Synthesis and Lithiation of γ,γ-Difunctionalised Ketene Dithioacetals. Access to a New Synthetic Equivalent of a β-Hydroxy-β-lithioacrylate. *X*-Ray Molecular Structure of 2-(1,3-Dithian-2-ylidenemethyl)-1,3-dithiane

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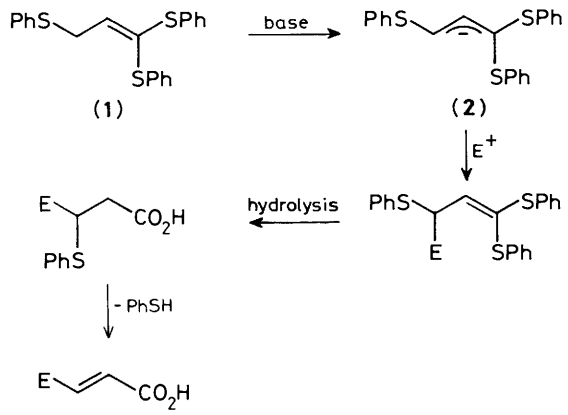
A series of γ,γ-dithioalkyl or dithioaryl ketene dithioacetals (**3a**), (**3b**), and (**3c**) has been prepared. Attempts to generate allylic anions under a variety of conditions from 1,1,3,3-tetrakis(phenylthio)-propene (**3a**) and 1,1,3,3-tetrakis(methylthio)propene (**3b**) failed but 2-(1,3-dithian-2-ylidene-methyl)-1,3-dithiane (**3c**) is readily deprotonated with lithium di-isopropylamide to give anion (**4c**). This species can function as an equivalent of β-hydroxy-β-lithioacrylate and this equivalence has been illustrated by a synthesis of (±)-dihydrokawain (**14**). The use of compound (**3c**) as a reagent in synthesis is, however, limited in some cases by the nature of the conditions required for dithioacetal–ketone conversion. The *X*-ray crystal structure of compound (**3c**) has been determined.

Allylic anions derived from ketene dithioacetals provide a range of reactivity that offers considerable potential in synthesis.[1] We have recently described how anion (**2**), derived from the now commercially available γ-functionalised ketene dithioacetal (**1**), behaves as a β-lithioacrylate equivalent.[2] This synthetic equivalence, which is outlined briefly in Scheme 1, is based on (i)

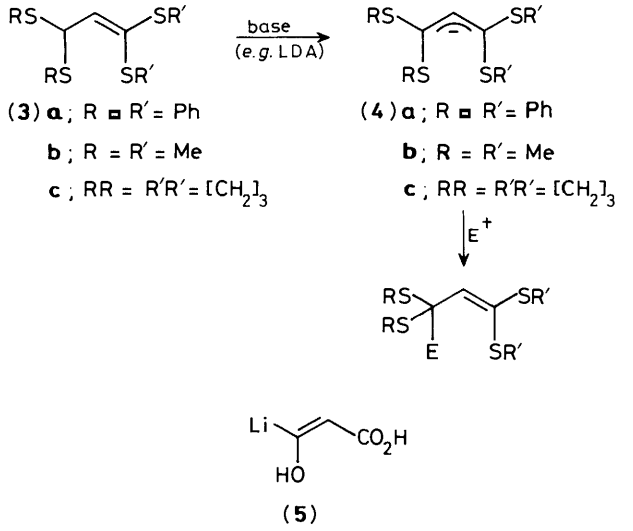


Scheme 1.

the high γ-regioselectivity exhibited by (**2**) towards a wide range of electrophiles and (ii) the relationship between the ketene dithioacetal, as a masked carboxylic acid, and the γ-SPh residue; upon hydrolysis of the ketene dithioacetal, this group becomes labile towards β-elimination.

In principle this methodology can be extended to provide access to a higher level of functionality (Scheme 2). Specifically, anions (**4**) derived from the γ,γ-bis(thioalkyl or thioaryl)ketene dithioacetals (**3**) should provide a reactivity equivalent to that of a β-hydroxy-β-lithioacrylate (**5**). This entity offers direct access to a structural subunit that occurs in a wide range of potential targets, with tetronic acids and related systems being obvious examples.[3] In addition, the symmetry of anions (**4**) dispenses with the need to control the α/γ-regioselectivity on which the success of the simpler anion (**2**) relies.

In this paper we describe the preparation of a series of ketene

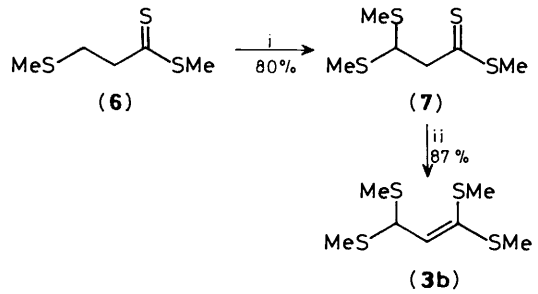


Scheme 2.

