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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Studies on the Double Alkylation of 2,2-Disubstituted-1,3-Dithiacycloalkane-S-oxides: Synthesis of Tertiary Thiol Derivatives

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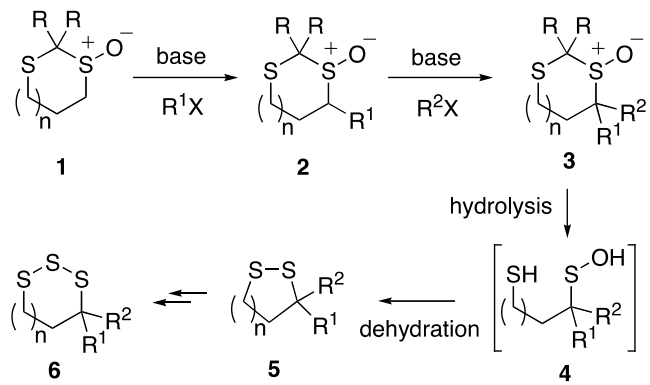
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Di-alkylation of 2,2-dimethyl-1,3-dithiacycloalkane-*S*-oxides has been achieved allowing the synthesis of two tertiary thiol centres. The diastereoisomers of the mono-alkylated products have been shown to react at different rates. The X-ray crystal structures of three substituted dithiane-*S*-oxides have been determined, and the conversion of the dialkylated products into cyclic disulfide derivatives of tertiary thiols (1,2-dithiolanes) has been achieved by treatment with acid.

Introduction

As part of an investigation into the synthesis of polysulfide natural products we required a method to generate a tertiary thiol group which would allow synthesis of tertiary di- and tri-sulfide derivatives. There are relatively few methods[1] for synthesising tertiary thiols, so we wished to study the sequential alkylation of cyclic dithioketal monosulfoxides **1** (Scheme 1) to allow controlled introduction of two substituents adjacent to a sulfur atom. Monoalkylation of a cyclic dithioketal monosulfoxide has been used in an elegant synthesis of lipoic acid,[2] and we wished to explore if further alkylation of this type of sulfoxide system could be employed to form a tertiary sulfoxide **3** which would generate the cyclic disulfide **5** on hydrolysis, and dehydration of the presumed mercaptosulfenic acid **4**. The disulfide would then have potential for ring expansion to a trisulfide **6** for example by mono-oxidation and treatment with *bis*-trimethylsilyl sulfide.[3] Use of a chiral auxiliary, and changing the sequence of introduction of substituents, should allow both enantiomers of the tertiary thiol to be produced. A series of experiments was therefore carried out to test if this was a viable approach to generate tertiary thiols protected as their cyclic disulfides.

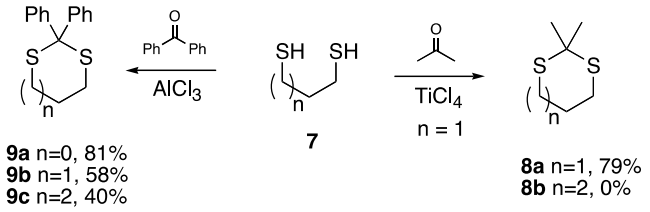


Scheme 1: proposed route to tertiary thiol based cyclic disulfides

Results and Discussion

Several cyclic dithioketals were prepared (Scheme 2) from either benzophenone or acetone as possible substrates for oxidation and alkylation. The 5-, 6- and 7-membered compounds derived from benzophenone **9a**,[4,5] **9b**,[6] **9c**,[7] were prepared in moderate to good yield by known methodology. The benzophenone derived 1,3-dithianes were chosen as they possess no aliphatic signals from the ketone moeity in the NMR spectra, and the derivatives were expected to be crystalline.

The dithiane **8a**[8] was prepared in good yield, but no pure product from the reaction of acetone and butane-1,4-dithiol in the presence of $TiCl_4$ could be obtained. Dithiepane **8b** could not be isolated, possibly due to slow closure of the seven-membered ring and formation of oligomers or polymers. The dithiepane **8b** may not crystallise as well as the corresponding diphenyl compound **9b** rendering separation from oligomeric or polymeric by-products difficult.



Scheme 2: Preparation of cyclic dithioketals employed.

The 14-membered dimer **10** (Figure 2) did however crystallise in low yield from the crude oily product after a prolonged period (16 months), and the structure was confirmed by X-ray crystallography (Figure 3). The dimer **10** was shown by ^{1}H NMR spectroscopy to convert in $CDCl_3$ to a similar compound (which could be either monomer **8b** or linear polymer) with a half-life time of about 1 day. The chemical shift of the methyl group changed from $\delta = 1.60$ in **10** to $\delta = 1.63$ in the new compound, but the structure could not be determined with certainty. The X-ray crystal structure was also obtained for the 1,3-dithiepane **9c** and is shown in Figure 4.

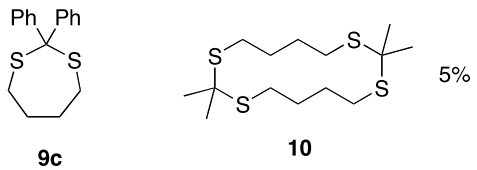


Figure 2: Structures of 1,3-dithiepane **9c** and 14-membered cyclic *bis*-dithioketal **10**.

