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TETRAHEDRON

4-(2,2-Dimethyldioxalan-4-yl)-5-(quinoxalin-2-yl)--1,3-dithiol-2-one, a Proligand Relating to the Cofactor of the Oxomolybdoenzymes

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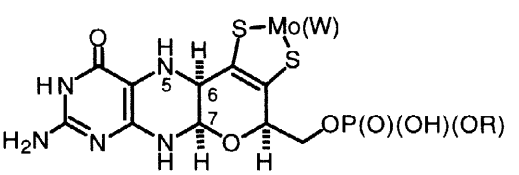
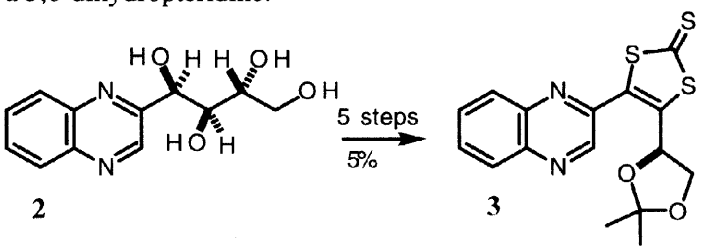
Abstract: The coupling of 2-iodoquinoxaline to 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-(tri-*n*-butylstannyl)-1,3-dithiol-2-one **5** gave 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one **4**.

Early degradative and spectroscopic work on the structure of the cofactors of the oxomolybdoenzymes by Rajagopalan *et al.*[1] concluded that they involve a reduced pterin carrying at C-6 a four-carbon side-chain having two sulfur atoms which ligate a molybdenum atom. Largely because the intrinsic instability of the cofactor once released from the enzyme precluded the isolation of the cofactor itself, further clarification had to wait for X-ray crystallographic determinations of whole enzymes. Since 1995, the X-ray determined crystal structures of three molybdenum- and one tungsten-containing enzyme have been published. The structures of aldehyde oxidase from *Desulfovibrio gigas*,[2] DMSO reductase from *Rhodobacter sphaeroides* and *R. capsulatus*[3] and formate dehydrogenase from *Escherichia coli*[4] and the hyperthermophilic tungsten enzyme, ferredoxin aldehyde oxidoreductase from *Pyrococcus furiosus*,[5] have clarified the structure of the cofactor.



1
(R = H or nucleoside)
(other ligands on metal not shown)

Thus, it is now generally considered that, in the family of molybdenum enzyme cofactors, each has a reduced tricyclic pyrano-pteridine nucleus in common – this substituted tricycle is termed molybdopterin. The structural evidence presently available is summarised in **1**; thus, the metal is chelated by an ene-1,2-dithiolate (dithiolene) which is attached at C-6 to a reduced pteridine ring, as originally proposed by Rajagopalan.[1] However, unsuspected from the degradative and spectroscopic examinations, all of the protein crystallographic studies have revealed the presence of a tetrahydropyran ring which can be viewed as resulting from cyclisation of a side-chain hydroxyl group to C-7 of a 5,6-dihydropteridine.

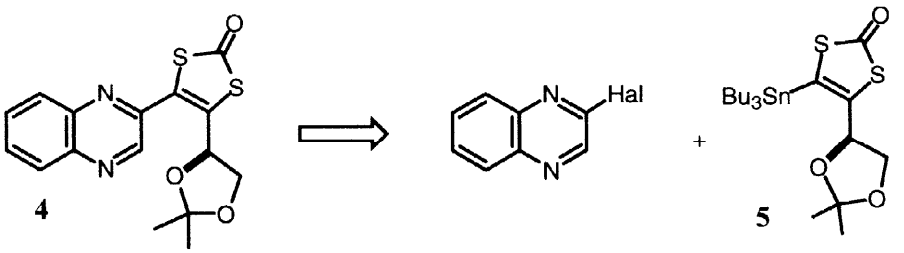


2 **3**

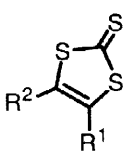
PII: S0040-4020(98)00072-6

Previously we have described[6] the synthesis of simple quinoxalin-2-yl and pteridin-6-yl dithiolene proligands and their conversion into cobalt and molybdenum complexes, culminating in a synthesis[6c] of the proligand **3**, a quinoxalin-2-yl 1,3-dithiole-2-thione which has a four-carbon side-chain, a dithiolene masked as a 1,3-dithiole-2-thione, and two hydroxyl groups (masked as a 1,3-dioxolane) located on the distal two carbons of the side-chain, as are the oxygens on the side-chain of the cofactor. This was produced *via* a linear sequence which started with the long known[7] and readily synthesised tetrol **2**, but which was not very efficient especially in the last step. We also developed a practicable synthesis[8] of the pterin analogue of **2**.

In the light of ambitions to synthesise ultimately not only molybdopterin itself, and complexes therefrom, but modified derivatives which may shed light on the mode of action of the cofactor, we sought a more convergent and potentially more versatile approach to compounds of the type **3** with the intention that it would then serve for pteridine systems, and this extrapolation is described in a sequel. The essential step in the successful route, the evolution of which is described in this paper, is a metal-catalysed coupling between a 2-haloquinoxaline and a stannylated derivative of the 'right-hand' portion, *i.e.* a four-carbon unit having both a masked dithiolene and a masked vicinal diol. Because other work[6e] had made us aware that hydrolytic release of a dithiolene from a 1,3-dithiole-2-thione such as **3**, is considerably more difficult than hydrolytic release from a 1,3-dithiol-2-*one*, our target was **4** which we envisaged as being available from a 'right-hand' unit such as **5**. However, since 1,3-dithiole-2-thiones can be readily transformed with $Hg(OAc)_2$ into 1,3-dithiol-2-ones,[9] and our earlier work had involved the thiones, it was with these that we began this present study.

