# The potential of sulfimides as chiral acyl anion equivalents

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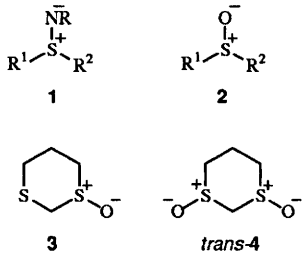
**Reaction of the tosyl imides 6 and 8 of 1,3-dithiane and 1,3,5-trithiane with sodium hydride and alkyl iodides in DMF yields *anti* alkylated products in all cases. In the case of the trithiane imide 8, both mono- and di-alkylation is observed. Preparation of cyclic sulfimide analogues of Eliel's oxathiane is shown to be problematic, but a new class of *O,S*-acetals, namely 4-bromophenylthiomethyl (BPTM) ethers, is introduced as a replacement for their troublesome phenylthiomethyl (PTM) analogues.†**

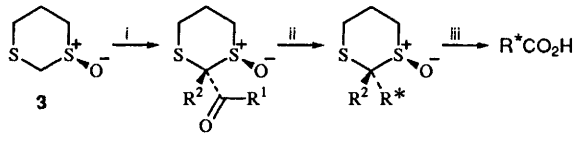
## Introduction

Sulfimides **1** (Chemical Abstracts name sulfilimines) are the nitrogen analogues of sulfoxides **2**.[1] Despite the fact that they are easy to prepare and that their chemistry parallels closely that of sulfoxides, which have many synthetic applications, sulfimides remain a relatively poorly studied class of compounds. Our particular interest is in the application of sulfimides to problems in asymmetric synthesis[2] where, again, chiral sulfoxides are prominent.[3]



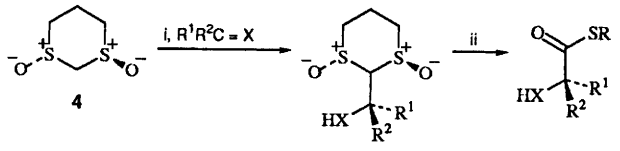

Chiral-at-sulfur chiral acyl anion equivalents have been developed by, in particular, the groups of Page and of Aggarwal, who have focussed on reactions of dithiane monoxide **3** and dithiane *trans* dioxide **4**, respectively.[4,5] These chiral acyl anion equivalents are now available in enantiomerically enriched form.[6]

Dithiane monoxide monitored syntheses generally proceed in three stages (Scheme 1): (i) diastereoselective condensation of

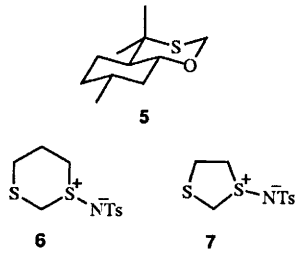



**Scheme 1**

the C-(2) carbanion to form a new chiral centre at C-(2) followed by further alkylation at C-(2) with $R^2I$; (ii) diastereoselective transformation of the acyl substituent $R^1CO$, which has no chiral centres, to a chiral group R*; (iii) unmasking of the carbonyl group.[4] Dithiane dioxide methodology typically involves two procedures (Scheme 2):



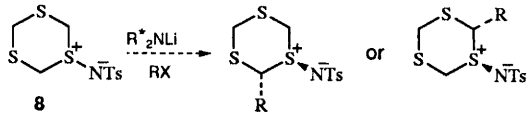

**Scheme 2**




(i) a diastereoselective addition which directly establishes the chirality of the final product; (ii) unmasking of the carbonyl group.[5]

The chiral oxathiane **5**, developed by the group of Eliel, has also been used to prepare chiral α-hydroxy carbonyl compounds,[7] using methodology very similar to that in Scheme 1. In this case, the chirality is not at sulfur, but in the hydrocarbon skeleton, which is derived from naturally occurring α-pulegone. Therefore, only one enantiomer of this chiral acyl anion equivalent is available.

Our experience with asymmetric reactions of sulfimidyl-stabilised carbanions[2] suggests that sulfimides have considerable potential as chiral acyl anion equivalents. We reasoned that the presence of the tosyl groups in the sulfimide analogues **6** and **7** of the sulfoxide **3** (diimide analogues of **4** have not been reported) would lead to improved diastereoselectivities in the methodology outlined in Schemes 1 and 2. The achiral acyl anion equivalent **5**, derived from trithiane, was also of interest, as we planned to use a chiral base to break the symmetry of **8**, thus yielding enantiomerically enriched products (Scheme 3).