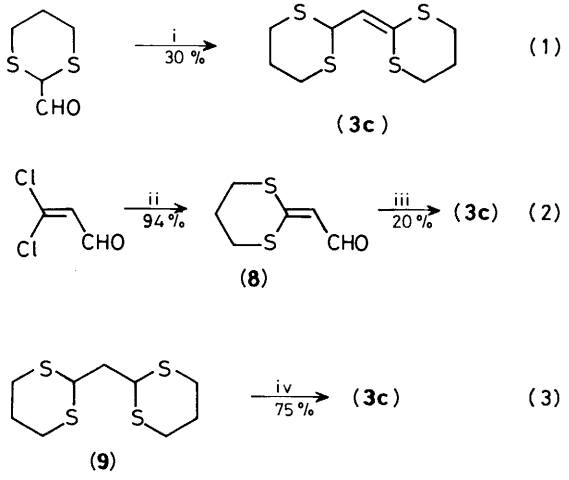
dithioacetals related to compounds (**3**) and we have evaluated the scope and limitations of these reagents, in terms of their equivalence to (**5**).

Results and Discussion

Our initial target was the tetrakis(phenylthio) derivative (**3a**). Following on from our earlier work,[2] reaction of anion (**2**) with diphenyl disulphide gave (**3a**) in 76% yield. The high steric demands imposed by the bulky SPh residues were expected to limit the variety of electrophiles that would trap the allylic anion (**4a**) but we did not anticipate that the initial deprotonation of (**3a**) would present an obstacle. However, using a wide range of amide bases and varying reaction conditions it was apparent, based on both D_2O and ICH_3 quenches, that this anion was not being formed in significant amounts. With the more strongly basic and more nucleophilic alkyl-lithiums (BuLi and MeLi) cleavage of an SPh residue from (**3a**), to give the trisubstituted anion (**2**), was observed.[4]



Scheme 3. *Reagents:* i, BuLi, then Bu^{s}Li, then MeSSMe; ii, LDA, MeI



Scheme 4. *Reagents and conditions:* i, 2-lithio-2-trimethylsilyl-1,3-dithiane, THF, −78 °C; ii, propane-1,3-dithiol, 1M-NaOH, Et_2O; iii, propane-1,3-dithiol, BF_3·Et_2O, CH_2Cl_2; iv, BuLi, then 2,2′-dipyridyl disulphide, −78 °C to room temperature

In an attempt to circumvent these problems, two other reagents, the tetrakis(methylthio)[5] and bis-(1,3-dithianyl) derivatives (**3b**) and (**3c**) were examined. Both of these ketene dithioacetals offer access to highly stabilised allylic anions, with a minimum of steric encumbrance for either the approach of a base or, once deprotonation has been achieved, to an incoming electrophile. The synthesis of compound (**3b**) (Scheme 3) was based on a method developed by Beslin.[6] Double deprotonation of methyl 3-(methylthio)dithiopropionate (**6**) followed by addition of dimethyl disulphide gave intermediate (**7**) in 80% yield. Reaction of this intermediate with lithium di-isopropylamide (LDA) and alkylation of the resulting anion on sulphur with iodomethane gave the desired ketene dithioacetal (**3b**) in 87% yield.* This procedure can also be carried out in one pot by treating the dianion of (**6**) with dimethyl disulphide followed by iodomethane without isolating the intermediate (**7**), but we have found that the stepwise procedure gave better yields.

Although some evidence (^{1}H n.m.r. spectroscopy) was obtained for the deprotonation of dithioacetal (**3b**) using LDA and subsequent methylation of anion (**4b**) with iodomethane, these results were not pursued. The reactions did not take place very cleanly and the relative instability of compound (**3b**) was an added complication to the use of this reagent in a general synthetic sense.

By contrast, the bis(1,3-dithianyl) derivative (**3c**) was obtained as a colourless, crystalline solid that had a good shelf life under normal laboratory conditions. Several routes for the synthesis of (**3c**) were evaluated and these are shown in Scheme 4. The Peterson reaction[7] has frequently been used to prepare ketene dithioacetals but the problem with this approach [equation (1)] was the competitive enolisation of 2-formyl-1,3-dithiane and the subsequent need to remove by-products by chromatography.[8] Use of 3,3-dichloropropenal[9] as a starting material was an attractive proposition [equation (2)]. The addition of propane-1,3-dithiol, under basic conditions,[10] to this reactive enal took place essentially quantitatively but the thioacetalisation of intermediate (**8**) (propane-1,3-dithiol, BF_3·Et_2O, CH_2Cl_2) proceeded in low yield (< 20%), and once again extensive chromatographic purification was required. The best procedure for the synthesis of compound (**3c**) involved oxidation of the readily available malonaldehyde bis(dithioacetal) (**9**)[11] using Fujita's conditions[12] [equation (3)]. In this way compound (**3c**) was obtained in 75% yield, following recrystallisation from methanol. As part of a more general interest in the structure of polyfunctionalised ketene dithioacetals, an *X*-ray crystallographic study of compound (**3c**) was undertaken. The crystal chosen for analysis was found to contain a small (≤ 10%) amount of the starting compound (**9**) which co-crystallised with (**3c**). This contaminant, which was presumably due to the use of insufficient base, was usually removed by a second recrystallisation step. The molecular structure of compound (**3c**), showing the split S4 site, is shown in the Figure.

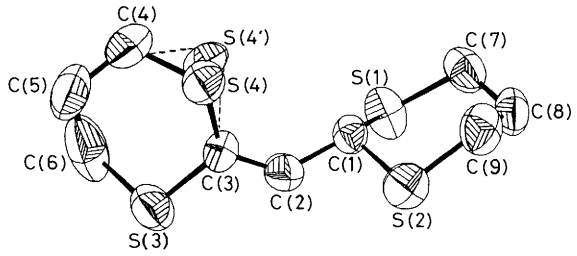


Figure.

