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# Enzyme-catalysed oxidation of 1,2-disulfides to yield chiral thiosulfinate, sulfoxide and*cis*-dihydrodiol metabolites

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## Supplementary information

## (i) Synthesis of compounds 8g-i, 12, 14, 9f-i, 13, 15

**General procedure for the synthesis of 1,2-disulfides 9f-i**

A solution of thiophenol (1.03 $cm^3$, 10 mmol) and pyridine (0.81 $cm^3$, 10 mmol) in $CH_2Cl_2$ (25 $cm^3$) was added dropwise, over 30 minutes, to a stirred solution of sulfuryl chloride (0.80 ml, 10 mmol) in $CH_2Cl_2$ (50 $cm^3$) maintained at -78 $^oC$. The mixture was stirred for a further 30 minutes. A solution of alkyl thiol (10 mmol) and pyridine (0.81 $cm^3$, 10 mmol) were dissolved in $CH_2Cl_2$ (25 $cm^3$) and added dropwise to the reaction mixture over 30 minutes. The reaction mixture was allowed to warm to room temperature, transferred to a separating funnel, washed successively with water (2 x 25 $cm^3$), 1N NaOH (2 x 25 $cm^3$) and again with water until neutral to pH paper. The organic layer was separated, dried ($CaCl_2$), filtered and the solvent removed under reduced pressure to yield the crude product which was purified by distillation.

**Ethyl phenyl disulfide 8g.** Colourless liquid (0.64 g, 38%); b.p. 92.$^o$C / 20 mmHg (*lit.*,[1a] 46 $^o$C at 0.1 mmHg); $R_f$ 0.88 (50% $CHCl_3$ / hexane); (Found: $M^+$, 170.0220. $C_8H_{10}S_2$ requires 170.0224); $\delta_H$ (500 MHz, $CDCl_3$) 1.32 (3 H, t, $J_{1,2}$ 7.3, $CH_2$*Me*), 2.73 (2 H, q, $J_{2,1}$ 7.3, C*H*$_2$-Me), 7.21 - 7.22 (1 H, m, Ar-H), 7.30 - 7.33 (2 H, m, 2 x Ar-H), 7.53 - 7.55 (2 H, m, Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 14.1, 32.7, 126.7, 127.4, 128.9, 137.7; *m/z* (EI) 170 ($M^+$, 100%), 154 (22), 141 (39), 109 (91), 78 (78), 65 (58); $\nu_{max}$ (KBr film) / $cm^{-1}$ 3059, 2973, 2926, 2869, 1580, 739, 689.

**Phenyl *n*-propyl disulfide 8h.** Colourless liquid (0.64 g, 35%); b.p. 128 $^o$C / 0.9 mmHg (*lit.*,[1b] 87-93 $^o$C / 0.1 mmHg);$R_f$ 0.85 (50% $CHCl_3$ / hexane); (Found: $M^+$, 184.0386. $C_9H_{12}S_2$ requires 184.0380); $\delta_H$ (500 MHz, $CDCl_3$) 0.97 (3 H, t, $J_{1,2}$ 7.3, $CH_2CH_2$*Me*), 1.70 (2 H, septet, $J_{2,1}$=$J_{2,3}$ 7.3, $CH_2$C*H*$_2$Me), 2.71 (2 H, t, $J_{3,2}$ 7.3, C*H*$_2$$CH_2$Me), 7.21 - 7.25 (1 H, m, Ar-H), 7.30 - 7.33 (2 H, m, 2 x Ar-H), 7.49 - 7.54 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 13.1, 22.2, 40.9, 126.6, 127.4, 128.9, 137.7; *m/z* (EI) 184 ($M^+$, 100%), 142 (79), 109 (66), 78 (88), 65 (39), 43 (52); $\nu_{max}$ (KBr film) / $cm^{-1}$ 3059, 2962, 2929, 2871, 1579, 739, 689.