**Scheme 3**

Furthermore, we felt that the sulfimides **11**, derived from *O,S*-acetals **10** of readily available norephedrine **9** were potentially useful analogues of Eliel's oxathiane **5**, with the advantage that both enantiomers would be available. Norephedrine was selected since, being a benzyl alcohol, the

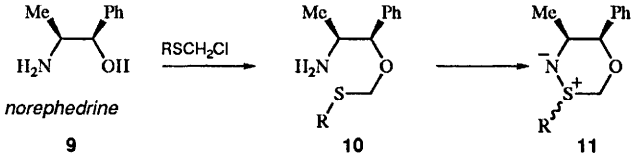
† The substituents denoted by phenylthiomethyl (PTM), bromophenylthiomethyl (BPTM) and methylthiomethyl (MTM) are now correctly named by IUPAC nomenclature as phenylsulfanylmethyl, bromophenylsulfanylmethyl and methylsulfanylmethyl, respectively. The previously-used names phenylthiomethyl (PTM) *etc.* have been retained for convenience.

**Table 1** Yields and diastereoselectivities for alkylations of the sulfimides **6** and **8**

| Sulfimide | R | Equivs. NaH/RI | Product | % Yield[a] | % De[b] |
|---|---|---|---|---|---|
| **6** | Me | 1 | **13a** | 55 | 93 |
| | Et | 1 | **13b** | *c* | 75 |
| | Pr | 1 | **13c** | *c* | 66 |
| **8** | Me | 4 | **16a** | 45 | > 75 |
| | Et | 1 | **15b** | 19 | > 85 |
| | | | **16b** | 15 | > 70 |
| | Pr | 1 | **15c** | 25 | > 85 |
| | | | **16c** | 23 | > 80 |

[a] Unoptimised yield of isolated product. [b] Des were assessed from the $^1$H NMR spectra of crude product mixtures. [c] Not isolated.

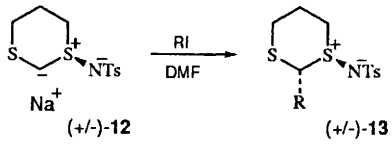
ether was expected to be readily cleaved at the unmasking stage. Although alkyl sulfimides are difficult to prepare, we felt that the conformational restraints of the system would result in the formation of a sulfimide (Scheme 4) being favoured over the usual by-products in this case.




Scheme 4

## Results and discussion

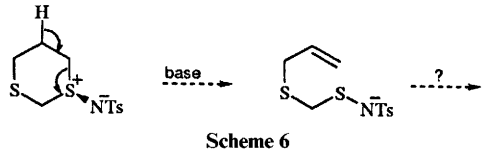
The sodium salt **12** of the dithiane imide **6** was successfully alkylated by alkyl iodides in DMF (Scheme 5). The reactions



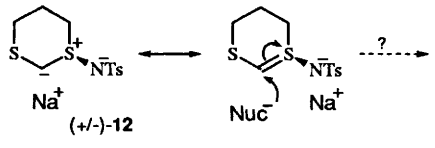

Scheme 5

were reasonably diastereoselective (Table 1), the *anti* products **13** predominating in all cases, as judged by comparison of their NMR data with those of compound **16a**. However, in our hands, alkylation of **6** was successful only under these conditions. With other bases (alkyllithiums, LDA or NaHMDS), solvents or alkyl halides (chlorides or bromides) the reactions failed. More importantly, the anion **12** did not react cleanly with prochiral electrophiles such as aldehydes or ketones, nor with esters or bifunctional alkyl iodides $ICH_2Z$ (Z = COCl, $CO_2H$, $SiMe_3$), thus precluding the use of **6** in place of the sulfoxides **3** and **4** in Schemes 1 and 2. In all these cases complex mixtures of products were observed, except with sterically demanding bases, when starting material was recovered unchanged.

We proposed that the unidentified by-products in reactions of **6** were due to eliminations such as that shown in Scheme 6 and/or nucleophilic interception of the anion **12** (Scheme 7).[8]



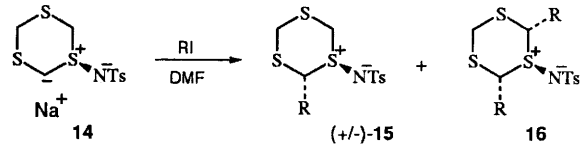

Scheme 6




Scheme 7

We thus expected the trithiane imide **8** to be a more useful acyl anion equivalent, since, as it has no β-protons, the first of these pathways is blocked.

In accord with our prediction, reactions of the sodium salt **14** of trithiane imide **8** with sodium hydride and alkyl iodides appeared to proceed much more cleanly. However, we were disappointed to find that the product mixture contained, as well as the desired products **15**, roughly equal amounts of the *meso* compounds **16**, which result from alkylation at both acidic α-sites (Scheme 8). With careful chromatography it was possible

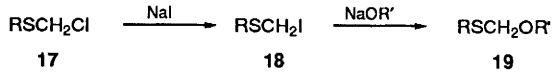



Scheme 8

to separate monoalkylated compounds **15b** and **15c** from the dialkylated products **16b** and **16c** (Table 1). We have only somewhat ambiguous NMR evidence for monomethyl compound **15a**, which could not be isolated.