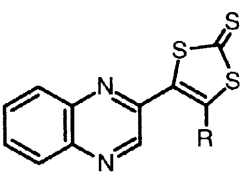


1,3-Dithiole-2-thione **6a** was lithiated then quenched with tri-*n*-butyltin chloride and the resulting stannane **6b** coupled with 2-chloroquinoxaline using $Pd(PPh_3)_4$ in refluxing toluene affording **7a**, previously prepared[6b] in four steps from quinoxaline. Encouraged by this result, we sought to produce a more elaborated 1,3-dithiole-3-thione, again *via* lithiation of **6a**. Thus, the lithiated intermediate was reacted with ethanal, as a model for the ultimately required dihydroxylated two-carbon extension, and produced the alcohol **6c** in 80% yield. Sequential treatment of **6a** with one mol equivalent of *n*-BuLi, then ethanal and then without isolation, a second mol equivalent of *n*-BuLi and finally *n*-Bu_3SnCl produced the alcohol-stannane **6d**.[10] Attempts to couple this stannane with 2-chloroquinoxaline were unsuccessful, possibly due to intramolecular protodestannylation. Therefore, the alcohol was protected giving **6e** which was then converted into stannane **6f**; however, this too could not be induced to couple with 2-chloroquinoxaline.



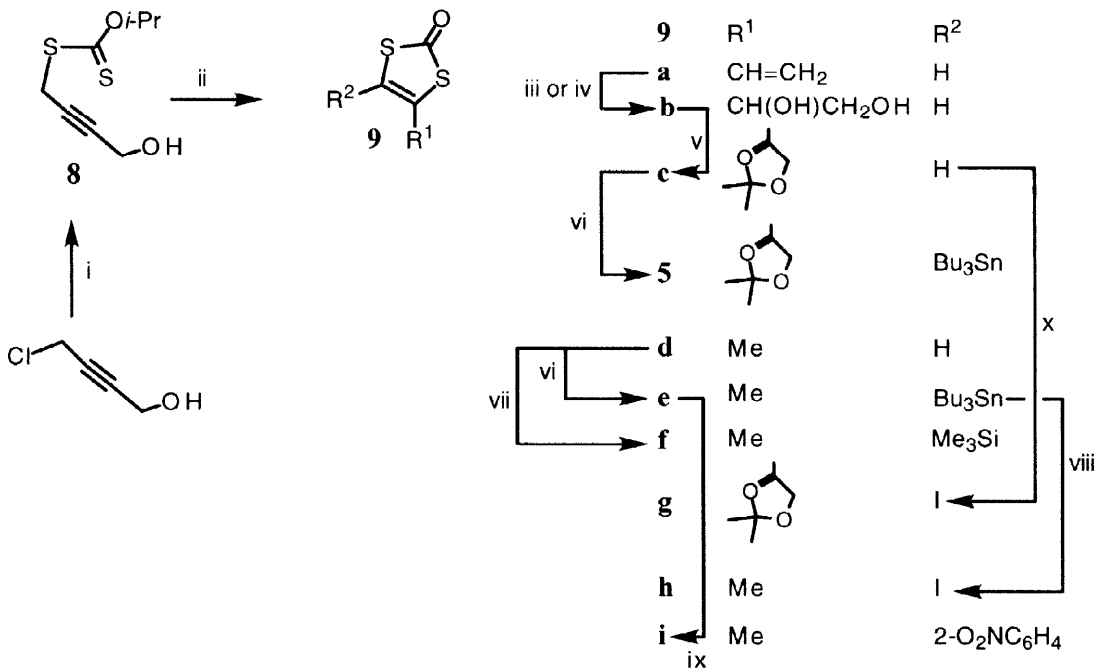
6	R^1	R^2
a	H	H
b	H	*n*-Bu_3Sn
c	MeCH(OH)	H
d	MeCH(OH)	*n*-Bu_3Sn
e	MeCH(OMEM)	H
f	MeCH(OMEM)	*n*-Bu_3Sn

7	R
a	H
b	Me



A route, to a four-carbon unit with both oxygen substituents installed, was conceived based on hydroxylation of a 4-ethenyl-1,3-dithiole (**Scheme 1**). Attempted dehydration of **6c** was unsuccessful so we turned to ring synthesis, following a precedent[11] in which the preparation of 4-ethenyl-1,3-dithiole-2-thione was described. We found that, although this substance could be prepared as described, yields were inferior to those reported, the thione was rather unstable and most importantly, we were unable to obtain derivatives *via* lithiation. Accordingly we modified the route to allow production 4-ethenyl-1,3-dithiol-2-*one* **9a**, which we found to be formed much more cleanly and in satisfactory yield, and to be more stable.

Reaction of 1-chlorobut-2-yn-4-ol[12] with isopropyl xanthate gave **8**, acid-catalysed ring closure of which produced the vinyl-substituted 1,3-dithiol-2-one **9a** in only moderate yield but sufficiently simply that multigram quantities could be prepared satisfactorily. OsO_4-Catalysed hydroxylation with *N*-methylmorpholine *N*-oxide as reoxidant proceeded efficiently (→ **9b**), as did subsequent protection as an acetal **9c**. Attempts at sequential lithiation of **9c** then trapping with a variety of electrophiles, including *n*-Bu_3SnCl, always led to the formation of polar sulfurous materials which could not be characterised. We believe that these failures, which contrast with successful lithiations of the thione **6a** are associated with nucleophilic attack by the lithiating agent at the carbonyl group of the ring. However, an *in situ* trapping protocol[13] did permit the conversion of **9c** into the target stannane **5**. The hydroxylation of **9a**, then protection and conversion to a stannane were repeated to produce homochiral materials, *R*-**9b**, *R*-**9c**, and *R*-**5** respectively, by carrying out the dihydroxylation with AD mix-α.[14] Chiral GC analysis of the acetonide *R*-**9c** showed *R*-**9b** to have been formed in 94.4% ee.



Scheme 1

Reagents: i, *i*-PrOC(S)SK, THF, 40 °C; ii, TFA, 4 °C; iii, OsO_4, NMO, Me_2CO, H_2O, <40 °C; iv, *t*-BuOH, H_2O, AD mix-α, 0 °C; v, $Me_2C(OMe)_2$, TsOH, rt; vi, *n*-Bu_3SnCl, THF, -70 °C, then LDA; vii, Me_3SiCl, THF, -70 °C, then LDA; viii, I_2, CH_2Cl_2, 0 °C; ix, 2-$IC_6H_4NO_2$, CuTC, rt; x, $ZnCl_2$, -70 °C, then *t*-BuLi, then I_2.

