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A Triple Umpolung Sequence For the Preparation of Highly Substituted Indanes.

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Abstract: The paper describes a new method for the diastereoselective construction of highly substituted indanes. The key step involves a triple umpolung sequence in which a 2-lithio-2-vinyl-1,3-dithiane is first united with an aryl halide to form a ketenedithioacetal. Transmetallation of the aryl halide with an alkyllithium reagent then generates an alkyl halide and a 2-indanyl-2-lithio-1,3-dithiane. Finally, these combine to complete the sequence. Copyright © 1996 Elsevier Science Ltd

We recently disclosed an approach to the *Podophyllum* lignans in which a Michael initiated ring closure (MIRC type II) featured as the key step (Figure 1).[1] This success lead us to consider how an analogous cyclopentannulation sequence might be accomplished. The problem did not appear to be a trivial one as it required the generation of an aryl cation equivalent in the presence of a lithiated dithiane. Reversing the polarisation of the system however, provided a potential solution (Figure 2).[2] For union of an *o*-bromobenzaldehyde and a 2-lithio-2-vinyl-1,3-dithiane would generate a ketenedithioacetal and, though unprecedented, we believed that an intramolecular cyclisation could then be induced by transmetallation of the halide.[3]

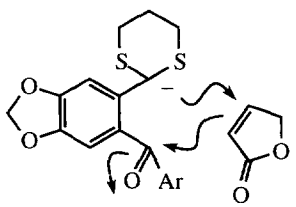


Figure 1

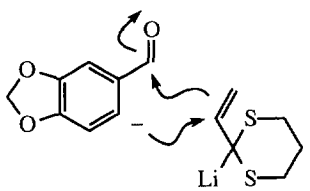
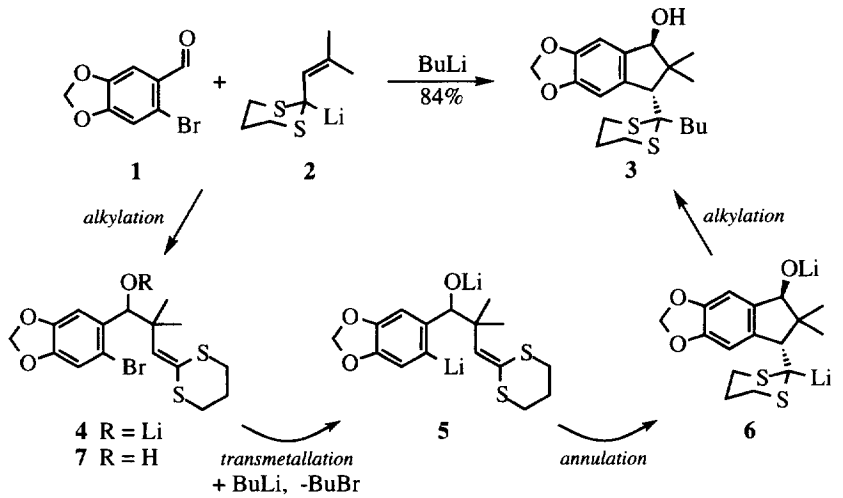


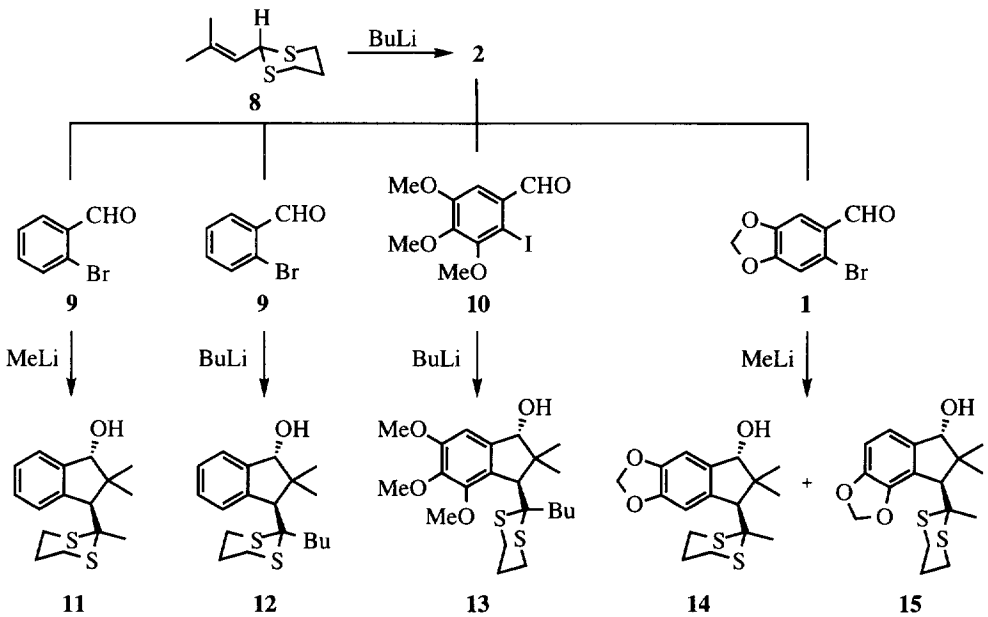
Figure 2

This general strategy was soon realised. Sequential addition of 6-bromopiperonal **1** and butyllithium to the lithiated 2-vinyl-1,3-dithiane **2**, for example, provided the indane **3** in 84% yield and as a single diastereoisomer (Scheme 1). Remarkably, in the one pot, three new carbon to carbon bonds had been established; each in an umpolung fashion.[4]



