The synthesis of pyrano[2,3-*b*]quinoxalines related to molybdopterin

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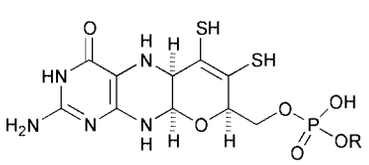
Two cobalt complexes, **5** and **7**, both containing 11,11a-dihydropyrano[2,3-*b*]quinoxaline nuclei, were synthesised as model substances for the molybdenum cofactor of the oxomolybdoenzymes. The organic proligands for the ene-1,2-dithiolates, from which these complexes were formed, were 1,3-dithiol-2-ones, the dianionic ligands being liberated by reaction with caesium hydroxide. The pyran ring in the tetracyclic 1,3-dithiol-2-one proligands, **4b** and **6**, was formed by ring closure of the side-chain alcohol in a 4-(1-hydroxyalkyl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one onto an aromatic quinoxaline *via* reaction with a chloroformate, generating 6-alkyloxycarbonyl-2-oxo-5a,6-dihydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxalines which were then reduced with cyanoborohydride to give 6-alkyloxycarbonyl-5a,6,11,11a-tetrahydro-2-oxo-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxalines – the proligands.

Introduction

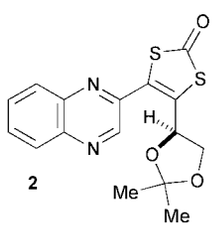
Molybdenum is an essential trace element for all living systems.[1,2,3] This metal acts as a vital component of the catalytic centre of the nitrogenases and of an extensive family of enzymes, each of which transfers an oxygen atom to, or from, the substrate. This latter family of molybdoenzymes includes xanthine dehydrogenases, aldehyde oxidases, sulfite oxidases, nitrate reductases, and DMSO reductases. Tungsten has also been shown to be present at the catalytic centre of enzymes, and it is notable that many of tungstoenzymes occur in thermophilic bacteria.[3,4] In all of the molybdo- and tungsto-enzymes, the metal atom is bound to the dianion(s) (ene-1,2-dithiolate) of one or two molecules of a special ligand, molybdopterin (MPT) **1**.



1
molybdopterin (MPT)
R = H or a dinucleotide

The nature of MPT has been established, following a series of biochemical investigations by Rajagopalan *et al.*[5] and several protein crystallographic studies of representative molybdo- and tungsto-enzymes.[1–4] MPT is chemically intriguing; it is a tricyclic pyranopterin, the pyran ring of which carries an ene-1,2-dithiol (or dithiolene) and the side-chain a phosphate group. In all of the native enzymes so far structurally characterised, the pterin is at the dihydro oxidation level and the dithiolene group acts as a bidentate ligand to bind Mo (or W); in some bacterial enzymes the phosphate group is covalently linked to a dinucleotide (R in **1**).

We have developed a strategy for the synthesis of MPT.[1,6,19] This approach should enable MPT to be characterised as an isolated, though protected, chemical species. Also, complexes of Mo and W (and other metals) could be synthesised, characterised, and their properties determined for comparison with those of the catalytic centres of the molybdo- and tungsto-enzymes. Additionally, these investigations should allow us to examine the possible roles[7,8] of MPT in the catalyses accomplished by these enzymes. In parallel with our work on pteridines, we have developed routes that permit the synthesis of the corresponding quinoxaline compounds. We have described linear syntheses[9] of such quinoxalines, but the most efficient route[10] to key intermediate **2**, is a coupling of 2-iodoquinoxaline with the tin compound **3**, using copper thiophene-2-carboxylate as stoichiometric mediator.[11]



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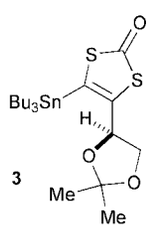

3

We have also described in preliminary form[12,13] our method for the construction of the third ring – the pyran ring. In this paper we detail the synthesis of pyrano-quinoxalines **4a** and **4b**, and from **4b**, cobalt complex **5**, and the latter stages of our synthetic route from **2** to proligand **6** and its conversion into a cobalt complex, **7**.

Results and discussion

For the synthesis of **4a** we chose to investigate an alternative route to a quinoxalin-2-yl-dithiole, based on the use of alkyne-ketone **9**. The Sonogashira coupling of 2-chloroquinoxaline[14] with but-3-yn-2-ol gave alcohol **8** in 79% yield. We showed that 2-tosyloxyquinoxaline or 2-trifluoromethylsulfonyloxyquinoxaline can also be utilised in this coupling (70% and 75% yields, respectively). Ketone **9**, obtained by Jones oxidation of **8**, was heated at 150 °C with 4-phenyl-1,3-dithiolane-2-thiole **12**[15]

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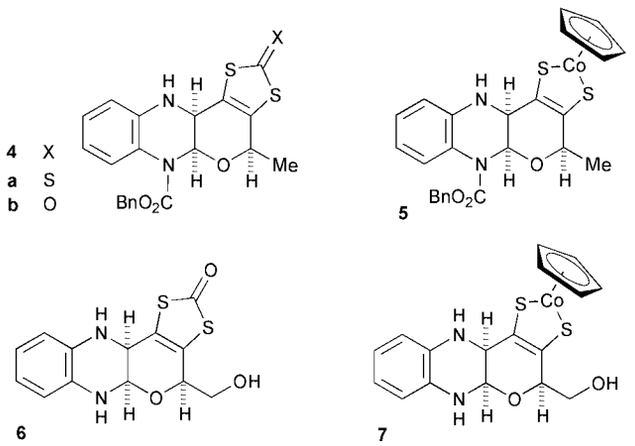
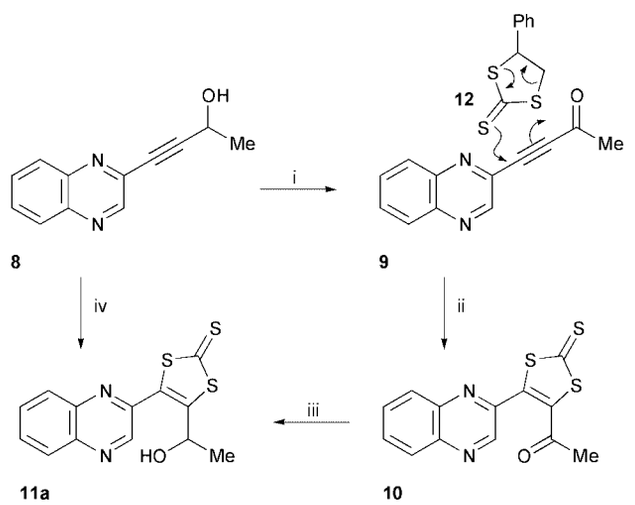


as reactant and solvent, leading to the formation of **10** in 81% yield. We assume that this process, which has clear precedents,[16,17] is electrocyclic in nature, and can be represented by the arrows in Scheme 1. It was reported[16] that the process proceeds better with the phenyl-substituted dithiolane used in the present work, than with 1,3-dithiolane-2-thiole itself, a conclusion consistent with our results, as the yield was only 27% using 1,3-dithiolane-2-thiole.