Since the *meso* products **16** are of no use to our asymmetric synthesis programme, we attempted to stop the alkylation at the chiral monoalkylated products **15**, but with little success. On the other hand, reaction of **8** with an excess of sodium hydride and excess of methyl iodide led exclusively to the dimethylated product **16a** with good diastereoselectivity (Table 1). The expected *anti,anti* relative stereochemistry of **16a** was confirmed by a single crystal X-ray diffraction study.[9] By comparison of the $^1$H NMR spectrum of compound **16a** with those of the other alkylated sulfimides **13**, **15** and **16**, we deduced that in all cases the major diastereoisomer has the *anti* stereochemistry shown.

The preparation of the *O,S*-acetals **10** was then attempted. *O,S*-Acetals **19** have found numerous synthetic uses, both as protective groups for alcohols and as acyl anion equivalents.[10] The simplest method for their preparation is by a Williamson type reaction of an alkoxide with activated alkylthiomethyl chlorides **17** (Scheme 9).[10] Activation is usually achieved with




**a** R = $CH_3$ ; **b** R = Ph ; **c** R = 4-bromophenyl

Scheme 9

sodium iodide which generates the corresponding alkylthiomethyl iodide **18** *in situ*. However, this procedure has proved to be very limited.[10] When R is methyl only primary alcohols can be alkylated[11] and when R is phenyl the process is restricted to phenol derivatives.[12]

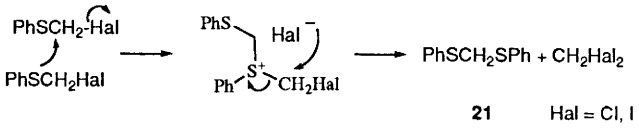
Our results with compounds **10** broadly confirm this previous experience. With R = Me, **10a** was isolated in 67% yield. However, with R = Ph, no *O,S*-acetal **10b** was observed. That secondary alcohols are particularly difficult substrates was demonstrated by the preparation, albeit in low yield, of the phenylthiomethyl (PTM) ether **20** of a primary alcohol analogue of **9**. These results were disappointing, since we considered derivative **10b**, with two conformationally restricting phenyl groups, to be the most likely to lead to a cyclic sulfimide target (Scheme 4). Indeed, under standard conditions for sulfimide synthesis, **10a** and **20** led only to complex mixtures of products.

The prohibitively low yields of PTM ethers **19b** observed in reaction of alkyl alcohols with phenylthiomethyl chloride (PTMCl **17b**) are due to competitive formation of the by-product **21**, probably by way of the mechanism shown in

**Table 2** Synthesis of BPSM ethers **19c**

| R′ | % Yield **19c**[a] | % Yield **22**[a] |
|---|---|---|
| $PhCH_2$ | 80 | 5 |
| Hexyl | 60 | 10 |
| Ph(Me)CH | 35 | 30 |
| Cyclohexyl | 55 | 20 |
| Bu$^t$ | 0 | Quantitative |
| Ph | 0 | *b* |

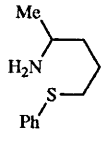
[a] Yields are of isolated pure material and are unoptimised. [b] Unidentified mixture of by-products.



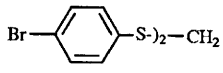

**Scheme 10**

Scheme 10.[13] Increasing the electron demand of the aryl substituent is expected to lower the electron density on sulfur and thus reduce the rate of by-product formation. We therefore speculated that using the potentially readily accessible bromophenylthiomethyl (BPTM) analogues of PTM *O,S*-acetals might obviate some of the problems associated with the troublesome PTM compounds. This hypothesis was tested by attempting the synthesis of the BPTM ethers of some simple alcohols.

4-Bromophenylthiomethyl chloride (BPTMCl) **17c** can be prepared by two literature procedures.[14] Both methods are high yielding, trivial and are amenable to scale-up. Reaction conditions for formation of BPTM ethers **19c** were essentially as used by Corey for methylthiomethyl (MTM) analogues **19a**.[11] A solution of BPTMCl **17c** in dimethoxyethane (DME) was added to a DME suspension of sodium iodide and the sodium alkoxide. After aqueous work-up the BPTM ethers **19c**




**20**




**22**

were purified by chromatography and/or distillation. The presence of compounds **19c** is most easily confirmed by their $^{13}C$ NMR spectra, where the methylene carbon is observed at 75.0 ppm (±1.0 ppm) as compared with BPTMCl **17c** (50.6 ppm) and the by-product **22** (40.7 ppm).

The scope of BPTMCl for formation of *O,S*-acetals is illustrated in Table 2. In all cases the by-product **22** (analogous to **21**) could be isolated from the reaction mixture. However, satisfactory yields of BPTM ethers were obtained from primary alcohols, from which PTM ethers **19b** are not readily accessible, and from secondary alcohols, from which neither MTM nor PTM ethers can be prepared. BPTM ethers of *tert*-butyl alcohol and phenol could not be synthesized by this method. Strangely, when norephedrine was treated with BPTMCl under our standard conditions, no *O,S*-acetal **10c** could be isolated from the mixture of products. We have no explanation for the failure of this reaction.

