The Synthesis of “Apo-Proteinic” Multidentate, N_2SS^* and N_2S, Ligands to Model Type I Trigonal and Trigonal-Pyramidal Copper Protein Sites

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The syntheses of the novel sterically highly hindered asymmetric tripodal tridentate N_2S and "distended" tripodal tetradentate N_2SS^* (S: thiolate; S*: thioether donor) ligands, 2-[bis(3′-isopropylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylbenzenethiol (**11**) and 3-{2′-[bis(3′′-isopropylpyrazol-1′′-yl)methyl]phenylsulfanyl}-1,1-diphenylpropane-1-thiol (**28**) are reported. These molecules possess the atom donor arrays of "trigonal" and "trigonal-pyramidal" type I "blue" copper proteins respectively. The success of the synthesis has transpired from the development of an effective flexible route to achieving the functional group interconversion of the phenolic group of the N_2O heteroscorpionate ligands based upon the already known 2-[bis(pyrazol-1′-yl)methyl]phenol framework to their benzenethiol analogs. This has been effected using the Newman–Kwart rearrangement of the thiocarbamic acid *O*-ester of the N_2O-phenol by a "*D*irect *I*nsertion *V*apour *P*hase *F*lash *V*acuum *P*yrolysis" (DIVPFVP) protocol which is highly effective despite the high involatility of the N_2O precursors/N_2S products. This process has been illustrated crystallographically for the sequence of conversions of 2-[bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenol (**3**) to *O*-{2-[bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenyl}-*N*,*N*-dimethylthiocarbamate (**4**) to *S*-{2-[bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenyl}-*N*,*N*-dimethylthiocarbamate (**5**). These "all-in-one" ligands represent a new strategy to modeling "blue" copper proteins and should be capable of complementing recent significant developments in the field since they are sterically somewhat less bulky than pre-existing ligands whilst maintaining viable coordination vectors and thus allow for the adoption of more "open" metal coordination environments.

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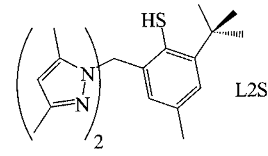
Introduction

Mixed [$N_xS_yO_z$] coordination arrays are almost ubiquitous in metalloproteins systems, notably with zinc[1−6] and copper.[7−16] Recently, considerable effort has been expended to synthesise unsymmetrical ligands possessing mixed N and/or S and/or O donor sets. Vahrenkamp et al.[17−21] have reported a number of tripodal N_3O and N_3S ligands that incorporate carboxylate, phenolate, or thiolate functionalities. Parkin et al.[22−24] have successfully synthesized a series of facially coordinating N_2O and N_2S heteroscorpionate ligands possessing thioether, thioimidazolyl, or carboxylate moieties attached to the B−H group. Riordan[25,26] and Fenton[27] have also pursued this goal with significant success. A recent noteworthy achievement in this field has been accomplished by Hammes, Carrano et al.[28−31] who have used the N_2S donor ligand, L2SH (Figure 1), to probe mechanisms of reactivity of Zn^{II} ligated by $N_2S_1S^*_1$ donor sets (S*: exogenous thiolate ligand) specifically in relation to alkylation of the exogenous RS* ligand. These studies are especially significant in light of the recent advances in recognizing the role of zinc metalloproteins in alkyl group transfer reactions.[32,33]



L2SH

Figure 1. The molecular structure of the N_2S donor ligand 2-[bis(3′,5′-dimethylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylbenzenethiol (L2SH)[28−31]

The simplicity of its method of synthesis and its considerable potential for future derivatization is a particularly attractive feature of this ligand design. To date though a definitive description of the synthetic protocols and experimental techniques required to produce ligands similar to L2SH has not been reported. Herein we finally report a definitive experimental method to produce these N_2S ligands, based upon a 2-[bis(pyrazol-1′-yl)methyl]benzenethiol skeleton, and our attempts to further derivatise these ligands to achieve a total synthesis of the "apo-proteinic"

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coordination sites of trigonal and trigonal-pyramidal type I copper proteins, recently described by Tolman and Spencer[34] as the "holy grail" of synthetic bioinorganic chemistry.

Type I "Blue" Copper Proteins (Cupredoxins)

Type I copper proteins, are found in bacterial and plant systems, having a role in biological electron transfer processes.[7−10,35−43] For this task they are ideally suited possessing a trigonal, N(his)$_2$S(cys)-ligated Cu$^{I/II}$ redox center in an "entatic state" with a coordination number/geometry intermediate between that preferred by the +I and +II Cu oxidation states. This "entatic" state is possibly enforced by the rack-induced bonding mechanism, first proposed by Malmström in the 1960s,[44] whereby the folding of the protein leading to a minimum overall energy conformation can stabilise a local energy maximum in the vicinity of the metal site (e.g. to support an unconventional arrangement of ligands). Considerable effort has been expended to support or challenge the rack hypothesis. Gray, Malmström et al.[8,45−48] have produced experimental evidence that supports it whereas Ryde et al.[49,50] have undertaken quantum chemical calculations that challenge it for the oxidized [Cu^{II}] protein.

Type I copper proteins exhibit extraordinarily anomalous spectroscopic properties with an intense absorption band at ca. 620 nm attributed to S(cys) → Cu^{II} CT.[10,38,41,42,51] The EPR spectroscopic properties are similarly intriguing with the observance of both rhombic and axial type spectra,[52,53] all possessing unusually small $A_{//}$ hyperfine coupling constants of $\leq 70\times10^{-4}$ cm^{-1} compared to $180-200\times10^{-4}$ cm^{-1} for "normal" tetragonal Cu^{II} complexes. Intensive studies using sulfur K-edge X-ray absorption spectroscopy have indicated this is due to extensive delocalization of the type I Cu^{II} site[10] with an unusually short (ca. 2.1 Å), covalent Cu^{II}−S(cys) bond which effectively delocalises the unpaired electron away from the Cu^{II} nucleus thus reducing the spin-coupling interaction of the former with the latter. Numerous members of this class of proteins possess subtle structural additions to the fundamental, commonal N(his)$_2$S(cys) Cu ligation, and the effect these variations have on the spectrochemical properties of these proteins are currently undergoing rigorous scrutiny. These variants include the "pure trigonal" site (fungal laccase,[54] ceruloplasmin[55,56]), the "trigonal-pyramidal" site wherein a weakly coordinated (ca. 2.6 Å) fourth ligand, typically a methionine-*S* thioether, occupies an axial site (plastocyanin[57]), and the "trigonal-bipyramidal" site wherein two ligands occupy axial positions at long distances, > 2.8 Å, with one again being methionine and the other a backbone carbonyl oxygen atom (azurin[58,59]).