Scheme 1 *Reagents and conditions*: i, CrO_3, H_2SO_4, Me_2CO, 0 °C ⟶ rt (76%); ii, **12**, 150 °C, N_2 (94%); iii, $NaBH_4$, *i*-PrOH, H_2O, rt (54%); iv, **12**, $BF_3{\cdot}OEt_2$ (37%).

The work of O'Connor and Jones[16] also suggested that a necessary condition for the success of the process is the presence of at least one electron-withdrawing substituent on the alkyne. An attempt to utilise the alcohol **8**, hoping that the heterocyclic ring would be a sufficiently electron-withdrawing substituent, was unsuccessful under the conditions employed for reaction with the ketone. However, incorporation of boron trifluoride etherate into the reaction mixture *did* bring about reaction and the formation of **11a** in 37% yield; we assume that the Lewis acid interacts with the pyrazine ring, increasing its electron-withdrawing effect and promoting the cycloaddition. Although the yield is not high, the direct nature of this route makes it an effective procedure for the preparation of **11a**.

Borohydride reduction of **10** produced the alcohol **11a**; care was needed to use only a little more than one equivalent of reducing agent, since the presence of an excess led to reduction of the pyrazine ring too.

In previous work[18,19,20] we had shown that hydride reduction of 2-substituted quinoxalines in the presence of chloroformates leads to 2-substituted-4-acylated-1,2,3,4-tetrahydroquinoxalines *via* initial 4-acylation and then nucleophilic hydride addition. Our plan for the production of the tricyclic pyranoquinoxaline ring system was that 4-acylation of a 2-substituted quinoxaline would be followed by intramolecular nucleophilic addition of a side-chain alcohol oxygen leading to a pyranodihydroquinoxaline. We believed that the urethane group at N-4 in the product tricyclic system would prevent N–C–O cleavage, pyran-ring opening, and the rearomatisation which would be a consequence of this. It was clear that the desired sequence would also need to compete with simple *O*-acylation.

The reactions of alcohol **11a** with various combinations of benzyl chloroformate and 4-dimethylaminopyridine (DMAP) in dichloromethane always produced both the *O*-acylated product and the desired cyclised material, comprising both the stereoisomers **13a** and **14a** (Scheme 2). After considerable experimentation it was found that the use of neat benzyl chloroformate, as reactant and solvent, led to no *O*-acylation and produced an 8 : 1 (as established by ^{1}H NMR analysis) mixture of **13a** and **14a** in 61% yield. These isomers could not be separated. For the desired and dominant *cis*-isomer, an NOE was observed between the protons C-4 and C-5a establishing their *cis*-relationship.

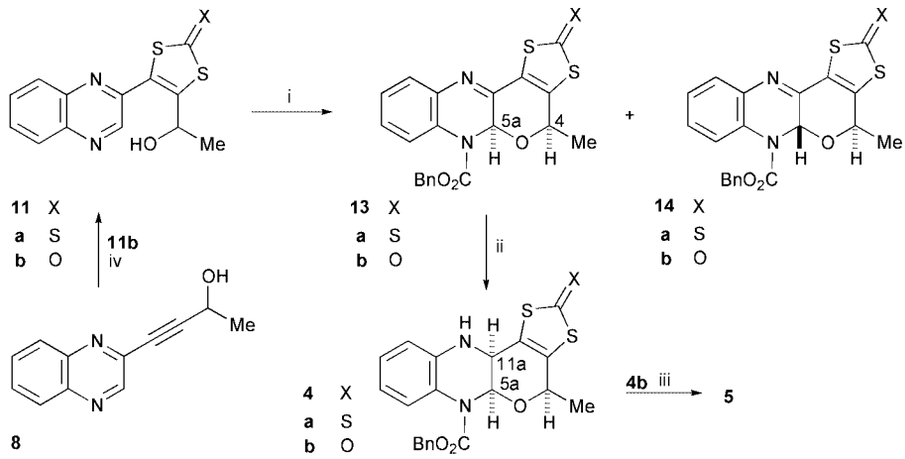
Reduction of the mixture of stereoisomers with sodium cyanoborohydride in the presence of acetic acid was stereospecific, a mixture of just two compounds being formed from which the major product, **4a** was isolated. The observed 1.4 Hz coupling constant between the protons at C-5a and at C-11a is consistent only with *cis* ring junction stereochemistry.

Attempted release of the dithiolate ligand from **4a** failed, the hydrolytic conditions required were too vigorous, the compound undergoing extensive degradation. We overcame this problem by using the carbonyl compound **4b**. To obtain **4b**, the sulfur of the alcohol **11a** was replaced with oxygen, using mercury(II) acetate, giving **11b**. The alcohol **11b** could also be obtained by a free radical synthesis[21,22] from the alkyne **8** by reaction with bis-isopropoxythiocarbonyldisulfane[23] which, despite a moderate yield, is the method of choice for the synthesis of this compound. Commencing with **11b**, a sequence of reactions comparable to that described above for the conversion of **11a** into **13a**–**14a** then led, presumably *via* a mixture of **13b** and **14b** (only **13b** was isolated) to **4b**. An NOE experiment established the *cis*-relationship between the protons at C-4 and C-5a in **13b** and both an NOE experiment and a coupling constant of 2.2 Hz for the protons at C-5a and C-11a in **4b** confirmed the relative stereochemistry.

Hydrolysis of the 1,3-dithiol-2-one unit in **4b** using caesium hydroxide followed by rapid trapping using cyclopentadienyldiiodocobalt(III)[24] produced compound **5** in an overall yield of 71% for the two chemical steps from **4b**.

