129.70, 132.15, 132.99, 133.04, 136.71, 136.80, 139.30, 192.27, 196.87. ν_{max} cm^{-1} 3069w, 2932w, 1773m, 1668s, 1599m, 1450m, 1317m, 1279s, 1265s, 1211s. *m/z* 209 (M – SCH_3, 100%), 180, 152, 105, 77.

Further elution with 80% petroleum ether/20% ethyl acetate, gave the *title compound* **14**, (80 mg, 50%) as a yellow oil. (Found: M – $TolSO_2(CH_3S)C{=}CH_2^{+\bullet}$ 240.0611; $C_{15}H_{12}OS$ requires: $M^{+\bullet}$ 240.0609 (the parent ion was not observed)). δ_H ($CDCl_3$) 1.32 (s, 3H), 2.23 (s, 3H), 2.35 (d, *J* 12.7, 1H), 2.38 (s, 3H), 2.87 (d, *J* 12.7, 1H), 7.21–7.48 (8H, m), 7.61–7.67 (m, 3H), 8.15 (dd, *J* 8.3, 1.5, 2H). δ_C ($CDCl_3$) 12.14, 14.91, 21.41, 46.42, 83.07, 92.53, 119.53, 122.86, 127.63, 127.70, 128.13, 128.21, 129.12, 129.76, 133.76, 135.84, 143.24, 143.91. ν_{max} cm^{-1} 2978m, 2930m, 1761w, 1448m, 1439m, 1144s, 1113s. *m/z* 266 (M – SO_2Tol – SCH_3), 240 (M – $TolSO_2(CH_3S)C{=}CH_2$, 100%), 228 ($TolSO_2(CH_3S)C{=}CH_2$), 226 197, 165, 139, 91 77, 73.

*Crystal Data and Structural Refinement for **16***

$C_{15}H_{12}O_2S$, *M* 256.31, crystal dimensions 0.79 × 0.33 × 0.03 mm^3; triclinic, *a* 7.9480(10), *b* 8.0680(10), *c* 11.0900 (10) Å; α 74.490(10)°, β 88.250(10)°, γ 69.980(10)°; *V* 642.37 (13) $Å^3$, space group *P*-1, *Z* 2, *F*(000) 268, D_{calc} 1.325 Mg m^{-3}, absorption coefficient 0.242 mm^{-1}, θ range for data collection 2.73 to 25.00; maximum and minimum transmissions 0.85 and 0.89, data/restraints/parameters 2231/0/163, goodness of fit on F^2 was 0.797, final *R* indices [$I > 2\sigma(I)$] R_1 0.0353, wR_2 0.0661, *R* indices (all data) R_1 0.0671, wR_2 0.0733, largest difference peak and hole 0.171 and −0.293 e$Å^{-3}$.

The unit cell parameters were obtained by least-squares refinement of the setting angles of 37 reflections with 8° < 2θ < 14°. A unique dataset was measured at 163(2) K within $2\theta_{max} = 50°$ limit (ω scans). Of the 2416 reflections obtained, 2235 were unique (R_{int} 0.0194) and were used in the full-matrix least-squares refinement after being corrected for absorption by using the psi-scan method. The intensities of three standard reflections, measured every 97 reflections throughout the data collection, showed only 8% decay.

*4-Hydroxy-3-methylthio-4-phenyl-4*H*-naphthalen-1-one (**15**)*

Compound **14** decomposed within a few hours in chloroform to give the titled compound, **15**, which recrystallized from methanol as white prisms mp 210°C (sublimes). (Found: $M^{+\bullet}$ 282.0716; $C_{17}H_{14}O_2S$ requires: $M^{+\bullet}$ 282.0715). δ_H ($CDCl_3$), 2.30 (s, 3H), 3.02 (br s, 1H), 6.24 (s, 1H), 7.22–7.31 (m, 3H), 7.36–7.49 (m, 5H), 8.12 (dd, *J* 6.9, 1.5, 1H). δ_C ((D_6)DMSO) 2.37 (s, 3H), 6.33 (s, 1H), 7.22 (s, 1H), 7.26 (ddd, *J* 6.8, 4.4, 1.4, 1H), 7.35 (t, *J* 7.3, 2H), 7.42 (dd, *J* 8.8, 1.5, 2H), 7.49–7.53 (m, 2H), 7.62 (td, *J* 7.3, 1.5, 1H), 8.06 (dd, *J* 8.3, 1.5, 1H). δ_C ((D_6) DMSO) 13.70, 74.03, 118.19, 124.66, 125.24, 127.18, 127.77, 127.86, 128.44, 129.07, 132.84, 144.81, 149.25, 173.18, 180.62. ν_{max} cm^{-1} 3580w, 1645s, 1601m, 1589w, 1564m, 1448w, 1321 (s) 1256w, 1132w. *m/z* 282 (M, 21%), 266 (M – O), 235 (M – SCH_3, 100%), 209, 181, 177, 152, 105, 77.

