

Synthesis and inclusion of *S*-aryl alkylthiosulfinates as stable allicin mimics

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Dedicated to Professor Berhanu M Abegaz on the occasion of his 60th birthday

Abstract

S-Aryl alkylthiosulfinates showing aromatic rings with varying electronic demand have been prepared by oxidation of the corresponding disulfide, the latter prepared using new one-pot methodology involving thiol oxidation with 1-chlorobenzotriazole. Whereas thiosulfinates with electron-withdrawing substituents in the aromatic ring were unstable towards isolation, those with a releasing substituent in the *para*-position have shown good stability as potential allicin mimics and one of them (*p*-OMe) has been characterised as its inclusion compound in the cyclodextrin, TRIMEB, by X-ray crystallography.

Keywords: Allicin mimic, unsymmetrical disulfide synthesis, *S*-aryl alkylthiosulfinate, cyclodextrin inclusion

Introduction

Modern organic chemistry has played a major role in elucidating the fascinating chemistry that goes on when a garlic clove is crushed or attacked by a pathogen to produce the thiosulfinate allicin, Figure 1.¹

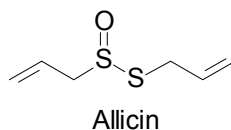


Figure 1

On the prospect of achieving enhanced stability, we were also encouraged by the recent paper by Brace⁹ on the fluorinated thiosulfinate **2** shown in Figure 3, which shows a significantly increased stability compared to its hydrogenated analogue.

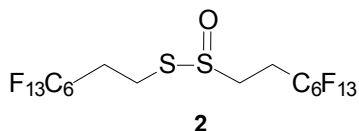
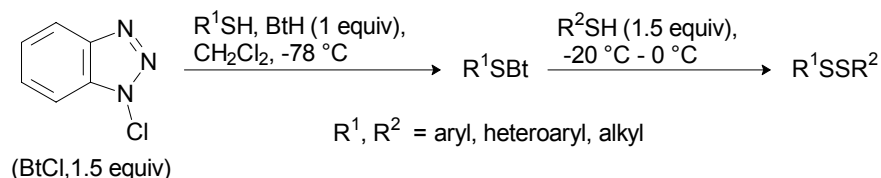


Figure 3

In this paper we report on the synthesis of aralkyl disulfides with either an electron-releasing or withdrawing group in the aromatic ring, and their oxidation to the corresponding thiosulfinate using *m*-CPBA.¹⁰ In addition, inclusion is described for one of the thiosulfينات into the permethylated β -cyclodextrin, TRIMEB.

Results and Discussion

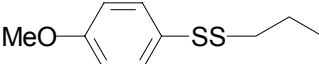
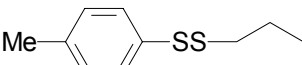
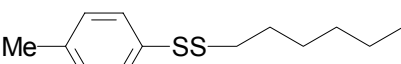
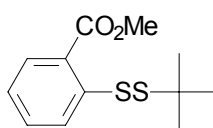
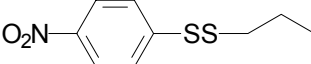
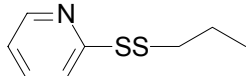
We have recently reported¹¹ novel methodology for unsymmetrical disulfide synthesis involving a one-pot oxidation with 1-chlorobenzotriazole (BtCl). The general sequence of events is shown in Scheme 2.



Scheme 2

This methodology was put to good use in preparing a range of disulfides for studying their oxidation to the thiosulfinate. Each case had R^1 as either an aromatic or pyridyl heteroaromatic ring, and R^2 as an alkyl chain. Each aromatic ring contained a substituent *ortho* or *para* to the sulfur for the expected attenuation of stability of target thiosulfinate. We decided to replace the allyl group of allicin with a fully saturated alkyl chain, as it was anticipated that this would not drastically affect any biological activity. Moreover, it had already been shown that yields of aralkyl disulfides were significantly lower than those of the aralkyl systems. Table 1 shows the structures synthesized together with the yield of each after chromatography.