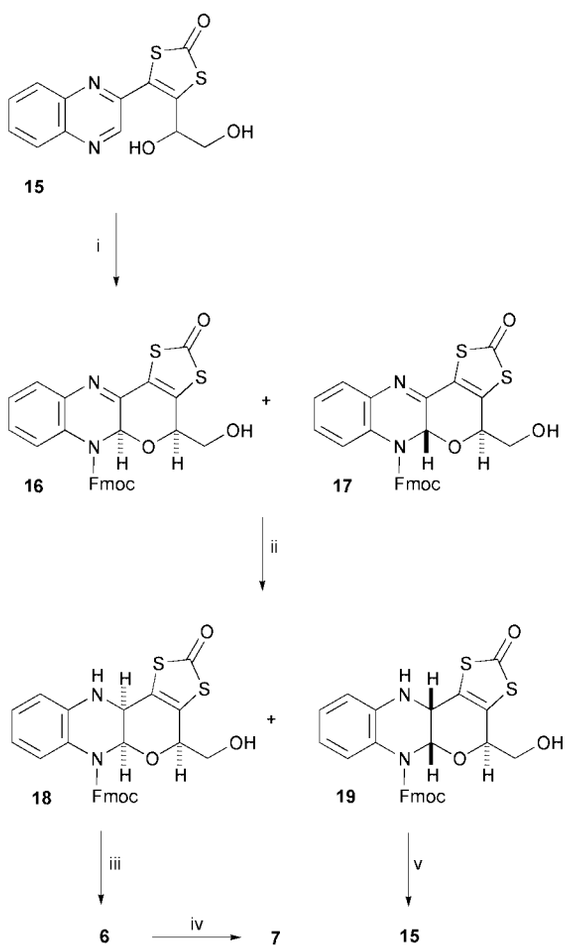
We now turned to the protected diol **2**,[10] a substance which more closely models the situation that we would have to face in approaching MPT itself, in giving us a substrate **15** with two side-chain alcohol groups, both of which could in principle participate in ring closure. Following removal of the acetal protection with toluene-*p*-sulfonic acid, giving **15**, reaction with 9*H*-fluoren-9-ylmethyl chloroformate (FmocCl) proceeded well under modified conditions – aqueous sodium hydrogen carbonate in dioxane at 35 °C – producing a 2 : 1 mixture of stereoisomers **16** and **17** which could not be separated. It is noteworthy that the terminal hydroxy group neither participated in ring closure, nor was it acylated by the chloroformate. Following cyanoborohydride reduction of the mixture of **16** and **17**, the desired all *cis* product **18** and its *trans* isomer **19** could be separated chromatographically, and each characterised. The successful synthesis of **18** allowed the stability of the pyranoquinoxaline system to be tested in the absence of the urethane protecting group.

A range of deprotection conditions were examined, which were successful in removing the protecting group, but not amenable to efficient isolation of the product. The best conditions for this purpose were diethylamine in THF[25] giving **6**, notably leaving the protected dithiolene and the pyran ring untouched. The undesired *trans*-isomer **19** could be recycled by removal of the Fmoc group in the same way and then exposure



Scheme 2 *Reagents and conditions*: i, $ClCO_2Bn$, rt (**13a** + **14a**, 61%; **13b**, 45%); ii, $NaB(CN)H_3$, AcOH, rt (**4a**, 62%; **4b**, 70%); iii, $CsOH{\cdot}H_2O$, MeOH, $CHCl_3$, rt then $cpCoI_2$ (71%); iv, $(i\text{-PrOCSS})_2$, AIBN, PhMe, reflux (41%).

to acidic conditions (silica chromatography) when pyran ring-opening and spontaneous oxidation returned the quinoxaline **15**. Hydrolysis of **6** with, caesium hydroxide followed by addition of cyclopentadienyldiiodocobalt(III) to the reaction solution afforded the cobalt dithiolene complex **7** in 55% yield from **6** (Scheme 3).



Scheme 3 *Reagents and conditions*: i, FmocCl, $NaHCO_3$, H_2O, 1,4-dioxane, 35 °C (**16** + **17**, 92%); ii, $NaB(CN)H_3$, AcOH, MeOH, CH_2Cl_2, 0 °C (**18**, 61%; **19**, 29%); iii, Et_2NH, THF, H_2O, 25 °C (80%); iv, $CsOH{\cdot}H_2O$, MeCN, CH_2Cl_2, rt then $cpCoI_2$ (55%); v, Et_2NH, THF, H_2O, 0 °C then SiO_2, air (~100%).

In the following paper, we describe how the synthetic strategy developed herein for this series of quinoxaline compounds has been applied to corresponding pteridine derivatives, leading to the synthesis of MPT in a protected form.

Experimental

General

Organic solutions were dried over anhydrous $MgSO_4$. Solid products were dried under reduced pressure using P_4O_{10} as a desiccant. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Inova-300 Athos (300 MHz) and Unity 500 (500 MHz) spectrometers. Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on an Inova-300 Athos spectrometer running at 75 MHz. All chemical shifts (δ) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). Signal splittings are reported as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), multiplet (m), and broad (br); *J* values are given in Hertz (Hz). UV spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer and are given in nm. IR spectra were recorded on an Ati Mattson Genesis Series FTIR spectrometer; only absorptions of importance to structure determination are listed. Mass spectra were recorded on a Fisons VG Trio 2000 (EI/CI{NH_3}/ES) (abundance relative to the base peak given in parenthesis as a percentage; only fragment ions of intensity ≥10% of the base peak are cited) and a Concept IS (MM/FAB) spectrometer for accurate mass determinations. Melting points were recorded on a Reichart heated stage microscope and are uncorrected. Flash column chromatography was carried out according to the method of Still *et al.*[26] using Merck 9385 silica gel 60 (230–400 mesh). All ethers were dried over Na wire and distilled under an atmosphere of dry Ar using benzophenone as an indicator of degree of hydration.

Dichloromethane, pyridine, and triethylamine were distilled from calcium hydride. Dimethylformamide was dried over 4 Å molecular sieves. Petroleum ether was the fraction bp 40–60 °C.