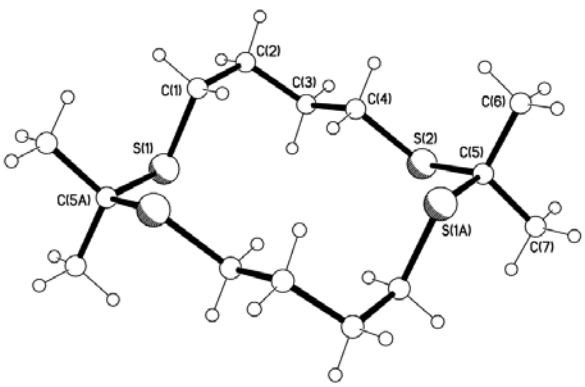


Figure 3. X-ray structure of **10**. The molecule lies on a centre of symmetry.

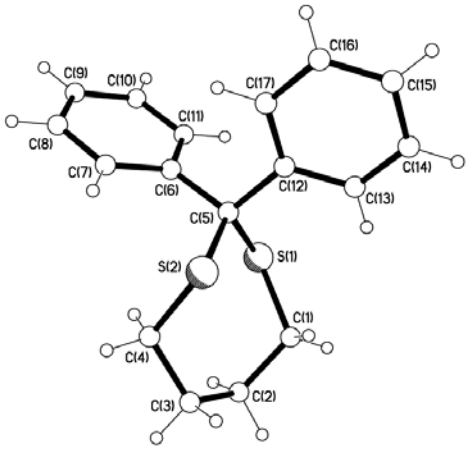
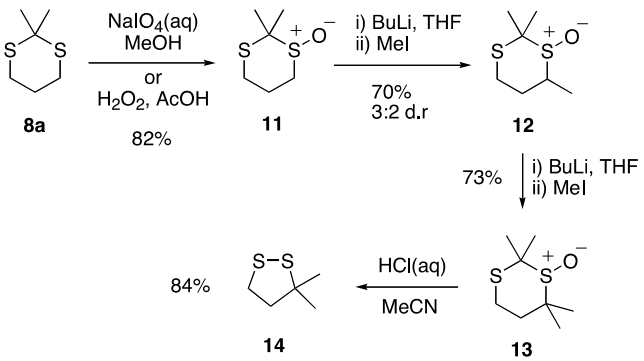


Figure 4. X-ray structure of dithiepane **9c**. One of two similar molecules in the asymmetric unit.

The 6-membered dithioketals **8a** and **9b** were easily oxidised to the mono-sulfoxide with methanolic sodium periodate, hydrogen peroxide in acetic acid[9] or best with hydrogen peroxide in methanol with a catalytic amount of HCl. Initial experiments with 2,2-dimethyl-1,3-dithiane-1-oxide **11** (Scheme 3) proved the viability of the double alkylation strategy and subsequent conversion to a cyclic disulfide.

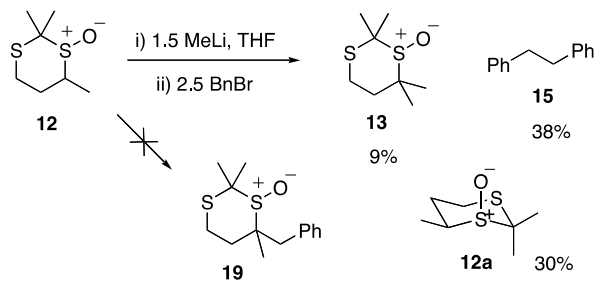


Scheme 3: Double alkylation of sulfoxide **11**

Thus treatment of **11** with n-butyllithium followed by addition of methyl iodide afforded monoalkylated sulfoxide **12** in 70% yield as a mixture of diastereoisomers (ratio ~ 3:2 by ^{1}H NMR spectroscopy). Further deprotonation and methylation then gave a 73% yield of the dimethylated sulfoxide **13** which, pleasingly, could be converted in high yield (84%), to the dimethyl 1,2-dithiolane **14** by treatment with acid. Reaction with hydrochloric acid in acetonitrile at room temperature[10] was found to give the best results; hydrochloric acid in methanol[13] gave lower yields,

while HCl in ether[14] or toluene returned only the starting sulfoxide.

When the deprotonation was carried out using n-BuLi, small amounts of impurities containing an n-butyl group were observed that were difficult to separate. This was witnessed by the presence of a triplet with $\delta = 0.97$ in the ^{1}H NMR spectrum, which did not disappear after purification by chromatography. In related reactions,[13,14] it was found that use of methyllithium instead of n-butyllithium as base gave higher yields and cleaner compounds. Thus methyllithium was investigated as a base to see if other substituents could be introduced by alkylation. This proved to be the case, and methyllithium as base gave similar yields of purer products. However, we were unable to isolate the benzyl adduct **19** (Scheme 4) on treatment of **12** (a mixture of diastereoisomers) with 1.5 equivalents of methyllithium, and subsequent addition of excess benzyl bromide. Surprisingly, a low yield (9%) of the dimethylated sulfoxide **13** was obtained, together with 1,2-diphenylethane (38%) and a 30% recovery of the starting sulfoxide isolated as a crystalline single diastereoisomer **12a**.



Scheme 4: Reaction of methylated sulfoxide **12** with methyllithium and benzyl bromide.

X-ray crystallography showed the oxygen atom, O(1), to be axial and the methyl group, C(5), equatorial (Figure 5).