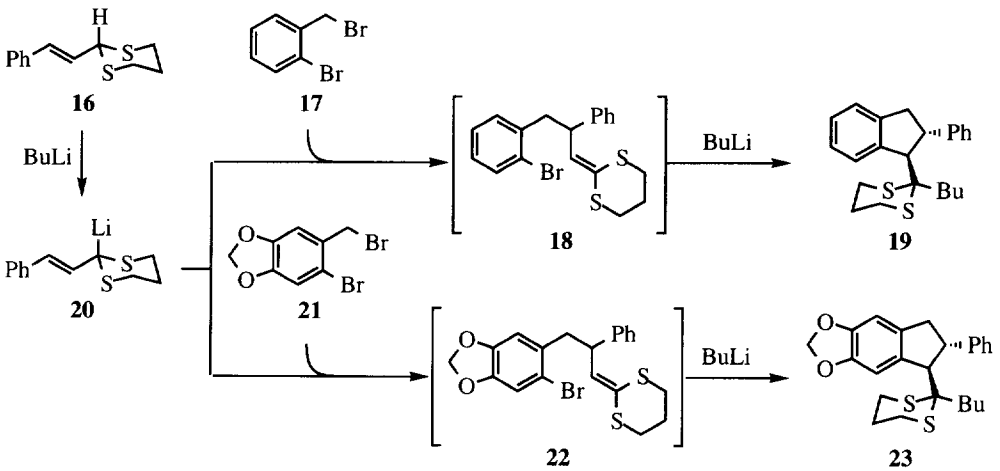
Scheme 1

The indanes **11** to **15** have also been prepared from the lithiodithiane **2** using the above procedure (Scheme 2). These experiments demonstrated that the reaction was i) effective with aryl bromides and aryl iodides; ii) tolerant of ethereal functions on the aromatic ring; iii) *trans*-1,3-diastereoselective and iv) more efficient with butyllithium than with methyllithium. One unexpected result occurred when **2** was combined with 6-bromopiperonal **1** and then treated with methyllithium. This provided the anticipated indane **14** together with significant quantities of its regioisomer **15**; presumably reflecting the relative efficiency of transmetallation reactions mediated by MeLi and BuLi.[5]



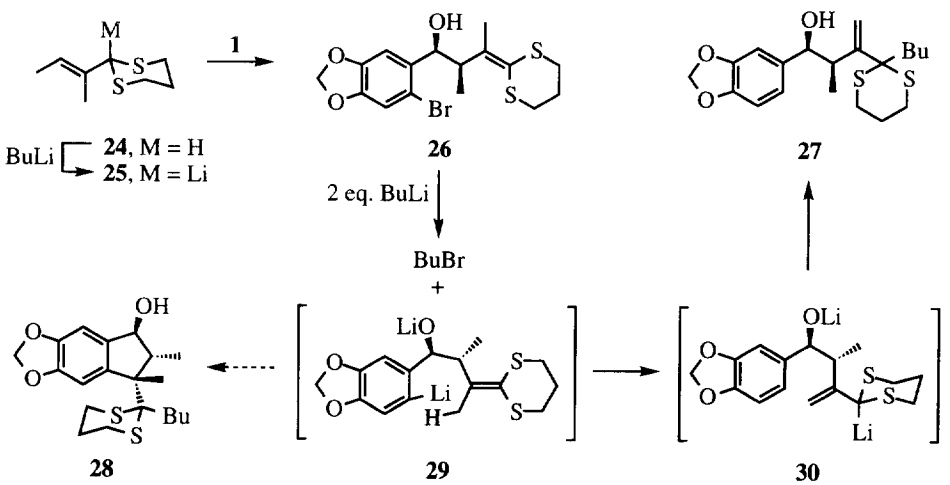
Scheme 2

We have also shown the reaction to be *trans*-1,2-diastereoselective through use of the 2-lithio-1,3-dithiane **20** derived from *trans*-cinnamaldehyde. Thus, addition of 2-bromobenzyl bromide **17** to **20** first gave the ketenedithioacetal **18**, which was transformed into the indane **19** on exposure to BuLi. Similarly the benzodioxole **21** provided access to the indanodioxole **23** *via* ketenedithioacetal **22**.



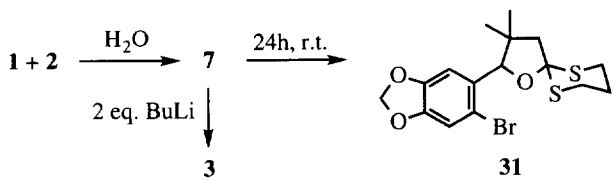
Scheme 3

Interestingly, the presence of a proton on the γ-carbon of the intermediate ketenedithioacetals had no discernible effect on the yield of the above reactions.[6] By way of contrast, when the lithiated dithiane **25** was employed in this sequence the major product attained was the 2-vinyl-1,3-dithiane **27** rather than the indane **28**. Thus it would seem that intermediates akin to **29** will effect deprotonation when it is kinetically favourable to do so (Scheme 4).



Scheme 4

Finally, we should mention that the intermediate ketenedithioacetals can be intercepted and that these too are responsive to cyclisation upon treatment with two equivalents of an alkyllithium reagent. That the γ-hydroxy derivatives are prone to isomerisation on standing to the corresponding tetrahydrofuran detracts from the appeal of this course (*e.g.* Scheme 5).[7]



Scheme 5

In conclusion, we have developed a new cyclopentannulation reaction for the synthesis of highly substituted indanes. The procedure adopted involves a triple umpolung sequence and features the unprecedented addition of an aryllithium to a ketenedithioacetal. The high yields, diastereoselectivity, atom efficiency and easy of experimental are noteworthy.

EXPERIMENTAL

General Remarks.

Melting points were obtained using a Mel-Temp (II) apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP800 spectrometer. Maxima and inflections (inf) are reported as λ_{max} followed in parentheses by the extinction coefficient ε ($dm^3mol^{-1}cm^{-1}$). IR spectra were recorded on a Perkin Elmer 1600 series Fourier transform infrared spectrometer using NaCl cells. Maxima are reported as ν_{max} followed by the signal intensity (described using the abbreviations s, strong; m, medium; w, weak; v, very; br, broad). ^1H n.m.r. spectra were recorded on a Bruker AC250 (250MHz) or a Jeol GX270 (270MHz) spectrometer. Chemical shifts (δ_H) are reported as values in parts per million relative to tetramethylsilane (δ 0.00) or residual $CHCl_3$ (δ 7.27). Multiplicities are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app., apparent. ^{13}C spectra were recorded on a Brucker AC250 (63MHz) or a Jeol GX270 (68MHz) spectrometer. Chemical shifts (δ_C) are reported as values in parts per million relative to tetramethylsilane (δ 0.00) or residual $CHCl_3$ (δ 77.2). Multiplicities refer to the signals in the off-resonance spectra, as determined by DEPT 135° and DEPT 90° experiments, and are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet. Two dimensional and n.O.e. experiments were recorded on a Jeol GX270 spectrometer. Mass spectra were recorded on a variety of instruments. Signals are reported as values in atomic mass units and are followed in parentheses by the peak intensity relative to the base peak (100%).