***tert*-Butyl phenyl disulfide 8i.** Colourless liquid (1.45 g, 80%); b.p. 56 $^o$C / 0.04 mmHg (*lit.*,[1c] 65 $^o$C at 0.5 mmHg); $R_f$ 0.92 ($CH_2Cl_2$); (Found: $M^+$, 198.0528. $C_{10}H_{14}S_2$ requires 198.0537); $\delta_H$ (500 MHz, $CDCl_3$) 1.30 (9 H, s, *t*-Bu), 7.15 (1 H, m, Ar-H), 7.25 - 7.30 (2 H, m, 2 x Ar-H), 7.55 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 29.9, 49.2, 126.2, 126.8, 128.7, 138.8; *m/z* (EI) 198 ($M^+$, 75%), 185 (10), 154 (11), 142 (86), 109 (87), 77 (56), 65 (68), 57 (100), 41 (70); $\nu_{max}$ (KBr film) / $cm^{-1}$ 3060, 2961, 2920, 2895, 2860, 1579, 739, 689.

**1,2-Dithiane 12.** Compound **12** was synthesised using the literature procedure[1d] and was found tohave similar characteristic as reported. Crystalline solid (3.1 g, 80%); m.p. 28-29 $^o$C ($CHCl_3$ / hexane) (*lit.*[1e] 30-31 $^o$C); (Found: $M^+$, 120.0071. $C_4H_8S_2$ requires 120.0067); $\delta_H$ (500 MHz, $CDCl_3$) 1.97 (4 H, m, 2x C*H*$_2$$CH_2$ ), 2.84 (4 H, m, 2 x $CH_2$C*H*$_2$S); $\delta_C$ (75 MHz, $CDCl_3$) 26.9, 32.4; *m/z* (EI) 120 ($M^+$, 46%), 97 (18), 91 (100), 87 (30), 64 (25), 63 (54), 55 (47), 41(52); $\nu_{max}$ (KBr) / $cm^{-1}$ 2905, 2844, 2796, 1729, 1431, 1406, 1280, 1224, 912, 869, 831, 658.

**1,4-Dihydrobenzo-2,3-dithiane 14.** Compound **14** was synthesised using the literature procedure and was found tohave similar characteristics as reported. Crystalline solid; m.p. 70-71 $^o$C ($CHCl_3$ / hexane) (*lit.*,[1f]77-78 $^o$C);$R_f$ 0.68 (10% EtOAc / hexane); (Found: C, 57.0; H, 4.7. $C_8H_8S_2$ requires C, 57.1; H, 4.8%); (Found: $M^+$, 168.0074. $C_8H_8S_2$ requires

168.0067); $\delta_H$ (500 MHz, $CDCl_3$) 4.07 (4 H, s, 2x $CH_2S$), 7.06 - 7.10 (2 H, m, 2 x Ar-H), 7.15 - 7.18 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 34.6, 126.8, 130.1, 132.9; *m/z* (EI) 168 ($M^+$, 99%), 134 (34), 104 (100), 91 (14), 78 (51), 64 (24), 51 (23); $\nu_{max}$ (KBr) / $cm^{-1}$ 3044, 2923, 2854, 1637, 733.

**General procedure for the synthesis of S-alkyl benzenethiosulfinates 9f-i**

Thionyl chloride (0.22 $cm^3$, 3.05 mmol) was added dropwise to benzenesulfinic acid sodium salt (0.50 g, 3.05 mmol) and the resulting mixture was stir for 20 minutes. Excess thionyl chloride was removed by vacuum distillation and the residue extracted with $CH_2Cl_2$ (2 x 20$cm^3$). The organic extract was concentrated under reduced pressure, diethyl ether (5 $cm^3$) and pyridine (0.28 $cm^3$, 3.05 mmol) were added to the concentrate and the reaction mixture cooled to 0 °C. A solution of alkylthiol (3.05 mmol) in dry diethyl ether (5 $cm^3$) was added dropwise to the cooled mixture over a period of 5 minutes. After stirring the reaction mixture for 10 minutes, it was neutralised with dilute (2 M) sulfuric acid and the stirring continued for another ten minutes. The ether layer was separated, dried ($CaCl_2$) and concentrated, to yield the crude product which was purified by flash chromatography or PLC ($CHCl_3$ / hexane).