The quantum chemical calculations of Ryde et al.[49,50] have led to a refinement of the rack-model for type I copper proteins. This revised model states that whilst protein folding has a minimal effect on the Cu^{II} coordination geometry it has a significant effect on the Cu^{I} site of the reduced protein, forcing the elongation of the axial methionine ligand in addition to shielding the metal from water and other potential ligands.[45,46] This rack-induced displacement of the apical methionine ligand often observed in this class of metalloprotein, relative to the Cu ion has been postulated as modulating the rather high redox potential of the Cu^{I}/Cu^{II} couple observed in these systems.[45,48,60] More evidence though is required to support such speculation and hence the need for viable model systems with accurate N$_x$S$_y$ donor sets, this latter requirement necessitating novel approaches to asymmetric ligand design.

Synthetic Bioinorganic Chemistry: Type I Copper Protein Models

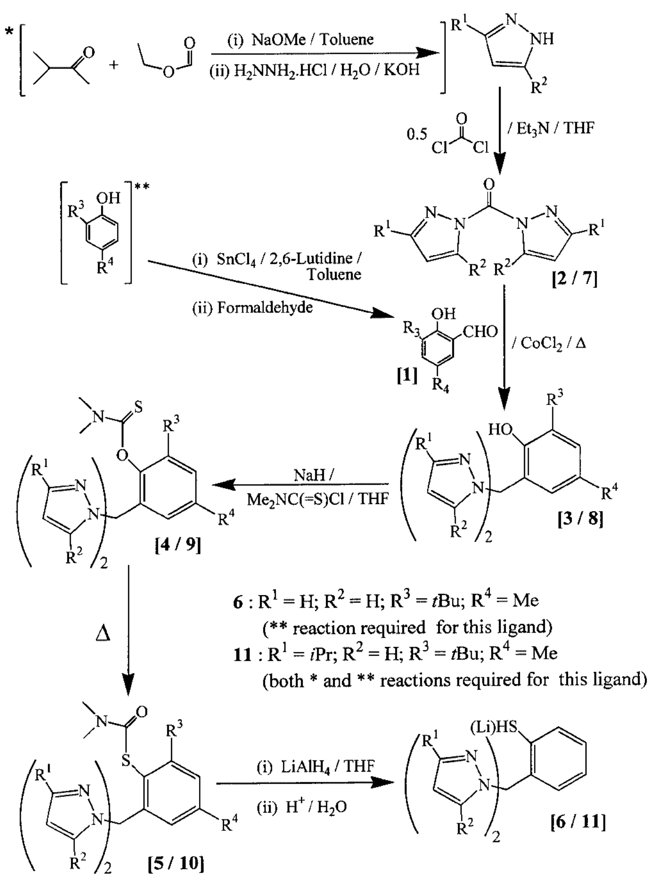
Synthesising a Cu^{II} complex that can simultaneously model the extraordinarily anomalous structural, spectroscopic, and electrochemical properties of type I copper proteins, is a considerable challenge and one that has preoccupied synthetic bioinorganic chemists for over 25 years. The situation is further complicated by the notorious extremely facile reduction of mercapto−Cu^{II} complexes, postulated to proceed by a two-step free-radical coupling mechanism.[61,62]

The initial homolytic cleavage (1) of the Cu^{II}−SR bond forming Cu^{I} and a thiolate radical is reversible being in dynamic equilibrium with the corresponding bond formation but (1) is driven completely to the right by subsequent irreversible 2 × RS$^{\cdot}$ radical coupling (2) which forms stable disulfide.

$$\mathrm{Cu^{II}{-}SR} \rightleftharpoons \mathrm{Cu^{I}} + \mathrm{RS^{\cdot}} \quad (1)$$