4-(Quinoxalin-2-yl)but-3-yn-2-ol 8

To a degassed solution of 2-chloroquinoxaline (20.0 g, 0.122 mol), butyn-2-ol (11.0 g, 0.157 mol), MeCN (300 ml) and Et_3N (150 ml) were added $Pd(OAc)_2$ (0.27 g, 1.2 mmol), Ph_3P (3.18 g, 0.012 mol) and CuI (2.31 g, 0.012 mol). The mixture was then refluxed for 2 h, cooled and filtered, and the filtrate was concentrated *in vacuo* and then the residue partitioned between H_2O (200 ml) and EtOAc (300 ml). The resulting mixture was filtered through Celite, the layers were separated and the aq. layer re-extracted with EtOAc (2 × 200 ml). The combined organic extracts were washed with brine (150 ml), dried and evaporated and the solid residue recrystallized from acetone to give *4-(quinoxalin-2-yl)but-3-yn-2-ol* **8** (13.2 g, 55%) as a light beige crystalline solid. A further quantity (6.0 g) was obtained by chromatography of the concentrated mother liquors (overall 19.2 g, 79%), mp 112–113 °C; λ_{max} (CH_2Cl_2)/nm 250, 310, 378, 456; ν_{max} (film)/cm^{-1} 3400, 2200, 1541; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.86 (1H, s, H-3′), 8.13 (2H, s, Ar*H*), 7.82 (2H, s, Ar*H*), 4.93 (1H, q, J = 6.6 Hz, H-2), 4.63 (1H, s, O*H*), 1.69 (3H, d, J = 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 141.8, 140.7, 138.8, 130.7, 130.6, 129.0, 96.1, 81.2, 58.3, 23.8; *m*/*z* (CI) 199 (MH^+, 100%), 183 (20), 155 (18); found C, 72.7; H, 5.2; N, 14.4%; HRMS, M^+, 198.0790. $C_{12}H_{10}N_2O$ requires C, 72.7; H, 5.1; N, 14.1%; *M*, 198.0793.

2-Tosyloxyquinoxaline

To a stirred solution of quinoxalin-2-one (2.5 g, 0.017 mol) DMAP (208 mg, 1.7 mmol) and toluene-*p*-sulfonyl chloride (6.42 g, 34 mmol) in CH_2Cl_2 at 0 °C was added Et_3N (5.9 ml, 43 mmol). After 1 h, sat. aq. $NaHCO_3$ (50 ml) was added, and the layers were separated and the aq. phase extracted with CH_2Cl_2 (2 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and the solvent removed. Purification by flash chromatography (silica, CH_2Cl_2) provided *2-tosyloxyquinoxaline* (4.34 g, 85%) as a brown solid, mp 83–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, s, H-3), 8.03 (2H, m, Ar*H*), 7.90 (2H, m, Ar*H*), 7.33 (2H, m, Ar*H*), 2.43 (3H, s, CH_3); *m*/*z* (CI) 301 (MH^+, 100%); found, HRMS, M^+, 300.3327. $C_{15}H_{12}N_2O_3S$ requires *M*, 300.3335.

2-Trifluoromethylsulfonyloxyquinoxaline

To a stirred solution of quinoxalin-2-one (1.7 g, 7.33 mmol) and Et_3N (1.32 ml, 9.53 mol) in CH_2Cl_2 (15 ml) at 0 °C was added Tf_2O (1.45 ml, 8.8 mmol) dropwise over 3 min. The mixture was stirred for 2 h then concentrated *in vacuo* and the residue purified by flash chromatography (silica, CH_2Cl_2) to provide *2-trifluoromethylsulfonyloxyquinoxaline* (1.59 g, 78%) as a brown oily solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, s, H-3), 8.24 (1H, m, Ar*H*), 8.09 (1H, m, Ar*H*), 7.92 (2H, m, Ar*H*); *m*/*z* (CI) 279 (MH^+, 100%); found, HRMS, M^+, 277.9968. $C_9H_5F_3N_2O_3S$ requires *M*, 277.9973.

4-(Quinoxalin-2-yl)but-3-yn-2-one 9

To a stirred solution of alcohol **8** (6.0 g, 0.03 mol) dissolved in acetone (250 ml) at 0 °C was added Jones' reagent (5.7 g, CrO_3, 23 ml H_2O, 8 ml H_2SO_4) dropwise. The mixture was stirred for 1 h and then allowed to warm to room temperature. H_2O (200 ml) and EtOAc (200 ml) were added, the layers were separated and the aq. layer was extracted with EtOAc (3 × 100 ml). The combined organic extracts were washed with sat. aq. $NaHCO_3$, brine (100 ml), and dried and the solvent evaporated. Purification by flash column chromatography (silica, 10–30% EtOAc in petroleum ether) provided *4-(quinoxalin-2-yl)but-3-yn-2-one* **9** (4.52 g, 76%) as a light beige crystalline solid, mp 205 °C; λ_{max} ($CHCl_3$)/nm 254, 266, 332; ν_{max} (film)/cm^{-1} 3295, 2370, 1673; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.2 (1H, s, H-3), 8.09 (2H, m, Ar*H*), 7.9 (2H, m, Ar*H*), 1.6 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 147.1, 142.1, 141.6, 136.8, 131.7, 131.1, 129.4, 129.3, 88.7, 84.8, 32.7; *m*/*z* (CI) 197 (MH^+, 100%), 183 (10), 145 (5); found C, 72.9; H, 4.2; N, 14.1%; HRMS, M^+ 196.0634. $C_{12}H_8N_2O$ requires C, 73.5; H, 4.1; N, 14.3%, *M*, 196.0634.

4-Acetyl-5-(quinoxalin-2-yl)-1,3-dithiole-2-thione 10

A solution of ketone **9** (400 mg, 2.04 mmol) and 4-phenyl-1,3-dithiolane-2-thione[15] (2.0 g, 9.4 mmol) in CH_2Cl_2 was concentrated on a rotary evaporator to produce a homogeneous solid. The flask was fitted with a condenser and then heated to 150 °C under N_2 for 35 min. Flash chromatography of the cooled reaction mixture (silica, CH_2Cl_2) provided *4-acetyl-5-(quinoxalin-2-yl)-1,3-dithiole-2-thione* **10** (0.58 g, 94%) as a yellow solid. Recrystallization from acetone gave **10** as fine yellow needles (0.5 g, 81%) mp 205 °C; λ_{max} (CH_2Cl_2)/nm 244, 364; ν_{max} (film)/cm^{-1} 1686, 1521; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.2 (1H, s, H-3′), 8.24 (1H, m, ArH), 8.15 (1H, m, ArH), 7.93 (2H, m, ArH), 2.35 (3H, s, Me); *m*/*z* (CI) 305 (MH^+, 100%), 231 (30), 199 (30); found C, 51.5; H, 2.4; N, 9.1; S, 31.0%; HRMS, M^+, 303.9799. $C_{13}H_8N_2S_3O$ requires C, 51.3; H, 2.7; N, 9.2; S, 31.6%, *M*, 303.9799.