**S-Methyl benzenethiosulfinate 9f.**[2a] Colourless liquid (0.17 g, 32%); $R_f$ 0.49 (85% $CHCl_3$ / hexane); (Found: $M^+$, 172.0009. $C_7H_8OS_2$ requires 172.0017); $\delta_H$ (500 MHz, $CDCl_3$) 2.59 (3 H, s, Me), 7.52 - 7.54 (3 H, m, 3 x Ar-H), 7.72 - 7.74 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 13.3, 123.8, 128.1, 130.5, 143.0; *m/z* (EI) 172 ($M^+$, 9%), 156 (14), 141 (10), 125 (100), 109 (40), 97 (64), 77 (81), 51 (71), 45 (60); $\nu_{max}$ (KBr film) / $cm^{-1}$ 3058, 2920, 1694, 1091 (S=O), 748, 689.

**S-Ethyl benzenethiosulfinate 9g.**[2b] Colourless liquid (0.17 g, 30%); $R_f$ 0.34 (50% $CHCl_3$ / hexane); (Found: $M^+$, 186.0170. $C_8H_{10}OS_2$ requires 186.0173); $\delta_H$ (500 MHz, $CDCl_3$) 1.45 (3 H, t, $J_{1,2}$ 7.4, $CH_2$*Me*), 3.07 - 3.14 (1 H, dq, $J_{2A,2B}$ 13.5, $J_{2A,1}$ 7.4, C$H_A$$H_B$Me), 3.20 - 3.27 (1 H, dq, $J_{2B,2A}$ 13.5, $J_{2B,1}$ 7.4, $CH_A$$H_B$Me), 7.46 - 7.51 (3 H, m, 3 x Ar-H), 7.72 - 7.74 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 16.4, 28.1, 124.8, 129.5, 131.8, 144.6; *m/z* (EI) 186 ($M^+$, 11%), 170 (73), 154 (34), 141 (90), 125, 77), 109 (86), 97 (43), 77 (100), 51 (88), 39 (60); $\nu_{max}$ (KBr film) / $cm^{-1}$ 3058, 2963, 2927, 2871, 1581, 1094 (S=O), 747, 689.

**S-*n*-Propyl benzenethiosulfinate 9h.**[2c]Colourless liquid (0.20 g, 32%); $R_f$ 0.40 (50% $CHCl_3$ / hexane, two elutions); (Found: $M^+$, 200.0331. $C_9H_{12}OS_2$ requires 200.0330); $\delta_H$ (500 MHz, $CDCl_3$) 1.04 (3 H, t, $J_{1,2}$ 7.3, $CH_2CH_2$*Me*), 1.83 (2 H, m, $CH_2$C$H_2$Me), 3.06 (1 H, m, C$H_A$$H_B$$CH_2$Me), 3.20 (1 H, m, $CH_A$$H_B$$CH_2$Me), 7.47 - 7.52 (3 H, m, 3 x Ar-H), 7.73 - 7.75 (2 H, m, 2 x Ar-H); $\delta_C$ (75 MHz, $CDCl_3$) 12.3, 23.2, 34.5, 123.5, 128.2, 130.6, 134.5; *m/z* (EI) 200 ($M^+$, 3%), 184 (PhSSC$H_2$C$H_2$Me$^+$, 15), 152 (58), 141 (PhS$S^+$, 24), 125 (PhS(O)$^+$, 100), 109 (Ph$S^+$, 71), 97 (32), 77 (Ph$^+$, 90), 65 (30), 51 (49); $\nu_{max}$ (KBr film) / $cm^{-1}$ 3059, 2963, 2930, 2872, 1581, 1061 (S=O), 748, 689.