$$2\ \mathrm{RS^{\cdot}} \rightarrow \mathrm{RSSR} \quad (2)$$

Early attempts at synthesising effective type I models, such as those of Bosnich et al.,[61][62] were thwarted by the facile mercapto-mediated reduction of Cu^{II}. Brader, Borchardt, and Dunn[63] elegantly avoided many of the synthetic difficulties associated with the required ligand systems by using an insulin-stabilized monomeric Cu^{II} chromophore as a framework onto which were introduced a series of exogenous thiolate-based ligands (C$_6$F$_5$S^{-}, C$_6$HF$_4$S^{-}). The resultant adducts effectively mimicked several of the spectroscopic properties (EPR, electronic spectroscopy) of type I sites. Unfortunately, these adducts still possessed redox instability over a time-scale of hours and X-ray characterization of these systems was not possible. Only with the seminal work of Kitajima et al.[64−67] in the early 1990s was the redox instability overcome to some extent by the use of the sterically highly hindered tridentate N$_3$-donor ligand hydrotris(3,5-ddiisopropylpyrazol-1-yl)borate and similarly sterically hindered thiol ligands, including *t*BuSH, Ph$_3$CSH, and C$_6$F$_5$SH. These ligands were used to synthesise "spectroscopically accurate" four-coordinate Cu^{II} complexes with N$_3$S ligation (S: thiolate), the sterically hindered nature of the ligands conferring at least low-temperature stability onto the complexes so that in a couple of cases, structural characterizations could be made. These model systems have several structural inaccuracies in that the N$_3$S coordination sphere is formerly incorrect, having one too many N-donors and no equivalent to the S(met) donor and the complexes exhibit flattened tetrahedral, not trigonal or trigonal-pyramidal, geometries. Tolman, Holland et al.[68−71] have recently reported a stunning breakthrough in this field, having successfully synthesized tractable, accurate structural model complexes of both three- (N_2S) and four-coordinate (N_2SS^*) "blue" copper sites. This again achieved by the use of sterically highly crowded ligands, the (1−)-bidentate N_2-donor ligand 2,4-bis(2,6-ddiisopropylphenylimido)pentane, the (1−)-monodentate ligand triphenylmethylthiolate (for the N_2S model) and the (1−)-bidentate thiolato−thioether donor 2-(methylsulfanyl)-1,1-diphenylethanethiolate (for the N_2SS^* model). The N_2S model closely mimics the spectroscopic properties of "trigonal" type I sites with a similar S(cys)→Cu^{II} LMCT band position and intensity and an "axial" type EPR spectrum with small $A_{//}$ values. The N_2SS^* model is the first to formerly model the ligation of the classic type I "blue" Cu^{II} site, and possesses many of the essential spectroscopic properties of these sites. This complex though does not accurately model the structure of "trigonal-pyramidal" sites, the $Cu^{II}N_2SS^*$ moiety being somewhat "squashed" by the extensive steric hindrance required to "redox-stabilise" the $Cu^{II}-S_{thiolate}$ bond, consequently forming a flattened tetrahedral geometry which more resembles the Cu sites of nitrite reductases and certain azurin mutants (His, or Glu replacing the Met ligand).[69] Therefore, there is still a requirement for "blue" copper ligands which allow for more "open" Cu^{II} coordination with a long "axial" S(met) interaction whilst maintaining the fundamental short S(cys)−Cu^{II} bond.



Scheme 1

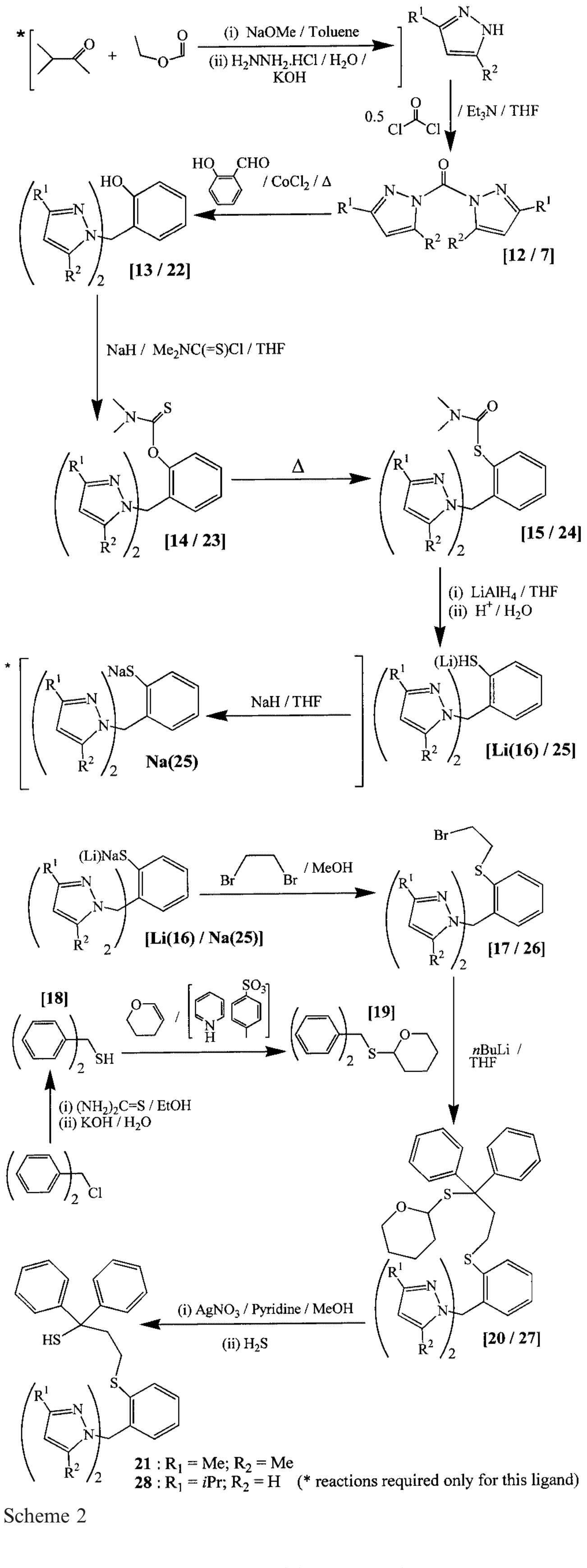
Results and Discussion

Total Synthesis of Flexible "Apo-proteinic" Type I Copper Protein Binding Sites

The development of ligands based upon a 2-[bis(pyrazol-1′-yl)methyl]phenol unit by the direct solventless reaction of various bis(pyrazolyl) ketones and salicylaldehyde,[72−76] and subsequent development of a thiol analog, 2-[bis(pyrazol-1′-yl)methyl]benzenethiol, by substituting 2-thiocyanatobenzaldehyde[77] for the salicylaldehyde led to the consideration of the latter's feasibility as a Cu^{II}-coordinating agent capable of forming complexes that model type I copper properties. Facile reduction of the coordinated Cu^{II} ion by the benzenethiolate group of the 2-[bis(pyrazol-1′-yl)methyl]benzenethiol ligand was the most pressing consideration. The precedents set by Kitajama et al.[64−67] and Tolman, Holland et al.[68−71] indicated that it would be necessary to introduce a high degree of steric hindrance onto this ligand system. Reactions of 2-thiocyanatobenzaldehyde with sterically hindered bis(pyrazolyl) ketones were unsuccessful (yields of ≤ 10% were typical after long workups). In addition, synthetic protocols for hindered analogs of 2-thiocyanatobenzaldehyde (e.g. with 3-*tert*-butyl substitution) are not available. This necessitated the development of a new, more flexible, approach to synthesizing these N_2S heteroscorpionate ligands, detailed in Schemes 1 and 2.