All reactions were magnetically stirred and conducted under a nitrogen atmosphere using flame dried glassware. Thin layer chromatography, using Macherey-Nagel Alugram Sil G/UV_{254} precoated aluminium foil plates of layer thickness 0.25mm, was used to monitor reactions. Compounds were visualised firstly by UV irradiation then by heating plates exposed to solutions of potassium permanganate in aq. sodium carbonate. Column chromatography was performed on Sorbsil 60 silica (230-400 mesh), slurry packed and run under low pressure. THF was dried and degassed by refluxing over sodium wire using benzophenone ketyl as indicator. All reagents used were purchased from Lancaster Synthesis Ltd. or The Aldrich Chemical Company Ltd. and used as supplied.

trans-7-(2-butyl-1,3-dithian-2-yl)-6,7-dihydro-6,6-dimethyl-5*H*-indeno[5,6-d]-1,3-dioxol-5-ol **3**

A hexane solution of *n*-butyllithium (1.6M, 9.7mL) was added over 10 min to a cooled (-20°C), THF solution (100mL) of 2-(2-methylprop-1-en-1-yl)-1,3-dithiane (2.45g, 14.1mmol). The resulting solution was warmed to 5°C over 2.5 h, then cooled to -50°C. A THF solution (40mL) of 6-bromopiperonal (3.23g, 14.1mmol) was then added over 15 min. After a further 30 min a hexane solution of *n*-butyllithium (1.6M, 9.7mL) added over 10 min. The resulting solution was allowed to warm to ambient temperature over 4 h then partitioned between ether (200mL) and water (200mL). The aqueous layer was extracted with further ether (2 x 100mL) and the combined organics washed with brine (200mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 10 to 50% ether in petrol) to yield the title compound (4.50g, 11.8mmol, 84%) as a white foam; **m.p.** 48-52°C; **FT-IR** (neat) υ_{max} 3420brm, 2960s, 2770w, 1475s, 1275s, 1040s, 910s and 730s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 242 (6630), 246 (6230), 246 (6210) and 295 (5970) nm; **^{1}H NMR** (270MHz, $CDCl_3$) δ_H 7.14 (1H, s, ArH), 6.82 (1H, s, ArH), 5.98 (1H, d, *J* 1.4Hz, OC*H*HO), 5.96 (1H, d, *J* 1.4Hz, OC*H*HO), 5.09 (1H, d, *J* 7.8Hz, C*H*OH), 3.31 (1H, s, C*H*CS), 2.96-2.86 (2H, m, 2xSC$H_{ax}H_{eq}$), 2.83-2.68 (2H, m, 2xSC$H_{ax}H_{eq}$), 2.22 (1H, m, C*H*HCH$_2$CH$_2$CH$_3$), 2.14 (1H, d, *J* 7.8Hz, O*H*), 2.14-1.77 (3H, m, SCH$_2$C*H*$_2$CH$_2$SCCH*H*), 1.60 (2H, m, C*H*$_2$CH$_2$CH$_3$), 1.53 (3H, s, CC*H*$_3$), 1.36 (2H, sextet, *J* 7.6Hz, CH$_2$CH$_3$), 1.00 (3H, s, CC*H*$_3$) and 0.94 (3H, t, *J* 7.6Hz, CH$_2$C*H*$_3$) ppm (these assignments were confirmed by a ^{1}H-^{1}H COSY experiment); **n.O.e.** Irradiation of the signal at δ_H 1.53 (CC*H*$_3$) caused an n.O.e. enhancement at δ_H 5.09 (C*H*OH) of 14% while irradiation of the signal at δ_H 1.00 (CC*H*$_3$) caused an n.O.e. enhancement at δ_H 3.31 (C*H*CS) of 10%; **^{13}C NMR** (68MHz, $CDCl_3$) δ_c 147.1 (s, *C*(Ar)), 146.4 (s, *C*(Ar)), 138.9 (s, *C*(Ar)), 134.3 (s, *C*(Ar)), 109.4 (d, *C*H(Ar)), 103.9 (d, *C*H(Ar)), 100.9 (t, OCH$_2$O), 81.9 (d, *C*HOH), 58.3 (d, *C*HCS), 58.2 (s, S*C*S), 50.5 (s, *C*(CH$_3$)$_2$), 36.7 (t, *C*H$_2$CS), 27.3 (t, *C*H$_2$CH$_2$CH$_3$), 26.4 (t, *C*H$_2$S), 25.9 (t, *C*H$_2$S), 25.2 (q, CCH$_3$), 24.3 (t, *C*H$_2$CH$_2$S), 23.8 (q, CCH$_3$), 22.8 (t, *C*H$_2$CH$_3$) and 14.0 (q, CH$_2$*C*H$_3$) ppm; **m/z** (EI) Found: 362.1423 (70%, $[M-H_2O]^+$); $C_{20}H_{26}S_2O_2$ requires 362.1408, 288 (7), 254 (16), 241 (38), 227 (16), 213 (39), 199 (55), 188 (28) and 175 (100, $[C_3H_6S_2CBu]^+$). (The intermediate ketenedithioacetal **7** could be intercepted and exhibited **^{1}H NMR** (270MHz, $CDCl_3$) δ_H 7.02 (1H, s, Ar*H*), 6.94 (1H, s, Ar*H*), 6.02 (s, =C*H*), 5.96 (2H, s, OC*H*$_2$O), 5.20 (1H, d, *J* 3.2Hz, C*H*OH), 2.94 - 2.82 (4H, m, 2xSC*H*$_2$), 2.41 (1H, d, *J* 3.2Hz, O*H*), 2.14 - 2.04 (2H, m, SCH$_2$C*H*$_2$), 1.26 (3H, s, C*H*$_3$) and 1.19 (3H, s, C*H*$_3$) ppm. This sample rapidly isomerised on standing to the tetrahydrofuran **31** which exhibited **^{1}H NMR** (270MHz, $CDCl_3$) δ_H 7.13 (1H, s, Ar*H*), 7.00 (1H, s, Ar*H*), 6.00 (2H, s, OC*H*$_2$O), 5.29 (1H, s, ArC*H*), 3.53 (1H, app. td, *J* 13.6, 2.9Hz, SC$H_{ax}H_{eq}$CH$_2$CH$_2$S), 3.42 (1H, app. td, *J* 13.6, 2.9Hz, SCH$_2$CH$_2$C$H_{ax}H_{eq}$S), 2.78 (1H, app. dt, *J* 13.6, 2.3Hz, SCH$_{ax}H_{eq}$CH$_2$CH$_2$S), 2.68 (1H, app. dt, *J* 13.6, 2.3Hz, SCH$_2$CH$_2$CH$_{ax}H_{eq}$S), 2.15 (2H, s, (CH$_3$)$_2$CC*H*$_2$C), 2.12-1.83 (2H, m, SCH$_2$C*H*$_2$CH$_2$S), 1.25 (3H, s, C*H*$_3$) and 0.88 (3H, s, C*H*$_3$) ppm.)