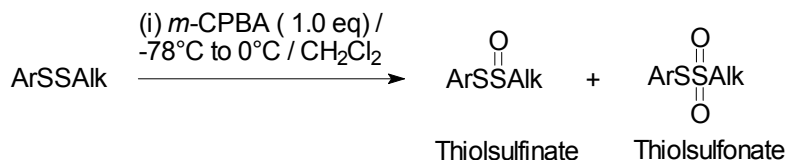
Table 1. Yields for disulfides from BtCl methodology

Entry	R ¹ SSR ² Product	Compound	Yield (%)
1		3	91 ^a
2		4	85 ^b
3		5	82
4		6	90
5		7	88
6		8	84 ^c

^a Reported in reference 11a and 11b, ^b reported in reference 11c, ^c reported in reference 11d.

Consistent with our previous study,^{11b} it was found that higher yields were obtained adding the aromatic thiol first, as the other way round resulted in the formation of large amounts of the aliphatic disulfide homodimer. Each product was fully characterised by both ¹H and ¹³C NMR to reveal the expected resonances, with the α -methylene protons and carbon diagnostic at $\sim \delta = 2.7$ ppm and 40 ppm for the two respective spectra.

We have previously reported a preliminary study regarding the oxidation of *p*-methoxyphenyl propyl disulfide using *m*-CPBA (1 equivalent) at low temperature,^{11a} in which oxidation took place chemoselectively at the more nucleophilic sulfur attached to the aliphatic group (alk) to form the desired thiosulfinate, as evidenced by ¹H NMR and ¹³C NMR shifts pertaining to the α -alkyl carbon. In addition, some thiosulfonate was also obtained. Scheme 3.

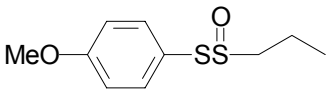
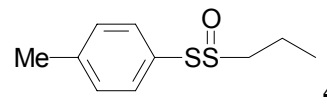
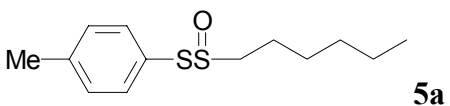
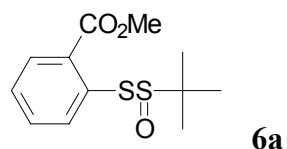
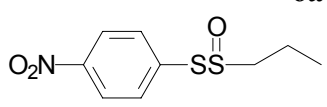
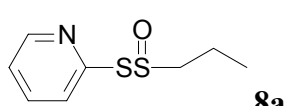


Scheme 3

In extending this study, it was found that marked differences between the substrates were observed, Table 2. For entries 2 and 3, oxidation occurred with similar profiles to those in the previous study already mentioned to produce **3a**.^{11a} Thus, the *S*-aryl alkylthiosulfonates **4a** and **5a** were obtained in good yield together with some thiosulfonate by-product as before. Assignment

of the regiochemistry of oxidation was based on comparison of the NMR data with that of compound **3a** as described previously.^{11a} The thiosulfonates were successfully chromatographed and found to have high stability at room temperature (see Table 3). Conversely, both compounds with electron-withdrawing substituents in the aromatic ring R¹ (CO₂Me and NO₂; entries 4 and 5 respectively), although producing a major product on tlc, failed to produce anything on purification involving a conventional work-up and chromatography. Tlc analysis of the column fractions revealed multiple spots indicating extensive breakdown. This strongly suggests that electron deficiency in the aromatic ring leads to instability of the thiosulfonate, precluding them as potential allicin mimics. Interestingly, the heteroaromatic pyridyl case (entry 6) gave an altogether different result. In spite of its aromatic ring being highly electron-withdrawing towards the sulfur atoms, oxidation proceeded to form two products that were stable to isolation by chromatography. The more polar of the two proved to be pyridyl disulfide, as evidenced by tlc, melting point and its ¹H NMR spectrum compared with an authentic sample. The less polar of the two products has a structure that has not been elucidated beyond reasonable doubt as yet but is clearly not *S*-pyridyl propylthiosulfonate as evidenced by ¹H and ¹³C NMR spectra, which indicate the presence of three propyl groups in the ratio 1:1:1 and each one in a significantly different chemical environment. Furthermore, NMR shifts indicate the pyridine nitrogen to be unoxidized. The structural elucidation of this interesting rearrangement will be reported elsewhere. An overview of the oxidation results is presented in Table 2.