## Conclusion

The sodium salt of sulfimide **6** can be alkylated by alkyl iodides in DMF. The major diastereoisomers **13** are shown to have *anti* stereochemistry. Analogous reactions of sulfimide **8** lead either to mono- or di-alkylated products. The major diastereoisomers **15** and **16** have *anti* and *anti,anti* stereochemistry, respectively. The potential of the sulfimides **6** and **7** as chiral acyl anion equivalents is limited by competing side-reactions, whereas introduction of chirality into the sulfimide **8** is thwarted by its facile dialkylation to yield *meso* products. An *O,S*-acetal of norephedrine can be prepared when R = Me, but not when R = aryl. The target cyclic sulfimides could not be prepared. The BPTM group is shown to be a satisfactory replacement for the troublesome PTM group for preparation of *O,S*-acetals **19** and may prove a useful protective group for alcohols, especially secondary ones for which *O,S*-acetal protection has not previously been generally available.

## Experimental

### General

IR spectra were recorded using a Perkin-Elmer 1720X FT IR spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded using a Bruker ACF 250 MHz instrument. Mass spectra were recorded on a Kratos MS 90 instrument. Reactions were monitored by TLC on silica gel plates ($G_{254}$). Column chromatography was performed using Merck silica gel 60. Compounds **6**, **7** and **8** were prepared as described previously.[15]

**4-Methyl-*N*-(2-methyl[1,3]dithian-1-ylidene)benzenesulfonamide 13a**

*N*-[1,3]Dithian-1-ylidene-4-methylbenzenesulfonamide **6**[16,17] (289 mg, 1.0 mmol), sodium hydride (33 mg, 1.1 mmol) and methyl iodide (0.69 $cm^3$, 1.1 mmol) were stirred in dry DMF (30 $cm^3$) at room temperature under nitrogen for 8 h. After careful dilution of the mixture with water (80 $cm^3$), followed by extraction with ethyl acetate (3 × 40 $cm^3$), the combined organic layers were washed with water (3 × 100 $cm^3$), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow residue from which the product was obtained as a white solid by crystallisation from chloroform–light petroleum (3:1) followed by suction filtration (167 mg, 55%); $\delta_H$(400 MHz; $CDCl_3$) 7.71 (2 H, m, Ar), 7.19 (2 H, m, Ar), 3.99 (1 H, q, *J* 6.9, 2-H), 3.25 (1 H, br m, 6e-H), 3.10 (1 H, ddd, *J* 2.8, 13.2, 13.2, 6a-H), 2.81 (1 H, ddd, *J* 2.3, 12.4, 14.5, 4a-H), 2.53 (1 H, br m, 4e-H), 2.46 (1 H, br m, 5e-H), 2.36 (3 H, s, ArMe), 2.20 (1 H, br m, 5a-H) and 1.38 (3 H, d, *J* 6.96, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 141.6 (Ar), 141.2 (Ar), 129.1 (Ar), 125.9 (Ar), 58.6 (C-2), 50.3 (C-6), 29.4 (C-4/5), 29.2 (C4/5), 21.2 (ArMe) and 15.5 (Me); *m/z* (CI/$NH_3$) 304 ($MH^+$).

***N*-(2-Ethyl[1,3]dithian-1-ylidene)-4-methylbenzenesulfonamide 13b and *N*-(2-propyl[1,3]dithian-1-ylidene)-4-methylbenzenesulfonamide 13c.** These compounds were prepared by a similar procedure to **13a**.

***N*-(2,6-Dimethyl[1,3,5]trithian-1-ylidene)-4-methylbenzenesulfonamide 16a**

*N*-[1,3,5]Trithian-1-ylidene-4-methylbenzenesulfonamide **8**[16] (614 mg, 2.0 mmol), sodium hydride (135 mg, 4.5 mmol) and methyl iodide (0.26 $cm^3$, 4.2 mmol) were stirred in dry DMF (60 $cm^3$) at room temperature under nitrogen for 15 h. After careful dilution of the mixture with water (150 $cm^3$) followed by extraction with ethyl acetate (3 × 60 $cm^3$), the combined organic layers were washed with water (3 × 120 $cm^3$), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow residue from which the product was obtained as a white solid by crystallisation from chloroform–light petroleum (3:1) followed by suction filtration (369 mg, 55%), mp 100–103 °C; $\delta_H$(250 MHz; $CDCl_3$) 7.73 (2 H, m, Ar), 7.23 (2 H, m, Ar), 4.50 (1 H, d, *J* 14.8, 4e-H), 4.48 (1 H, q, *J* 7.0, 2/6a-H), 3.48 (1 H, d, *J* 14.8, 4a-H), 2.36 (3 H, s, ArMe) and 1.42 (6 H, d, *J* 7.0, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 142.0 (Ar), 140.7 (Ar), 129.3 (Ar), 126.1 (Ar), 61.5 (C-2/6), 34.0 (C-4), 21.4 (ArMe) and 16.1 (Me); *m/z* (CI/NH3) 336 ($MH^+$).