**S-*tert*-Butyl benzenethiosulfinate 9i.**[2d] Colourless solid (0.43 g, 66%); m.p. 44-46 °C ($CHCl_3$ / hexane) (*lit.*,[20d] 51-52 °C); $R_f$ 0.30 ($CH_2Cl_2$); (Found: $M^+$, 214.0484. $C_{10}H_{14}OS_2$ requires 214.0486); $\delta_H$ (500 MHz, $CDCl_3$) 1.65 (9 H, s, *t*-Bu), 7.47 - 7.52 (3 H, m, 3 x Ar-H), 7.72 - 7.74 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 32.2, 50.6, 124.5, 129.0, 131.1, 144.1; *m/z* (EI) 214 ($M^+$, 8), 198 (15), 159 (76), 142 (33), 125 (74), 109 (43), 97 (67), 89 (94), 77 (84), 57 (100); $\nu_{max}$ (KBr) / $cm^{-1}$ 3003, 2962, 1637, 1088 (S=O), 758, 689.

**General procedure for the synthesis of 1,2-dithiane-1-oxide 13, 1,4-Dihydrobenzo- 2,3-dithiane-2-oxide 15 and 1,3-dihydrobenzo[*c*]thiophene-2 oxide 25**

1,2-Dithiane-1-oxide **13**, 1,4-dihydrobenzo-2,3-dithiane-2-oxide **15** and 1,3-dihydrobenzo[*c*]thiophene-2-oxide **25** were synthesised by the following general procedure. A solution of sodium periodate (0.12 g, 0.55 mmol, 1.1 eq) in water (10 $cm^3$) was added dropwise, to a stirred solution of 1,2-disulfide (0.50 mmol) in methanol (30 $cm^3$) at 0 $^oC$. The mixture was stirred overnight, warmed to room temperature and the sodium iodate salt formed was removed by filtration. The filtrate was concentrated under reduced pressure, to remove most of the methanol, and the remaining aqueous solution was saturated (NaCl) and extracted with $CHCl_3$ (3 x 10 $cm^3$). The combined $CHCl_3$ extract was dried ($Na_2SO_4$) and the solvent removed under reduced pressure, to yield the crude thiosulfinate which was purified by flash chromatography.

**1,2-Dithiane-1-oxide 13.** White solid (60% yield); m.p. 83-85 $^oC$ ($CHCl_3$ / hexane) (*lit*.,[3a] 85 $^oC$); $R_f$ 0.32 (2% MeOH / $CH_2Cl_2$); (Found: $M^+$, 136.0014. $C_4H_8OS$ requires 136.0017); $\delta_H$ (500 MHz, $CDCl_3$) 1.83 - 1.90 (1 H, m, 3-$H_{eq}$), 1.97 - 2.06 (1 H, dtt, $J_{5eq,5ax}$ 14.2, $J_{5eq,4ax\&6ax}$ 12.8, $J_{5eq,4eq\&6eq}$ 3.0, 5-$H_{eq}$), 2.10 - 2.16 (1 H, qdd, $J_{4eq,4ax,3ax,6ax}$ 7.1, $J_{4eq,5eq}$ 4.2, $J_{4eq,3eq}$ 2.9, 4-$H_{eq}$), 2.61 - 2.71 (1 H, dtt, $J_{4ax,4eq}$ 15.0, $J_{4ax,3ax\&5ax}$ 13.0, $J_{4ax,3eq,5eq}$ 3.1, 4-$H_{ax}$), 2.67 - 2.71 (1 H, m, 3-$H_{ax}$), 3.05 - 3.11 (1 H, dt, $J_{6eq,6ax}$ 13.2, $J_{6eq,5ax,5eq}$ 3.0, 6-$H_{eq}$), 3.18 - 3.22 (1 H, dt, $J_{6ax,6eq}$ 13.3, $J_{6ax,5ax\&5eq}$ 3.6, 6-$H_{ax}$), 3.62 - 3.69 (1 H, ddd, $J_{5ax,5eq}$ 14.1, $J_{5ax,4ax}$ 12.7, $J_{5ax,4eq}$ 2.5, 5-$H_{ax}$); $\delta_C$ (125 MHz, $CDCl_3$) 15.2, 23.4, 25.6, 51.8; *m/z* (EI) 136 ($M^+$, 32%), 87 (28), 80 (59), 60 (44), 54 (100), 45 (83), 41 (38), 27 (65); $\nu_{max}$ (KBr) / $cm^{-1}$ 2916, 2848, 1066 (S=O).