For the study of coupling reactions it was convenient to compare results obtained with the elaborated **5** with those using the much simpler stannane **9e** which was obtained, using the *in situ* trapping protocol, from 4-

methyl-1,3-dithiol-2-one **9d**, itself readily available in two steps from chloroacetone.[9] It is significant that although the *in situ* trapping regime also allowed the synthesis of silane **9f**, it failed completely in an attempt to convert **9d** into the corresponding boronic acid, starting material being recovered after exposure of a mixture of **9d** and trimethyl (or tri-*i*-propyl) borate to LDA.

It was very disappointing to find that all attempts to achieve a cross-coupling between 2-chloroquinoxaline and either the simple stannane **9e** or the elaborated stannane **5** using palladium(0) catalysis failed – various combinations of catalyst and ligand were examined including $Pd(OAc)_2/PPh_3$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3/AsPh_3(Pfur_3)$, with variations in solvent (PhMe, DMF, MeCN, THF, Et_3N, *N*-methylpyrrolidinone (NMP)) and promotor (CuI, $AgNO_3$). No coupled product was detected in any case. An attempt to couple iodobenzene with stannane **9e** ($Pd(OAc)_2/Pfur_3$/NMP/100 °C) gave none of the desired product.

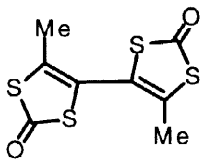
In an attempt to generate a zinc derivative of a 1,3-dithiol-2-one, and knowing that simple lithiation (as a prelude to exchange with $ZnCl_2$) was not possible (see above), we attempted *in situ* generation of a zinc derivative. Treatment of a THF solution of $ZnCl_2$ with LDA generated heat; addition of **9d** to the mixture followed by TMEDA, and after one hour d_4-acetic acid, resulted in a good recovery of **9d** with a significant (50%) incorporation (MS and ^1H NMR) of deuterium on the ring. Addition of *t*-BuLi to a mixture of **9c** and $ZnCl_2$ then quenching with I_2 gave the iodide **9g**. Thus, it was apparently possible to generate significant quantities of zinc derivatives using this approach which follows Eaton's protocol in the cubane field.[15] With this evidence for the formation of the organozinc intermediate we attempted a coupling with iodobenzene using Farina's catalyst[16] ($Pd_2(dba)_3/Pfur_3$) in NMP, however no trace of coupled product was found. An analogous sequence to generate the zinc derivative of **9d**, followed by addition of chloroquinoxaline and $Pd(PPh_3)_4$ gave principally unreacted starting materials, together with a trace (1.7% yield) of the desired coupled product **7b**, but this yield could not be improved upon.

Treatment of the stannane **9e** with I_2 produced the iodide **9h**. Having two iodo-1,3-dithiol-2-ones in hand we attempted their conversion into the corresponding zinc species. It was encouraging that exposure of **9h** to activated zinc then water gave the de-iodinated material **9d** in good yield, indicating formation of an organozinc intermediate however, when we attempted to capitalise on this by adding 2-chloroquinoxaline and $Pd(PPh_3)_2Cl_2$ to the solution containing the putative organozinc intermediate from **9h**, no coupled product was formed.

Having synthesised iodides **9g** and **9h**, attempts were made to carry out cross-couplings *via* the generation of a 2-zincio quinoxaline, but again no coupled products were obtained. Reaction of 2-chloroquinoxaline with Riecke zinc[17] was exothermic but addition of iodobenzene and palladium catalyst gave no coupled products and indeed simple addition of water after the exotherm with zinc produced no quinoxaline, casting doubt on the formation of a quinoxalin-2-ylzinc species. In passing, we noted that addition of $ZnEt_2$ to 2-chloroquinoxaline in the presence of $Pd(PPh_3)_2Cl_2$, with the intention of generating a 2-zincio quinoxaline,[18] resulted in an exothermic reaction then, after the addition of water, not quinoxaline, but 2-ethylquinoxaline in 94% yield. No reaction occurred in the absence of the catalyst – this result merits further study.

No reaction occurred when $ZnEt_2$, $Pd(PPh_3)_2Cl_2$ and iodide **9h** were mixed. This result can be taken to indicate that the presence of *two* substituents on the five-membered ring retards both the rate of oxidative insertion of Pd(0) from substrates such as **9g** and **9h** and transmetallation by Pd(II), from the corresponding stannane or zincio-derivative.

A solution to the impasse arrived in the form of Liebskind's report[19] of the use of copper thiophene-2-carboxylate (CuTC) in cross-coupling processes. When we attempted the coupling of the simpler stannane **9e** with 2-chloroquinoxaline using this methodology, although no cross-coupled product was produced, a homo-coupled product **10** was obtained from the stannane in 50% yield. This clearly indicated that reaction had taken place between the CuTC and the stannane. This encouraging result prompted examination of the interaction between **9e** and 2-iodonitrobenzene, a substrate successfully utilised by Liebskind, and here, at last, an acceptable yield of product **9i** was obtained in which an aromatic partner had been linked to a 1,3-dithiol-2-one, though **9i** was accompanied by the homocoupled product **10**.



10

It seemed that the use of an aryl iodide might provide the means to link a 1,3-dithiole to a quinoxaline. 2-Chloroquinoxaline was converted into the corresponding iodide,[20] by heating with NaI and acid. To our delight, the iodide reacted with stannanes **5** and **9e** using the CuTC coupling conditions, and the cross-coupled products **4** and **7b** were obtained in yields of 45% and 44% respectively, with formation of no homo-coupled product **10**.

We shall utilise proligands **4** and **7b** in our further research to develop chemical analogues of the catalytic centres of the oxomolybdoenzymes.

EXPERIMENTAL

General

Organic extracts were dried with anhydrous $MgSO_4$ then filtered before evaporation. Chromatography refers to 'flash' chromatography on silica gel.