Table 2: Oxidation of unsymmetrical disulfides to thiosulfonates

Entry	R ¹ SSR ²	ArSSO(Alk)	Yield (%)
1	3		66 ^a
2	4		54 ^b
3	5		70 ^c
4	6		Unstable
5	7		Unstable
6	8		Unstable

^aWith 23% of thiosulfonate; ^bWith 14% of thiosulfonate; ^cWith 15% of thiosulfonate

Regarding stability studies, samples of the thiosulfinates **3a** and **4a** were left at room temperature (around 20°C) on the bench in a neat form, in the refrigerator (-5°C) in a neat form and in solution (CDCl₃) at room temperature. 400 MHz ¹H NMR spectroscopy was used to evaluate the % conversion after 1, 3 and 5 months, using signals in the aromatic and methyl regions. After 1 month neat at room temperature, less than 5% decomposition was noted for the samples. This contrasts with allicin, which has a half-life of 16 hours under the same conditions. Both thiosulfinates proved to be significantly more stable in the neat form at room temperature than in solution in CDCl₃, Table 3. Tlc indicated the decomposition to involve disproportionation⁸ to the corresponding disulfide and thiosulfonate according to reference samples. Interestingly, the results indicate that whilst **3a** is more stable than **4a** in the neat form, the reverse applies in solution.

Table 3: Decomposition studies of thiosulfinates **3a** and **4a**

Cpd	Time ^a	0°C ^{b, c}	Time	RT ^{b, c}	Time	RT, CDCl ₃ ^b
3a	1	< 1	1	< 3	1	60
3a	3	< 3	3	^d	3	100
3a	5	10	5	50	5	^d
4a	1	< 5	1	5	1	10
4a	3	6	2	12	3	75
4a	5	15	5	75	5	^d

^a In Months; ^b as a % of conversion determined by 400 MHz ¹H NMR; ^c Neat; ^d Not recorded

Following our successful inclusion of the isomers of ajoene in cyclodextrins,¹² it was of interest to establish whether the novel *S*-aryl alkylthiosulfinates would show a similar affinity for these host molecules. The oxidation product of entry 1 (Table 2), namely *S*-*p*-methoxyphenyl propylthiosulfinate **3a**, as a representative of this series, was accordingly added to a saturated aqueous solution of an equimolar amount of heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) and the mixture stirred in a vial for 24 h. Following incubation of the vial at 50°C for 72 h, colourless prismatic crystals of the inclusion compound appeared. These were harvested and characterised by elemental analysis, hot stage microscopy (HSM), thermogravimetry (TGA), differential scanning calorimetry (DSC) and single crystal X-ray diffraction, as described below.

Elemental analysis yielded %C 52.2, %H 7.4, %S 3.9, consistent with 1:1 host-guest stoichiometry (calcd. for C₆₃H₁₁₂O₃₅·C₁₀H₁₄O₂S₂: %C 52.82, %H 7.65, %S 3.86). HSM revealed melting of the complex crystals at ~134°C. In the DSC trace, onset and peak temperatures corresponding to the melting endotherm were recorded as 132.6 and 136.9 °C respectively. The TGA trace showed negligible mass loss in the temperature range 25-160 °C followed by a mass loss of ~13.2% between 160 and 325 °C. The latter corresponds to release of the guest from the inclusion complex (calcd. for 1:1 host-guest stoichiometry 13.9%). Above 325°C, the host

compound decomposed. Details of the X-ray analysis are listed in the experimental Section and in Table 4.