This involved the synthesis of the N_2O phenol analog (based upon a 2-[bis(pyrazol-1′-yl)methyl]phenol framework) of the desired benzenethiol ligand with the required alkyl-substitution pattern, on the pyrazole rings and/or the phenol (using an appropriately substituted salicylaldehyde, typically 3-*tert*-butyl-2-hydroxy-5-methylbenzaldehyde). Synthesis of a thiocarbamic acid *O*-ester from this phenol, then its pyrolytic conversion by Newman−Kwart rearrangement[78−80] into the isomeric thiocarbamic acid *S*-ester and lastly cleavage of this by either base hydrolysis (KOH) or reduction ($LiAlH_4$) yielded the benzenethiol ligand. This sequence of synthetic conversions is illustrated by crystallographic plots of molecules **3**, **4**, and **5** (Scheme 1) in Figure 2.

The Newman−Kwart rearrangement is normally performed (i) in high-boiling solvents (diphenyl ether, benzaldehyde, anisole, etc.), (ii) as a "melt" in the absence of solvent, (iii) in the vapour phase at atmospheric pressure by a flash pyrolysis process with the thiocarbamic acid *O*/*S*-ester being transported through the furnace by an inert carrier gas.[80] Neither of these methods worked satisfactorily for sterically substituted 2-[bis(pyrazol-1′-yl)methyl]phenol-based thiocarbamic acid *O*-esters, in order: (i) primarily due to the limitations on the amount of material that could converted in a realistic (i.e. small) amount of solvent, (ii) due to rapid thermal decomposition of the melt, (iii) due to the extremely low volatility of these compounds at atmospheric



Scheme 2

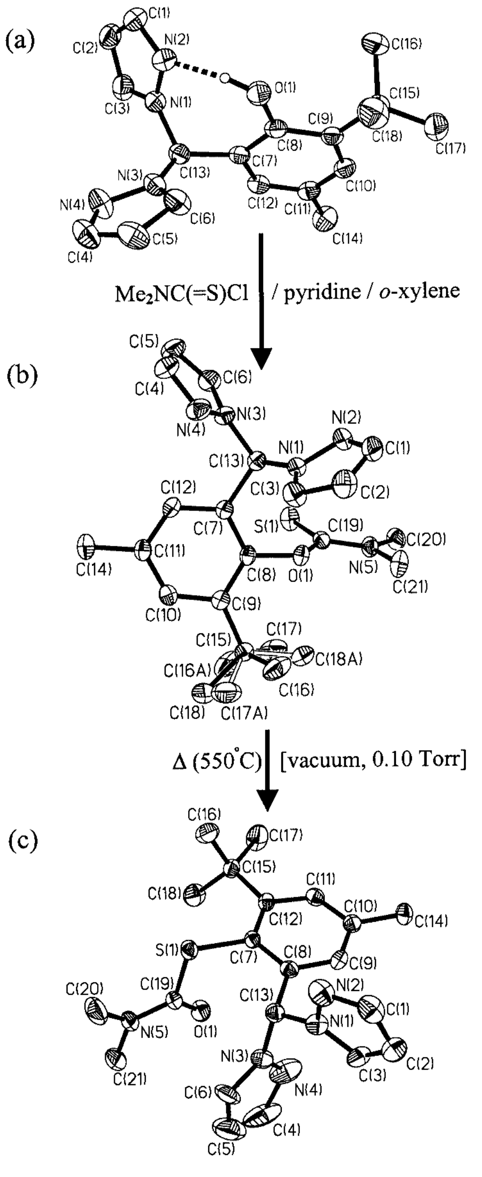


Figure 2. Crystallographic plots (ORTEP, 30% thermal ellipsoids) of molecules **3** (a), **4** (b), and **5** (c), illustrating the conversion of 2-[bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenol to its benzenethiol analog by Newman−Kwart rearrangement

pressure (thermal decomposition occurring long before vapourization). Thus, we have had to develop a variant of the above vapour pyrolysis method wherein the thiocarbamic acid *O*-ester is volatilized at high temperature in vacuo and passed through a quartz tube inserted into a furnace at very high temperature (typically > 500°C). Conventional vapour phase pyrolysis protocols often involve pre-vapourization of the starting material before its transfer into the pyrolysis vessel, this proved impractical with our thiocarbamic acid *O*-esters, again due to their very low volatility, even under vacuum, at "easily accessible" elevated temperatures (i.e. ≤ 200 °C). Therefore, a modification to these conventional procedures was developed whereby the starting thiocarbamic acid *O*-ester (typically 1.0−2.0 g) was packed into a 5-g weighing vial and packed down with glass wool. This sample loading vial was inserted into the end of the quartz-vacuum tube which was then securely stoppered. The apparatus was then assembled at room temp. and placed under vacuum (0.10 Torr) with the end of the quartz tube containing the loading vial outside of the tube furnace. The tube furnace was then activated and heated to the required temperature (dependent on the steric bulk on the ligand) and once the apparatus had thermally equilibrated the portion of the quartz tube containing the loading vial was inserted directly into the furnace (***CAUTION!*** *Care required!*). Under these low-pressure and high-temperature conditions the *O*-ester rapidly volatilised, underwent the pyrolytic rearrangement reaction and the product [and side product(s)] condensed on the far side of the furnace (see Exp. Sect.). By careful control of these "*D*irect *I*nsertion *V*apour *P*hase *F*lash *V*acuum *P*yrolysis" (DIVPFVP) conditions complete reaction of the thiocarbamic acid *O*-ester can be achieved with only two significant products, the desired thiocarbamic acid *S*-ester and 1*H*-pyrazole resulting from thermal decomposition of the *O*/*S* ester (usually 20−40% depending on temperature, higher temperatures leading to more degradation). The efficacy of this batch technique is a trade-off between the furnace temperature and the amount of starting material converted per run. Greater steric bulk in the starting material requires higher furnace temperatures for complete rearrangement, but temperatures above 600 °C tended to lead to excessive thermal decomposition of the thiocarbamic acid *O*-ester (predominantly in the loading vial). A solution to this development was to use smaller amounts of material at lower temperatures ($\leq$ 1.0 g for sterically very bulky *O*-esters such as **8**). Using this method this group has managed to synthesize numerous 2-[bis(pyrazol-1′-yl)methyl]benzenethiol-based ligands with various permutations of alkyl substitition (Me, *i*Pr, *t*Bu) on the pyrazoles and/or the thiophenol. The ^{1}H NMR spectrum ($CDCl_3$) for the most hindered ligand synthesized to date using this procedure, 2-[bis(3′-isopropylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylbenzenethiol (**11**), is shown in Figure 3.