4-Tri-*n*-butylstannyl-1,3-dithiole-2-thione 6b

1,3-Dithiole-2-thione (0.54 g, 4.02 mmol), dried by azeotropic removal of residual water (2xbenzene, 10 ml) was dissolved in dry THF (6 ml) under nitrogen. The solution was cooled in a dry ice/Me_2CO bath and LDA (3.2 ml, 1.5 M in hexanes, 4.8 mmol) was added dropwise by syringe with efficient stirring. After 1 h, tri-*n*-butylstannyl chloride (1.3 ml, 4.8 mmol) was added by syringe, with stirring, and the resultant solution allowed to warm to rt over 2 h. The reaction was quenched by addition of sat. aq. NH_4Cl (10 ml), the organic phase diluted with hexane (20 ml), separated and the aq. phase re-extracted with hexane (20 ml). The combined organic phases were washed with brine (15 ml), dried and the solvent evaporated *in vacuo* giving a brown oil which was further purified by chromatography, eluting with petroleum ether (40/60):EtOAc, 96:4 to give *4-tri-n-butylstannyl-1,3-dithiole-2-thione* **6b** as a yellow oil (1.35 g, 80%); δ_H (300 MHz, $CDCl_3$) 7.03 (1H, s, *H*CS), 1.65-0.90 (27H, $Sn(C_4H_9)_3$); *m/z* (EI) 424 (M^+, 35%), 367 (40), 291 (90), 177 (100); found M^+ 424.0378; $C_{15}H_{28}S_3Sn$ requires *M* 424.0371.

4-(Quinoxalin-2-yl)-1,3-dithiole-2-thione 7a

To 4-tri-*n*-butylstannyl-1,3-dithiole-2-thione **6b** (0.15 ml, 0.47 mmol) and 2-chloroquinoxaline (63 mg, 0.38 mmol) in degassed PhMe (2 ml) was added $Pd(PPh_3)_4$ (*ca.* 5 mg) then the solution was heated at reflux under

argon for 2 h. After concentration *in vacuo*, the resultant brown oil was purified by chromatography, eluting with CH_2Cl_2, to give 4-(quinoxalin-2-yl)-1,3-dithiole-2-thione **7a** as a yellow solid (10 mg, 10 % or 24 % on the basis of recovered chloroquinoxaline) which was identical with previously prepared material.[6b]

4-(1-Hydroxyethyl)-1,3-dithiole-2-thione 6c

To 1,3-dithiole-2-thione **6a** (0.348 g, 2.6 mmol) in THF (3 ml), under nitrogen at dry ice/Me_2CO bath temperature was added LDA (2.07 ml, 1.5 M in hexanes, 3.1 mmol) dropwise by syringe, with efficient stirring, and the solution was allowed to stand for 1 h. Ethanal (0.19 ml freshly distilled from $NaHCO_3$, 3.4 mmol) was added with stirring, the mixture allowed to warm to rt over 20 min then quenched by addition of sat. aq. NH_4Cl (10 ml). The aq. phase was separated and extracted with EtOAc (15 ml). The combined organic phases were washed with brine (15 ml), dried and the solvent evaporated *in vacuo* to give a yellow oil which was purified by chromatography when CH_2Cl_2:MeOH, 97:3 eluted *4-(1-hydroxyethyl)-1,3-dithiole-2-thione* **6c** as a yellow oil (0.372 g, 81%), δ_H (200 MHz, $CDCl_3$) 6.89 (1H, s, *H*CS), 4.85 (1H, m, MeC*H*OH), 2.55 (1H, bs, O*H*), 1.54 (3H, d, J 6.4, CH_3); *m/z* (CI) 179 (MH^+, 100%); found M^+ 177.9586, $C_5H_6OS_3$ requires M 177.95808.

4-(1-Hydroxyethyl)-5-tri-*n*-butylstannyl-1,3-dithiole-2-thione 6d

To 1,3-dithiole-2-thione **6a** (204 mg, 1.52 mmol) in dry THF (4 ml) under nitrogen at dry ice/Me_2CO bath temperature LDA (1.06 ml, 1.5 M in cyclohexane, 1.6 mmol) was added dropwise by syringe with efficient stirring. After 30 min freshly distilled ethanal (90µl, 1.6 mmol) was added by cold syringe, followed after a further 30 min by LDA (1.06 ml, 1.6 mmol). The oily solution was stirred for 15 min then warmed to dry ice/MeCN bath temperature, and after 40 min tri-*n*-butyltin chloride (0.43 ml, 1.6 mmol) was added by syringe. The solution was warmed to -3 °C over 40 min then quenched with sat. aq. NH_4Cl (15 ml). The organic phase was diluted with EtOAc (15 ml), separated and the aq. phase re-extracted with EtOAc (15 ml). The organic phases were washed with brine (15 ml), dried and evaporated *in vacuo* to yield a red oil which was purified by chromatography, eluting with EtOAc:petroleum ether (40/60), 1: 9. After elution of an unidentified byproduct, *4-(1-hydroxyethyl)-5-tri-n-butylstannyl-1,3-dithiole-2-thione* **6d** (285 mg, 40%) was obtained as an oil, δ_H (200 MHz, $CDCl_3$) 4.75 (1H, m, MeC*H*OH), 2.2 (1H, bs, O*H*), 1.7-0.8 (30H, m, $(C_4H_9)_3Sn$, CH_3CHOH); *m/z* (EI) 468 (M^+, 5%), 411 (50), 269 (62); found $[M\text{-}Bu]^+$ 410.9929; $C_{13}H_{23}S_3OSn$ requires [*M-Bu*] 410.9932.

4-(1-([2-Methoxyethoxy]methoxy)ethyl)-1,3-dithiole-2-thione 6e

4-(1-Hydroxyethyl)-1,3-dithiole-2-thione **6c** (143 mg, 0.8 mmol), dried by azeotroping once with toluene, in dry THF (3 ml) under nitrogen at rt was reacted with LDA (0.59 ml, 1.5M in hexanes, 0.9 mmol), followed after 3 min by MEM chloride (110 µl, 0.96 mmol). After 21 h at rt the solution was diluted with EtOAc (15 ml), washed with sat. aq. NH_4Cl then with brine (15 ml) dried and the solvent removed *in vacuo* to give a tan oil which was purified by chromatography, eluting with CH_2Cl_2 to give *4-(1-([2-methoxyethoxy]methoxy)ethyl)-1,3-dithiole-2-thione* **6e** as a pale yellow oil (55 mg, 26%), δ_H (200MHz, $CDCl_3$) 6.88 (1H, s, *H*CS), 4.79 (1H, m, partially obscured by overlapping adjacent singlet, C*H*), 4.75 (2H, s, CH_2), 3.82-3.52 (4H, overlapping ms, 2xCH_2), 3.40 (3H, s, CH_3), 1.52 (3H, d, J 6.2 Hz, CH_3CHO); *m/z* (CI) 284 (MNH_4^+, 20%), 267 (MH^+, 100), 161 (15), 146 (15); found M^+ 266.01009, $C_9H_{14}O_3S_3$ requires *M* 266.0105.