trans-3-(2-methyl-1,3-dithian-2-yl)-2,3-dihydro-2,2-dimethyl-1*H*-inden-1-ol **11**

A hexane solution of *n*-butyllithium (1.6M, 4.8mL) was added over 5 min to a cooled (-20°C), THF solution (50mL) of 2-(2-methylprop-1-en-1-yl)-1,3-dithiane (1.22g, 7.05mmol). The resulting solution was warmed to ambient temperature over 3 h, then cooled to -78°C. A THF solution (10mL) of 2-bromobenzaldehyde (1.31g, 7.08mmol) was then added over 2 min. After a further 45 min a hexane solution of *n*-methyllithium (1.4M, 5.5mL) was added. The resulting solution was allowed to warm to 0°C over 2 h then maintained at that temperature for 24h. The whole was partitioned between ether (200mL) and water (200mL), the aqueous layer was extracted with ether (100mL) and the combined organics were washed with brine (200mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 5 to 30% ether in petrol) to yield the title compound (1.49g, 5.07mmol, 72%) as colourless oil; **FT-IR** (neat) υ_{max} 3400brm, 3070w, 3035w, 2970s, 2930s, 2900s, 1605w, 1475m, 1455m, 1420m, 1055s and 755s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 320inf

(210), 314inf (250), 309inf (260), 304inf (280), 292 (290), 274 (740), 264 (1130), 252 (1480) and 242 (1920) nm; **^{1}H NMR** (270MHz, $CDCl_3$) δ_H 7.80 (1H, d, *J* 8.2, Ar*H*), 7.38-7.18 (3H, m, 3xAr*H*), 4.91 (1H, brs, C*H*OH), 3.50 (1H, s, C*H*CS), 3.06-2.95 (2H, m, 2xSC$H_{ax}H_{eq}$), 2.87-2.76 (2H, m, 2xSC$H_{ax}H_{eq}$), 2.10-1.80 (3H, m, SCH_2CH_2 & O*H*), 1.80 (3H, s, SCCH_3), 1.43 (3H, s, CH_3) and 1.14 (3H, s, CH_3) ppm; **^{13}C NMR** (68MHz, $CDCl_3$) δ_c 144.7 (s, *C*(Ar)), 141.1 (s, *C*(Ar)), 128.9 (d, *C*H(Ar)), 127.2 (d, *C*H(Ar)), 126.5 (d, *C*H(Ar)), 123.8 (d, *C*H(Ar)), 82.4 (d, *C*HOH), 60.4 (d, *C*HCS), 52.7 (s, *S*CS), 50.0 (s, $C(CH_3)_2$), 26.7 (t, CH_2S), 26.6 (t, CH_2S), 26.0 (q, SCCH_3), 25.0 (q, CCH_3), 24.9 (t, CH_2CH_2S) and 23.5 (q, CCH_3) ppm; **m/z** (EI) Found: 276.1044 (2%, $[M-H_2O]^+$); $C_{16}H_{20}S_2$ requires 276.1007, 187 (9) and 133 (100, $[C_3H_6S_2CMe]^+$).

trans-3-(2-butyl-1,3-dithian-2-yl)-2,3-dihydro-2,2-dimethyl-1*H*-inden-1-ol **12**

A hexane solution of *n*-butyllithium (1.6M, 4.6mL) was added over 10 min to a cooled (-20°C), THF solution (50mL) of 2-(2-methylprop-1-en-1-yl)-1,3-dithiane (1.23g, 7.07mmol). The resulting solution was warmed to ambient temperature over 3 h, then cooled to -78°C. A THF solution (10mL) of 2-bromobenzaldehyde (1.30g, 7.03mmol) was then added over 15 min. After a further 45 min a hexane solution of *n*-butyllithium (1.6M, 4.6mL) was added, dropwise over 10 min. The resulting solution was allowed to warm to ambient temperature over 6h then partitioned between ether (200mL) and water (200mL). The aqueous layer was extracted with further ether (2 x 100mL) and the combined organics were dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 5 to 30% ether in petrol) to yield the title compound (2.11g, 6.28mmol, 89%) as a pale yellow oil; **FT-IR** (neat) υ_{max} 3415brm, 3070w, 2955s, 2920s, 2870, 1920w, 1605w, 1460m, 1215m, 1050m and 755s cm^{-1}; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 7.61 (1H, d, *J* 7.4, Ar*H*), 7.35-7.18 (3H, m, 3xAr*H*), 5.23 (1H, brs, C*H*OH), 3.42 (1H, s, C*H*CS), 2.95-2.80 (2H, m, 2xSC$H_{ax}H_{eq}$), 2.73-2.58 (2H, m, 2xSC$H_{ax}H_{eq}$), 2.25 (1H, m, C*H*HCH$_2$CH$_2$CH$_3$), 2.08-1.73 (3H, m, $SCH_2CH_2CH_2S$-CCH*H*), 1.69-1.15 (3H, m, $CH_2CH_2CH_3$ & O*H*), 1.57 (3H, s, CCH_3), 1.36 (2H, sextet, *J* 7.2Hz, CH_2CH_3), 0.98 (3H, s, CCH_3) and 0.97 (3H, t, *J* 7.2Hz, CH_2CH_3) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_c 145.5 (s, *C*(Ar)), 141.4 (s, *C*(Ar)), 129.0 (d, *C*H(Ar)), 127.7 (d, *C*H(Ar)), 126.7 (d, *C*H(Ar)), 123.4 (d, *C*H(Ar)), 82.4 (d, *C*HOH), 58.6 (d, *C*HCS), 58.2 (s, *S*CS), 50.2 (s, $C(CH_3)_2$), 36.9 (t, CH_2CS), 27.5 (t, $CH_2CH_2CH_3$), 26.5 (t, CH_2S), 26.0 (t, CH_2S), 25.1 (q, CCH_3), 24.5 (t, CH_2CH_2S), 23.8 (q, CCH_3), 22.9 (t, CH_2CH_3) and 14.1 (q, CH_2CH_3) ppm; **m/z** (CI, NH_3) Found: 337.1660 (7%, $[MH]^+$); $C_{19}H_{29}S_2O$ requires 337.1660, 319 (12, $[MH-H_2O]^+$), 229 (6) and 175 (100, $[C_3H_6S_2CBu]^+$).

trans-3-(2-methyl-1,3-dithian-2-yl)-2,3-dihydro-2,2-dimethyl-4,5,6-trimethoxy-1*H*-inden-1-ol **13**