4-(1-Hydroxyethyl)-5-(quinoxalin-2-yl)-1,3-dithiole-2-thione 11a

Method 1. To ketone **10** (1.32 g, 4.34 mmol) dissolved/suspended in THF (75 ml) was added $NaBH_4$ (60 mg, 1.58 mmol) dissolved in isopropanol (propan-2-ol) (9 ml) and H_2O (9 ml). After 15 min, sat. aq. NH_4Cl (25 ml) and EtOAc (100 ml) were added and the layers separated. The aq. layer was extracted with EtOAc (2 × 50 ml) and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), and the solvent evaporated, and the residue purified by flash chromatography (silica, 2 ⟶ 25% EtOAc in CH_2Cl_2) to provide *4-(1-hydroxyethyl)-5-(quinoxalin-2-yl)-1,3-dithiole-2-thione* **11a** (720 mg, 54%) as a yellow crystalline solid, mp 177 °C; λ_{max} (CH_2Cl_2)/nm 242, 314, 378; ν_{max} (film)/cm^{-1} 3320, 1648; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (1H, s, H-3′), 8.11 (1H, m, Ar*H*), 8.03 (1H, s, Ar*H*), 7.8 (2H, m, Ar*H*), 5.13 (1H, q, J = 6.7 Hz, CH_3CHOH), 4.9 (1H, s, O*H*), 1.57 (3H, d, J = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 157.5, 144.5, 141.2, 134.2, 131.8, 131.7, 129.3, 65.4, 55.3, 24.8; *m*/*z* (CI) 307 (MH^+, 100%), 289 (10), 263 (10), 203 (12); found C, 50.9; H, 3.3; N, 8.8%; HRMS, M^+, 305.9955. $C_{13}H_{10}N_2OS_3$ requires C, 51.0; H, 3.3; N, 9.1%, *M*, 305.99553.

Method 2. To 3-phenyldithiolane-2-thione **12** (960 mg, 4.53 mmol) dissolved/suspended in THF (5 ml) at 40 °C was added $BF_3{\cdot}Et_2O$ (3 ml). To this solution was added a solution of alkyne-alcohol **8** (300 mg, 1.51 mmol) in THF (3 ml) dropwise *via* syringe. After 15 min TLC analysis indicated the complete consumption of the alcohol **8**. The reaction mixture was poured into H_2O (50 ml) and made basic by the addition of solid $NaHCO_3$ and then the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were washed with brine (30 ml), dried and then concentrated *in vacuo*. Purification by flash chromatography provided *4-(1-hydroxyethyl)-5-(quinoxalin-2-yl)-1,3-dithiole-2-thione* **11a** (172 mg, 37%), identical with that prepared by Method 1.

cis-6-Benzyloxycarbonyl-4-methyl-2-thioxo-5a,6-dihydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 13a and *trans*-6-benzyloxycarbonyl-4-methyl-2-thioxo-5a,6-dihydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 14a

Alcohol **11a** (333 mg, 1.09 mmol) was dissolved in benzyl chloroformate (12 ml) and the solution stirred for 24 h at room temperature. The chloroformate was removed under high vacuum to leave a yellow residue which was purified by flash chromatography (silica, EtOAc in petroleum ether) to provide a mixture of the *pyrano-quinoxalines* **13a** and **14a** (8 : 1, 293 mg, 61%) as a yellow solid mp 180–181 °C; λ_{max} (CH_2Cl_2)/nm 250, 334: ν_{max} (film)/cm^{-1} 2351, 2321, 1732, 1643; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, m, Ar*H*), 7.4–7.0 (8H, m Ar*H*), 6.15 (0.11H, s, H-5a), 6.03 (0.11H, s, H-5a), 5.34 (0.89H, d, J = 12.1 Hz, COHC*H*Ph), 5.30 (0.88H, d, J = 12.1 Hz, CO*H*-CHPh), 5.29 (0.11H, d, J = 11.7 Hz, COHC*H*Ph), 5.22 (0.11H, d, J = 11.7 Hz, CO*H*CHPh), 4.95 (0.89H, q, J = 6.6 Hz, H-4), 4.78 (0.11H, d, J = 7.0 Hz, H-4), 1.40 (2.7H, d, J = 7.0 Hz, CH_3), 1.35 (0.3H, d, J = 7.0 Hz, CH_3); *m*/*z* (CI) 441 (MH^+, 100%), 291 (15), 229 (70), 152 (50); found, HRMS, M^+, 440.0333. $C_{21}H_{16}N_2O_3S_2$ requires *M*, 440.03230.

cis,cis-6-Benzyloxycarbonyl-4-methyl-2-thioxo-5a,6,11,11a-tetrahydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]-quinoxaline 4a

The mixture of imines **13a** and **14a** (450 mg, 1.02 mmol) was added to MeOH (100 ml) to form a yellow suspension to which was then added $NaB(CN)H_3$ (193 mg, 3 mmol) and glacial

acetic acid (3 ml). The starting material slowly dissolved and the solution was allowed to stir for 18 h. The mixture was concentrated *in vacuo*, CH_2Cl_2 (30 ml) was added and the resulting solution washed with sat. aq. $NaHCO_3$. The layers were separated and the aq. layer extracted with CH_2Cl_2 (2 × 20 ml). The combined organic fractions were washed with brine (20 ml), dried and evaporated and the resulting solid was purified by flash chromatography (silica, 10 ⟶ 20% EtOAc in petroleum ether) to provide *cis,cis-6-benzyloxycarbonyl-4-methyl-2-thioxo-5a,6,11,11a-tetrahydro-4H-[1,3]dithiolo[4′,5′:4,5]pyrano-[2,3-b]quinoxaline* **4a** as a yellow oil (280 mg, 62%) which was triturated with Et_2O to give a yellow crystalline solid, mp 165–167 °C, λ_{max} (CH_2Cl_2)/nm 246, 298, 378; ν_{max} (film)/cm^{-1} 3370, 1712, 1604; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, d, J = 8.5 Hz, Ar*H*), 7.42 (5H, m, Ar*H*), 7.02 (1H, m, Ar*H*), 6.9 (1H, m, Ar*H*), 6.72 (1H, m, Ar*H*), 6.33 (1 H, d, J = 1.4 Hz, H-5a), 5.35 (2H, m, CH_2Ph), 4.81 (1H, q, J = 6.3 Hz, H-4), 4.15 (1H, d, J = 1.4 Hz, H-11a), 3.70 (1H, br s, NH), 1.46 (3H, d, J = 6.3 Hz, CH_3); *m*/*z* (CI) 443 (MH^+, 100%), 413 (20), 291 (30), 217 (18), 131 (30); found, HRMS, M^+, 442.0479. $C_{20}H_{18}N_2O_3S_2$ requires *M*, 442.0480.