4-(1-([2-Methoxyethoxy]methoxy)ethyl)-5-tri-*n*-butylstannyl-1,3-dithiole-2-thione 6f

To 4-(1-([2-methoxyethoxy]methoxy)ethyl)-1,3-dithiole-2-thione **6e** (90 mg, 0.34 mmol) in THF (2 ml) under nitrogen and at dry ice/Me_2CO bath temperature was added LDA (0.34 ml, 1.5 M in hexanes, 0.5 mmol)

dropwise by syringe. After stirring for 1 h, Bu_3SnCl (0.12 ml, 0.4 mmol) was added, the mixture was allowed to warm to rt over 2 h. Sat. aq. NH_4Cl (15 ml) was added, the organic phase was diluted with EtOAc (20 ml), separated, and the the aq. phase re-extracted with EtOAc. The combined organic phases were washed once with brine, dried and the solvent evaporated *in vacuo* to give a brown oil. This was purified by chromatography, eluting with EtOAc:petroleum ether (40/60) 1:9. The first major eluting component was *4-(1-([2-methoxyethoxy]methoxy)ethyl)-5-tri-n-butylstannyl-1,3-dithiole-2-thione* **6f** (88 mg, 47%) as an oil, δ_H (200MHz, $CDCl_3$) 4.69 (2H, s, CH_2), 4.64 (1H, partially obscured by overlapping singlets, q, J 6.5, OC*H*CH_3), 3.83-3.51(4H, overlapping ms, 2xCH_2), 3.37 (3H, s, OCH_3), 1.7-0.8 (30H, overlapping ms, $(C_4H_9)_3Sn$, CH_3); *m/z* (EI) 555 (M^+, 5%), 499 (25), 469 (10), 395 (20), 319 (30), 267 (40); found $[M\text{-}Bu]^+$ 499.0451, $C_{19}H_{31}O_3S_3Sn$ requires [*M-Bu*] 499.0456.

i-Propyl ([4-hydroxybut-2-yn-1-yl]sulfanyl)methanethioate 8

To 1-chlorobut-2-yn-4-ol[12] (14.58 g, 0.139 mol) in THF (100 ml) was added potassium *iso*-propyl xanthate (29.5 g, 0.153 mol) portionwise over 10 min with efficient stirring. A slow exothermic reaction occurred over the following 30 min, the temperature of the mixture reaching 40 °C. The mixture was stirred for 90 min then washed with sat. aq. NH_4Cl (70 ml). The aq. phase was separated and re-extracted with Et_2O (2x50 ml); the combined organic phases were washed with brine (2x20 ml), dried and evaporated *in vacuo* to give *i-propyl ([4-hydroxybut-2-yn-1-yl]sulfanyl)methanethioate* **8** (27.87 g, 98%) as a pale yellow oil, which was of sufficient purity for direct use in the next reaction, δ_H (300 MHz, $CDCl_3$) 5.80 (1H, m, C*H*), 4.33 (2H, t, J 2.2, CH_2), 3.93 (2H, t, J 2.2, CH_2), 1.70 (1H, bs, O*H*), 1.46 (6H, d, J 6.1, $CH(CH_3)_2$); *m/z* (CI) 222 (MNH_4^+, 50%), 205 (MH^+, 100); found M^+ 204.0282, $C_8H_{12}O_2S_2$ requires *M* 204.0279.

4-Ethenyl-1,3-dithiol-2-one 9a

Isopropyl ([4-hydroxybut-2-yn-1-yl]sulfanyl)methanethioate **8** (5.52 g, 27 mmol) in CH_2Cl_2 (15 ml) was added dropwise over 1.5 h to CF_3CO_2H (25 ml) cooled in an ice-bath under nitrogen and with efficient stirring. The mixture was maintained at 4 °C for 48 h, then the trifluroacetic acid evaporated *in vacuo* and traces of acid removed by azeotroping twice with Et_2O. The resultant oil was absorbed onto silica and further purified by chromatography, elution with CH_2Cl_2:petroleum ether (40/60), 1:3 giving *4-ethenyl-1,3-dithiol-2-one* **9a** (2.0 g, 51%) as a colourless oil, δ_H (300 MHz, $CDCl_3$) 6.64 (1H, d, J 0.5, *H*CS), 6.53 (1H, ddd, J 0.7, 10.8, 17.2, C*H*), 5.39 (1H, dd, J 0.4, 10.7, one of CH_2), 5.32 (1H, dd, J 0.5, 17.2, one of CH_2); *m/z* (CI) 162 (MNH_4^+, 30%), 145 (MH^+, 100), 116 (30); found M^+ 143.9708, $C_5H_4S_2O$ requires *M* 143.9704.

4-(1,2-Dihydroxyethyl)-1,3-dithiol-2-one 9b

4-Ethenyl-1,3-dithiol-2-one **9a** (2 g, 13.8 mmol) was dissolved in Me_2CO:H_2O, 1:1 (20 ml) and to this was added *N*-methylmorpholine *N*-oxide (1.95 g, 16.6 mmol) and OsO_4 (64 mg, 0.25 mmol). The mixture was stirred for 5.5 h at rt, evaporated *in vacuo* below 40 °C and the resultant oil purified by chromatography eluting with CH_2Cl_2:MeOH, 92:8 to give *4-(1,2-dihydroxyethyl)-1,3-dithiol-2-one* **9b** as a colourless oil (2.05 g, 83%), δ_H (300 MHz, CD_3OD) 6.92 (1H, s, C*H*S), 4.63 (1H, t, J 5.5, C*H*OH), 3.30 (2H, d, J 5.7, CH_2); *m/z* (CI) 196 (MNH_4^+, 100%), 178 (MH^+, 20); found M^+ 177.9759, $C_5H_6O_3S_2$ requires *M* 177.9758.