Deprotonation of (**3c**) occurred readily (LDA, tetrahydrofuran; −78 to −40 °C; 1 h) and the resulting anion (**4c**) was trapped with a variety of electrophiles to give adducts (**10**) in good yield (Table 1). Although an emphasis was placed on the reactions of anion (**4c**) with aldehydes and epoxides, alkylation reactions also proceeded smoothly.

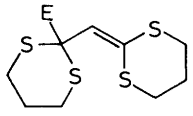
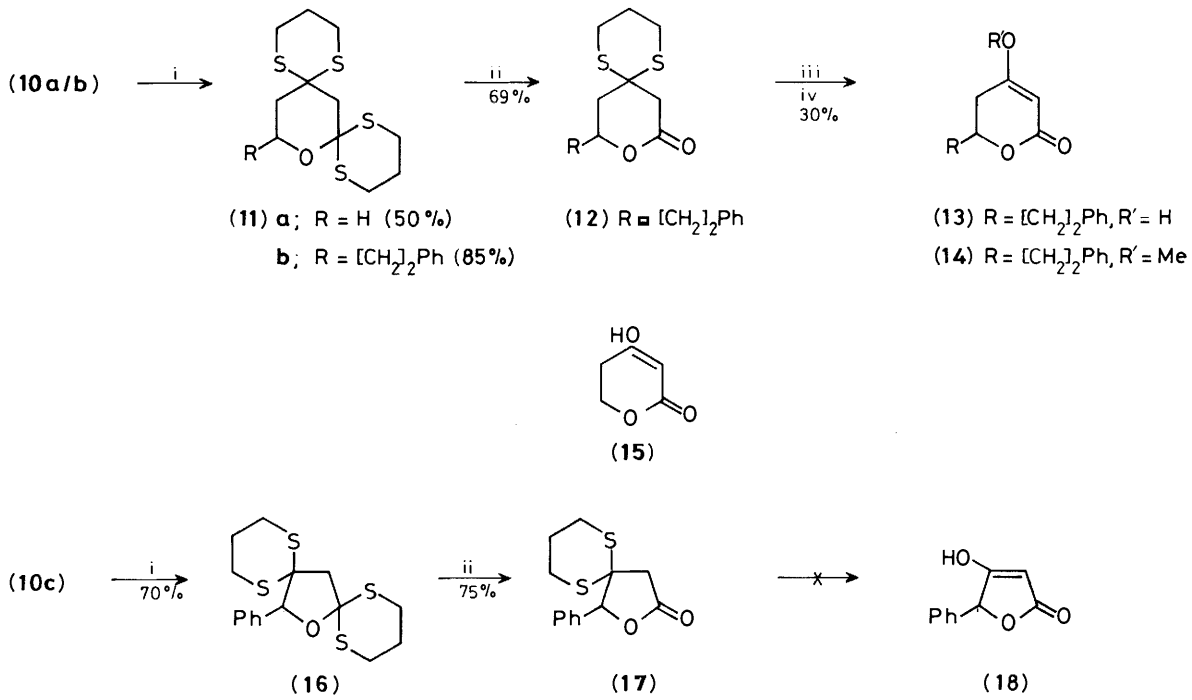


Table 1.

Electrophile	Adduct (**10**)	Yield (%)
Ethylene oxide	(**10a**) E = CH_2CH_2OH	78
Phenethyloxirane	(**10b**) E = $CH_2CH(OH)CH_2CH_2Ph$	78
Benzaldehyde	(**10c**) E = $CH(OH)Ph$	76
Hexanal	(**10d**) E = $CH(OH)C_5H_{11}$	76
Iodomethane	(**10e**) E = CH_3	98
1-Iodopentane	(**10f**) E = $CH_2[CH_2]_3CH_3$	70

In order to express the equivalence of anion (**4c**) to a β-hydroxy-β-lithioacrylate (**5**), hydrolysis of both 1,3-dithianyl residues of compound (**10**) was required. This has been examined in the case of three systems (**10a**), (**10b**), and (**10c**)

* A synthesis of (**3b**) has been reported,[5] starting from 2-bromo-1,1,3,3-tetraethoxypropane. The related system (**3**; R = Et), together with the corresponding sulphones, have also been described.



Scheme 5. *Reagents:* i, TFA, CH_2Cl_2; ii, $HgCl_2$, $CaCO_3$, aq. MeCN; iii, NBS, aq. acetone; iv, Me_2SO_4, K_2CO_3, acetone

(Scheme 5). Treatment of both (**10a**) and (**10b**) with trifluoroacetic acid (TFA) in CH_2Cl_2 [13] smoothly led to doubly masked β-keto lactones (**11a**) and (**11b**) in 50 and 85% yield respectively. We planned to effect simultaneous hydrolysis of both 1,3-dithianyl residues, although the enhanced lability of the dithio-ortho ester portion of (**11a**) and (**11b**) should allow for a selective hydrolysis sequence. This stepwise cleavage turned out to be the method of choice and attention was focused on compound (**11b**), given the known instability of 5,6-dihydro-4-hydroxy-2*H*-pyran-2-one (**15**). Mercury(II) chloride-mediated hydrolysis of (**11b**) gave lactone (**12**) in 69% yield, but even under forcing conditions no cleavage of the remaining 1,3-dithianyl group was observed when using Hg^{II}. The oxidative method for cleavage of ketene thioacetals [*N*-bromosuccinimide (NBS), aqueous acetone] described by Corey [14] was, however, successfully used to liberate lactone (**13**) and this product was treated directly with dimethyl sulphate, in the presence of K_2CO_3, to give (±)-dihydrokawain (**14**) [15] in 30% overall yield. The 1,3-dithianyl cleavage step appeared to proceed both rapidly and cleanly and it is not clear which step was responsible for this poor yield. Losses were also experienced during the purification of dihydrokawain, which is relatively volatile and can in fact be readily purified by sublimation.