**1,4-Dihydrobenzo-2,3-dithiane-2-oxide 15.** Colourless crystalline solid (2.47 g, 75%); m.p. 130-132 $^oC$ ($CHCl_3$ / hexane) (*lit*.,[3b]128-129 $^oC$); $R_f$ 0.18 (30% EtOAc / hexane); (Found: C, 51.7; H, 4.3. $C_8H_8OS_2$ requires C, 52.1; H, 4.4%); (Found: $M^+$, 184.0010. $C_8H_8OS_2$ requires 184.0017); $\delta_H$ (500 MHz, $CDCl_3$) 3.96 (1 H, d, $J_{A,B}$ 13.5, C$H_A$H$_B$SO), 4.23 (1 H, d, $J_{A,B}$ 13.1, C$H_A$H$_B$S), 4.32 (1 H, d, $J_{B,A}$ 13.1, CH$_A$$H_B$S), 4.37 (1 H, d, $J_{B,A}$ 13.5, CH$_A$$H_B$SO), 7.37 - 7.43 (4 H, m, 4 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 33.0, 59.7, 127.7, 127.9, 128.47, 129.3, 131.8, 135.6; *m/z* (EI) 184 ($M^+$, 9%), 168 (4), 136 (63), 135 (100), 104 (87), 91 (25), 78 (37); $\nu_{max}$ (KBr) / $cm^{-1}$ 3040, 2987, 2926, 1637, 1072 (S=O), 757.

**1,3-Dihydrobenzo[*c*]thiophene-2-oxide 25.** White crystalline solid (53% yield); m.p. 84-85 $^oC$ ($CHCl_3$ / hexane) (*lit*.,[3c] 90-91 $^oC$); $R_f$ 0.48 (10% MeOH / $CHCl_3$); (Found: C, 63.0; H 5.2. $C_8H_8OS$ requires C, 63.1; H, 5.3%); (Found: $M^+$, 152.0293. $C_8H_8OS$ requires 152.0296); $\delta_H$ (500 MHz, $CDCl_3$) 4.15 (2 H, d, $J_{A,B}$ 16.1, 2 x C$H_A$H$_B$), 4.29 (2 H, d, $J_{B,A}$16.1, 2 x CH$_A$$H_B$), 7.30 - 7.34 (2 H, m, 2 x Ar-H), 7.35 - 7.38 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 59.4, 126.6, 128.4, 135.1; *m/z* (EI) 152 ($M^+$, 99%), 136 (4), 135 (22), 134 (15), 104 (100), 103 (67), 91 (11), 78 (69), 63 (17), 51 (33), 39 (27); $\nu_{max}$ (KBr) / $cm^{-1}$ 3057, 3029, 2921, 2848, 1636, 1033 (S=O), 741.