4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one 9c

4-(1,2-Dihydroxyethyl)-1,3-dithiol-2-one **9b** (2.05 g, 11.5 mmol) dried by azeotroping (2xMeCN) was dissolved in dimethoxypropane (10 ml) and toluene-*para*-sulfonic acid (50 mg) added. After standing for 16 h,

the mixture was concentrated to a small volume *in vacuo* and purified by chromatography eluting with CH_2Cl_2 to give *4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one* **9c** as a colourless oil (2.09 g, 83%), δ_H (300 MHz, $CDCl_3$) 6.61 (1H, d, J 0.8, *H*CS), 4.89 (1H, t, J 6.2, OC*H*), 4.19 (1H, dd, J 6.5, 8.8, CH_2), 3.85 (1H, dd, J 8.8, 6.0, CH_2), 1.42 (3H, s, CH_3), 1.34 (3H, s, CH_3); *m/z* (CI) 236 (MNH_4^+, 40%), 219 (MH^+, 30), 178 (70), 161 (100); found M^+ 218.0070, $C_8H_{10}O_3S_2$ requires *M* 218.0071.

4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-tri-*n*-butylstannyl-1,3-dithiol-2-one 5

To 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one **9c** (281 mg, 1.29 mmol) and tri-*n*-butylstannyl chloride (0.42 ml, 1.55 mmol) in dry THF (2 ml) under nitrogen at liquid nitrogen/EtOAc bath temperature, LDA (1.03 ml, 1.5M in hexanes, 1.55 mmol) was added dropwise over two minutes and the resultant solution allowed to warm to -8 °C during 1 h. Sat. aq. NH_4Cl (15 ml) was added, the organic phase was diluted with EtOAc (20 ml), separated and the aq. phase re-extracted with EtOAc (2x15 ml). The combined organic extracts were dried and the solvents evaporated *in vacuo* to give a yellow oil which was purified by chromatography, eluting with CH_2Cl_2:petroleum ether (40/60), 1:1 to give *4-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-tri-n-butylstannyl-1,3-dithiol-2-one* **5** (438 mg, 67%), δ_H (200 MHz, $CDCl_3$) 4.71 (1H, m, C*H*), 4.18 (1H, dd, J 6.3 and 8.7, CH_2), 3.90 (1H, dd, J 7.4, 8.6, CH_2), 1.59-0.88 (33H, $(C_4H_9)_3Sn$, $C(CH_3)_2$); *m/z* (CI) 526 (MNH_4^+, 30%), 509 (MH^+, 95), 432 (10), 393 (30), 308 (100); found $[M\text{-}Bu]^+$ 451.0421, $C_{16}H_{27}S_2O_3Sn$ requires [*M-Bu*] 451.0422.

4-(1*R*-1,2-Dihydroxyethyl)-1,3-dithiol-2-one *R*-9b

4-Ethenyl-1,3-dithiol-2-one **9a** (3.125 g, 21.7 mmol) was added to a well stirred mixture of *t*-butanol (108 ml) and water (108 ml) containing AD mix-α (30.4 g) and precooled to ice-bath temperature. Stirring at 4 °C was continued for 17 h, after which Na_2SO_3 (30 g) was added and stirring continued for 15 min. The mixture was filtered through celite washed through with EtOAc:*t*-butanol, 1:1 (2x50 ml). The combined filtrate and washings were separated, and the resultant aq. phase re-extracted with EtOAc:*tert*-butanol, 1:1 (20 ml). The combined organic phases were washed with brine (2x20 ml), dried and the solvents evaporated *in vacuo* to give an oil identified as *4-(1R-1,2-dihydroxyethyl)-1,3-dithiol-2-one R*-**9b** (3.65 g, 96%), $[\alpha]_D^{23}$ +6.8 (*c* 3.4, MeOH), which was identical as judged by ^1H NMR spectroscopic and TLC analysis to the racemic sample obtained above and of sufficient purity for the next reaction; the enantioselectivity was determined by chiral GC analysis of the resultant acetonide *R*-**9c** to be 94.4%.

4-(4*R*-2,2-Dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one *R*-9c

To 4-(1*R*-1,2-dihydroxyethyl)-1,3-dithiol-2-one *R*-**9b** (3.65 g, 20.7 mmol) pre-dried by azeotroping (2x acetonitrile) was added dimethoxypropane (10 ml) and toluene-*para*-sulfonic acid (50 mg) added. An oily suspension was formed, which during 16 h stirring did not disperse. However, removal of excess dimethoxypropane *in vacuo*, absorption of the oily product onto silica and purification by chromatography yielded a colourless oil, *4-(4R-2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one R*-**9c** (2.8 g, 62%), $[\alpha]_D^{23}$ +15.5 (c 2.4, $CHCl_3$) which was spectroscopically identical to the racemic material, **9c**. Chiral GC analysis of the material showed the ratio of enantiomers to be 97.2:2.8 (CP-Chirasil-DEX-CB) and hence the enantioselectivity of the dihydroxylation was determined to be 94.4%.

4-(4*R*-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-tri-*n*-butylstannyl-1,3-dithiol-2-one *R*-5

4-(4R-2,2-Dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one R-**9c** (2.75 g, 12.6 mmol), dried by azeotroping (3xPhH) and tri-*n*-butylstannyl chloride were dissolved in dry THF (25 ml) under argon. The solution was

cooled to liquid nitrogen/EtOAc bath temperature and LDA (9.7 ml, 1.5M in hexanes, 14.5 mmol) was added portionwise over 5 min by syringe and with efficient stirring. The solution was allowed to warm to -10 °C over 30 min then quenched by addition of sat. aq NH_4Cl (20 ml) and after 5 min vigorous stirring, the organic phase was diluted with EtOAc (20 ml), separated and the aq. phase re-extracted with EtOAc (2x30 ml). The combined organic phases were dried and evaporated *in vacuo* to give a yellow oil which was purified by chromatography, eluting with CH_2Cl_2:petroleum ether (40/60), 1:1 to give *4-(4R-2,2-dimethyl-1,3-dioxolan-4-yl)-5-tri-n-butylstannyl-1,3-dithiol-2-one R*-**5** (6.2 g, 97%), $[\alpha]_D^{23}$ +7.3 (c 1.7, $CHCl_3$), identical by spectroscopic analyses to the racemic material **5**.