As a more stringent test of the flexibility of reagent (**3c**) we have also studied the conversion of the benzaldehyde adduct (**10c**) into phenyltetronic acid (**18**), using the procedures described above. TFA-catalysed cyclisation of (**10c**) gave compound (**16**) in 70% yield, and hydrolysis of this with mercury(II) chloride also proceeded smoothly to give lactone (**17**) in 75% yield. It was at this stage that the limitations of the Corey procedure became evident. Control experiments showed that phenyltetronic acid was unstable to NBS and although a large number of other methods for ketene thioacetal cleavage were applied to compound (**17**), in no case was the tetronic acid (**18**) detected.

This latter case, a synthesis of phenyltetronic acid, illustrates one of the problems associated with the thioacetal–ketone conversion and although we have successfully demonstrated the use of anion (**4c**) as a synthetic equivalent of β-hydroxy-β-lithioacrylate (**5**), the applications of this reagent are limited. We are currently developing alternative reagents, still based on the principles outlined above, that will allow for the full expression of this β-keto ester subunit under mild and more generally applicable reaction conditions.*

Experimental

General experimental procedures have already been described.[2] All ^1H n.m.r. spectra were run using $CDCl_3$ as solvent. Mass spectra were obtained under either electron impact (EI) or chemical ionisation (CI) using isobutane as the ionising medium.

1,1,3,3-*Tetrakis(phenylthio)propene* (**3a**).—A solution of LDA prepared from butyl-lithium (1.6M in hexane; 0.69 ml, 1.1 mmol) and di-isopropylamine (0.196 ml, 1.4 mmol)] in tetrahydrofuran (THF) (3 ml) was cooled to −78 °C and a solution of ketene dithioacetal (**1**) (366 mg, 1 mmol) in THF (3 ml) was added dropwise. The solution was then warmed to −40 °C during 1.5 h and maintained at this temperature for 30 min. After this time the solution was recooled to −78 °C and a solution of diphenyl disulphide (240 mg, 1.1 mmol) in THF (2 ml) was added dropwise. The reaction mixture was slowly warmed to room temperature and then quenched with saturated aqueous ammonium chloride (2 ml). Water (2 ml) was then added and the product was extracted using ethyl acetate (3 × 25 ml). The combined extracts were washed with water (10 ml) and dried (Na_2SO_4), and purification by flash chromatography gave *tetrasulphide* (**3a**) as an oil (362 mg, 76%) (Found: $M^+ - SPh$, 365.045. $C_{21}H_{17}S_3$ requires *m/z* 365.049); $\nu_{max.}$(thin film) 1 580 cm^{-1}; δ_H(100 MHz) 5.76 (1 H, d, *J* 10.5 Hz), 6.04 (1 H,

* Hydrolysis of bis(dithioacetal) (**10f**) was also examined. Use of Hg^{II} or Ag^{I}-mediated hydrolysis of the ketene dithioacetal was accompanied by fragmentation of the remaining 1,3-dithianyl ring by β-elimination. This resulted in the formation of mixtures that proved difficult to purify.

d, *J* 10.5 Hz), and 6.77—7.65 (20 H, m); *m/z* (EI) 365 (M^+ − SPh, 100).

1,1,3,3-*Tetrakis(methylthio)propene* (**3b**).—A solution of butyl-lithium (1.6M in hexane; 2.1 ml, 3.31 mmol) was slowly added to a solution of methyl 3-(methylthio)dithiopropionate (**6**) (500 mg, 3 mmol) in THF (20 ml) at −78 °C. The solution was then warmed to −50 °C and s-butyl-lithium (1.125M in cyclohexane; 2.9 ml, 3.31 mmol) was added to give a deep red solution. After warming to −40 °C and being stirred for 1 h, the reaction mixture was recooled to −78 °C and dimethyl disulphide (0.3 ml, 3.31 mmol) was added. After 30 min saturated aqueous ammonium chloride (5 ml) was added and the mixture was warmed to room temperature. Water (30 ml) was added and the product was extracted with ethyl acetate (2 × 20 ml). The combined extracts were washed with brine and dried (Na_2SO_4) and, after removal of solvent, the residue was purified by distillation to give *methyl* 3,3-*bis(methylthio)dithiopropionate* (**7**) (512 mg, 80%), b.p. 200 °C at 0.05 mmHg (Kugelrohr) (Found: M^+, 211.980. $C_6H_{12}S_4$ requires *M*, 211.982); $\nu_{max.}$(thin film) 1 530 cm^{-1}; δ_H(60 MHz) 2.19 (6 H, s), 2.71 (3 H, s), 3.44 (2 H, d, *J* 7 Hz), and 4.53 (1 H, t, *J* 7 Hz); *m/z* (EI) 212 (M^+, 57%), and 165 (M^+ − SMe, 100).