Table 4. Crystal data and details of refinement for the complex TRIMEB·(*S*)-*S*-*p*-methoxyphenyl propylthiosulfinate^a

Complex formula	C ₆₃ H ₁₁₂ O ₃₅ ·C ₁₀ H ₁₄ O ₂ S ₂
<i>M</i>	1659.88
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	14.7750(2)
<i>b</i> /Å	21.3329(3)
<i>c</i> /Å	27.872 (1)
<i>V</i> _{cell} /Å ³	8785.2(4)
<i>Z</i>	4
<i>T</i> /K	113(2)
Absorption coefficient/mm ⁻¹	0.145
<i>F</i> (000)	3568
Theta range °	2.8 - 25.7
Index ranges	-17 ≤ <i>h</i> ≤ 18, -25 ≤ <i>k</i> ≤ 26, -33 ≤ <i>l</i> ≤ 33
Reflections collected	16562
Observed reflections [<i>I</i> >2σ(<i>I</i>)]	11196
Data/parameters	16562/939
Goodness-of-fit on <i>F</i> ²	1.04
Final <i>R</i> indices [<i>I</i> >2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0877, <i>wR</i> ₂ = 0.2674
Largest diff. peak and hole	-0.96, 1.58 e Å ⁻³

^a Full crystallographic data (CCDC 616365)

A perspective view of the complex structure is shown in Figure 4, with the host in ball-and-stick mode and the guest in space-filling representation. The TRIMEB molecule displays the usual elliptical distortion,¹² stabilised by several C-H...O hydrogen bonds, with the methoxyl groups on the primary rim acting as a lid, presenting the guest with a cup-shaped hydrophobic surface for inclusion. The guest molecule adopts a hairpin conformation with the moiety -S-S=O located near the cavity 'roof' and the methoxyphenyl and propyl residues directed towards the secondary rim of the host molecule.

Interestingly, in each of the TRIMEB inclusion complexes of (*E*)- and (*Z*)-ajoene, a disordered arrangement, comprising both the *R*- and *S*-enantiomers of the guest, was identified within the host cavity.¹² In contrast, for the crystal selected, only the *S*-enantiomer of *S*-*p*-methoxyphenyl propylthiosulfinate was evident in the present complex.

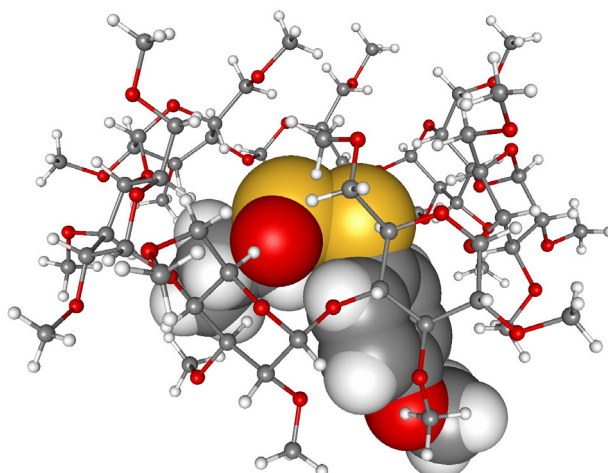


Figure 4. Molecular structure of the complex TRIMEB·(*S*)-*S*-*p*-methoxyphenyl propylthiosulfinate

In summary, the present study opens up the way for further work to be carried out on *S*-aryl alkylthiosulfonates bearing electron-releasing groups in the aromatic ring, with the emphasis on investigating potential biological activity and associated structure-activity relationships. Work will also continue towards attempting to produce even more stable thiosulfonates of this type,¹³ with the incorporation of fluorinated alkylsulfinyl groups an attractive option to pursue.⁹

Acknowledgements

We thank the National Research Foundation for funding.

Experimental Section

General Procedures. Thin layer chromatography (Tlc) was used to monitor reactions using aluminium-backed plates coated with Merck silica-gel F₂₅₄. Compounds on tlc plates were observed by UV lamp and iodine vapour. Column chromatography was performed using Merck silica-gel 60-230 mesh. Melting points were measured on a Reichert-Jung Thermovar hot-stage microscope. Infrared spectra were recorded on sodium chloride plates on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. High resolution mass spectrometry data was obtained using a VG70-SEQ micromass spectrometer. ¹H and ¹³C NMR spectra were recorded on either a Varian VXR-300 (at 300.08 MHz for ¹H and 75.5 MHz for ¹³C) or a Varian Unity 400 (at 399.95 MHz for ¹H and 100.58 MHz for ¹³C) spectrometer in deuteriochloroform (CDCl₃). Chemical

shifts are quoted using residual chloroform (δ 7.24 in ^1H NMR and δ 77.00 in ^{13}C NMR) as an internal standard. All chemical shifts are reported in ppm and all coupling constants are quoted in Hz. All solvents were purified using standard methods and freshly distilled.