4-Methyl-5-tri-*n*-butylstannyl-1,3-dithiol-2-one 9e

4-Methyl-1,3-dithiol-2-one **9d**[9] (1.177 g, 8.92 mmol) and tri-*n*-butylstannyl chloride (2.9 ml, 10.7 mmol) in dry THF (10 ml) under argon were cooled to dry ice/Et_2O bath temperature and LDA (6.5 ml, 1.5M in hexanes, 9.8 mmol) was added dropwise over 3 min then the mixture allowed to stand for 35 min, warmed to ice-bath temperature and after a further 10 min quenched with sat. aq. NH_4Cl (20 ml). The organic phase was diluted with EtOAc, separated and the aq. phase re-extracted with Et_2O (2x15 ml). The combined organic phases were washed with brine, dried and the solvents evaporated *in vacuo* to give a tan oil. This was purified by chromatography, eluting with EtOAc:petroleum ether (40/60), 3:97 to give *4-methyl-5-tri-n-butylstannyl-1,3-dithiol-2-one* **9e** (3.33 g, 89%), δ_H (300 MHz, $CDCl_3$) 2.24 (3H, s, CH_3), 1.7-0.9 (27H, m, $Sn(C_4H_9)$); *m/z* (CI) 423 (MH^+, 100%), 308 (20); found M^+ 422.0758, $C_{16}H_{30}S_2OSn$ requires *M* 422.0759.

4-Methyl-5-trimethylsilyl-1,3-dithiol-2-one 9f

A mixture of 4-methyl-1,3-dithiol-2-one **9d** (0.544 g, 4.12 mmol) and trimethylsilyl chloride (freshly distilled from CaH_2; 0.78 ml, 6.2 mmol) in dry THF (5 ml) under argon was cooled to dry ice/Et_2O bath temperature. LDA (3.3 ml, 4.9 mmol) was added dropwise by syringe over two min and the solution was allowed to warm to 0 °C over 2 h. Sat. aq. NH_4Cl was added, the organic phase was diluted with EtOAc (20 ml), separated and the aq. phase re-extracted with EtOAc (15 ml). The combined organic phases were washed with brine, dried and the solvents were evaporated *in vacuo* to give a red oil which was purified by chromatography, eluting with EtOAc:petroleum ether (40/60), 3:97 to give *4-methyl-5-trimethylsilyl-1,3-dithiol-2-one* **9f** (541 mg, 64%) as a colourless oil which crystallised on standing. An analytical sample was recrystallised (95% EtOH) to mp 31-34 °C, found C, 40.66; H, 5.79; S, 31.37%; M^+ 204.0098. $C_7H_{12}S_2OSi$ requires C, 41.14; H, 5.92; S, 31.37%; *M* 204.0088; δ_H (300 MHz, $CDCl_3$) 2.25 (3H, s, CH_3), 0.2 (9H, s, $Si(CH_3)_3$); *m/z* (CI) 222 (MNH_4^+, 25%), 205 (MH^+, 100%).

4-Iodo-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one 9g

4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one (0.205 g, 0.94 mmol) and $ZnCl_2$ (0.52 ml, 1M in Et_2O, 0.52 mmol) were dissolved in dry THF (2.5 ml) under argon. The solution was cooled to dry ice/Me_2CO bath temperature and *t*-BuLi (0.82 ml, 1.5M in hexanes, 1.22 mmol) was added dropwise over 1.5 minutes by syringe. The solution was stirred for 15 min, warmed to rt over 5 min and then I_2 (285 mg, 1.1 mmol) was added, under a positive pressure of argon. After five min stirring, sat. aq. NH_4Cl (15 ml) was added, the organic phase was diluted with EtOAc (15 ml), separated and the aq. phase re-extracted with EtOAc (15 ml). The combined organic phases were washed with aq. $Na_2S_2O_4$ (1M, 20 ml), once with brine (20 ml), then dried and the solvents evaporated *in vacuo* to give a tan oil which was purified by chromatography, eluting with CH_2Cl_2/petroleum ether (40/60); 7:3 to give *4-iodo-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one* **9g** as

a pale yellow oil (120 mg, 37%); δ_H (200 MHz, $CDCl_3$) 5.09 (1H, t, J 6.4, C*H*), 4.37 (1H, dd, J 6.5, 8.8, CH_2), 3.83 (1H, dd, J 6.35, 8.8, CH_2), 1.5 (3H, s, CH_3), 1.42 (3H, s, CH_3); *m/z* (+ve FAB, 3-nba) 344 (M^+, 100%), 221 (65); found M^+ 343.9042, $C_8H_9S_2O_3I$ requires *M* 343.9040.

4-Iodo-5-methyl-1,3-dithiol-2-one 9h

To 4-methyl-5-tri-*n*-butylstannyl-1,3-dithiol-2-one **9e** (3.33 g, 7.9 mmol) in CH_2Cl_2 (24 ml) at ice-bath temperature, I_2 (2.09 g, 7.9 mmol) was added with efficient stirring. After 30 min, 1M aq. $Na_2S_2O_3$ (20 ml) was added and the mixture stirred until colourless. The aq. phase was separated and extracted with CH_2Cl_2 (2x15 ml). The combined organic phases were washed with brine (15 ml), dried and the solvent evaporated *in vacuo* to give a yellow oil which crystallised slowly on standing. Recrystallisation from petroleum ether (40/60) gave *4-iodo-5-methyl-1,3-dithiol-2-one* **9h** as pale yellow crystals (1.158 g). The mother liquors were concentrated *in vacuo* and purified by chromatography, eluting with EtOAc:petroleum ether (40/60); 3:97, to give a further quantity of product (0.52 g, combined yield 1.678 g, 83%), mp (95% EtOH) 41-42 °C; δ_H (200 MHz, $CDCl_3$) 2.29 (s, CH_3); *m/z* (CI) 276 (MNH_4^+, 40%), 258 (MH^+, 100), 234 (20), 230 (20), 120 (30); found C, 18.94; H, 1.22; S, 25.01%, $C_4H_3S_2OI$ requires C, 18.61; H, 1.17; S, 24.84%.