*Crystal Data and Structural Refinement for **15***

$C_{17}H_{14}O_2S$, *M* 282.34, crystal dimensions 0.76 × 0.33 × 0.13 mm^3; monoclinic, *a* 7.216(2), *b* 22.708(5), *c* 8.544(2) Å; α 90°, β 104.51(3)°, γ 90°; *V* 1355.4(6) $Å^3$, space group $P2_1/c$, *Z* 4, *F*(000) 592, D_{calc} 1.384 Mg m^{-3}, absorption coefficient 0.236 mm^{-1}, θ range for data collection 2.62 to 25.00; data/restraints/parameters 2369/0/185, goodness of fit on F^2 was 0.877, final *R* indices [$I > 2\sigma(I)$] R_1 0.0720, wR_2 0.1699, *R* indices (all data) R_1 0.1249, wR_2 0.1999, largest difference peak and hole 0.623 and −0.570 e $Å^{-3}$.

The unit cell parameters were obtained by least-squares refinement of the setting angles of 30 reflections with 13° > 2θ > 7°. A unique dataset was measured at 163(2) K within $2\theta_{max}$ 50° limit (ω scans). Of the 2441 reflections obtained, 2372

were unique (R_{int} 0.0640) and were used in the full-matrix least-squares refinement. The intensities of three standard reflections, measured every 97 reflections throughout the data collection, showed only 2% decay.

*1,9-Bis(methylthio)-11-oxa-9-(*p*-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene (**18**) and 1,10-Bis(methylthio)-11-oxa-10-(*p*-tolylsulfonyl)tricyclo-[6.2.1.0^{2,7}]undeca-2,4,6-triene (**19**)*

n-Butyl lithium (0.24 mL of a 1.6 mol L^{-1} solution in hexanes, 0.38 mmol, 1.2 equiv.) was added dropwise to a stirred solution of diisopropylamine (49 μL, 0.35 mmol, 1.1 equiv.) in tetrahydrofuran (3.3 mL) cooled in an ice-salt bath. The solution was stirred for 20 min at this temperature and then cooled further in an acetone/dry ice bath. A solution of 1,3-dihydroisobenzofuran-1-thione[2] (48 mg, 0.32 mmol, 1.0 equiv.) in tetrahydrofuran (3.3 mL) was added dropwise. The solution was stirred at −78°C for 1 h. Iodomethane (24 μL, 0.38 mmol, 1.2 equiv.) was added dropwise and the resulting mixture allowed to warm to room temperature over 2 h. A solution of **1** (87 mg, 0.38 mmol, 1.2 equiv.) in tetrahydrofuran (0.9 mL) was added. The reaction solution was left stirring overnight at room temperature. The solution was then concentrated under vacuum to remove excess tetrahydrofuran. The residue was partitioned between water (8 mL) and dichloromethane (8 mL). The aqueous layer was further extracted with dichloromethane (2 × 8 mL). The combined organic layers where dried ($MgSO_4$), filtered, and concentrated under vacuum. Purification by radial chromatography, eluting with 80% petroleum ether/20% ethyl acetate gave *1*,endo-*9-bis(methylthio)-11-oxa*-exo-*9-(*p*-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene* (**18b**) (75 mg, 60%) as a white solid, mp 67.5–69°C. (Found: M – $TolSO_2H^{+\bullet}$ 236.0330; $C_{12}H_{12}OS_2$ requires: $M^{+\bullet}$ 236.0330 (the parent ion was not observed)). δ_H (C_6D_6) 1.69 (d, *J* 13.1, *endo* H), 1.84 (s, CH_3S–CO), 1.96 (s, CH_3–Ø), 2.15 (s, CH_3S–C–SO_2), 3.13 (d, *J* 13.1, *exo* H), 6.01 (s, H–CO), 6.92 (d, *J* 7.8, 2H), 6.99–7.09 (m, 3H), 7.20 (d, *J* 5.9, 1H), 8.01 (d, *J* 8.3, 2H). *m/z* 236 (M – $TolSO_2H$, 100%), 221 (M – $TolSO_2H$ – CH_3), 189 (M – $TolSO_2H$ – SCH_3), 177, 164, 139, 91, 73.