The unsymmetrical disulfides were synthesized using the following method^{11b}. To a stirred solution of 1-chlorobenzotriazole (0.46 g, 3 mmol) and benzotriazole (0.24 g, 2 mmol) in CH_2Cl_2 (10 ml) under N_2 at -78°C was added weighed thiol R^1SH (2 mmol) dissolved in CH_2Cl_2 (1 ml) drop-wise. The solution was allowed to stir for 2 hours (slowly warming to -20°C). Thiol R^2SH (3 mmol) was added slowly neat via a syringe at -20°C and stirred at 0°C for 20 min. The reaction was quenched with a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (0.50 g in 10 ml water) and saturated NaHCO_3 , (20 ml), and the mixture rapidly stirred at 0°C for 20 minutes before being extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (40 g silica) with petroleum ether-ethyl acetate mixtures.

Compound 3 (0.391 g, 91%) was obtained as a pale yellow oil; IR ν_{max} (CHCl_3)/ cm^{-1} 496 (S-S); δ_{H} (400 MHz, CDCl_3): 0.96 (3H, t, J 7.3 Hz, H-3), 1.70 (2H, sextet, J 7.3 Hz, H-2), 2.71 (2H, t, J 7.3 Hz, H-1), 3.80 (3H, s, OCH_3), 6.86 (2H, d, J 8.9 Hz, H_m), 7.48 (2H, d, J 8.9 Hz, H_o); δ_{C} (100.57 MHz, CDCl_3): 13.1 (C-3), 22.1 (C-2), 40.9 (C-1), 55.4 ($-\text{OCH}_3$), 114.6 (C_m), 128.6 (C_s), 131.6 (C_o), 159.5 (C_p); HRMS: m/z 214.0487 (M^+). $\text{C}_{10}\text{H}_{14}\text{OS}_2$ requires 214.0486.

Compound 4 (0.337 g, 85%) was obtained as a pale yellow oil; IR ν_{max} (CHCl_3)/ cm^{-1} 488 (S-S); δ_{H} (400 MHz, CDCl_3): 0.97 (3H, t, J 7.3 Hz, H-3), 1.70 (2H, sextet, J 7.3 Hz, H-2), 2.34 (3H, s, CH_3), 2.71 (2H, t, J 7.3 Hz, H-1), 7.13 (2H, d, J 8.1 Hz, H_m), 7.43 (2H, d, J 8.1 Hz, H_o); δ_{C} (100.57 MHz, CDCl_3): 13.1 (C-3), 21.0 (Ar- CH_3), 22.2 (C-2), 40.9 (C-1), 128.4 (C_m), 129.7 (C_o), 134.5 (C_s), 137.1 (C_p); HRMS: m/z 198.0511 (M^+). $\text{C}_{10}\text{H}_{14}\text{S}_2$ requires 198.0537.

Compound 5 (0.393 g, 82%) was obtained as a pale yellow oil; IR ν_{max} (CHCl_3)/ cm^{-1} 488 (S-S); δ_{H} (300 MHz, CDCl_3): 0.91 (3H, t, J 6.8 Hz, H-6), 1.25-1.44 (6H, m, H-3, H-4, H-5), 1.70 (2H, quintet, J 7.4 Hz, H-2), 2.36 (3H, s, CH_3), 2.76 (2H, t, J 7.4 Hz, H-1), 7.15 (2H, d, J 7.8 Hz, H_m), 7.46 (2H, d, J 7.8 Hz, H_o); δ_{C} (100.57 MHz, CDCl_3): 14.0 (C-6), 21.0 (CH_3), 22.6 (C-5), 28.2 (C-4), 28.8 (C-2), 31.4 (C-3), 39.0 (C-1), 128.4 (C_m), 129.7 (C_o), 134.4 (C_s), 136.9 (C_p); HRMS: m/z 240.1010 (M^+). $\text{C}_{13}\text{H}_{20}\text{S}_2$ requires 240.1006.