2-Ethylquinoxaline

2-Chloroquinoxaline (95 mg, 0.58 mmol) and $Pd(PPh_3)_2Cl_2$ (12 mg, 0.017 mmol) were dissolved in dry THF (3 ml) at rt with stirring and under argon. Diethylzinc (1.16 ml, 1M in hexanes, 1.16 mmol) was added causing an immediate exothermic reaction and darkening, then iodobenzene (100 µl, 0.89 mmol) was added, hoping for a coupling process. After a further 115 min stirring (when TLC analysis had shown complete consumption of 2-chloroquinoxaline), sat. aq. NH_4Cl (15 ml) was added, the organic phase was diluted with EtOAc, separated and washed with aq. 5% TMEDA (15 ml), the biphasic mixture filtered through celite to break up an emulsion, the aq. phase separated and re-extracted with EtOAc (15 ml). The extracts were washed with brine (15 ml), dried and evaporated *in vacuo* to give an oil, which was purified by chromatography when CH_2Cl_2:MeOH, 98.5:1.5 gave 2-ethylquinoxaline as a colourless oil (83 mg, 94%), the ^1H NMR and other spectroscopic properties of which were identical to those reported.[21]

4-Methyl-5-(2-nitrophenyl)-1,3-dithiol-2-one 9i and *bis*-(5-methyl-1,3-dithiol-2-on-4-yl) 10

To 4-methyl-5-tri-*n*-butylstannyl-1,3-dithiol-2-one **9e** (183 mg, 0.43 mmol) and 2-iodonitrobenzene (108 mg, 0.43 mmol) in NMP (3 ml) was added CuTC (124 mg, 6.5 mmol) and vigourous stirring was continued for 40 min at rt. The reaction mixture was poured into water (20 ml) and extracted with EtOAc (15 ml), the biphasic mixture filtered through celite to remove solid material, the aq. phase separated and extracted with EtOAc (2x15 ml) and the combined organic phases washed with brine (15 ml), dried and the solvent evaporated *in vacuo* to give a yellow oil. This was subjected to chromatography, eluting initially with EtOAc:petroleum ether (40/60), 1:9, then 15:85 then 1:4. Both products were contaminated by tin compound residues, as judged by ^1H NMR spectroscopic analysis. The first eluted was *bis-(5-methyl-1,3-dithiol-2-on-4-yl)* **10**, (45 mg, 40%) an analytical sample of which was obtained by recrystallisation (95% EtOH); mp 130-132 °C; δ_H (200 MHz, $CDCl_3$) 2.25 (s, CH_3); *m/z* (CI) 279 (MNH_4^+, 20%), 263 (MH^+, 100), 165 (40); found C, 36.62; H, 2.36; S, 48.20%; $C_8H_6O_2S_4$ requires C, 36.62; H, 2.31; S, 48.88%. The second eluted was *4-methyl-5-(2-nitrophenyl)-1,3-dithiol-2-one* **9i** (59 mg, 54%), δ_H (200 MHz, $CDCl_3$) 8.05 (1H, dd, J 1.6, 7.9, Ar*H*), 7.71-7.62 (2H, m, Ar*H*), 7.50 (1H, dd, J 2.1, 6.9, Ar*H*), 2.02 (3H, s, CH_3) (an impurity was present (~ 30 % by integration) which gave a number of minor signals in the aromatic region); *m/z* (EI) 253 (M^+, 25%), 223 (20) 198 (30), 59 (100); found M^+ 252.9868, $C_{10}H_7NO_3S_2$ requires *M* 252.9867.

4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one 4

To (±)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-tri-*n*-butylstannyl-1,3-dithiol-2-one **5** (250 mg, 0.49 mmol) and 2-iodoquinoxaline[20] (152 mg, 0.59 mmol) in NMP (3 ml) under argon at ice bath temperature, CuTC (141 mg, 0.74 mmol) was added under a positive pressure of argon. After vigorous stirring for 35 min, the mixture was diluted with CH_2Cl_2 and filtered through a plug of alumina washed through with CH_2Cl_2:MeOH, 92:8 and the resultant filtrate and washings were concentrated *in vacuo* to give an oil which partially crystallised on standing. This was purified by chromatography when CH_2Cl_2:MeOH, 98:2 gave a mobile oil which contained a substantial quantity of tin compound residues, judging by the appearance. Crystallisation from EtOAc gave *4-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one* **4** (76 mg, 45%), mp 150-152 °C; δ_H (300 MHz, $CDCl_3$) 8.83 (1H, s, quinoxalin-2-yl-*H*), 8.10-7.96 (2H, m, Ar*H*), 7.8-7.74 (2H, m, Ar*H*), 5.67 (1H, t, J 6, *CH*(O)CH_2), 4.68 (1H, dd, J 6.8, 8.9, one of *CH*$_2$), 4.05 (1H, dd, J 5.9, 8.9, one of *CH*$_2$), 1.50 (3H, s, *CH*$_3$), 1.37 (3H, s, *CH*$_3$); *m/z* (CI) 347 (MH^+, 100%); found C, 55.46; H, 4.07; N, 8.01; S, 18.47%; $C_{16}H_{14}N_2S_2O_3$ requires C, 55.47; H, 4.07; N, 8.09; S, 18.51%.

4-Methyl-5-(quinoxalin-2-yl)-1,3-dithiol-2-one 7b

A mixture of 2-iodoquinoxaline (421 mg, 1.64 mmol) and 4-methyl-5-tri-*n*-butylstannyl-1,3-dithiol-2-one (760 mg, 1.8 mmol) in NMP (5 ml) under argon, was cooled to ice-bath temperature then CuTC (470 mg, 2.46 mmol) added and the resultant mixture vigorously stirred for 35 min. The mixture was diluted with CH_2Cl_2 (20 ml), filtered to remove a bulky red brown solid which was then washed thoroughly with CH_2Cl_2. The combined filtrate and washings were shaken for 5 min with 5% aq. TMEDA (20 ml). The biphasic mixture was filtered through a plug of alumina to obtain a coppery solid which retained the product. The solid was thoroughly shaken twice with aq. TMEDA (5%) and CH_2Cl_2, then organic extract washied with aq. $Na_2S_2O_5$ (1M), a further time with aq. TMEDA, once with brine, then dried and the solvent evaporated to give a green solid which was further purified by flash chromatography to give *4-methyl-5-(quinoxalin-2-yl)-1,3-dithiol-2-one* **7b** as a tan solid (188 mg, 44%); mp (EtOH) 134-136 °C, δ_H (300 MHz, $CDCl_3$) 8.96 (1H, s, quinoxalin-3-yl–H), 8.05 (2H, m, ArH), 7.75 (2H, m, ArH), 2.55 (3H, s, CH_3); *m/z* (CI) 261 (MH^+, 100%), 203 (20); found M^+ 260.0068; C, 55.21; H, 3.00; N, 10.54; S, 24.90%; $C_{11}H_8N_2S_2O$ requires *M* 260.0078; C, 55.36; H, 3.10; N, 10.76; S, 24.63%.

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