**N-(2-Ethyl[1,3,5]trithian-1-ylidene)-4-methylbenzenesulfonamide 15b and N-(2,6-diethyl[1,3,5]trithian-1-ylidene)-4-methylbenzenesulfonamide 16b**

Compound **8**[16] (154 mg, 0.5 mmol), sodium hydride (21 mg, 0.7 mmol) and ethyl iodide (0.48 $cm^3$, 0.6 mmol) were stirred in dry DMF (15 $cm^3$) at room temperature under nitrogen for 5 h. After careful dilution of the mixture with water (40 $cm^3$), followed by extraction with ethyl acetate (3 × 20 $cm^3$), the combined organic layers were washed with water (3 × 50 $cm^3$), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow residue. Separation from this of mono- and di-alkylated products using flash chromatography on silica with ethyl acetate–light petroleum (3:1) as eluent gave **15b** (33 mg, 19%) and **16b** (28 mg, 15%): **15b** $R_F$ 0.35 ethyl acetate–light petroleum (3:1); $\delta_H$(250 MHz; $CDCl_3$) 7.77 (2 H, m, Ar), 7.24 (2 H, m, Ar), 4.53 (1 H, d, *J* 13.2, 6e-H), 4.50 (1 H, dd, *J* 3.2, 7.9, 2a-H), 4.36 (1 H, d, *J* 14.5, 4e-H), 4.15 (1 H, d, *J* 2.3, 13.2, 6a-H), 3.47 (1 H, d, *J* 2.3, 14.5, 4a-H), 2.38 (3 H, s, ArMe), 2.11 (1 H, ~dq, *J* 3.2, 7.9, $CH_2$), 1.79 (1 H, ~dq, *J* 3.2, 7.9, $CH_2$) and 0.86 (3 H, t, *J* 7.6, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 141.9 (Ar), 140.8 (Ar), 129.3 (Ar), 126.1 (Ar), 67.8 (C-2), 52.2 (C-6), 33.6 (C-4), 22.4 ($CH_2$), 21.4 (ArMe) and 9.3 (Me); **16b** $R_F$ 0.52 EtOAc–light petroleum (3:1); $\delta_H$(250 MHz; $CDCl_3$) 7.76 (2 H, m, Ar), 7.24 (2 H, m, Ar), 4.25 (2 H, dd, *J* 3.2, 7.6, 2a-H), 4.24 (1 H, d, *J* 14.7, 4e-H), 3.53 (1 H, d, *J* 14.7, 4a-H), 2.38 (3 H, s, ArMe), 2.12 (2 H, ~dq, *J* 3.2, 7.6, $CH_2$), 1.79 (2 H, ~dq, *J* 3.2, 7.6, $CH_2$) and 0.89 (6 H, t, *J* 7.6, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 141.9 (Ar), 140.7 (Ar), 129.2 (Ar), 126.2 (Ar), 69.6 (C-2), 33.7 (C-4), 22.7 ($CH_2$), 21.4 (ArMe) and 9.8 (Me).

**4-Methyl-N-(2-propyl[1,3,5]trithian-1-ylidene)benzenesulfonamide 15c and N-(2,6-dipropyl[1,3,5]trithian-1-ylidene)-4-methylbenzenesulfonamide 16c**