4-(1-Hydroxyethyl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one 11b

Method 1. To the alcohol **11a** (290 mg, 1.0 mmol) dissolved/suspended in acetone (25 ml) and AcOH (6 ml) was added $Hg(OAc)_2$ (0.48 g, 1.5 mmol) and the solution was stirred for 2 h and then filtered through Celite and the filter cake washed with a portion of EtOAc (20 ml). Sat. aq. $NaHCO_3$ was added to the filtrate, followed by solid $NaHCO_3$ until a neutral pH was attained. The organic layer was separated and the aq. layer was re-extracted with EtOAc (2 × 20 ml), the combined organic extracts were washed with brine (20 ml), dried and evaporated to leave *4-(1-hydroxyethyl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one* **11b** as a creamy brown–pink crystalline solid (270 mg, 98%), mp 196–197 °C; λ_{max} (CH_2Cl_2)/nm 250, 263; ν_{max} (film)/cm^{-1} 3250, 1644, 1625; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (1H, s, H-3′), 8.1 (1H, m, Ar*H*), 8.04 (1H, m, Ar*H*), 7.8 (2H, m, Ar*H*), 5.1 (1H, dq, J = 3.5, 6.5 Hz, C*H*OHCH$_3$), 4.85 (1H, br s, O*H*), 1.55 (1H, d, J = 6.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 145.0, 144.4, 141.5, 140.8, 131.5, 131.1, 129.4, 129.0, 125.1, 64.5, 29.6, 22.6; *m*/*z* (CI) 291 (MH^+, 100%), 275 (15), 91 (100), 74 (70); found, HRMS 290.0174. $C_{13}H_{10}N_2O_2S_2$ requires *M* 290.0184.

Method 2. Alkyne-alcohol **8** (2.0 g, 0.01 mol), bis-isopropoxythiocarbonyldisulfane (3.0 g, 11 mmol), and azobisisobutyronitrile (0.75 g, 4.55 mmol) in toluene (1 ml) were heated at reflux for 6 h. Purification of the reaction mixture by flash chromatography (silica, 0 ⟶ 5 ⟶ 10% EtOAc in CH_2Cl_2) gave the alcohol **11b** (320 mg, 41%) as a yellow crystalline solid with spectroscopic properties identical to those reported above.

cis-6-Benzyloxycarbonyl-4-methyl-2-oxo-5a,6-dihydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 13b

To alcohol **11b** (70 mg, 0.24 mmol) in CH_2Cl_2 (2 ml) was added benzyl chloroformate (8 ml) and the mixture was stirred for 36 h. The chloroformate was removed on a rotary evaporator (70 °C, 5 mmHg) and the residue was purified by flash chromatography (silica, 5 ⟶ 20% EtOAc in petroleum ether) to provide *cis-6-benzyloxycarbonyl-4-methyl-2-oxo-5a,6-dihydro-4H-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-b]quinoxaline* **13b** as white fine needles (46 mg, 45%), mp 176–177 °C; λ_{max} (CH_2Cl_2)/nm 252, 332; ν_{max} (film)/cm^{-1} 3420, 1731, 1677, 1639; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, m, Ar*H*), 7.4–7.0 (8H, m, Ar*H*), 6.02 (1H, s, H-5a), 5.17–5.4 (2H, m, CH_2Ph), 4.92 (1H, q, J = 6.6 Hz, H-4), 1.4 (3H, d, J = 6.6 Hz, CH_3); *m*/*z* (CI) 425 (MH^+, 40%), 185 (15), 91 (60); found, HRMS, M^+, 424.0548. $C_{21}H_{16}N_2O_4S_2$ requires *M* 424.0551.

cis,cis-6-Benzyloxycarbonyl-4-methyl-2-oxo-5a,6,11,11a-tetrahydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]-quinoxaline 4b

The imine **13b** (100 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (~2 ml) then acetic acid (0.3 ml) and $NaB(CN)H_3$ (43 mg, 0.68 mmol) dissolved in MeOH (3 ml) were added to the stirred solution. After 5–10 min a white precipitate was evident, the solvent was removed carefully by pipette, the remaining solid washed with several portions of Et_2O and dried to leave *cis,cis-6-benzyloxycarbonyl-4-methyl-2-oxo-5a,6,11,11a-tetrahydro-4H-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-b]quinoxaline* **4b** (70 mg, 70%) as a white solid. A portion of Et_2O was added to the removed reaction solution and a further quantity of product (20 mg) precipitated during 24 h (overall 95%), mp 210 °C; λ_{max} (CH_2Cl_2)/nm 246, 298; ν_{max} (film)/cm^{-1} 1712, 1604; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63, (1H, d, J = 8.1 Hz, Ar*H*), 7.2–7.4 (5H, m, CH$_2$*Ph*), 6.9 (1H, m, Ar*H*), 6.7 (1H, m, Ar*H*), 6.48 (1H, m, Ar*H*), 5.95 (1H, d, J = 2.2 Hz, H-5a), 5.23 (2H, m, CH_2Ph), 4.75 (1H, q, J = 6.6 Hz, H-4), 4.0 (1H, d, J = 2.2 Hz, H-11a), 3.7 (1H, s, N*H*), 1.37 (3H, d, J = 6.6, CH_3); *m*/*z* (CI) 427 (MH^+, 100%), 383 (20), 275 (17), 215 (10), 108 (20), 92 (70), 74 (100); found C, 58.9; H, 4.2; N, 6.6; S, 15.1%; HRMS, M^+, 426.0712. $C_{21}H_{18}N_2S_2O_4$ requires C, 59.1; H, 4.3; N, 6.6; S, 15.0%, *M*, 426.07079.