Ligands **6** and **11**, each of which possesses *tert*-butyl substitution on the carbon atom adjacent to the thiophenol group, both have N_2S donor capability, i.e. that observed in "trigonal" type I copper proteins. The *tert*-butyl group "covering" the −SH group of the ligand (Figure 1) should inhibit oligomerization of its Cu^{II} complex through μ_2-S bridging, and more critically dimerization of $R{-}S^{\cdot}$ radicals, resulting from reductive homolysis of the $Cu^{II}{-}SR$ bond, thereby increasing the redox solution stability of the complex. Furthermore the complementary 3-*i*Pr substitution on the pyrazolyl rings will assist in constraining the coordination number of the Cu^{II} complex such as preventing "sandwich" complex formation[72,73] and reducing exogenous ligation (e.g. by solvent) therefore promoting the formation of low-coordination number complexes relevant to the redox-active centers in "blue" copper systems.

An exogenous monodentate thioether ligand would be unlikely to insert into the coordination sphere of the Cu^{II} atoms coordinated to **6** or **11** N_2S-donor ligands due to the poor Cu^{II}-ligating ability of thioether-*S*.[69] Therefore, to utilise these N_2S ligands for modeling N_2SS^* "trigonal-pyramidal" type I ligation spheres, an "all-in-one" adaptive strategy was required. The critical thioether-*S** ligand was incorporated into the pre-synthesized N_2S ligand to form an N_2SS^* donor tetradentate asymmetric "distended" tripod ligand. This was achieved relatively simply as shown in Scheme 2 by treating an appropriate 2-[bis(pyrazol-1′-yl)-methyl]benzenethiol-based ligand (with 3,5-dimethyl- or 3-isopropylpyrazole substitution and no thiophenol substitution) with a vast excess of 1,2-dibromoethane thus converting the thiophenol to a thioether-*S**, and subsequent substitution of the 2-bromo group of the ethyl chain for a lithiated 2-[(diphenylmethyl)thio]tetrahydropyran group. Deprotection of the tetrahydropyran yielded a 3-(1,1-diphenyl-1-mercaptopropane) chain tethered to the sulfanyl group of the tripod phenyl ring. The ^{1}H NMR spectrum of the sterically most hindered ligand of this type synthesized to date, **28**, is shown in Figure 4.

These "all-in-one" N_2SS^* ligands retain all the advantages of the ligands employed for the Katjima et al.[64−67] and Holland, Tolman et al.[68−71] type I copper protein model systems in that they possess a high degree of steric hindrance (especially in the case of the **28** ligand), thus restraining the adoption of higher coordination numbers (i.e. > 4). The sterically bulky 1,1-diphenyl substitution of the