Compound **8**[16] (307 mg, 1.0 mmol), sodium hydride (36 mg, 1.2 mmol) and propyl iodide (0.11 $cm^3$, 1.1 mmol) were stirred in dry DMF (30 $cm^3$) at room temperature under nitrogen for 8 h. After careful dilution of the mixture with water (50 $cm^3$) followed by extraction with ethyl acetate (3 × 20 $cm^3$) the combined organic layers were washed with water (3 × 60 $cm^3$), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow residue. Separation from this of mono- and di-alkylated products using flash chromatography on silica with ethyl acetate–$CH_2Cl_2$ (3:1) as eluent gave **15c** (80 mg, 23%) and **16c** (90 mg, 23%): **15c** mp 119–122 °C, $R_F$ 0.35 $CH_2Cl_2$–EtOAc (3:1) (Found: C, 44.7; H, 5.5; N, 4.0. $C_{10}H_{19}NO_2S_4$ requires C, 44.75; H, 5.54; N, 3.93); $\delta_H$(250 MHz; $CDCl_3$) 7.77 (2 H, m, Ar), 7.25 (2 H, m, Ar), 4.50 (1 H, d, *J* 13.3, 6a-H), 4.48 (1 H, dd, *J* 3.2, 8.4, 2a-H), 4.31 (1 H, d, *J* 14.5, 4a-H), 4.19 (1 H, d, *J* 2.2, 13.3, 6e-H), 3.46 (1 H, d, *J* 2.2, 14.5, 4a-H), 2.38 (3 H, s, ArMe), 1.9 (1 H, m, C$H_2$CH), 1.6 (1 H, m, C$H_2$CH), 1.27 (2 H, m, C$H_2$Me) and 0.75 (3 H, t, *J* 7.3, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 142.1 (Ar), 140.8 (Ar), 129.4 (Ar), 126.1 (Ar), 66.3 (C-2), 52.4 (C-6), 33.8 (C-4), 30.7 (*C*$H_2$CH), 21.3 (ArMe), 18.2 (*C*$H_2$Me) and 13.4 (C-9); **16c** $R_F$ 0.64 $CH_2Cl_2$–EtOAc (3:1); $\delta_H$(250 MHz; $CDCl_3$) 7.76 (2 H, m, Ar), 7.24 (2 H, m, Ar), 4.23 (1 H, dd, *J* 3.5, 12.2, 2a-H), 4.19 (1 H, d, *J* 14.7, 4e-H), 3.50 (1 H, d, *J* 14.7, 4a-H), 2.38 (3 H, s, ArMe), 1.98 (1 H, m, C$H_2$CH), 1.60 (2 H, m, C$H_2$CH), 1.44 (2 H, m, C$H_2$Me), 1.25 (2 H, m, C$H_2$Me) and 0.77 (6 H, t, *J* 7.3, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 141.9 (Ar), 140.8 (Ar), 129.3 (Ar), 126.2 (Ar), 68.0 (C-2), 30.98 (*C*$H_2$CH), 21.3 (ArMe), 18.7 (*C*$H_2$Me) and 13.4 (Me).

**(1R,2S)-1-Methyl-2-(methylsulfanylmethoxy)phenylethylamine 10a**

(1*R*,2*S*)-(−)-Norephedrine (1.51 g, 10 mmol) and sodium hydride (60%, hexane washed; 0.48 g, 20 mmol) were heated to reflux in THF (20 $cm^3$) for 2 h. The reaction mixture was cooled to 0 °C, and treated with sodium iodide (1.50 g, 10 mmol) and chloromethyl phenyl sulfide (0.84 $cm^3$, 10 mmol) after which stirring was continued at room temperature for 20 h. The reaction mixture was then diluted with water (20 $cm^3$) to quench the reaction and extracted with ether (3 × 20 $cm^3$). The combined extracts were then extracted with 5% HCl (3 × 20 $cm^3$) and the latter neutralised with 10% aqueous sodium carbonate and extracted with ether (3 × 20 $cm^3$). The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Bulb-to-bulb distillation of this *in vacuo* afforded a colourless oil (1.41 g, 67%), bp 110 °C/10 mmHg (Found $M^+$, 212.1109. $MH^+$ requires 212.1110); $\nu_{max}$(neat)/$cm^{-1}$ 3366, 1493, 1302, 1054 and 960; $\delta_H$(250 MHz; $CDCl_3$) 7.27 (5 H, m, Ph), 4.67 (1 H, d, *J* 11.5, $CH_2S$), 4.46 (1 H, d, *J* 6.0, 2-H), 4.27 (1 H, d, *J* 11.5, $CH_2S$), 3.13 (1 H, m, 1-H), 2.14 (3 H, s, MeS), 1.5 (2 H, br s, $NH_2$) and 1.09 (3 H, d, *J* 6.3, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 138.1 (Ph), 128.3 (Ph), 127.95 (Ph), 126.1 (Ph), 83.0 ($CH_2S$), 72.6 (C-2), 51.4 (C-1), 19.4 (Me) and 14.0 (MeS); *m*/*z* (CI) 212 (100%, $MH^+$) and 164 (25).