A hexane solution of *n*-butyllithium (1.6M, 4.8mL) was added over 5 min to a cooled (-20°C), THF solution (50mL) of 2-(2-methylprop-1-en-1-yl)-1,3-dithiane (1.22g, 7.05mmol). The resulting solution was warmed to ambient temperature over 3 h, then cooled to -60°C. A THF solution (10mL) of 2-iodo-3,4,5-trimethoxybenzaldehyde (2.27g, 7.05mmol) was then added over 5 min. After a further 45 min a hexane solution of methyllithium (1.4M, 5.5mL) added. The resulting solution was allowed to warm to ambient temperature over 3 h then maintained at that temperature for 15h. The whole was partitioned between ether (200mL) and water (200mL), the aqueous layer was extracted with ether (2x100mL) and the combined organics were washed with ammonium chloride (200mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 5 to 50% ether in petrol) to yield the title compound (1.84g, 4.79mmol, 68%) as a colourless oil; **FT-IR** ($CHCl_3$) υ_{max} 3420brm, 2935s, 1602m, 1465s, 1410s, 1335s, 1235m, 1195m, 1115s, 1050m and 755s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 280 (4600) and 242 (12000) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 6.71 (1H, s, Ar*H*), 5.46 (1H, brs, C*H*OH), 3.87 (3H, s, OCH_3), 3.84 (6H, s, 2xOCH_3), 3.20 (1H, s, C*H*CS), 3.11 (1H, ddd, *J* 14.4, 11.8, 2.5Hz, SC$H_{ax}H_{eq}$), 2.96 (1H, ddd, *J* 14.4, 11.8, 2.5Hz, SC$H_{ax}H_{eq}$), 2.75 (1H, app.dt, *J* 14.4,

4.0Hz, $SCH_{ax}H_{eq}$), 2.61 (1H, app.dt, *J* 14.4, 4.0Hz, $SCH_{ax}H_{eq}$), 2.20 (1H, brs, O*H*), 2.09 (1H, m, $SCH_2CH_{ax}H_{eq}$), 1.86 (3H, s, SCC*H*$_3$), 1.80 (1H, m, $SCH_2CH_{ax}H_{eq}$), 1.74 (3H, s, C*H*$_3$) and 0.86 (3H, s, C*H*$_3$) ppm; **^{13}C NMR** (68MHz, $CDCl_3$) δ_C 154.2 (s, *C*(Ar)), 151.6 (s, *C*(Ar)), 141.7 (s, *C*(Ar)), 140.9 (s, *C*(Ar)), 125.9 (s, *C*(Ar)), 102.4 (d, *C*H(Ar)), 81.3 (d, *C*HOH), 61.2 (q, O*C*H$_3$), 60.8 (q, O*C*H$_3$), 60.5 (q, O*C*H$_3$), 55.9 (d, *C*HCS), 55.5 (s, S*C*S), 51.5 (s, *C*(CH$_3$)$_2$), 28.5 (q, SC*C*H$_3$), 27.5 (t, *C*H$_2$S), 26.4 (t, *C*H$_2$S), 25.5 (t, *C*H$_2$CH$_2$S), 25.5 (q, CC*H*$_3$), and 23.4 (q, CC*H*$_3$) ppm; **m/z** (CI, NH_3) Found: 385.1507 (13%, [MH]$^+$); $C_{19}H_{29}O_4S_2$ requires 385.1507, 367 (3, [MH-H_2O]$^+$), 251 (18, [M-$C_3H_6S_2CMe$]$^+$) and 133 (100, [$C_3H_6S_2CMe$]$^+$).

trans-7-(2-methyl-1,3-dithian-2-yl)-6,7-dihydro-6,6-dimethyl-5*H*-indeno[5,6-d]-1,3-dioxol-5-ol **14** and *trans*-8-(2-methyl-1,3-dithian-2-yl)-7,8-dihydro-7,7-dimethyl-6*H*-indeno[4,5-d]-1,3-dioxol-6-ol **15**