(η^5-Cyclopenta-2,4-dienyl)(10-benzyloxycarbonyl-2-methyl-4a,5,10,10a-tetrahydro-2*H*-pyrano[2,3-*b*]quinoxaline-3,4-dithiolato-κ^2*S*,*S*)cobalt(III) 5

1,3-Dithiol-2-one **4b** (30 mg, 0.070 mmol) was suspended in MeOH–$CHCl_3$ (1 : 1; 5 ml). To this solution was added $CsOH{\cdot}H_2O$ (22 mg, 0.15 mol) previously dissolved in 1 ml of the solvent mixture and then the mixture was stirred for 20 min. Cyclopentadienyldiiodocobalt(III) (52 mg, 0.136 mmol) was added (dark purple–black solution) and the solution was stirred for 15 min. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (15 ml) and H_2O (15 ml). The aq. layer was separated and extracted with CH_2Cl_2 (2 × 20 ml). The combined organic fractions were washed with brine (10 ml), dried and concentrated *in vacuo* to give the title compound as a blue–black crystalline solid (27 mg, 71%), mp 101–103 °C; λ_{max} (CH_2Cl_2)/nm 238, 244, 288, 408, 578; ν_{max} (CH_2Cl_2)/cm^{-1} 2995, 1710, 1604; *m*/*z* (CI) 427 (MH^+, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, m, Ar*H*), 7.1–7.3 (5H, m, CH$_2$*Ph*), 6.9 (1H, m, Ar*H*), 6.6 (1H, m, Ar*H*), 6.4 (1H, m, Ar*H*), 5.75 (1H, br s, H-5a), 5.33 (5H, s, C$_5H_5$), 5.2 (2H, m, CH_2Ph), 4.68 (1H, q, J = 6.9 Hz, H-4), 4.45 (1H, br s, H-11a), 3.8 (1H, s, N*H*), 1.6 (3H, d, J = 6.9 Hz, CH_3); *m*/*z* (CI) 523 (MH^+, 50%), 389 (10), 283 (16), 243 (19), 201 (14), 152 (39), 131 (60), 82 (100); found, HRMS, M^+, 522.0494. $C_{25}H_{23}N_2O_3S_2Co$ requires *M*, 522.0482.

4-[(1*R*)-1,2-Dihydroxyethyl]-5-(quinoxalin-2-yl)-1,3-dithiol-2-one 15

A stirred solution of acetal **2** (440 mg, 1.27 mmol) in MeOH (20 ml) was treated with $TsOH{\cdot}H_2O$ (240 mg, 1.27 mmol) and the mixture was refluxed for 1 h. Et_3N (2 ml) was added, and the solvents were evaporated. The residue was dissolved in CH_2Cl_2, and washed with H_2O, and the aq. layer re-extracted with CH_2Cl_2 (2 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to provide pure *diol* **15** as a beige solid (358 mg, 92%). A small sample was recrystallised from MeCN to give **15** as white needles, mp 140 °C; λ_{max} ($CHCl_3$)/nm 252, 364; ν_{max} (film)/cm^{-1} 3259 (br), 1638; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (1H, s, H-3′), 8.19 (1H, m, Ar*H*), 8.10 (1H, m, Ar*H*), 7.89 (2H, m, Ar*H*), 5.29 (1H, m, C*H*CH$_2$OH), 4.59 (1H, br d, OH), 4.05 (1H, m, one of CH_2OH), 3.95 (1H, m, one of CH_2OH), 2.79 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 145.8, 144.1, 141.7, 141.4, 140.9, 130.9, 130.7, 128.9, 128.4, 125.6, 69.9, 65.5; *m*/*z* (CI) 307 (MH^+, 100%), 289 (10), 273 (12), 247 (8), 102 (10); found

C, 51.1; H, 3.1; N, 9.1; S, 21.3%; HRMS, M^+ 306.0135. $C_{13}H_{10}N_2O_3S_2$ requires C, 51.0; H, 3.3; N, 9.1; S, 20.9%, *M* 306.0133.

(4*R*,5a*R*)-*cis*-6-(9*H*-Fluoren-9-ylmethyloxycarbonyl)-4-hydroxymethyl-2-oxo-5a,6-dihydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 16 and (4*R*,5a*S*)-*trans*-6-(9*H*-fluoren-9-ylmethyloxycarbonyl)-4-hydroxymethyl-2-oxo-5a,6-dihydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 17

A stirred solution of diol **15** (300 mg, 0.98 mmol), 9*H*-fluoren-9-ylmethyl chloroformate (10 g, 38.7 mmol), solid $NaHCO_3$ (3 g) and 1,4-dioxane–H_2O (10 ml, 19 : 1) was heated at 35 °C for 14 h. The reaction mixture was diluted with petroleum ether (200 ml) and the resulting mixture was passed through a pad of silica, eluting with petroleum ether to remove excess chloroformate reagent. Elution of the product (10% MeOH in CH_2Cl_2) and further purification by flash chromatography (silica, 20 ⟶ 25% EtOAc in petroleum ether) provided the mixture of *pyranoquinoxalines* **16** and **17** as a white solid (457 mg, 92%, 2 : 1), λ_{max} ($CHCl_3$)/nm 258, 292, 302, 336; ν_{max} (film)/cm^{-1} 3426, 1729, 1682, 1638; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–6.80 (12H, m, Ar*H*), 6.28 (0.33H, s, H-5a), 5.28 (0.66H, s, H-5a), 5.16–4.8 (2H, m, CHCH_2OCON), 3.9–3.5 (3H, series of overlapping multiplets, H-4 and CHCH_2OH); *m*/*z* (ES+) 529 (MH^+, 100%), 511 (11), 367 (22), 331 (16), 282 (12), 233 (20); found C, 63.9; H, 3.6; N, 5.3; S, 12.2%; $C_{28}H_{20}N_2O_5S_2$ requires C, 63.6; H, 3.8; N, 5.3; S, 12.1%.