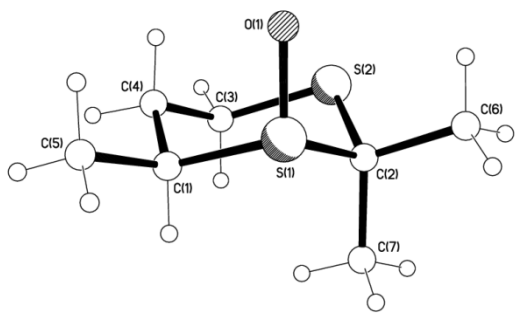
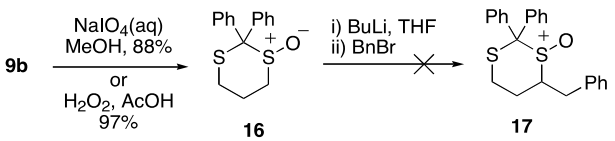


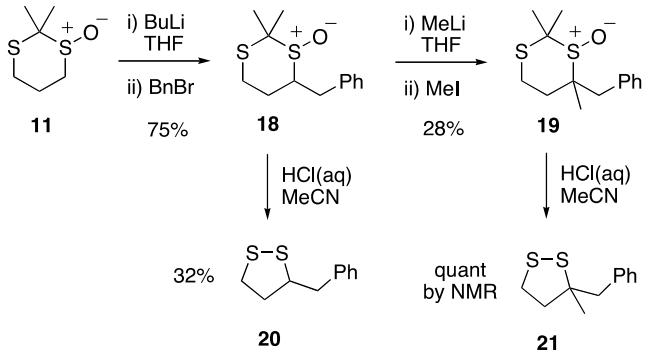
Figure 5: X-ray crystal structure of sulfoxide **12a**.

The formation of **13** can be explained by a metal-halogen exchange between the excess methyllithium and benzyl bromide with subsequent methylation of the anion of **12** by the resulting methyl bromide. Coupling between the benzyllithium formed and the benzyl bromide present would then form 1,2-diphenylethane **15**. The reaction between the anion of **12** and benzyl bromide must be slow as no evidence for the formation of any benzylated product **19** was obtained. Similarly the 2,2-diphenyl 1,3-dithiane-1-oxide **16**[10] (Scheme 5) could not be alkylated with benzyl bromide in an attempt to generate **17** (n-BuLi used as base); a complex mixture was obtained and no pure substance or starting material could be isolated. The presence of a bulky axial phenyl substituent may have blocked approach of the electrophile preventing alkylation, and the anion must have then degraded by other pathways leading to consumption of the starting material.



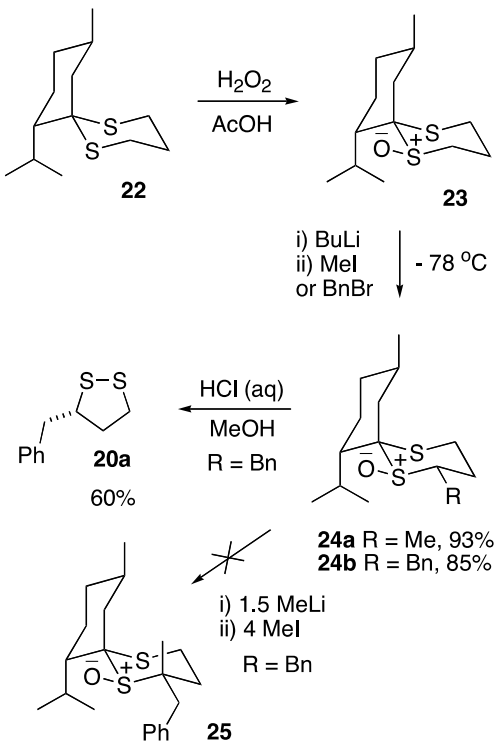
Scheme 5: Attempted benzylation of 2,2-diphenyldithiane-1-oxide **16**.

Introduction of benzyl as first substituent was successful with sulfoxide **11** (Scheme 6), after lithiation with n-butyllithium, forming **18** as a mixture of diastereoisomers. Subsequent deprotonation with methyllithium and treatment with methyl iodide revealed, however, that only one of the diastereoisomers of **18** was methylated with the other diastereoisomer being recovered in pure form. Neither **18** nor **19** are solid, so no assignment of stereochemistry by X-ray crystallography was possible. Both the mono- and di-alkylated dithiane oxides **18** and **19** were smoothly converted into the 1,2-dithiolanes **20** and **21** respectively by treatment with aqueous hydrochloric acid in acetonitrile, again illustrating the viability of the approach. It was observed that the diastereoisomers of **18** are cleaved at different rates, with the ratio changing from initially 43:57 to 93:7 when the reaction was followed by ^{1}H NMR spectroscopy. The diastereomer that is cleaved faster is the one that failed to alkylate, but we were unable to determine the relative stereochemistry of the compound.



Scheme 6: Double alkylation of sulfoxide **11** and 1,2-dithiolane formation.

We then investigated alkylation of the dithiane derived from menthone as a chiral auxiliary (Scheme 7). The dithioacetal **22** formed[2] from menthone and 1,3-propanedithiol on oxidation with $NaIO_4$ in methanol gave only the sulfoxide **23** as a single diastereoisomer, the structure being confirmed by X-ray crystallography (Figure 6).



Scheme 7: Alkylation of menthone derived sulfoxide **23**.

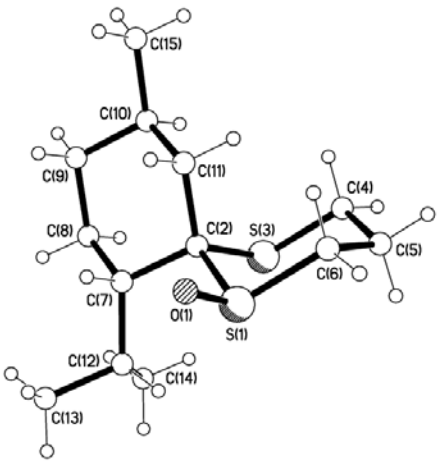


Figure 6: X-ray crystal structure of sulfoxide **23**.

Alkylation was found to be completely diastereoselective for both methyl iodide and benzyl bromide, yielding only **24a** or **24b** respectively when methyllithium was employed as base. The structures of the two alkylation products **24a** and **24b** were established by single crystal X-ray diffraction and are shown in Figures 7 and 8.