A solution of compound (**7**) (419 mg, 1.98 mmol) in THF (5 ml) was slowly added to a solution of LDA (2.37 mmol) in THF (15 ml) at −78 °C. After 15 min iodomethane (0.14 ml, 2.17 mmol) was added and after a further 15 min the mixture was quenched with saturated aqueous ammonium chloride (5 ml) and allowed to warm to room temperature. Water (30 ml) was added and the product was extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and the residue was distilled to give tetrasulphide (**3b**) (390 mg, 87%) as a pale orange liquid, b.p. 150—200 °C at 0.05 mmHg (Kugelrohr) (lit.[5], 130—140 °C at 0.25 mmHg); δ_H(60 MHz) 2.20 (6 H, s), 2.36 (3 H, s), 2.38 (3 H, s), 5.13 (1 H, d, *J* 10 Hz), and 5.85 (1 H, d, *J* 10 Hz).

2-(1,3-*Dithian*-2-*ylidene)propenal* (**8**).—A solution of 3,3-dichloropropenal (500 mg, 4 mmol) and propane-1,3-dithiol (463 mg, 4.3 mmol) in ether (20 ml) at 0 °C was treated with 1M-NaOH (9 ml) and the mixture was stirred rapidly for 1.25 h at this temperature. After this time the organic solution was separated and the aqueous phase was extracted with ether (2 × 10 ml). The combined extracts were dried ($MgSO_4$), and removal of the solvent under reduced pressure gave aldehyde (**8**) as a pale yellow solid (600 mg, 94%), which was not purified further; $\nu_{max.}$(thin film) 1 620 cm^{-1}; δ_H(60 MHz) 1.90—2.35 (2 H, m), 2.90—3.25 (4 H, m), 6.40 (1 H, d, *J* 7 Hz), and 10.00 (1 H, d, *J* 7 Hz).

2-(1,3-*Dithian*-2-*ylidenemethyl*)-1,3-*dithiane* (**3c**).—A solution of 2,2′-methylenebis-1,3-dithiane (**9**) (2.50 g, 20 mmol) in THF (30 ml) was cooled to −30 °C and BuLi (1.6M in hexane; 13.5 ml, 22 mmol) was added. After 2 h at this temperature the solution was cooled to −78 °C and a solution of 2,2′-dipyridyl disulphide (5.29 g, 24 mmol) in THF (10 ml) was added slowly. The reaction mixture was allowed to warm slowly to room temperature and was then quenched with saturated aqueous ammonium chloride (10 ml). Water (10 ml) was added and the product was extracted with CH_2Cl_2 (4 × 20 ml). The combined extracts were washed successively with 1M-NaOH (2 × 10 ml), water (10 ml), and brine, and dried (Na_2SO_4). Removal of solvent gave a residue, which rapidly crystallised on trituration with methanol. Recrystallisation gave the bis-1,3-dithiane (**3c**) (1.90 g, 75%), m.p. 76—77 °C (from MeOH or Et_2O–hexane) (Found: C, 43.4; H, 5.75. $C_9H_{14}S_4$ requires C, 43.16; H, 5.6%); $\nu_{max.}$(Nujol) 1 535 cm^{-1}; δ_H(270 MHz) 1.90—2.14 (4 H, m), 2.85—2.96 (8 H, m), 5.15 (1 H, d, *J* 10 Hz), and 5.84 (1 H, d, *J* 10 Hz); *m/z* (EI) 250 (M^+, 100).

General Procedure for the Lithiation of Compound (**3c**) *and Reaction of Anion* (**4c**) *with Electrophiles* (*Table* 1).—A solution of LDA (2 mmol) in THF (10 ml) was cooled to −78 °C and a solution of compound (**3c**) (250 mg, 1 mmol) in THF (2 ml) was added. The mixture was warmed to −50 °C during 30 min and was then recooled to −78 °C and a solution of the electrophilic component (1.1 mol equiv.) in THF was added. The reaction mixture was then warmed to room temperature before being quenched with saturated aqueous ammonium chloride (3 ml). Water (20 ml) was added, the product was extracted with ethyl acetate (3 × 20 ml), the combined extracts were dried (Na_2SO_4), and after removal of the solvent the product (**10**) was purified by flash chromatography.

2-[2-(1,3-*Dithian*-2-*ylidenemethyl*)-1,3-*dithian*-2-*yl*]*ethanol* (**10a**). This was prepared from ethylene oxide in 78% yield as an oil (Found: C, 45.1; H, 6.2. $C_{11}H_{18}OS_4$ requires C, 44.86; H, 6.16%); $\nu_{max.}$(thin film) 3 460 and 1 540 cm^{-1}; δ_H(60 MHz) 1.85—2.30 (5 H, m, containing OH), 2.50 (2 H, t, *J* 6 Hz), 2.80—3.10 (8 H, m), 3.83 (2 H, t, *J* 6 Hz), and 6.13 (1 H, s); *m/z* (CI) 295 (M^+ + 1, 100).