Compound 6 (0.461 g, 90%) was obtained as a clear oil; IR ν_{max} (CHCl_3)/ cm^{-1} 487 (S-S), 1710 (C=O); δ_{H} (400 MHz, CDCl_3): 1.32 (9H, s, (H-2')), 3.95 (3H, s, OCH_3), 7.19 (1H, m, H-5), 7.49 (1H, m, H-4), 7.97 (1H, dd, J 8.1 Hz and 1.2 Hz, H-6), 8.22 (1H, dd, J 8.1 Hz and 1.2 Hz, H-3); δ_{C} (100.57 MHz, CDCl_3): 30.0 (C-2'), 49.2 (C-1'), 52.1 (OCH_3), 124.9 (C-5), 126.5 (C-3), 127.1 (C-1), 131.1 (C-6), 132.2 (C-4), 142.9 (C-2), 166.8 (C=O); HRMS: m/z 256.0597 (M^+). $\text{C}_{12}\text{H}_{16}\text{O}_2\text{S}_2$ requires 256.0592.

Compound 7 (0.404 g, 88%) was obtained as a pale yellow oil; IR ν_{max} (CHCl_3)/ cm^{-1} 468 (S-S), 1340 (NO_2), 1515 (NO_2); δ_{H} (300 MHz, CDCl_3): 0.99 (3H, t, J 7.2 Hz, H-3), 1.69 (2H, sextet, J 7.2 Hz, H-2), 2.74 (2H, t, J 7.4 Hz, H-1), 7.65 (2H, d, J 8.7 Hz, H_o), 8.16 (2H, d, J 8.7 Hz, H_m); δ_{C} (75.45 MHz, CDCl_3): 13.0 (C-3), 22.3 (C-2), 41.0 (C-1), 123.9 (C_o), 125.7 (C_m), 146.1 (C_s), 147.3 (C_p); HRMS: m/z 229.0239 (M^+). $\text{C}_9\text{H}_{11}\text{NO}_2\text{S}_2$ requires 229.0231.

Compound 8 (0.311 g, 84%) was obtained as a yellow oil; IR ν_{\max} (CHCl₃)/ cm⁻¹ 478 (S-S); δ_{H} (400 MHz, CDCl₃): 1.00 (3H, t, *J* 7.4 Hz, H-3'), 1.73 (2H, sextet, *J* 7.3 Hz, H-2'), 2.78 (2H, t, *J* 7.4, Hz, H-1'), 7.07 (1H, m, H-5), 7.64 (1H, td, *J* 7.6 Hz and 1.6 Hz, H-4), 7.74 (1H, dt, *J* 7.6 and 0.8 Hz, H-3), 8.46 (1H, m, H-6); δ_{C} (MHz, CDCl₃): 13.0 (C-3'), 22.3 (C-2'), 41.0 (C-1'), 119.6 (C-3), 120.4 (C-5), 136.9 (C-4), 149.5 (C-6), 161.4 (C-2); HRMS: *m/z* 185.0339 (M⁺). C₈H₁₁NS₂ requires 185.0333.

The thiosulfates were synthesized using the following method

To a stirred solution of the unsymmetrical disulfide (2 mmol) in CH₂Cl₂ (5 ml) under N₂ at -78 °C was added *m*-CPBA (2 mmol, 1.0 eq). The reaction was allowed to stir for 3 hours slowly warming to 0 °C, then quenched with saturated aqueous NaHCO₃ (20 ml) and extracted with CH₂Cl₂ (3 x 50ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and evaporated under reduced pressure. The crude material was purified by chromatography as before.