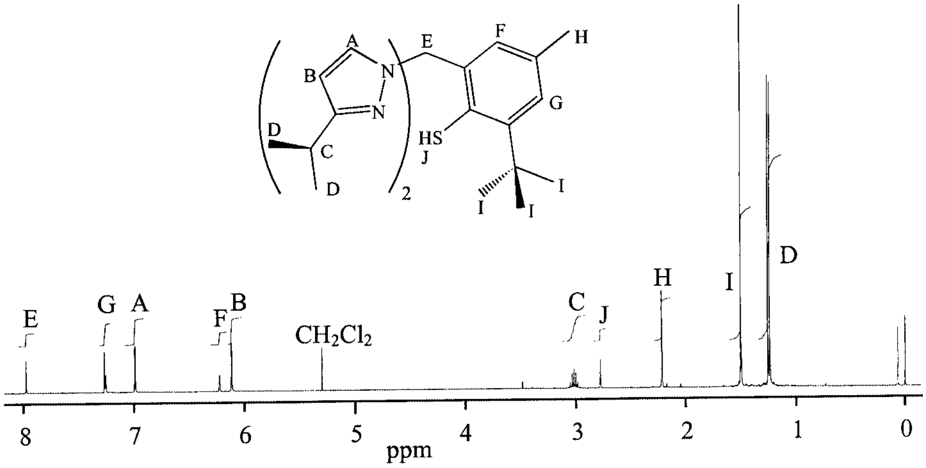


Figure 3. 400 MHz ^{1}H NMR spectrum of **11** in $CDCl_3$

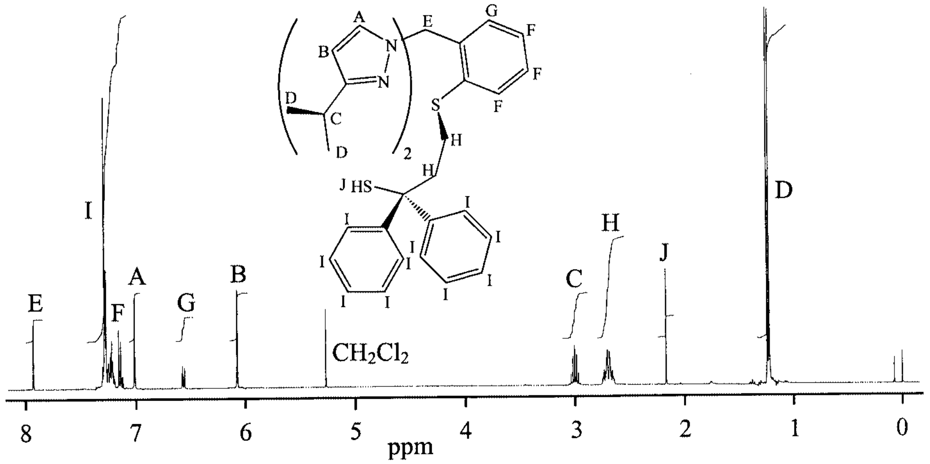


Figure 4. 400 MHz ^1H NMR spectrum of **28** in $CDCl_3$

$-C(Ph)_2SH$ group should confer at least low-temperature solution redox metastability, by inhibiting inter-radical $R-S^{\cdot}$ close contacts (these would favor disulfide formation concomitant with irreversible reduction of $Cu^{II} \rightarrow Cu^{I}$), onto any Cu^{II} complex of this N_2SS^* ligand. The steric bulk, whilst still encouraging distorted coordination geometries, is not as nearly great as that employed on the N-donor ligands of the Holland, Tolman et al.[68−71] systems (2,6-diisopropylphenyl groups) and so should allow more "open" tetraligated Cu^{II} coordination modes (i.e. less "squashed" or "flattened"). Furthermore, Cu^{II} ligation by this thioether-*S** ligand will be strongly encouraged due to its internalized position within the N_2SS^* ligand at the "trichelating pivot" of the ligand, able to form three simultaneous chelate rings when the the ligand is fully coordinated, two seven-membered rings with the pyrazole-*N* donors and one six-membered ring with the thiolate-*S* donor. The incorporation of the thiolate ligand into a six-membered chelate ring (with the thioether-*S** donor via the linking alkylpropyl chain) upon coordination should assist in enhancing the stability of its Cu^{II} complex. Although the homolytic cleavage/formation equilibrium of the $Cu^{II}-SR$ bond will be unaffected, the resultant thiolate radical will be effectively tethered to its "parent" Cu^{I} complex making the long-range dissociation of $R-S^{\cdot}$ from its "parent" Cu^{I} and subsequent radical disulfide coupling less facile.

Conclusion

Herein we have reported the hitherto unspecified synthetic protocol used by Hammes, Carrano et al.[28−31] to produce ligands of the type L2SH which they have employed successfully in the elucidation of possible exogenous thiolate alkylation reaction mechanisms of Zn^{II} complexes. Further to this we have described the extension of these procedures to encompass sterically highly hindered tripodal heteroscorpionate N_2S (**11**) and asymmetric "distended" tripod N_2SS^* **(28)** ligands which possess identical ligand donor arrays to those observed in type I "trigonal" and "trigonal-pyramidal" copper proteins. We anticipate that such ligand systems or ones based upon them could complement the seminal work of Kitajima et al.[64−67] and Holland, Tolman et al.[68−71] in elucidating structural-spectroscopic-redox relationships in this class of metalloprotein.

Experimental Section

General: All reactions were run under a blanket of argon, using standard anaerobic protocols, unless stated otherwise. Anhydrous, degassed THF was freshly distilled from sodium/benzophenone, whilst all other solvents were purchased from Aldrich Chemical Co. and used as received. ^1H NMR spectra were acquired using a 400 MHz Varian NMR spectrometer. All reagents were purchased from Aldrich Chemical Company unless otherwise stated. The 400 MHz ^1H NMR spectroscopic characterizations are tabulated in Tables 1−4, each one summarising a particular synthetic sequence. The analytical integrity of ligands synthesized by this flash vacuum pyrolysis strategy was confirmed by Hammes, Carrano et al.[28−31] through the Zn^{II} complexes of their similarly synthesized L2SH ligand.

Ligand Syntheses

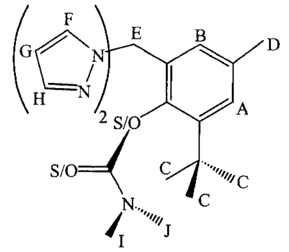
(1) 2-[Bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylbenzenethiol

(a) 3-*tert*-Butyl-2-hydroxy-5-methylbenzaldehyde (1): This was prepared according to a previously published method.[81]

(b) Bis(pyrazol-1-yl) Ketone (2): This synthesis has been previously reported by this group.[72]

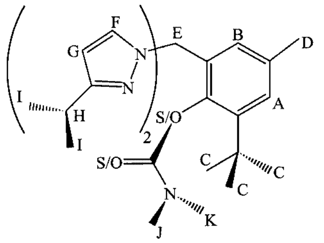
(c) 2-[Bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenol (3): 1 (6.93 g, 0.036 mol), **2** (3.90 g, 0.024 mol), and a catalytic amount of $CoCl_2$ (anhydrous, 0.05 g) were placed together in a 100-mL round-bottom flask fitted with a reflux condenser. The reaction mixture was then steadily brought to a temperature of 90−120 °C during which time a deep blue "melt" formed which effervesced due to evolution of $CO_2(g)$. The heating was continued for 90 min before the reaction mixture was allowed to cool to room temp. The resultant thick, viscous dark blue oil was dissolved in CH_2Cl_2 (70 mL)

Table 1. Proposed ^{1}H NMR assignments for **3**, **4**, **5**, **6**; chemical shifts δ in ppm; ambiguous assignments are represented by merging the cells of the possible contributors; for overlapping peaks the individual components are deconvoluted in the table (dd: doublet of doublets; td: triplet of doublets; bs: broad singlet; qd: quadruplet of doublets; cm: complex multiplet)

	3[a]	**4**	**5**	**6**[b]
				