1-[(1,3-*Dithian*-2-*ylidenemethyl*)-1,3-*dithian*-2-*yl*]-4-*phenylbutan*-2-*ol* (**10b**). This was prepared from phenethyloxirane in 78% yield as an oil (Found: C, 57.6; H, 6.7. $C_{19}H_{26}OS_4$ requires C, 57.24; H, 6.57%); $\nu_{max.}$(thin film) 3 470 and 1 545 cm^{-1}; δ_H(270 MHz) 1.84—2.46 (7 H, m, containing OH), 2.70 2.96 (12 H, m), 4.05 (1 H, m), 6.17 (1 H, s), and 7.17—7.31 (5 H, m); *m/z* (CI) 399 (M^+ + 1, 44).

[2-(1,3-*Dithian*-2-*ylidenemethyl*)-1,3-*dithian*-2-*yl*](*phenyl*)*methanol* (**10c**). This was prepared from benzaldehyde in 76% yield as a liquid (Found: M^+, 356.036. $C_{16}H_{20}OS_4$ requires *M*, 356.039); $\nu_{max.}$(thin film) 3 450 and 1 550 cm^{-1}; δ_H(60 MHz) 1.90—2.35 (4 H, m), 2.74—3.08 (8 H, m), 3.29 (1 H, br s, OH), 5.25 (1 H, s), 5.92 (1 H, s), and 7.32—7.62 (5 H, m); *m/z* (EI) 356 (M^+, 1%) and 249 (M^+ − C_7H_7O, 100).

1-[2-(1,3-*Dithian*-2-*ylidenemethyl*)-1,3-*dithian*-2-*yl*]*hexan*-1-*ol* (**10d**). This was prepared from hexanal in 76% yield as an oil (Found: M^+, 350.087. $C_{15}H_{26}OS_4$ requires *M*, 350.087); $\nu_{max.}$(thin film) 3 450 and 1 555 cm^{-1}; δ_H(60 MHz) 0.64—2.34 (15 H, m), 2.53—3.12 (9 H, m, containing OH), 4.04 (1 H, br d), and 5.97 (1 H, s); *m/z* (CI) 351 (M^+ + 1, 50%) and 249 (M^+ − $C_6H_{13}O$, 100).

2-(1,3-*Dithian*-2-*ylidenemethyl*)-2-*methyl*-1,3-*dithiane* (**10e**). This was prepared from iodomethane in 98% yield as an oil (Found: M^+, 264.011. $C_{10}H_{16}S_4$ requires *M*, 264.013); $\nu_{max.}$(thin film) 1 540 cm^{-1}; δ_H(60 MHz) 1.84 (3 H, s), 1.74—2.30 (4 H, m), 2.64—3.10 (8 H, m), and 6.22 (1 H, s); *m/z* (EI) 264 (M^+, 55).

2-(1,3-*Dithian*-2-*ylidenemethyl*)-2-*pentyl*-1,3-*dithiane* (**10f**). This was prepared from 1-iodopentane in 70% yield as an oil (Found: M^+, 320.073. $C_{14}H_{24}S_4$ requires *M*, 320.076); $\nu_{max.}$(thin film) 1 550 cm^{-1}; δ_H(270 MHz) 0.95 (3 H, t, *J* 7 Hz), 1.22—1.60 (8 H, m), 1.92—2.21 (4 H, m), 2.74—2.90 (2 H, m), 2.92—3.05 (6 H, m), and 6.20 (1 H, s); *m/z* (EI) 320 (M^+, 100).

Tetrahydropyran-2,4-*dispiro*-(2′-[1′,3′]-*dithiane*) (**11a**).—A solution of compound (**10a**) (100mg, 0.34 mmol) in CH_2Cl_2 (7 ml) was cooled to −18 °C and treated with TFA (0.17 ml, 2.2 mmol). After 30 min water (4 ml) was added and the organic phase was washed successively with saturated aqueous sodium hydrogencarbonate (2 ml) followed by water (2 ml) and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography gave the *pyran* (**11a**) (50 mg, 50%) as needles, m.p. 110—112 °C (from Et_2O–hexane) (Found: C, 44.7; H, 6.3. $C_{11}H_{18}OS_4$ requires C, 44.86; H, 6.16%); $\nu_{max.}$($CHCl_3$) 1 435, 1 190, and 1 070 cm^{-1}; δ_H(270 MHz) 1.91—2.14 (4 H, m), 2.20 (2 H, t, *J* 5 Hz), 2.55 (2 H, s), 2.62 (2 H, dt, *J* 14 and 8 Hz), 2.85—2.94 (4 H, m), 3.22—3.33 (2 H, m), and 4.05 (2 H, d, *J* 5 Hz); *m/z* (EI) 294 (M^+, 100).

Table 2. Fractional atomic co-ordinates ($\times 10^4$) for compound (**3c**)

	x	*y*	*z*
S(1)	1 368(1)	7 734(1)	70(1)
S(2)	−425(1)	8 957(1)	1 820(2)
S(3)	3 962(2)	11 221(1)	1 410(2)
S(4)	3 801(3)	9 336(2)	3 311(2)
S(4′)	4 249(13)	8 905(12)	2 691(23)
C(1)	1 269(5)	8 593(4)	1 471(5)
C(2)	2 067(6)	9 630(5)	1 274(6)
C(3)	3 225(5)	9 922(4)	1 839(5)
C(4)	5 638(7)	9 348(7)	3 190(9)
C(5)	6 227(7)	10 511(7)	2 955(10)
C(6)	5 758(8)	10 929(7)	1 636(11)
C(7)	317(7)	6 545(5)	436(7)
C(8)	−1 083(7)	6 865(7)	759(7)
C(9)	−1 159(5)	7 549(6)	1 952(6)