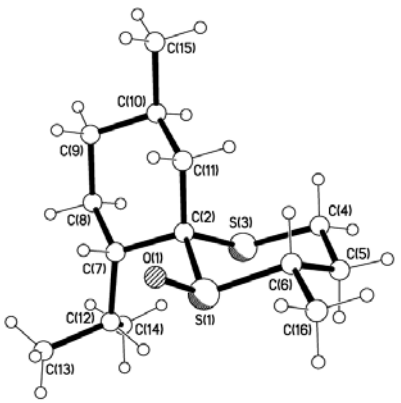


Figure 7: X-ray crystal structure of methylated sulfoxide **24a**.

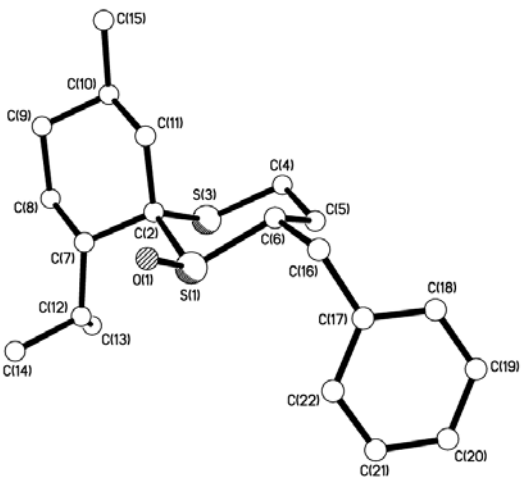


Figure 8: X-ray crystal structure of benzylated sulfoxide **24b**. Hydrogen atoms omitted for clarity. One of two similar molecules in the asymmetric unit.

The benzylated product **24b** could be cleanly converted to the dithiolane **20a**, which was shown to be the pure *S*-enantiomer by chiral HPLC, conditions having been established to separate the racemic product **20** generated from **18** (Scheme 6).

It was not possible to effect a second alkylation with methyllithium as base and methyl iodide as alkylating agent, **24b** being recovered unchanged in 69% yield, and no evidence for the formation of **25** was obtained. This may have been due to the axial methylene group of the menthyl auxillary group blocking approach of the electrophile.

Conclusions

In conclusion, we have shown that it is possible in two cases so far, to effect di-alkylation of dithioketal-*S*-oxides, and that the diastereoisomers of the mono-alkylated products react at different rates. We have determined the X-ray crystal structures of a cyclic dithiane and three substituted dithiane-*S*-oxides, and shown that the dialkylated products can be converted into cyclic disulfide derivatives of tertiary thiols on treatment with aqueous hydrochloric acid in acetonitrile. Further studies on increasing the range of alkylating agents, and applying the method to natural product synthesis are in progress.

Acknowledgements

We thank Mr J.A Daley for performing CHN analyses, and Mr E. Simpson for help with electronic plots of NMR spectra. We thank Loughborough University for financial support, and the EPSRC National Mass Spectrometry Service at Swansea for mass spectra.

Experimental Section

Reactions involving sodium hydride, n-butyl- or methyllithium were performed in oven-dried glassware (150 °C overnight) under an atmosphere of nitrogen. Tetrahydrofuran and diethyl ether were distilled from Na/Ph_2CO immediately before use. Petrol, methanol, and dichloromethane were distilled, while all other solvents were used as received unless otherwise stated. Column chromatography was performed on silica-gel 60 with gradient elution using petrol:ethyl acetate mixtures. Thin layer chromatography was performed on silica-gel 60, and the visualizing method is quoted. Chiral HPLC was performed using a Eurocel 01 5µm column, 250 x 4.6 mm with pre-column, and UV detection.

^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker DPX 400MHz or Bruker Advance 400MHz instruments using $CDCl_3$ as solvent and TMS as standard unless otherwise stated. Chemical shifts are reported as δ_H or δ_C in ppm relative to TMS. Assignments were assisted by COSY, DEPT, HMBC and HMQC analysis. For ^1H spectra coupling patterns are reported as s, d, t, q or m with coupling constants, *J*, in hertz. For ^{13}C spectra the term in brackets indicates the proton attachment based on the DEPT-135 experiment.

IR-spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer or on a PerkinElmer Spectrum 65 FT-IR spectrometer, for neat liquids, and as Nujol-mulls, or KBr discs for solids, with wavenumbers reported in cm^{-1}.

HRMS was carried out using a Thermo Scientific Orbitrap Exactive with Advion Triversa Nanomate, or by the EPSRC National Mass Spectrometry Service Centre in Swansea.

Melting points were measured on a Stuart Scientific Melting Point apparatus SMP3 and are uncorrected.

Elemental Analyses were determined on a Perkin-Elmer 2400 analyser.

2,2-Diphenyl-1,3-dithiolane 9a

Benzophenone (1.88 g, 10.3 mmol) and 1,2-ethanedithiol (1.30 g, 13.8 mmol) were dissolved in CH_2Cl_2 (12 ml). The solution was stirred at room temperature and aluminium trichloride (0.51 g, 3.7 mmol) was added. The mixture turned yellow and boiled. After 30 min aq. HCl (5 ml, 2 M) was added. The organic layer was separated, washed with water, dried and rotary evaporated to give a white solid (2.58 g, 100%), m.p. 102-103 ºC (lit.[6]: 104-105 ºC). Recrystallisation from CH_2Cl_2/petrol gave pure crystalline product (2.07 g, 8.0 mmol, 78%, m.p. 104-105 ºC) in two crops.