**Synthesis of 1,3-dihydrobenzo[*c*]thiophene 24.** It was synthesised following the literature procedure.[4a] Colourless oil (0.45 g, 88%); b.p. 78 °C / 0.15 mmHg) (*lit*.,[4b] 94 °C / 7 mmHg); $R_f$0.88 (4% MeOH / $CHCl_3$); (Found: $M^+$, 136.0341. $C_8H_8S$ requires 136.0347); $\delta_H$ (500 MHz, $CDCl_3$) 4.27 (4 H, s, 2 x $CH_2$), 7.18 - 7.22 (2 H, m, 2 x Ar-H), 7.23 - 7.25 (2 H, m, 2 x Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 38.0, 124.7, 126.7, 140.4; *m/z* (EI) 136 ($M^+$, 100%), 135 (91), 134 (74), 118 (35), 104 (92), 91 (53), 78 (30), 51 (25), 28 (27); $\nu_{max}$ (KBr) $cm^{-1}$ 3063, 3024, 2912, 2841, 1696, 1487, 1454, 743.

**Synthesis of benzo[*c*]thiophene 19.** It was synthesised by the literature procedure[4a] and stored at -78 °C, under nitrogen in the dark, until required. White crystalline solid (0.13 g, 26%); m.p. 56-58 °C (*lit*.,[4a] 54-57 °C); (Found: C, 71.2; H, 4.4. $C_8H_6S$ requires C, 71.6; H, 4.5%); (Found: $M^+$, 134.0187. $C_8H_6S$ requires 134.0190); $\delta_H$ (500 MHz, $CDCl_3$) 7.03 - 7.05 (2 H, dd, *J* 6.9, *J* 2.9, 5-H, 6-H), 7.59 - 7.61 (2 H, dd, *J* 6.8, *J* 3.0, 4-H, 7-H), 7.65 (2 H, s, 1-H, 3-H); $\delta_C$ (125 MHz, $CDCl_3$) 116.5, 121.9, 123.4, 138.1; *m/z* (EI) 134 ($M^+$, 100%), 133 (13), 108 (14), 102 (6), 90 (26), 89 (40), 69 (20), 45 (25), 39 (17), 28 (10); $\nu_{max}$ (KBr) / $cm^{-1}$ 3065, 3024, 1689, 1454, 1259, 1201, 759.

## References


1 (*a*) A. K. Bhattacharya and A. G. Hortmann, *J. Org. Chem*., 1978, **43**, 2728; (*b*) D. N. Harpp, D. K. Ash, T. G. Back and J. G. Gleason, *Tetrahedron Lett*., 1970, 3441; (*c*) W. G. Bentrude, T. Kawashima, B. A. Keys, M. Garroussian, W. Heide and D. A. Wedgaertner, *J. Am. Chem. Soc*., 1987, **109**, 1227; (*d*) N. A. Noureldin, M. Caldwell, J. Hendry and D. G. Lee, *Synthesis*, 1998, 1587; (*e*) D. N. Harpp, S. J. Bodzay, T. Aida and T. H. Chan, *Tetrahedron Lett*., 1986, **27**, 441; (*f*) B. Milligan and J. M. Swan, *J. Chem. Soc*., 1965, 2901.

2 (*a*) S. Oae, T. Takata and Y. H. Kim, *Bull. Chem. Soc. Jpn*, 1982, **55**, 2484; (*b*) T. Takata and S. Oae, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3937; (*c*) T. Takata, Y. H. Kim and S. Oae, *Tetrahedron Lett.*, 1978, 4303; (*d*) T-L. Ju, J. L. Kice and C.G.Venier, *J. Org. Chem.*, 1979, **44**, 610.

3 (*a*) R. Louw, H. P. W. Vermeeren, J. J. A. van Asten and W. J. Ultée, *J. Chem. Soc., Chem. Commun.*, 1976, 496; (*b*) P. K. Singh, L. Field and B. J. Sweetman, *Phosphorus and Sulfur*, 1988, **39**, 61; (*c*) M. P. Cava, N. M. Pollack, O. A. Mamer and M. J. Mitchell, *J. Org. Chem.*, 1971, **36**, 3932.

4 (a) R. P. Kreher and J. Kalischko, *Chem. Ber.*, 1991, **124**, 645; (*b*) M. Yamato, Y. Takeuchi, K. Hattori and K. Hashigaki, *Synthesis*, 1982, 1014.