Table 3. Bond lengths and angles for compound (**3c**)

Bond lengths (Å)

C(1)–S(1)	1.799(7)	C(7)–S(1)	1.804(8)
C(1)–S(2)	1.792(7)	C(9)–S(2)	1.821(8)
C(3)–S(3)	1.769(7)	C(6)–S(3)	1.809(10)
C(3)–S(4)	1.758(7)	C(4)–S(4)	1.830(10)
C(3)–S(4′)	1.774(14)	C(4)–S(4′)	1.529(17)
C(2)–C(1)	1.477(8)	C(3)–C(2)	1.300(8)
C(5)–C(4)	1.517(12)	C(6)–C(5)	1.518(14)
C(8)–C(7)	1.497(10)	C(9)–C(8)	1.501(11)

Bond angles (deg)

C(7)–S(1)–C(1)	101.4(4)	C(9)–S(2)–C(1)	100.4(3)
C(6)–S(3)–C(3)	102.7(4)	C(4)–S(4)–C(3)	101.5(4)
C(4)–S(4′)–C(3)	114.3(9)	S(2)–C(1)–S(1)	114.0(4)
C(2)–C(1)–S(1)	106.9(5)	C(2)–C(1)–S(2)	110.3(5)
C(3)–C(2)–C(1)	128.1(6)	S(4)–C(3)–S(3)	116.9(4)
S(4′)–C(3)–S(3)	119.0(6)	C(2)–C(3)–S(3)	118.5(5)
C(2)–C(3)–S(4)	121.5(5)	C(2)–C(3)–C(4′)	120.5(7)
C(5)–C(4)–S(4)	114.3(6)	C(5)–C(4)–S(4′)	126.8(8)
C(6)–C(5)–C(4)	110.2(8)	C(5)–C(6)–S(3)	114.7(6)
C(8)–C(7)–S(1)	114.1(6)	C(9)–C(8)–C(7)	115.2(6)
C(8)–C(9)–S(2)	112.5(5)		

6-*Phenethyltetrahydropyran*-2,4′-*dispiro*-(2′-[1′,3′]*dithiane*) (**11b**).—A solution of compound (**10b**) (210 mg, 0.53 mmol) in CH_2Cl_2 (16 ml) was cooled to −20 °C and treated with TFA (0.26 ml, 3.26 mmol). After 15 min, water (10 ml) was added and the reaction mixture was worked up, using the same procedure as described for compound (**11a**), to give the *pyran* (**11b**) (179 mg, 85%) as crystals, m.p. 125—126 °C (from CH_2Cl_2–hexane) (Found: C, 56.9; H, 6.6. $C_{19}H_{26}OS_4$ requires C, 57.24; H, 6.57%); $\nu_{max.}$($CHCl_3$) 1 430, 1 180, 1 070, and 960 cm^{-1}; δ_H(270 MHz) 1.75—2.14 (6 H, m), 2.17—2.33 (2 H, m), 2.50—3.55 (12 H, m), 4.30 (1 H, m), and 7.18—7.32 (5 H, m); *m/z* (EI) 398 (M^+, 100).

6-*Phenethyltetrahydropyran*-4-*spiro*-2′-[1′,3′]*dithian*-2-*one* (**12**).—A solution of compound (**11b**) (45 mg, 0.113 mmol) in water–acetonitrile (1:4) (2 ml) was added slowly to a rapidly stirred solution of mercury(II) chloride (140 mg, 0.5 mmol) in water–acetonitrile (1:4) (2 ml) containing calcium carbonate (50 mg, 0.5 mmol). After 30 min the solution was filtered through a Celite pad, the solids were washed thoroughly with CH_2Cl_2, and these washings were combined with the filtrate. The organic layer was separated and washed successively with 5M-aqueous ammonium acetate (1 ml) and water (1 ml), and then dried (Na_2SO_4). Removal of the solvent and purification of the residue by flash chromatography gave *lactone* (**12**) (24 mg, 69%) as a viscous oil (Found: M^+, 308.090. $C_{16}H_{20}O_2S_2$ requires *M*, 308.090); $\nu_{max.}$(thin film) 1 730 cm^{-1}; δ_H(270 MHz) 1.86—2.15 (4 H, m), 2.26 (1 H, m), 2.45 (1 H, ddd, *J* 14, 3, and 2 Hz), 2.70—3.05 (7 H, m), 3.21 (1 H, dd, *J* 17 and 2 Hz, part of AB system), 4.63 (1 H, m), and 7.19—7.33 (5 H, m); *m/z* (EI) 308 (M^+, 100).

5,6-*Dihydro*-4-*methoxy*-6-*phenethyl*-2H-*pyran*-2-*one* [(±)-*Dihydrokawain*] (**14**).—A solution of lactone (**12**) (37 mg, 0.12 mmol) in acetone (0.5 ml) was slowly added to a solution of NBS (170 mg, 0.96 mmol) in water–acetone (5:95) (3 ml) at −5 °C. After 5 min saturated aqueous sodium sulphite (1.5 ml) was added followed by hexane (1 ml) and CH_2Cl_2 (1 ml). The organic phase was washed with water (1.5 ml) and dried (Na_2SO_4). Removal of solvent gave the enol (**13**) as an opaque residue, which was immediately dissolved in acetone (0.5 ml) containing potassium carbonate (30 mg, 0.24 mmol) and dimethyl sulphate (0.02 ml, 0.24 mmol). After 20 h, water (1 ml) was added and the product was extracted with ethyl acetate (4 × 1 ml). The combined extracts were dried (Na_2SO_4) and, after removal of the solvent, the residue was purified by flash chromatography followed by sublimation at reduced pressure to give (±)-dihydrokawain (**14**) (9 mg, 30%) as needles, m.p. 67—69 °C (lit.,[15] 69—71 °C, 65—69 °C). Spectral data obtained for (**14**) were identical with those reported previously.