^1H NMR (400 MHz, $CDCl_3$) δ_H = 3.40 (4H, s), 7.15-7.35 (m, 6H), 7.55-7.65 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 40.1 (CH_2), 76.8 (Cq), 127.2 (CH), 127.9 (CH), 128.2 (CH), 144.6 (Cq).

2,2-Diphenyl-1,3-dithiane 9b

2,2-Diphenyl-1,3-dithiane was prepared as above from benzophenone (1.91g, 10.5 mmol) and 1,3-propanedithiol (1.31 g, 12 mmol). Crude product was obtained as a white solid (2.84 g, 99%). Recrystallisation from CH_2Cl_2/petrol gave pure crystalline product (1.66 g, 6 mmol, 58%, m.p. 109-110 ºC).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.95-2.05 (m, 2H, $SCH_2C\underline{H}_2$), 2.74-2.83 (m, 4H, SCH_2), 7.20-7.30 (m, 2H), 7.30-7.40 (m, 4H), 7.65-7.75 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 24.5 (CH_2), 29.4 (CH_2), 62.8 (Cq), 127.6 (CH), 128.4 (CH), 129.3 (CH), 142.5 (Cq).

2,2-Diphenyl-1,3-dithiepane 9c

2,2-Diphenyl-1,3-dithiepane was prepared as above from benzophenone (1.87 g, 10.3 mmol) and 1,4-butanedithiol (1.54 g, 12.6 mmol). The crude product (3.03 g) was an oil that showed no signals for thiol or carbonyl in the IR spectrum, but was impure by NMR spectroscopy. The oil solidified on standing and crystallisation from CH_2Cl_2 at -20 ºC yielded product (472 mg, 1.7 mmol, 16%) with minor impurities. The substance recovered from the mother liquor was subjected to chromatography (40 g silica, 97:3 petrol:EtOAc, 40 ml fore-run, fractions 15 ml). Fractions 6 and 7 deposited crystals. Fractions 5-9 afforded pure compound (469 mg, 1.6 mmol, 16%) and material with minor impurities (228 mg, 0.83 mmol, 8%). Combined yield 40%.

R_f (97:3 petrol:EtOAc) 0.53 [UV_{254} quenched].

m.p. 106-108 ºC (from petrol/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.95-2.10 (m, 4H, $SCH_2C\underline{H}_2$), 2.90-3.05 (m, 4H, SCH_2), 7.18-7.26 (m, 2H), 7.26-7.35 (m, 4H), 7.50-7.60 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 31.2 (CH_2), 31.4 (CH_2), 70.2 (Cq), 127.2 (CH), 128.1 (CH), 128.2 (CH), 145.1 (Cq).

HRMS (ESI): Calcd. for $C_{17}H_{18}S_2$ $[MNa]^+$ 309.0738 ; found 309.0742.

2,2,9,9-Tetramethyl-1,3,8,10-tetrathiacyclotetradecane 10

Acetone (0.76 g, 13 mmol) and 1,4-butanedithiol (1.32 g, 11 mmol) were dissolved in CH_2Cl_2 (5 ml) and stirred at 0 ºC. $TiCl_4$ (1.0 ml, 1.0 M solution in CH_2Cl_2) was added. The mixture turned white and turbid. After stirring overnight the mixture was washed with NaOH (aq) (2 M, 1 ml) and brine (1 ml). The dichloromethane layer was dried over $MgSO_4$. Evaporation yielded a clear colourless oil (1.57 g), which turned into a white jelly. Attempted kugelrohr distillation yielded no identifiable products. After 16 months crystals were deposited (86 mg, 0.53 mmol, 4.9%). Single crystal X-ray analysis showed these to be the dimer. ^{1}H NMR spectroscopy in $CDCl_3$ showed the dimer to rapidly convert into another compound of similar structure (δ = 1.60 to 1.63 for the methyl signal).

m.p. 144-147 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.60 (s, 12H), 1.75-1.85 (m, 8H, $SCH_2C\underline{H}_2$), 2.65-2.72 (m, 8H, SCH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 25.5 ($SCH_2\underline{C}H_2$), 28.2 (SCH_2), 31.0 (CH_3), 55.3 (Cq).

Converts into another compound (50% conversion at room temperature overnight):

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.63 (s, 6H), 1.90-2.00 (m, 4H), 2.75-2.85 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 29.0 (CH_2), 32.0 (CH_2), 33.4 (CH_3), 54.4 (Cq).

2,2,6-Trimethyl-1,3-dithiane-1-oxides 12/12a

2,2-Dimethyldithiane-1-oxide (0.51 g, 3.1 mmol) was dissolved in THF (6 ml) and the solution stirred at -78 ºC. n-Butyllithium solution (2.0 ml, 2.0 M in hexanes, 4.0 mmol) was added dropwise. After 15 min methyl iodide (0.25 ml, 4.0 mmol) was added. After a further 45 min, the reaction mixture was quenched by addition of ammonium chloride (0.5 ml sat. aq. solution) and warmed to room temperature. Water (15 ml) was added and the mixture extracted with dichloromethane (3 x 15 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Chromatography, eluting with $CHCl_3$:MeOH (24:1), gave a 3:2 mixture of diastereoisomers as a clear yellow liquid (0.39 mg, 70%), which partially crystallised.