**DL-1-Methyl-2-(phenylsulfanylmethoxy)ethylamine 20**

A mixture of DL-2-aminopropan-1-ol (150 mg, 2.0 mmol), sodium hydride (51 mg, 2.1 mmol), chloromethyl phenyl sulfide (301 mg, 1.9 mmol) and sodium iodide (28 mg, 0.19 mmol) in THF (16 $cm^3$)–acetonitrile (2 $cm^3$) was stirred at 0 °C for 1 h. The reaction mixture was then stirred at room temperature for 24 h, after which it was poured into water (30 $cm^3$) and extracted with ether (3 × 20 $cm^3$). The combined extracts were extracted with 5% aqueous HCl (3 × 30 $cm^3$) and the combined aqueous phases neutralised with 10% aqueous sodium carbonate. The aqueous phases were extracted with ether (3 × 20 $cm^3$) and the combined extracts dried ($MgSO_4$) and concentrated under reduced pressure to afford a pale yellow oil. Bulb-to-bulb distillation of this under reduced pressure afforded a colourless oil (90 mg, 24%), bp 85 °C/10 mmHg (Found: $M^+$, 198.0953. $MH^+$ requires 198.0949); $\nu_{max}$(neat)/$cm^{-1}$ 3368, 2964, 2924, 1734, 1584, 1481, 1457, 1440, 1374, 1245, 1076, 1026, 740, 704 and 692; $\delta_H$(250 MHz; $CDCl_3$) 7.26 (5 H, m, Ph), 5.02 (2 H, ~s, $CH_2S$), 3.58 (1 H, dd, *J* 3.4, 8.9, 2-H), 3.34 (1 H, dd, *J* 8.9, 8.9, 2-H), 3.16 (1 H, m, 1-H), 2.20 (2 H, br s, $NH_2$) and 1.07 (3 H, d, *J* 6.3, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 135.7 (Ph), 130.0 (Ph), 128.9 (Ph), 126.6 (Ph), 76.2 ($CH_2S$), 74.7 (C-2), 46.3 (C-1) and 19.4 (Me); *m*/*z* (CI/$NH_3$) 198 (100%, $MH^+$) and 123 (64).

**Benzyloxymethyl 4-bromophenyl sulfide 19c (R′ = PhCH$_2$)**

Sodium hydride (0.75 g, 31 mmol) was added to a solution of benzyl alcohol (1.35 $cm^3$, 31 mmol) in dimethoxyethane (DME) (7.5 $cm^3$) at 0 °C under nitrogen followed by BPTMCl (3.0 g, 12.6 mmol) in DME (7.5 $cm^3$). The mixture was then stirred for 1 h at 0 °C followed by 40 h at room temperature. It was then diluted with water (40 $cm^3$) and extracted with ether (3 × 25 $cm^3$). The combined extracts were washed with brine (25 $cm^3$), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Column chromatography of this on silica using dichloromethane–light petroleum (2:3) gave a colourless oil (3.12 g, 80%) (Found: C, 54.1; H, 4.4. $C_{14}H_{13}BrOS$ requires C, 54.38; H, 4.24%); $\nu_{max}$(neat)/$cm^{-1}$ 3064, 3031, 2926, 1474, 1095, 1068, 1029, 1009 and 698; $\delta_H$(250 MHz; $CDCl_3$) 7.3–7.5 (9 H, m, Ar), 5.04 (2 H, s, $CH_2S$) and 4.72 (2 H, s, $CH_2Ph$); $\delta_C$(62.9 MHz; $CDCl_3$) 136.9 (Ar), 135.1 (Ar), 131.9 (Ar), 131.5 (Ar), 128.5 (Ar), 128.2 (Ar), 127.95 (Ar), 120.7 (Ar), 74.8 ($CH_2S$) and 69.8 ($CH_2Ph$); *m*/*z* (EI) 310 (7, [$^{81}$Br]$M^+$), 308 (7, [$^{79}$Br]$M^+$), 280 (19), 278 (18), 108 (10), 91 (100) and 65 (11).

**4-Bromophenyl hexyloxymethyl sulfide 19c (R′ = hexyl)**

Sodium hydride (0.80 g, 33 mmol) was added to a solution of hexan-1-ol (1.58 $cm^3$, 12 mmol) in dimethoxyethane (DME) (7.5 $cm^3$) at 0 °C under nitrogen followed by BPTMCl (3.0 g, 12.6 mmol) in DME (7.5 $cm^3$). The mixture was then stirred for 1 h at 0 °C followed by 80 h at room temperature. It was then

diluted with water (40 $cm^3$) and extracted with ether (3 × 25 $cm^3$). The combined extracts were washed with brine (25 $cm^3$), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Column chromatography of this on silica using 1% ethyl acetate in light petroleum gave a pale yellow oil which, upon bulb-to-bulb distillation *in vacuo*, afforded a colourless oil (2.18 g, 60%), bp 140 °C/10 mmHg (Found: C, 51.6; H, 6.5. $C_{13}H_{19}BrOS$ requires C, 51.49; H, 6.31%); $\nu_{max}$(neat)/$cm^{-1}$ 2955, 2930, 2858, 1474, 1099, 1084, 1009 and 813; $\delta_H$(250 MHz; $CDCl_3$) 7.50 (2 H, AA′ of AA′BB′, Ar), 7.22 (2 H, BB′ of AA′BB′, Ar), 4.97 (2 H, s, $CH_2S$), 3.59 (1 H, t, *J* 6.7, 1-H) 1.59 (2 H, m, 2-H), 1.29 (6 H, m, 3/4/5-H) and 0.88 (3 H, t, *J* 6.8, $CH_3$); $\delta_C$(62.9 MHz; $CDCl_3$) 135.4 (Ar), 131.8 (Ar), 131.4 (Ar), 120.5 (Ar), 75.90 ($CH_2S$), 65.6 (C-1), 31.5 (C-2), 29.2 (C-3), 25.8 (C-4), 22.5 (C-5) and 14.0 (C-6); *m*/*z* (EI) 304 (71, [$^{81}$Br]$M^+$), 302 (71, [$^{79}$Br]$M^+$), 203 (44), 201 (45), 190 (71), 188 (70), 115 (71), 85 (100), 69 (23), 57 (62) and 43 (94).