A hexane solution of *n*-butyllithium (1.6M, 9.4mL) was added over 5 min to a cooled (-20°C), THF solution (50mL) of 2-(2-methylprop-1-en-1-yl)-1,3-dithiane (2.45g, 14.1mmol). The resulting solution was warmed to ambient temperature over 4 h, then cooled to -78°C. A THF solution (20mL) of 6-bromopiperonal (3.23g, 14.1mmol) was then added over 2 min. After a further 15 min a hexane solution of *n*-methyllithium (1.4M, 13mL) added over 2 min. The resulting solution was warm to ambient temperature, stirred for 8 h then partitioned between ether (200mL) and water (200mL). The aqueous layer was extracted with a aliquot of ether (100mL) and the combined organics were washed with brine (200mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 10 to 50% ether in petrol) to yield firstly *trans*-8-(2-methyl-1,3-dithian-2-yl)-7,8-dihydro-7,7-dimethyl-6*H*-indeno[4,5-d]-1,3-dioxol-6-ol (1.52g, 4.51mmol, 32%) as a white solid; **m.p.** 152-155°C; **CHN** Found: C 59.9%, H 6.5%; $C_{17}H_{22}S_2O_3$ requires C 60.3%, H 6.6%; **FT-IR** ($CHCl_3$) υ_{max} 3420brm, 2915s, 2865s, 2770m, 1870w, 1465s, 1365s, 1300s, 1280m, 990m and 945s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 295 (4810), 251 (4340) and 247 (4510) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 7.36 (1H, s, Ar*H*), 6.93 (1H, s, Ar*H*), 5.97 (2H, s, O*CH*$_2$O), 4.78 (1H, brd, *J* 6.9Hz, *CH*OH), 3.39 (1H, s, *CH*CS), 3.03 (2H, ddd, *J* 14.5, 9.7, 3.4Hz, $2xSCH_{ax}H_{eq}$), 2.83 (2H, ddd, *J* 14.5, 6.4, 3.6Hz, $2xSCH_{ax}H_{eq}$), 2.03 (1H, m, $SCH_2CH_{ax}H_{eq}$), 1.94 (1H, m, $SCH_2CH_{ax}H_{eq}$), 1.82 (3H, s, C*H*$_3$), 1.70 (1H, brd, *J* 6.9Hz, OH), 1.43 (3H, s, C*H*$_3$) and 1.18 (3H, s, C*H*$_3$) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 147.1 (s, *C*(Ar)), 146.8 (s, *C*(Ar)), 138.4 (s, *C*(Ar)), 134.6 (s, *C*(Ar)), 109.9 (d, *C*H(Ar)), 104.4 (d, *C*H(Ar)), 101.1 (t, O*C*H$_2$O), 82.8 (d, *C*HOH), 60.6 (d, *C*HCS), 53.2 (s, S*C*S), 50.7 (s, *C*(CH$_3$)$_2$), 27.0 (t, *C*H$_2$S), 26.8 (t, *C*H$_2$S), 26.3 (q, SC*C*H$_3$), 25.2 (q, CC*H*$_3$), 24.9 (t, *C*H$_2$CH$_2$S) and 23.9 (q, CC*H*$_3$) ppm; **m/z** (EI) Found: 320.0869 (8%, [M-H_2O]$^+$); $C_{17}H_{20}S_2O_2$ requires 320.0904, 214 (10), 199 (10), 187 (6, [M-H_2O-$C_3H_6S_2CMe$]$^+$) and 133 (100, [$C_3H_6S_2CMe$]$^+$) then *trans*-7-(2-methyl-1,3-dithian-2-yl)-6,7-dihydro-6,6-dimethyl-5*H*-indeno[5,6-d]-1,3-dioxol-5-ol (2.47g, 7.31mmol, 52%) as a colourless oil; **FT-IR** ($CHCl_3$) υ_{max} 3425brm, 2965s, 2895s, 2830w, 2780w, 1840w, 1605w, 1500m, 1460s, 1245s, 1045s, 910s and 730s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 291 (4900), 288 (4910), 251inf (5220) and 249 (5240) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 6.82 (1H, dd, *J* 7.8, 1.1Hz, Ar*H*), 6.76 (1H, d, *J* 7.8Hz, Ar*H*), 5.93 (1H, d, *J* 1.4Hz, OC*H*HO), 5.88 (1H, d, *J* 1.4Hz, OCH*H*O), 5.25 (1H, brs, *CH*OH), 3.30 (1H, s, *CH*CS), 3.04 (1H, ddd, *J* 14.4, 10.4, 3.1Hz, $SCH_{ax}H_{eq}$), 2.93 (1H, ddd, *J* 14.4, 10.5, 3.1Hz, $SCH_{ax}H_{eq}$), 2.84 (1H, ddd, *J* 14.4, 5.9, 3.4Hz, $SCH_{ax}H_{eq}$), 2.71 (1H, ddd, *J* 14.4, 5.9, 3.3Hz, $SCH_{ax}H_{eq}$), 2.10-1.80 (3H, m, SCH_2CH_2 & O*H*), 1.80 (3H, s, SCC*H*$_3$), 1.64 (3H, s, C*H*$_3$) and 0.85 (3H, s, C*H*$_3$) ppm; **^{13}C NMR** (68MHz, $CDCl_3$) δ_C 146.7 (s, *C*(Ar)), 144.5 (s, *C*(Ar)), 140.6 (s, *C*(Ar)), 122.2 (s, *C*(Ar)), 116.1 (d, *C*H(Ar)), 107.8 (d, *C*H(Ar)), 100.1 (t, O*C*H$_2$O), 80.5 (d, *C*HOH), 59.8 (d, *C*HCS), 54.4 (s, S*C*S), 50.7 (s, *C*(CH$_3$)$_2$), 27.6 (q, SC*C*H$_3$), 27.1 (t, *C*H$_2$S), 26.2 (t, *C*H$_2$S), 25.2 (q, CC*H*$_3$), 24.9 (t, *C*H$_2$CH$_2$S) and 23.2 (q, CC*H*$_3$) ppm (the structural assignment was confirmed by ^{13}C-^{1}H COSY and ^{13}C-^{1}H COLOC experiments); **m/z** (EI) Found: 231.1006 (12%, [M-$C_3H_7S_2$]$^+$); $C_{14}H_{15}O_3$ requires 231.1021, 189 (5) and 133 (100, [$C_3H_6S_2CMe$]$^+$).

trans-3-(2-butyl-1,3-dithian-2-yl)-2,3-dihydro-2-phenyl-1*H*-indene **18**

A hexane solution of *n*-butyllithium (1.6M, 3.1mL) was added over 3 min to a cooled (-78°C), THF solution (50mL) of 2-(2-phenyleth-1-en-1-yl)-1,3-dithiane (1.00g, 4.5mmol) resulting in an orange coloured solution. After 30 min 2-bromobenzyl bromide (1.13g, 4.5mmol), as a solution in THF (10mL), was added over 5 min and the solution stirred for 30 min. A hexane solution of *n*-butyllithium (1.6M, 3.1mL) was then added over 5 min. The resulting solution was stirred for 30 min at -78°C then warmed to ambient temperature over 1 h. Water (6mL) was added and the whole partitioned between ether (200mL) and water (200mL). The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 2 to 10% ether in petrol) to yield the title compound (1.31g, 3.56mmol, 79%) as a white solid; **m.p.** 131-133°C (ether / petrol); **FT-IR** ($CHCl_3$) υ_{max} 3025w, 2955m, 2940m, 2870m, 2845m, 1960w, 1750w, 1610w, 1490m, 1460m and 910m cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 239 (2620), 256 (1420), 261 (1430), 269 (1440) and 276 (1190) nm; **^{1}H NMR** (270MHz, $CDCl_3$) δ_H 7.66 (1H, d, *J* 7.6Hz, Ar*H*), 7.41-7.21 (8H, m, 8xAr*H*), 4.15 (1H, brd, *J* 8.9Hz, C*H*Ph), 3.97 (1H, brs, C*H*CHPh), 3.73 (1H, dd, *J* 16.8, 8.9Hz, C*H*HCHPh), 3.05 (1H, brd, *J* 16.8Hz, CH*H*CHPh), 2.94 (2H, m, 2xSC$H_{ax}H_{eq}$), 2.78 (2H, m, 2xSCH$_{ax}H_{eq}$), 2.00 (3H, m, SCH_2CH_2 & SCC*H*H), 1.80-1.55 (3H, m, SCCH*HCH*$_2$), 1.36 (2H, sextet, *J* 7.3Hz, CH_2CH_3) and 0.98 (3H, t, *J* 7.3Hz, CH_3) ppm (these assignments were confirmed by ^{1}H-^{1}H COSY and ^{13}C-^{1}H COSY experiments); **^{13}C NMR** (68MHz, $CDCl_3$) δ_C 149.1 (s, *C*(Ph)), 145.3 (s, *C*(Ar)), 140.7 (s, *C*(Ar)), 128.4 (d, 2x*C*H(Ph)), 127.9 (d, *C*H(Ar)), 127.6 (d, *C*H(Ar)), 126.2 (d, 2x*C*H(Ph)), 125.9 (d, *C*H(Ph)), 125.8 (d, *C*H(Ar)), 124.1 (d, *C*H(Ar)), 60.0 (d, *C*HCHPh), 59.6 (s, *SCS*), 46.4 (d, *C*HPh), 41.0 (t, CH_2CHPh), 34.9 (t, CH_2CS), 26.8 (t, $CH_2CH_2CH_3$), 25.9 (t, CH_2S), 25.8 (t, CH_2S), 24.6 (t, CH_2CH_2S), 23.0 (t, CH_2CH_3) and 14.0 (q, CH_2CH_3) ppm (these assignments were confirmed by a ^{13}C-^{1}H COSY experiment); **m/z** (EI) Found: 368.1677 (4%, $[M]^+$); $C_{23}H_{28}S_2$ requires 368.1666, 293 (3, $[M\text{-}C_3H_6SH]^+$), 261 (4, $[M\text{-}SC_3H_6SH]^+$), 193 (9, $[M\text{-}C_3H_6S_2CBu]^+$), 175 (100, $[C_3H_6S_2CBu]^+$), 115 (14) and 91 (20).