Mixture of diastereomers:

m.p. slightly above room temperature.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.33 (d, J = 7 Hz, 3H, CH_3-6, major isomer) + 1.41 (d, J = 7 Hz, 3H, CH_3-6, minor isomer), 1.47 + 1.59 (2 × s, 2 × 3H, CH_3-2, major isomer), 1.53 + 1.65 (2 × s, 2 ×3H, CH_3-2, minor isomer), 1.58-1.67 (m, 1H, H-5, both isomers), 1.95-2.12 (m, 1H, H-5, both isomers), 2.30-2.40 (m, 1H, H-4, minor isomer), 2.51 (app dt, J = 14, 3 Hz, 1H, H-4, major isomer), 2.60-2.76 (m, 1H, H-6, both isomers), 2.82-2.98 (m, 1H, H-4, both isomers).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 16.0 (CH_3), 16.6 (CH_3), 17.9 (CH_3), 21.7 (CH_2), 22.5 (CH_3), 25.3 (CH_2), 25.4 (CH_2), 25.7

(CH_3), 25.9 (CH_3), 37.6 (CH_2), 46.1 (CH), 52.6 (CH), 57.6 (C_q), 58.5 (C_q).

Z-2,2-Dimethyl-6-methyl-1,3-dithiane-1-oxide 12a (the diastereoisomer that failed to alkylate; oxygen axial, methyl equatorial):

m.p. 102-103 ºC (from Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.34 (d, *J* = 7 Hz, 3H, CH_3-6), 1.50 (s, 3H, CH_3-2), 1.57 (s, 3H, CH_3-2), 1.52-1.68 (m, 1H, H-5), 2.02-2.15 (m, 1H, H-5), 2.52 (app dt, *J* = 14, 3 Hz, 1H, H-4), 2.53-2.65 (m, 1H, H-6), 2.89 (ddd, *J* = 15, 13, 2 Hz, 1H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 18.1 (CH_3), 22.0 (CH_2), 22.7 (CH_3), 25.6 (CH_2), 26.1 (CH_3), 46.5 (CH), 58.7 (Cq).

HRMS: calcd. for $C_7H_{14}NaOS_2$ $[MNa]^+$ 201.0378; found 201.0377.

2,2,6,6-Tetramethyl-1,3-dithiane-1-oxide 13

A solution of sulfoxide **12** (3:2 mixture of diastereoisomers) (0.37 g, 2.1 mmol) in THF (7 ml) was stirred at -78 ºC and treated with n-butyllithium solution (1.0 ml, 2.0 M in hexanes, 2.5 mmol). After 15 min methyl iodide (0.20 ml, 3.2 mmol) was added and the mixture allowed to warm to room temperature. Saturated ammonium chloride solution (0.5 ml) and then water (10 ml) were added. The mixture was extracted with dichloromethane (2 x 10 ml) and the organic extracts dried and evaporated to give a pale yellow oil (0.4 g). Chromatography over silica afforded the product as a clear colourless oil (0.29 g, 73%).

R_f (1:1 Petrol:EtOAc) = 0.33 [stains with cold $KMnO_4$ (aq)].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.28 (s, 3H), 1.38 (s, 3H), 1.53 (s, 3H), 1.60 (s, 3H), 2.09-2.25 (m, 2H), 2.35 (ddd, 1H, *J* = 15, 5, 3 Hz,), 2.80 (ddd, 1H, *J* = 15, 11, 3 Hz,).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 18.0 (CH_3), 20.0 (CH_3), 22.2 (CH_2), 27.6 (CH_3), 28.8 (CH_3), 40.8 (CH_2), 55.9 (Cq), 58.3 (Cq).

ν_{max}/cm^{-1} 2962, 2927, 1719, 1448, 1376, 1362, 1236, 1164, 1110, 1041, 1005.

6-Benzyl-2,2-dimethyl-1,3-dithiane-1-oxide 18

Sulfoxide **13** (0.51 g, 3.1 mmol) was dissolved in THF (12 ml) and the solution stirred at -75 °C. Methyllithium (3.0 ml, 1.5 M in Et_2O, 4.5 mmol) was added and the mixture stirred for 1 h. Benzyl chloride (0.59 g, 4.7 mmol) was added and the pale yellow green solution was left to warm to room temperature. Aqueous work-up and chromatography (1:1 petrol:EtOAc + 0.2% MeOH) yielded product (0.59 g, 2.3 mmol, 75%) as a sticky oil consisting of two diastereoisomers (43:57) which did not separate.

R_f (1:1 petrol:EtOAc + 0.2% MeOH) = 0.38 (stains with hot phosphomolybdic acid).

HRMS: Calcd. for $C_{13}H_{18}OS_2$ $[MNa]^+$ 277.0691; found 277.0686 .

The diastereoisomer that could not be alkylated:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H =1.49 (s, 3H), 1.53 (s, 3H), 1.60-1.70 (m, 1H, one of C$\underline{H_2}$CH$_2$S), 2.05-2.20 (m, 1H, one of C$\underline{H_2}$CH$_2$S), 2.45-2.55 (m, 1H, one of SC$\underline{H_2}$), 2.65-2.75 (m, 1H, PhCH$_2$C$\underline{H}$), 2.75-2.85 (m, 2H, one of SC$\underline{H_2}$ and one of PhC$\underline{H_2}$), 3.11 (dd, 1H, *J* = 14, 7 Hz, one of PhC$\underline{H_2}$), 7.15-7.35 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 20.1 (CH_2), 22.6 (CH_3), 25.5 (CH_2), 26.1 (CH_3), 38.3 (PhCH$_2$), 53.8 (CH), 58.9 (Cq), 126.9 (CH), 128.7 (CH), 129.4 (CH), 137.0 (Cq).

The diastereoisomer that was cleaved more slowly by acid: (some integrals could not be determined accurately as the compound could not be obtained pure)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.60 (s, 3H), 1.69 (s, 3H), 1.85-1.95 (m, 1H), 2.15-2.35 (m), 2.55-2.80 (m), 2.80-2.90 (m), 3.10-3.20 (m, 1H), 3.50-3.60 (m, 1H), 7.10-7.40 (m, 5H).