A	7.22, d, 1 H	7.29, bs, 1 H	7.52, bs, 1H	7.30, d, 1H (+ see F)
B	6.99, d, 1 H	6.48, bs, 1 H	7.15, bs, 1 H	6.46, bs, 1 H
C	1.46, s, 9 H	1.31, s, 9 H	1.47, s, 9 H	1.52, s, 9 H
D	2.27, s, 3 H	2.27, s, 3 H	2.29, s, 3 H	2.24, s, 3 H
E	7.24, s, 1 H	7.99, s, 1 H	8.27, s, 1 H	8.22, s, 1 H
F	7.57, d, 2 H	7.60, d, 1 H[c] 7.37, d, 1 H[c]	7.39, bs, 1 H[c] 6.78, bs, 1 H[c]	7.30, d, 2 H (+ see A)
G	6.28, t, 2 H	6.32, t, 1 H[c] 6.27, t, 1 H[c]	6.27, bs, 2 H	6.34, t, 2 H
H	7.80, d, 2 H	7.62, d, 1 H[c] 7.57, d, 1 H[c]	7.61, bs, 2 H	7.66, d, 2 H
I		3.47, s, 3 H 2.93, s, 3 H	3.10, bs, 3 H 2.84, bs, 3 H	
J				

[a] **3** phenolic, −OH, a singlet at δ = 11.52 ppm. [b] **6** thiophenolic, −SH, a singlet at δ = 2.68 ppm. [c] Carbon atom possesses diastereotopic protons.

Table 2. Proposed ^{1}H NMR assignments for **8**, **9**, **10**, **11**; chemical shifts δ in ppm; ambiguous assignments are represented by merging the cells of the possible contributors; for overlapping peaks the individual components are deconvoluted in the table (dd: doublet of doublets; td: triplet of doublets; bs: broad singlet; qd: quadruplet of doublets; cm: complex multiplet)

	8[a]	**9**	**10**	**11**[b]
				
A	7.18, d, 1 H	7.25, d, 1 H	7.36, d, 1 H	7.26, d, 1 H
B	6.98, d, 1 H	6.36, d, 1 H	6.47, d, 1 H	6.23, d, 1 H
C	1.45, s, 9 H	1.30, s, 9 H	1.45, s, 9 H	1.50, s, 9 H
D	2.25, s, 3 H	2.25, s, 3 H	2.27, s, 3 H	2.22, s, 3 H
E	7.10, s, 1 H	7.81, s, 1 H	8.14, s, 1 H	7.97, s, 1 H
F	7.75, d, 2 H	7.33, d, 1 H[c] 7.22, d, 1 H[c]	7.20, bs, 1 H[c] 6.68, bs, 1 H[c]	6.99, d, 2 H
G	6.05, d, 2 H	6.09, d, 1 H[c] 6.05, d, 1 H[c]	6.03, bs, 2 H	6.12, d, 2 H
H	2.93, sp, 2 H	2.95, sp, 2 H	3.00, m, 2 H (+ see J/K)	3.02, sp, 2 H
I	1.20, d, 12 H	1.20–1.26, m, 12 H[c]	1.24, m, 12 H[c]	1.25, d, 12 H
J		3.44, s, 3 H 2.92, s, 3 H	3.04, bs, 3 H 2.72, bs, 3 H (+ see H)	
K				

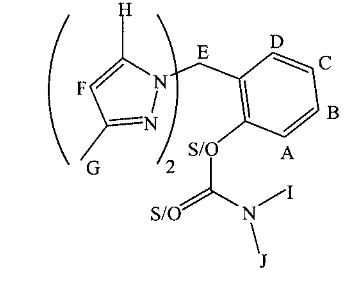
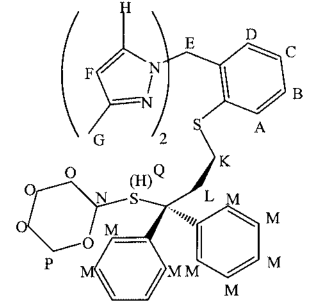
[a] **8** phenolic, −OH, a singlet at δ = 12.33 ppm. [b] **11** thiophenolic, −SH, a singlet at δ = 2.78 ppm. [c] Carbon atom possesses diastereotopic protons.

and this was extracted with distilled water (2 × 200 mL). The CH_2Cl_2 layer was separated and dried with anhydrous $MgSO_4$, and the solution subsequently concentrated to dryness in a rotary evaporator yielding a yellow oil which was distilled under a reduced pressure removing approximately 3.2 g of **1** (which was recycled for use in later syntheses). The brown residual oil in the distillation flask was dissolved in CH_2Cl_2 (20 mL) and *n*-hexane (30 mL) added, this solution was then transferred to a crystallising dish and the product was allowed to crystallise as large colorless crystals (X-ray quality). These were collected by filtration, washed with *n*-hexane (10 mL) and dried in vacuo. Yield: 4.1 g (42%), subsequent ^{1}H NMR spectroscopy and crystal structure analysis of this material indicated a significant component of it was (pz)$_2$CH[3-*t*Bu-5-Me-PhOC(=O)pz] (**3e**), an ester of the desired phenol ligand. **3e** (4.00 g, 9.90×10^{-3} mol) and KOH (3.00 g, 0.053 mol) were refluxed in MeOH (80 mL) for 1 h. The volume of the reaction mixture was then reduced to about 15 mL under a reduced pressure and distilled water (80 mL) then added. The solution was then acidified to pH = 6 with 6 M HCl(aq) which caused a dense white microcrystalline solid to deposit. This water/MeOH/**3** suspension was extracted with CH_2Cl_2 (40 mL) and the organic layer was separated and washed with distilled water (2 × 100 mL). The CH_2Cl_2 layer was then separated and dried with anhydrous $MgSO_4$, *n*-hexane (100 mL) was added and the volume of the solution was reduced to about 20 mL in a rotary evaporator. The solution was transferred to a crystallising dish and overnight large colorless block crystals developed (of crystallographic quality), these were collected by filtration, washed with *n*-hexane (5 mL) and dried in vacuo. Yield: 2.4 g (78%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 1. IR (KBr disk): ṽ = 3050 s, 2947 s, 2721 s, 2618 s, 1778 w, 1727 w, 1064 w, 1515 m, 1478 s, 1435 s, 1384 s, 1356 w, 1304 s, 1252 s, 1210 s, 1149 m, 1087 s, 1050 s, 975 m, 914 w, 834 m, 806 s, 754 s, 707 s, 651 w, 614 w, 561 w, 528 w, 467 w cm^{-1}.