### *p*-Bromophenyl 1-phenylethoxymethyl sulfide 19c [R′ = Ph(Me)CH]

Sodium hydride (0.80 g, 33 mmol) was added to a solution of 1-phenylethanol (1.54 $cm^3$, 12.6 mmol) in dimethoxyethane (DME) (7.5 $cm^3$) at 0 °C under nitrogen followed by BPTMCl (3.0 g, 12.6 mmol) in DME (7.5 $cm^3$). The mixture was then stirred for 1 h at 0 °C followed by 24 h at room temperature. It was then diluted with water (40 $cm^3$) and extracted with ether (3 × 25 $cm^3$). The combined extracts were washed with brine (25 $cm^3$), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Column chromatography of this on silica using dichloromethane–light petroleum (1:3) gave a pale yellow oil which, upon bulb-to-bulb distillation *in vacuo*, afforded a colourless oil (1.27 g, 35%), bp 145 °C/10 mmHg; $\nu_{max}$(neat)/$cm^{-1}$ 3062, 3029, 2975, 2928, 1474, 1094, 1070, 1049, 1009 and 813; $\delta_H$(250 MHz; $CDCl_3$) 7.35 (9 H, m, Ar), 5.04 (1 H, d, *J* 11.6, $CH_2$), 4.95 (1 H, q, *J* 6.4, CH) 4.64 (1 H, d, *J* 11.6, $CH_2$) and 1.48 (3 H, d, *J* 6.4, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 142.1 (Ar), 135.3 (Ar), 131.9 (Ar), 131.5 (Ar), 128.6 (Ar), 127.9 (Ar), 126.7 (Ar), 120.6 (Ar), 74.6 ($CH_2$), 72.9 (CH) and 23.6 (Me); *m*/*z* (EI) 324 (7, [$^{81}$Br]$M^+$), 322 (7, [$^{79}$Br]-$M^+$), 294 (25), 292 (25), 203 (12), 201 (12), 122 (10), 105 (100), 77 (38) and 51 (11).

### *p*-Bromophenyl cyclohexyloxymethyl sulfide 19c (R′ = cyclohexyl)

Sodium hydride (0.75 g, 31 mmol) was added to a solution of cyclohexanol (1.31 $cm^3$, 12.6 mmol) in dimethoxyethane (DME) (7.5 $cm^3$) at 0 °C under nitrogen followed by BPTMCl (3.0 g, 12.6 mmol) in DME (7.5 $cm^3$). The mixture was then stirred for 1 h at 0 °C followed by 60 h at room temperature. It was then diluted with water (40 $cm^3$) and extracted with ether (3 × 25 $cm^3$). The combined extracts were washed with brine (25 $cm^3$), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Column chromatography of this on silica using 1% acetone in light petroleum gave a pale yellow oil which, upon bulb-to-bulb distillation *in vacuo* afforded a colourless oil (2.09 g, 55%), bp 145 °C/10 mmHg; $\nu_{max}$(neat)/$cm^{-1}$ 2932, 2856, 1474, 1094, 1068, 1035, 1009 and 813; $\delta_H$(250 MHz; $CDCl_3$) 7.41 (2 H, AA′ of AA′BB′, Ar), 7.32 (2 H, BB′ of AA′BB′, Ar), 5.00 (2 H, s, $CH_2S$), 3.69 (1 H, m, 1-H) 1.80 (2 H, m, 2/3-H), 1.55 (2 H, m, 2/3-H), 1.25 (4 H, m, 2/3-H) and 0.87 (2 H, m, 4-H); $\delta_C$(62.9 MHz; $CDCl_3$) 135.5 (Ar), 131.7 (Ar), 131.3 (Ar), 120.3 (Ar), 74.8 ($CH_2S$), 72.7 (C-1), 31.7 (C-2/3), 25.5 (C-4) and 23.9 (C-2/3); *m*/*z* (EI) 302 (43, [$^{81}$Br]$M^+$), 300 (41, [$^{79}$Br]$M^+$), 203 (52), 201 (51), 190 (85), 188 (85), 113 (77), 83 (100), 69 (29), 55 (86) and 41 (59).

## Acknowledgements

We thank the EPSRC for financial support (to T. J. S.) and Dr J. J. Hastings for NMR.

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*Paper* 5/05934H
*Received* 7*th September* 1995
*Accepted* 25*th September* 1995