Further elution gave *1*,exo-*10-bis(methylthio)-11-oxa*-endo-*10-(*p*-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene* (**19a**) (6 mg, 5%) as a white solid, mp 126–128°C. δ_H ($CDCl_3$) 2.05 (s, CH_3S–CO), 2.10 (s, CH_3–Ø), 2.43 (s, CH_3S–C–SO_2), 2.60 (d, *J* 12.7, *endo* H), 2.75, dd, *J* 12.7, 5.4, *exo* H), 5.52 (d, *J* 5.4, H–CO), 7.29–7.38 (m, 5H), 7.54 (d, *J* 7.3, 1H), 7.78 (d, *J* 8.3, 2H).

Further elution gave *1*,endo-*10-bis(methylthio)-11-oxa*-exo-*10-(*p*-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene* (**19b**) (25 mg 20%), which recrystallized from ethanol as white needles, mp 148–152°C. (Found: M – $TolSO_2H^{+\bullet}$ 236.0329; $C_{12}H_{12}OS_2$ requires: $M^{+\bullet}$ 236.0330 (the parent ion was not observed)). δ_H ($CDCl_3$) 1.38 (d, *J* 13.2, *endo* H), 2.11 (s, CH_3S–CO), 2.42 (s, CH_3–Ø), 2.48 (s, CH_3S–C–SO_2), 3.05 (dd, *J* 13.2, 5.4, *exo* H), 5.33 (d, *J* 4.9, H–CO), 7.22–7.32 (m, 5H), 7.49 (d, *J* 6.4, 1H), 7.99 (d, *J* 8.3, 2H). δ_C ($CDCl_3$) 13.94, 15.83, 21.66, 43.64, 77.12, 78.96, 101.20, 119.39, 121.86, 126.94, 128.24, 128.90, 131.52, 135.30, 141.69, 144.56, 145.41. ν_{max} cm^{-1} 2932m, 1597m, 1302m, 1142s. *m/z* 236 (M – $TolSO_2H$, 37%), 228, 221, 164, 139, 121 91, 73 (100%).

*1,3-Bis(methylthio)naphthalen-4-ol (**20**)*

Compound **18a** decomposed within hours upon standing in chloroform. Purification by radial chromatography, eluting with petroleum ether, gave the titled compound **20**[13] (6 mg, 43%) as white needles, mp 57–58°C. (Found: 236.0329; $C_{12}H_{12}OS_2$ requires: 236.0329). δ_H ($CDCl_3$) 2.36 (s, 3H), 2.48 (s, 3H), 7.24 (s, 1H), 7.54 (dd, *J* 8.3, 1.4, 1H), 7.58 (dd, *J* 8.3, 1.4, 1H), 7.62 (s, 1H), 8.28 (t, *J* 8.3, 2H). δ_C ($CDCl_3$) 18.42, 19.98, 113.40, 123.51, 124.06, 125.03, 126.04, 126.11, 127.75, 132.87, 134.05, 152.88 ν_{max} cm^{-1} 3398br m, 2926m, 1578s, 1499m, 1437m, 1418m, 1366s, 1333s, 1238s. *m/z* 236 (M, 100%), 221 (M – CH_3), 177.

*2-(Methylthio)naphthalen-1,4-dione (**21**)*

Compound **20** slowly oxidized to naphthoquinone **21** upon exposure to air. Purification by radial chromatography, eluting with 90% petroleum ether/10% ethyl acetate, gave the titled compound, **21**,[14] which crystallized from ethanol as yellow needles mp 161–163°C. δ_H ($CDCl_3$) 2.37 (s, SCH_3), 6.56 (s, CHCO), 7.69 (td, *J* 7.3, 1.5, ArH), 7.74 (td, *J* 7.3, 2.0, ArH), 8.08 (dd, *J* 7.3, 2.0, ArH), 8.10 (dd, *J* 7.3, 1.5, ArH).

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