6-Benzyl-2,2,4-trimethyl-1,3-dithiane-1-oxide 19

6-Benzyl-2,2-dimethyl-1,3-dithiane-1-oxide (256 mg, 1.0 mmol, mixture of diastereomers) was dissolved in THF (5 ml) and stirred at -78 °C. Methyllithium (1.0 ml, 1.5 M in Et_2O, 1.5 mmol) was added and the solution stirred for 1 h. Methyl iodide (0.25 ml, 4.0 mmol) was added and the mixture left to warm to room temperature over 3 h. Aqueous workup and chromatography (1:1 petrol:EtOAc + 0.2% MeOH) yielded product (75 mg, 0.28 mmol, 28%, one diastereomer) and starting material (91 mg, 0.36 mmol, 35%, one diastereomer).

R_f (1:1 petrol:EtOAc + 0.2% MeOH) = 0.47 (stains with hot phosphomolybdic acid).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H =1.25 (s, 3H), 1.53 (s, 3H), 1.64 (s, 3H), 2.01-2.13 (m, 1H, one of SCH$_2$), 2.17-2.34 (m, 2H, one of SCH$_2$ and one of CqCH$_2$), 2.72-2.85 (m, 1H, one of CqCH$_2$), 3.00 (d, *J* = 13 Hz, 1H, one of PhCH$_2$), 3.06 (d, *J* = 13 Hz, 1H, one of PhCH$_2$), 7.10-7.40 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C =14.2 (CH_3), 19.7 (CH_3), 21.9 ($SCH_2\underline{C}H_2$), 28.3 (CH_3), 38.8 (SCH_2), 46.1 ($PhCH_2$), 58.4 (Cq), 60.0 (Cq), 127.0 (CH), 128.1 (CH), 131.2 (CH), 134.7 (Cq).

HRMS: Calcd. for $C_{14}H_{20}OS_2$ $[MNa]^+$ 291.0848; found 291.0843.

(1*R*,6*R*,7*S*,10*R*)-7-Isopropyl-10-methyl-1,5-dithia-spiro[5.5]undecane 1-oxide 23

(1*R*,6*R*,7*S*,10*R*)-7-Isopropyl-10-methyl-1,5-dithia-spiro[5.5]undecane 1-oxide **23** was prepared from menthone and 1,3-propanedithol followed by treatment with $NaIO_4$ following a literature procedure.[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 0.88 (d, *J* = 6.8 Hz, 3H), 0.90-1.10 (m, 7H), 1.45-1.65 (m, 2H), 1.65-1.85 (m, 2H), 1.95-2.50 (m, 7H), 2.60-2.75 (m, 1H), 2.80-2.90 (m, 1H), 3.00-3.10 (m, 1H).

(1*R*,2*S*,6*R*,7*S*,10*R*)-2-Benzyl-7-isopropyl-10-methyl-1,5-dithia-spiro[5.5]undecane-1-oxide 24b

Sulfoxide **23** (653 mg, 2.5 mmol) was dissolved in 15 ml THF (15 ml) and the mixture stirred under nitrogen at -78 ºC. Methyllithium (2.0 ml, 1.5 M in Et_2O, 3.0 mmol) was added, and after 15 min, benzyl bromide (0.85 g, 5.0 mmol) was added. Aqueous workup after 2 h and chromatography (CH_2Cl_2 + 1%MeOH) yielded a yellow oil (751 mg, 85%) that solidified. Purification by crystallisation was achieved by dissolution in CH_2Cl_2 (1 ml), addition of petrol (3 ml) and cooling to -20 ºC.

m.p. 161-168 ºC (from CH_2Cl_2/petrol).

R_f (CH_2Cl_2 + 1% MeOH) = 0.11 (stains with hot phosphomolybdic acid).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 0.88 (d, *J* = 6.8 Hz, 3H), 0.95-1.10 (m, 7H), 1.45-1.65 (m, 2H), 1.70-1.90 (m, 3H), 2.00-2.25 (m, 5H), 2.35-2.50 (m, 1H, $C\underline{H}(CH_3)_2$), 2.50-2.60 (m, 1H), 2.60-2.70 (m, 1H, one of $PhCH_2$), 2.85-3.00 (m, 1H, SCH), 3.50-3.60 (m, 1H, one of $PhCH_2$), 7.15-7.25 (m, 3H), 7.25-7.35 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 19.3 (CH_3), 21.4 (CH_2), 22.2 (CH_3), 23.5 (CH_2), 24.4 (CH_3), 25.5 (CH), 27.2 (CH), 30.9 (CH_2), 33.7 (CH_2), 34.3 (CH_2), 36.5 ($PhCH_2$), 44.7 (CH), 57.1 (SCH), 70.1 (Cq), 126.7 (CH), 128.5 (CH), 129.6 (CH), 137.3 (Cq).

Calcd. for $C_{20}H_{30}OS_2$ 68.5 %C, 8.63 %H; found 68.1, 8.59.

HRMS: Calcd. for $C_{20}H_{30}OS_2$ $[MNa]^+$ 373.1622 ; found 373.1630.