Compound 3a (66%) was obtained as a pale yellow oil; IR ν_{\max} (CHCl₃)/ cm⁻¹ 1079 (S=O stretch); δ_{H} (400 MHz, CDCl₃): 1.09 (3H, t, *J* 7.4 Hz, H-3), 1.88 (2H, m, H-2), 3.04 (2H, m, H-1), 3.83 (3H, s, OCH₃), 6.93 (2H, d, *J* 8.8 Hz, H_m), 7.53 (2H, d, *J* 8.8 Hz, H_o); δ_{C} (100.57 MHz, CDCl₃): 13.2 (C-3), 17.2 (C-2), 55.4 (OCH₃), 57.7 (C-1), 115.0 (C_m), 119.2 (C_s), 137.3 (C_o), 161.6 (C_p); HRMS: *m/z* 230.0440 (M⁺). C₁₀H₁₄O₂S₂ requires 230.0435.

Compound 4a (54%) was obtained as a pale yellow oil; IR ν_{\max} (CHCl₃)/ cm⁻¹ 1086 (S=O stretch); δ_{H} (400 MHz, CDCl₃): 1.09 (3H, t, *J* 7.6 Hz, H-3), 1.89 (2H, m, H-2), 2.38 (3H, s, CH₃), 3.07 (2H, m, H-1), 7.22 (2H, d, *J* 8.0 Hz, H_m), 7.49 (2H, d, *J* 8.0 Hz, H_o); δ_{C} (100.57 MHz, CDCl₃): 13.2 (C-3), 17.3 (CH₃), 21.3 (C-2), 57.9 (C-1), 125.6 (C_s), 130.3 (C_m), 135.3 (C_o), 140.7 (C_p); HRMS: *m/z* 214.0478 (M⁺). C₁₀H₁₄OS₂ requires 214.0486.

Compound 5a (70%) was obtained as a pale yellow oil; IR ν_{\max} (CHCl₃)/ cm⁻¹ 1087 (S=O stretch); δ_{H} (400 MHz, CDCl₃): 0.89 (3H, m, H-6), 1.30-1.48 (6H, m, H-3, H-4, H-5), 1.83 (2H, m, H-2), 2.36 (3H, s, CH₃), 3.07 (2H, t, *J* 7.6 Hz, H-1), 7.20 (2H, d, *J* 8.0 Hz, H_m), 7.48 (2H, d, *J* 8.0 Hz, H_o); δ_{C} (100.57 MHz, CDCl₃): 13.9 (C-6), 21.3 (CH₃), 22.4 (C-5), 23.5 (C-4), 28.3 (C-2), 31.2 (C-3), 56.1 (C-1), 125.6 (C_s), 130.3 (C_m), 135.3 (C_o), 140.6 (C_p); HRMS: *m/z* 256.0933 (M⁺). C₁₃H₂₀OS₂ requires 256.0956.

X-ray analysis

A single crystal of dimensions 0.30 x 0.30 x 0.30 mm was mounted on a Nonius Kappa CCD diffractometer for intensity data-collection with MoK α X-rays ($\lambda = 0.71073$ Å). The crystal was cooled to 113 ± 2 K in a stream of nitrogen vapour to enhance diffraction quality and data were collected using ϕ - and ω -scans of 1.0 and 1.2° (program COLLECT¹⁴). Unit cell refinement and data reduction were performed with DENZO-SMN¹⁵ and the structure was solved by isomorphous replacement using the rigid skeleton of the host molecule of the TRIMEB·(Z)-ajoene complex as a trial model.¹² All remaining non-H atoms of the host and guest were located in successive difference electron-density maps. All but one of the host atoms refined anisotropically. The phenyl ring of the guest molecule was modelled as a regular hexagon with a common variable isotropic thermal parameter. One of the sulfur atoms refined anisotropically

while the remaining guest atoms were treated isotropically. Full-matrix least-squares refinement on F^2 was performed using the program SHELXL-97¹⁶ with weights of the form $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$ and $P = [\max(F_o^2, 0) + 2F_c^2]/3$. The configuration at the stereogenic sulfur atom was found to be (*S*-). The largest peak in the final difference electron-density map was located at 1.9 Å from this centre, its position suggesting the presence of a trace of the (*R*-) enantiomer. However, the latter could not be modelled due to its low site-occupancy.

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