(4*R*,5a*R*,11a*R*)-*cis,cis*-6-(9*H*-Fluoren-9-ylmethyloxycarbonyl)-4-hydroxymethyl-2-oxo-5a,6,11,11a-tetrahydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 18 and (4*R*,5a*S*,11a*S*)-*trans,cis*-6-(9*H*-fluoren-9-ylmethyloxycarbonyl)-4-hydroxymethyl-2-oxo-5a,6,11,11a-tetrahydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 19

To a stirred solution of the mixture of **16** and **17** (450 mg, 0.852 mmol, 2 : 1) in CH_2Cl_2 (20 ml) and MeOH (20 ml) at 0 °C was added AcOH (107 μl, 205 mg, 1.89 mmol) and after 5 min $NaB(CN)H_3$ (214 mg, 3.41 mmol) was added and the resulting mixture was stirred for 2 h. The mixture was diluted with CH_2Cl_2 (50 ml), sat. aq. $NaHCO_3$ (30 ml) was added followed by solid $NaHCO_3$ until a neutral pH was attained, separation of the aq. layer and re-extraction with CH_2Cl_2 (2 × 30 ml) gave combined extracts which were washed with brine (30 ml), dried and evaporated. Purification and separation of the diastereoisomers by flash column chromatography (silica, 20 ⟶ 25 ⟶ 50% EtOAc in petroleum ether ⟶100% CH_2Cl_2) provided *cis-pyrano-quinoxaline* **18** as a yellow solid (277 mg, 61%), then the minor *trans-pyrano-quinoxaline* **19** (130 mg, 29%). Data for **18**: mp 207–208 °C; λ_{max} ($CHCl_3$)/nm 266, 302, 336; ν_{max} (film)/cm^{-1} 3368, 2926, 1705, 1640, 1606; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–7.20 (9H, m, Ar*H*), 6.6–6.95 (3H, m, Ar*H*), 5.35 (1H, d, *J* = 1.1 Hz, H-5a), 5.0 (1H, dd, *J* = 4.0, 11.0 Hz, one of CHCH_2OCON), 4.80 (1H, dd, *J* = 3.6, 11.0 Hz, one of CHCH_2OCON), 4.30 (2H, m, C*H*CH_2OCON and H-4), 3.80–3.55 (3H, m, CHCH_2OH and H-11a); *m*/*z* (ES+) 531 (MH^+, 100%), 513 (12), 342 (10), 321 (14), 242 (17); found C, 62.0; H, 4.1; N, 5.0; S, 11.8%. $C_{28}H_{22}N_2O_5S_2$ requires C, 63.4; H, 4.2; N, 5.3; S, 12.1%. Data for **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–7.20 (9H, m, Ar*H*), 6.95–6.5 (3H, m, Ar*H*), 5.98 (1H, d, *J* = 4.8 Hz, H-5a), 4.80 (1H, dd, *J* = 5.2, 11.0 Hz, one of CHCH_2OCON), 4.60 (1H, dd, *J* = 5.3, 11.0 Hz, one of CHCH_2OCON), 4.42 (1H, t, *J* = 5.2 Hz, H-4), 4.20 (2H, m, CHCH_2OCON and one of CH_2OH), 3.80–3.55 (2H, m, one of CH_2OH and H-11a).

***cis,cis*-(4*R*,5a*R*,11a*R*)-4-Hydroxymethyl-2-oxo-5a,6,11,11a-tetrahydro-4*H*-[1,3]dithiolo[4′,5′:4,5]pyrano[2,3-*b*]quinoxaline 6**

A solution of Fmoc derivative **18** (100 mg, 0.189 mmol) in THF–H_2O (10 ml, 25 : 1) at 25 °C was treated with excess Et_2NH (3 ml), and the mixture was stirred for 2 h. The reaction was diluted with Et_2O–CH_2Cl_2 ((1 : 1), 80 ml) and dried with Na_2SO_4. The solution was concentrated *in vacuo*. Flash chromatography (alumina, 0 ⟶ 2% MeOH in CH_2Cl_2) gave the deprotected *pyrano-quinoxaline* **6** (47 mg, 80%) as a white solid, λ_{max} ($CHCl_3$)/nm 244; ν_{max} (film)/cm^{-1} 3337, 2922, 1636; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.8–6.5 (4H, m, Ar-*H*), 5.30 (1H, br s, N-6-H), 5.09 (1H, d, *J* = 1.5 Hz, H-5a), 4.66 (1H, dd, *J* = 3.3, 4.4 Hz, H-4), 3.96 (1H, d, *J* = 1.5 Hz, H-11a), 3.8 (1H, dd, *J* = 3.3, 12.0 Hz, one of CH_2OH), 3.67 (1H, dd, *J* = 4.4, 12.0 Hz, one of CH_2OH), 3.62 (1H, br s, N-11-H); *m*/*z* (CI) 309 (MH^+, 18%), 166 (100), 149 (40), 131 (39), 103 (40), 74 (40); found, HRMS, M^+ 308.0296. $C_{13}H_{12}N_2O_3S_2$ requires *M* 308.0289.

(η^5-Cyclopenta-2,4-dienyl)(2-hydroxymethyl-4a,5,10,10a-tetrahydro-2*H*-pyrano[2,3-*b*]quinoxaline-3,4-dithiolato-κ^2*S*,*S*)-cobalt(III) 7

A solution of amine **6** (20 mg, 0.065 mmol) in CH_2Cl_2–MeCN was treated with $CsOH·H_2O$ (33 mg, 0.195 mmol) and the mixture was stirred for 20 min. Cyclopentadienyldiiodocobalt(III) (38 mg, 0.098 mol) was then added and the mixture was stirred for a further 20 min. The solvent was evaporated *in vacuo* and the residue was partitioned between CH_2Cl_2 and H_2O. The aq. layer was separated and re-extracted with CH_2Cl_2 (2 × 10 ml), the combined organic extracts were washed with brine (5 ml), dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (alumina, 0 ⟶ 2% MeOH in CH_2Cl_2) provided the cobalt complex (14 mg, 55%) as a green–purple solid, λ_{max} ($CHCl_3$)/nm 234, 290, 576; ν_{max} (film)/cm^{-1} 3330, 2953, 1742, 1703; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63–6.40 (4H, m, H-7, 8, 9, 10), 5.42 (1H, br s, N-6-H), 5.37 (1H, d, *J* = 1.6 Hz, H-5a), 5.23 (5H, s, C_5H_5), 4.75 (1H, br s, H-4), 4.42 (1H, br s, N-11-H), 4.40 (1H, br s, H-11a), 4.22 (1H, br s, one of CH_2OH), 3.97 (1H, dd, *J* = 4.8, 12.2 Hz, one of CH_2OH); *m*/*z* (CI) 405 (MH^+, 15%), 389 (10), 280 (12), 201 (50), 183 (60), 145 (50), 74 (100); found, HRMS, M^+ 404.0056. $C_{17}H_{17}N_2O_2S_2Co$ requires *M* 404.0063.

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