(1*R*,2*S*,6*R*,7*S*,10*R*) 7-Isopropyl-2,10-dimethyl-1,5-dithia-spiro[5.5]undecane-1-oxide 24a

Compound **24a** was prepared as above in 93% yield using methyl iodide instead of benzyl bromide.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 0.88 (d, *J* = 6.8 Hz, 3H), 0.92-1.05 (m, 7H), 1.44 (d, *J* = 6.8 Hz, 3H, $C\underline{H}_3CHS$), 1.48-1.65 (m, 2H), 1.70-1.85 (m, 2H), 1.90-2.15 (m, 4H, one of $SCHC\underline{H}_2$), 2.25-2.35 (m, 2H, one of $SCHC\underline{H}_2$), 2.35-2.45 (m, 1H), 2.70-2.85 (m, 1H), 2.90-3.00 (m, 1H, SCH).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 17.4 (CH_3), 19.3 (CH_3), 21.5 (CH_2), 22.2 (CH_3), 23.7 (CH_2), 24.4 (CH_3), 25.6 (CH), 27.3 (CH), 31.0 (CH_2), 34.4 (CH_2), 37.3 (CH_2), 44.6 (CH), 50.7 (CH), 69.9 (Cq).

Calcd. for $C_{14}H_{26}OS_2$ 61.26 %C, 9.55 %H; found 60.97, 9.51.

HRMS: Calcd. for $C_{14}H_{26}OS_2$ $[MNa]^+$ 297.1312; found 297.1317.

m.p. 121-122 ºC (from petrol).

3,3-Dimethyl-1,2-dithiolane 14

Sulfoxide **13** (190 mg, 0.99 mmol) was dissolved in CH_3CN (5 ml) and HCl (aq) (0.25 ml, 2 M) was added. The mixture was maintained at 0 ºC for 18 h and then at room temperature for 72 h. ^{1}H NMR spectroscopy showed the product:starting material ratio to change as follows: 18 h at 0 ºC, trace product formed; 6 h at room temperature ~ 1:3; 23 h ~ 7:3; 72 h ~ 100:0. After 72 h the mixture was evaporated, and the residue taken up in dichloromethane. After washing with water, the organic layer was dried, filtered and evaporated to give a clear yellow liquid (111 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.55 (s, 6H), 2.11 (t, *J* = 6.6 Hz, 2H, $SCH_2C\underline{H}_2$), 3.24 (t, *J* = 6.6 Hz, 2H, SCH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 28.2 (CH_3), 37.9 (SCH_2), 48.6 (CH_2), 60.5 (Cq).

ν_{max} /cm^{-1} 2965, 2919, 2859, 1452, 1363, 1261, 1115.

3-Benzyl-1,2-dithiolane 20

3-Benzyl-1,2-dithiolane was prepared using the method above in 60% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.95-2.05 (m, 1H, one of $SCH_2C\underline{H}_2$), 2.30-2.40 (m, 1H, one of $SCH_2C\underline{H}_2$), 2.96 (d, *J* = 7.6 Hz, 2H, $PhCH_2$), 3.05-3.15 (m, 1H, one of SCH_2), 3.15-3.25 (m, 1H, one of SCH_2), 3.82 (quint, *J* = 6.8 Hz, 1H, SCH), 7.15-7.35 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 38.4 (SCH_2), 39.6 (CH_2), 40.9 ($PhCH_2$), 57.5 (CH), 126.7 (CH), 128.5 (CH), 128.8 (CH), 139.5 (Cq).

Chiral HPLC: 5.38 min + 5.87 min (chiralcel OD ; 9:1 hexanes:isopropanol ; 1.0ml/min ; detection at 254 nm). The optical rotation could not be determined due to the instability of the product.

3-Methyl-3-benzyl-1,2-dithiolane 21

3-Methyl-3-benzyl-1,2-dithiolane was prepared as above. The reaction was shown to be quantitative by NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.43 (s, 3H), 2.00-2.12 (m, 1H, SCH_2CH_2), 2.15-2.30 (m, 1H, SCH_2CH_2), 3.00 (d, J = 13.6 Hz, 1H, one of $PhCH_2$), 3.14 (d, J = 13.6 Hz, 1H, one of $PhCH_2$), 3.26 (td, J = 7.6, 0.6 Hz, 2H), 7.20-7.35 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 25.2 (CH_3), 37.4 (SCH_2), 45.8 ($PhCH_2$), 46.6 (SCH_2CH_2), 65.1 (Cq), 126.7, 128.0, 130.4, 137.9 (Cq).

Crystallography.

For each sample, a crystal was mounted in oil on a glass fibre and fixed in the cold nitrogen stream (150 K) on a Bruker APEX 2 CCD diffractometer equipped with MoKα radiation (λ = 0.71073 Å) and a graphite monochromator. Intensity data were measured by thin-slice *ω*–scans and corrected for Lp and absorption effects. Data were reduced using the SAINT program[15]. The structures were determined by the direct methods routine in the SHELXS-97 program and refined by full-matrix least-squares methods, on F^2, in SHELXL-97[16,17]. The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were constrained.

*******Table 1 near here*******

Crystals of **9c** were merohedrally twinned into two domains related by twin law [-1 0 0, 0 -1 0, 1 0 1] with major component occupancy of 80.57(8)%. In **9c** there are two similar molecules in the asymmetric unit. In **10** the molecule lies on a centre of symmetry. The absolute structures of **23** and **24a** were reliably determined with Flack parameters x = –0.04(5) and 0.04(4)% respectively. Crystals of **24b** were merohedrally twinned into two domains via twin law [–1 0 0, 0 –1 0, 0 0 1] with major component = 52.9(2)% and had two similar molecules in the asymmetric units. The absolute structure was not very reliably determined in this case with x = –0.30(14). Crystal data and refinement results are collated in Table 1. CCDC 896890–896895 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Notes and references

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† Electronic Supplementary Information (ESI) available: NMR spectra for compounds **9a**-**9c**, **10**, **12**, **12a**, **13**, **14**, **18**, **19**, **20**, **21**, **23**, **24a**, **24b**. Crystallographic data for compounds **9c**, **10**, **12a**, **23**, **24a**, and **24b**. See DOI: 10.1039/b000000x/

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