The intermediate ketenedithioacetal **22**, a pale yellow oil, could be intercepted and exhibited **UV** ($CHCl_3$) λ_{max} (ε) 295 (4600), 261 inf (6180), 256 inf (6730), 252 (7620), 248 (8340) and 243 (9060) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 7.43 - 7.18 (5H, m, C_6H_5), 6.98 (1H, s, ArH), 6.58 (1H, s, ArH), 6.19 (1H, d, *J* 9.9Hz, =CH), 5.92 (2H, s, OC*H*HO), 4.26 (1H, ddd, *J* 9.9, 9.2, 6.1Hz, PhC*H*), 3.07 (1H, dd, *J* 13.6, 6.1Hz, ArC*H*H), 2.94 (1H, dd, *J* 13.6, 9.2Hz, ArCH*H*), 2.85 - 2.55 (4H, m, 2xSCH_2) and 2.07 (2H, m, $SCH_2CH_2CH_2$) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 146.9 (s, *C*(Ph)), 146.7 (s, *C*(Ar)), 143.1 (s, *C*(Ar)), 135.6 (d, =CH), 131.9 (s, *C*(Ar)), 128.6 (d, 2x*C*H(Ph)), 127.8 (s, *C*(Ar)), 127.5 (d, 2x*C*H(Ph)), 126.5 (d, *C*H(Ph)), 115.2 (s, $=CS_2$), 112.5 (d, *C*H(Ar)), 111.1 (d, *C*H(Ar)), 101.5 (t, OCH_2O), 45.6 (d, *C*HPh), 42.7 (t, CH_2CHPh), 30.3 (t, CH_2S), 29.6 (t, CH_2S) and 25.1 (t, CH_2CH_2S) ppm; **m/z** sample suffered hydrolysis prior to analysis.

trans-5-(2-butyl-1,3-dithian-2-yl)-6,7-dihydro-6-phenyl-5*H*-indeno[5,6-d]-1,3-dioxole **23**

A hexane solution of *n*-butyllithium (1.6M, 3.1mL) was added over 3 min to a cooled (-78°C), THF solution (50mL) of 2-(2-phenyleth-1-en-1-yl)-1,3-dithiane (1.00g, 4.5mmol) resulting in deep red solution. After 10 min a THF solution (10mL) of 6-bromopiperonyl bromide (1.10g, 3.74mmol) was added and the solution stirred for 30 min. A hexane solution of *n*-butyllithium (1.6M, 3.1mL) was then added over 5 min, the resulting solution was warmed to 0°C over 30 min, then partitioned between ether (200mL) and water (200mL). The aqueous layer was extracted with further aliquots of ether (2 x 100mL) then the combined organics were washed with brine (200mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 5 to 15% ether in petrol) to yield the title compound (1.31g, 3.18mmol, 85%) as a white solid; **m.p.** 128-129°C (ether / petrol); **FT-IR** ($CHCl_3$) υ_{max} 2955m, 2925m, 2870m, 1605w, 1500m, 1475s, 1295m, 1245m, 1040m, 940m, 755m and 700m cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 240 (7820), 243 inf (7030) and 299 (11000) nm; **^{1}H NMR**

(250MHz, $CDCl_3$) δ_H 7.25-7.11 (5H, m, C_6H_5), 7.16 (1H, s, ArH), 7.04 (1H, s, ArH), 5.99 (1H, d, *J* 1.3Hz, OC*H*HO), 5.96 (1H, d, *J* 1.3Hz, OC*H*HO), 4.01 (1H, d, *J* 8.9Hz, C*H*HCHPh), 3.73 (1H, s, C*H*CHPh), 3.51 (1H, dd, *J* 16.6, 8.9Hz, C*H*Ph), 2.98-2-63 (4H, m, $SCH_2CH_2CH_2S$), 2.83 (1H, d, *J* 16.6Hz, CH*H*CHPh), 1.97-1.80 (3H, m, $SCH_2CH_2CH_2SCCHH$), 1.72-1.40 (3H, m, $CHHCH_2CH_2CH_3$), 1.28 (3H, sextet, *J* 7.2Hz, CH_2CH_3) and 0.89 (3H, t, *J* 7.2Hz, CH_3) ppm (these assignments were confirmed by a ^1H-^1H COSY experiment); **^{13}C NMR** (63MHz, $CDCl_3$) δ_c 149.2 (s, *C*(Ph)), 147.6 (s, *C*(Ar)), 146.3 (s, *C*(Ar)), 138.3 (s, *C*(Ar)), 133.3 (s, *C*(Ar)), 128.5 (d, 2x*C*H(Ph)), 126.3 (d, 2x*C*H(Ph)), 126.0 (d, *C*H(Ph)), 108.1 (d, *C*H(Ar)), 104.2 (d, *C*H(Ar)), 101.0 (t, OCH_2O), 59.7 (d, *C*HCHPh), 59.6 (s, *SCS*), 47.2 (d, *C*HPh), 40.8 (t, CH_2CHPh), 34.9 (t, CH_2CS), 26.8 (t, $CH_2CH_2CH_3$), 25.9 (t, CH_2S), 25.8 (t, CH_2S), 24.6 (t, CH_2CH_2S), 23.1 (t, CH_2CH_3) and 14.0 (q, CH_2CH_3) ppm; **$m/_z$** (EI) 237 (13%, [M-$C_3H_6S_2CBu$]$^+$), 207 (7), 175 (100, [$C_3H_6S_2CBu$]$^+$) and 136 (38).