5-*Phenyltetrahydrofuran*-2,4-*dispiro*-(2′-[1′,3′]*dithiane*) (**16**).—To a stirred solution of compound (**10c**) (800 mg, 2.25 mmol) in CH_2Cl_2 (2 ml) at −10 °C was added TFA (0.15 ml). After 5 min saturated aqueous sodium hydrogencarbonate (5 ml) was added and the organic phase was separated and dried (Na_2SO_4). Removal of solvent followed by flash chromatography gave the *tetrahydrofuran* (**16**) (553 mg, 70%), m.p. 145—146 °C (from EtOAc–hexane) (Found: C, 53.55: H, 5.7. $C_{16}H_{20}OS_4$ requires C, 53.89; H, 5.65%); $\nu_{max.}$($CHCl_3$) 1 420, 1 275, and 1 025 cm^{-1}; δ_H(270 MHz) 1.75—2.12 (4 H, m), 2.45—2.95 (4 H, m), 2.81 (1 H, d, *J* 15 Hz, part of AB system), 3.01 (1 H, dd, *J* 15 Hz, part of AB system), 3.28—3.65 (4 H, m), 5.28 (1 H, s), and 7.36—7.41 (5 H, m); *m/z* (EI) 356 (M^+, 5%) and 250 ($M^+ - C_7H_6O$, 80).

5-*Phenyltetrahydrofuran*-4-*spiro*-2′-[1′,3′]*dithian*-2-*one* (**17**).—Using the same procedure described above for the conversion of (**11b**) to (**12**), compound (**16**) (90 mg, 0.25 mmol) gave, after purification, the *tetrahydrofuranone* (**17**) (50 mg, 75%), m.p. 121—122 °C (from benzene–hexane) (Found: M^+, 266.042. $C_{13}H_{14}O_2S_2$ requires *M*, 266.043); $\nu_{max.}$($CHCl_3$) 1 760 cm^{-1}; δ_H(270 MHz) 1.83 (1 Hm, m), 1.95 (1 H, m), 2.29 (1 H, m), 2.63 (1 H, m), 2.85—2.97 (2 H, m), 3.23 (1 H, d, *J* 17 Hz, part of AB system), 3.34 (1 H, d, *J* 17 Hz, part of AB system), 5.55 (1 H, s), and 7.40—7.53 (5 H, m); *m/z* (EI) 299 (M^+, 5).

X-*Ray Crystallography*—*Structure determination of compound* (**3c**). *Crystal data.* $C_9H_{14}S_4$, M = 250.45, monoclinic, a = 9.890(1), b = 11.792(2), c = 10.533(4) Å, β = 93.93(5)°, V = 1 225.64 $Å^3$, space group $P2_1/c$, Z = 4, D_c = 1.35 g cm^{-3}, $F(000)$ = 528, μ(Mo-K_α) = 7.03 cm^{-1}, λ = 0.710 69 Å, T = 293 K.

All crystallographic measurements were made on a crystal sealed in a thin-walled glass capillary using a CAD4 diffractometer operating in the ω/2θ scan mode with graphite-monochromated Mo-K_α radiation, in a manner previously described in detail.[16] Of the 2 154 unique data measured, 1 600 were deemed observed [$I > 1.5\sigma(I)$]. The data were corrected for absorption on the basis of psi-scan measurements.

The structure was solved by direct methods (SHELXS86) and developed and refined by standard difference-Fourier and least-squares procedures. Difference syntheses computed towards the end of the refinement showed a significant peak in the

neighbourhood of S(4). This was interpreted as a partial sulphur atom due to the presence of a small amount of the saturated starting material as impurity (see main text). Accordingly, S(4) was represented by a split site with linked occupancies; these refined to values of 0.808 and 0.192. The carbons and other atoms of the related part of the molecule showed extended displacement ellipsoids consistent with the mixing in of a ring with a conformation different to that of the major component, but not extensive enough to produce split sites as for the sulphur. The final refinement cycle employed anisotropic displacement factors for non-hydrogen atoms and isotropic for hydrogens: only those on the ring of the fully saturated side of the molecule were included. The final R and R_w values were 0.062 and 0.075 respectively. Reflections were weighted according to the scheme $w = [\sigma^2(F_o) + 0.000\,025F_o^2]$.

Table 2 lists the atomic fractional co-ordinates and Table 3 the bond lengths and angles. Displacement factor coefficients, hydrogen co-ordinates, and bond lengths and angles have been deposited as Supplementary data.*

Acknowledgements

We thank S.E.R.C. and ICI Pharmaceuticals (CASE award to W. O. M.) and University of Bath for their financial support of this work. S.E.R.C.-funded access to the *X*-ray crystallographic service is also acknowledged.

* See section 5.6.3, in the Instructions for Authors, January issue.

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Received 5th January 1989; *Paper* 9/00099B