6-bromo-5-(3-(1,3-dithian-2-ylidene)-1*S**-hydroxy-2*S**-methylbut-1-yl)benzo[1,3]-dioxole **26**

A hexane solution of *n*-butyllithium (1.6M, 3.8mL) was added over 5 min to a cooled (-20°C), THF solution (50mL) of 2-(but-2-en-2-yl)-1,3-dithiane (1.00g, 5.75mmol). The resulting solution was warmed to ambient temperature over 3 h, then cooled to -60°C. A THF solution (10mL) of 6-bromopiperonal (1.30g, 5.68mmol) was then added over 5 min. The resulting solution was allowed to warm to ambient temperature over 3 h then partitioned between ether (200mL) and water (200mL). The aqueous layer was extracted with ether (2x100mL) and the combined organics were dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 5 to 50% ether in petrol) to yield the title compound (2.11g, 5.24mmol, 92%) as a white solid; **m.p.** 156-157°C; **CHN** Found: C 47.5%, H 4.7%, Br 19.7%, S 15.9; $C_{16}H_{19}S_2O_3Br$ requires C 47.7%, H 4.8%, Br 19.8%, S 15.9; **FT-IR** ($CHCl_3$) υ_{max} 3415brm, 2990w, 2910m, 2850m, 2770m, 2070w, 1860w, 1625m, 1500m, 1485m, 1465m, 1375m, 1110s, 995s and 965s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 319 (420), 290inf (4500), 257inf (10400), 254 (10500) and 245 (9970) nm; **^1H NMR** (250MHz, $CDCl_3$) δ_H 7.09 (1H, s, Ar*H*), 6.95 (1H, s, Ar*H*), 5.97 (1H, d, *J* 1.4Hz, OC*H*HO), 5.95 (1H, d, *J* 1.4Hz, OCH*H*O), 4.95 (1H, d, *J* 8.7Hz, C*H*OH), 3.71 (1H, dq, *J* 8.7, 6.7Hz, C*H*CH_3), 2.90-2.63 (4H, m, 2xSCH_2), 2.12-1.85 (2H, m, SCH_2CH_2), 1.76 (3H, s, =CCH_2) and 1.20 (3H, d, *J* 6.7Hz, CHC*H*$_3$) ppm; **^{13}C NMR** (68MHz, $CDCl_3$) δ_c 147.6 (s, *C*(Ar)), 147.3 (s, *C*(Ar)), 140.5 (s, *C*(Ar)), 135.1 (*SCS*), 121.5 (s, *C*(Ar)), 113.8 (s, *C*(Ar)), 112.2 (d, *C*H(Ar)), 108.6 (d, *C*H(Ar)), 101.7 (t, OCH_2O), 75.5 (d, *C*HOH), 43.2 (d, *C*HCH_3), 30.3 (t, CH_2S), 29.9 (t, CH_2S), 24.9 (t, CH_2CH_2S), 16.2 (q, $CHCH_3$) and 15.1 (q, CCH_3) ppm; **$m/_z$** (EI) Found: 404.0004 (9%, [M(^{81}Br)]$^+$) and 401.9921 (8%, [M(^{79}Br)]$^+$); $C_{16}H_{19}BrO_3S_2$ requires 403.9939 (^{81}Br) and 401.9959 (^{79}Br); 386 (25, [M(^{81}Br)-H_2O]$^+$), 384 (23, [M(^{79}Br)-H_2O]$^+$), 339 (18), 337 (17), 305 (17, [M-Br-H_2O]$^+$), 242 (30), 240 (28), 230 (29), 228 (29), 173 (68), 125 (58), 106 (51) and 40 (100).

5-(2-(2-butyl-1,3-dithian-2-yl)-4*S**-hydroxy-3*S**-methylbut-1-en-4-yl)benzo[1,3]dioxole **27**

A hexane solution of *n*-butyllithium (1.6M, 3.4mL) was added over 2 min to a cooled (-78°C), THF solution (50mL) of **26** (1.00g, 2.48mmol). The resulting solution was warmed to 0°C over 30 min, stirred for a further 4h then partitioned between ether (200mL) and water (200mL). The organics were washed with brine (200mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (gradient elution, 10 to 25% ether in petrol) to yield the title compound (395mg, 1.04mmol, 42%) as a colourless oil; **FT-IR** (neat) υ_{max} 3445brm, 2965m, 2930m, 2900m, 2865m, 1500m, 1485m, 1440m, 1235m, 1040s and 930m cm^{-1}; **^1H NMR** (250MHz, $CDCl_3$) δ_H 6.98 (1H, d, *J* 1.5Hz, Ar*H*), 6.90 (1H, dd, *J* 8.0, 1.5Hz, Ar*H*), 6.81 (1H, d, *J* 8.0, Ar*H*), 5.98 (2H, s, OCH_2O), 5.85 (1H, brs, =C*H*H), 5.65 (1H, d, *J* 0.7Hz, =CH*H*), 4.84 (1H, brd, *J* 2.4Hz, C*H*OH), 2.97-2.65 (5H, m, 2xSCH_2 & C*H*CH_3), 2.25 (1H, s, O*H*), 2.13-1.82 (4H, m, SCH_2CH_2 & $CH_2CH_2CH_2CH_3$), 1.40-1.22 (4H,

m, $CH_2CH_2CH_3$), 0.98 (3H, d, *J* 6.7Hz, $CHCH_3$) and 0.89 (3H, t, *J* 7.1Hz, CH_2CH_3) ppm (these assignments were confirmed by a ^1H-^1H COSY experiment); **^{13}C NMR** (68MHz, $CDCl_3$) δ_C 149.8 (s, =CH), 147.4 (s, *C*(Ar)), 146.3 (s, *C*(Ar)), 137.6 (s, *C*(Ar)), 119.0 (d, *C*H(Ar)), 117.8 (t, $=CH_2$), 107.8 (d, *C*H(Ar)), 106.7 (d, *C*H(Ar)), 100.8 (t, OCH_2O), 75.1 (d, *C*HOH), 60.0 (s, S*C*S), 41.8 (d, $CHCH_3$), 39.5 ($CH_2CH_2CH_2CH_3$), 27.9 (t, CH_2S), 27.6 (t, CH_2S), 26.0 (t, $CH_2CH_2CH_3$), 25.4 (t, CH_2CH_2S), 22.8 (t, CH_2CH_3), 15.1 (q, $CHCH_3$) and 13.9 (q, CCH_3) ppm (these assignments were confirmed by a ^{13}C -^1H COSY experiment); **$m/_z$** (ES+) 363 (100%, $[MH\text{-}H_2O]^+$)

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