(d) *O*-{2-[Bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenyl}-*N*,*N*-dimethylthiocarbamate (4): 3 (3.60 g, 11.6×10^{-3} mol), pyridine (0.94 mL, 11.6×10^{-3} mol), and dimethylthiocarbamoyl chloride (1.51 g, 0.122 mol) were dissolved in *o*-xylene (75 mL) in a 250-mL round-bottom flask fitted for reflux. The reaction mixture was brought to reflux for 24 h before being allowed to cool to room temp. and the solvents were evaporated to dryness under a reduced pressure. The resultant residual green oil was dissolved in CH_2Cl_2 (50 mL) and this solution washed with distilled water (3 × 300 mL). The organic layer was separated and dried with anhydrous $MgSO_4$ and then concentrated to dryness in a rotary evaporator yielding a yellow oil which was triturated with *n*-hexane (30 mL). This material recrystallized from CH_2Cl_2/*n*-hexane to yield yellow blocks of the product (of crystallographic quality). Yield: 3.3 g (71%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 1. IR (KBr disk): ṽ = 3396 w, 3123 w, 2965 m, 2860 m, 1632 s, 1432 s, 1390 s, 1286 s, 1207 s, 1170 s, 1133 s, 1086 s, 1044 s, 970 m, 913 w, 865 w, 807 m, 744 s, 708 m, 655 m, 613 m, 503 w, 445 w cm^{-1}.

(e) *S*-{2-[Bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenyl}-*N*,*N*-dimethylthiocarbamate (5): 4 (0.20 g, 5.04×10^{-4} mol) was converted into **5** by "direct insertion vapour phase flash vacuum pyrolysis" (DIVPFVP) at a furnace temperature of 550 °C (0.10 Torr). The product condensed on the far side of the furnace as a yellow/

Table 3. Proposed ^{1}H NMR assignments for **14**, **15**, **Li[16]·THF**, **17**, **20**, **21**; all spectra were run in $CDCl_3$ except for **Li[16]·THF** which was run in CD_3OD; chemical shifts δ in ppm; ambiguous assignments are represented by merging the cells of the possible contributors; for overlapping peaks the individual components are deconvoluted in the table (dd: doublet of doublets; td: triplet of doublets; bs: broad singlet; qd: quadruplet of doublets; cm: complex multiplet)

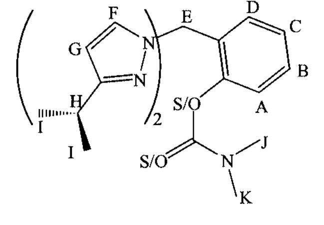
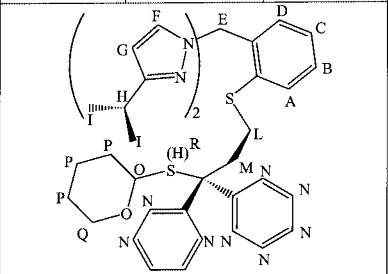
	14	15	Li[16]·THF[a]	17	20	21
						
A	7.01, dd, 1 H	7.51, m, 1 H 7.33, m, 2 H	7.51, d, 1 H 6.93, m, 1 H 6.75, d, 2 H	7.48, d, 1 H	7.01, d, 1 H	7.22, t, 3 H (+ see M)
B	7.39, td, 1 H			7.34, t, 1 H	7.17, t, 1 H	
C	7.20, td, 1 H			7.26, t, 1 H.	7.08, t, 1 H	
D	6.55, dd, 1 H	6.71, m, 1 H		6.80, s, 1 H	6.68, s, 1 H	6.73, d, 1 H
E	7.68, s, 1 H	7.68, s, 1 H	8.36, s, 1 H	7.79, s, 1 H	7.64, s, 1 H	7.69, s, 1 H
F	5.83, s, 2 H	5.83, s, 2 H	5.88, s, 2 H	5.88, s, 2 H	5.84, s,2 H	5.85, s, 1 H
G	2.20, s, 6 H	2.19, s, 6 H	2.17, s, 12 H	2.18, s, 6 H	2.18, d, 6 H	2.17, s, 6 H
H	2.16, s, 6 H	2.09, s, 6 H		2.16, s, 6 H	7.08, d, 6 H	2.08, s, 6 H
I	3.41, s, 3 H	2.96, bs, 6 H				
J	2.89, s, 3 H					
K				2.96, t, 2 H	2.52, qd, 2 H	7.62–2.74, cm, 4 H
L				3.27, t, 2 H	2.97, td, 1 H[b] 2.83, td, 1 H[b]	
M					7.18–7.34, cm, 10 H	7.20–7.35*, cm, 10 H (+ see B/C/A)
N					4.05, m, 1 H	
O					1.35–1.82, cm, 6 H	
P					3.84, m, 1 H[b] 3.20, m, 1 H[b]	
Q						2.20, s, 1 H

[a] THF solvate: δ = 1.89 (m, ca. 3 H, 2,3-CH_2 of THF), 3.75 (m, ca. 3 H, 1,4-CH_2 of THF) ppm. [b] Carbon atom possesses diastereotopic protons.

orange glass (further along the quartz tube, dendritic clumps of white crystals of pyrazole condensed). The condensate was removed from the quartz glass tube by solvation with CH_2Cl_2 (100 mL), this solution was then concentrated to dryness in a rotary evaporator. The ^{1}H NMR (400 MHz, $CDCl_3$) of the crude product indicated the only significant contaminant was free pyrazole, resulting from thermal decomposition. After five more pyrolysis runs of **4**, the batches of crude product were then combined and dissolved in CH_2Cl_2 (30 mL) and this was extracted with distilled water (3 × 75 mL) to remove the pyrazole impurity. The organic layer was separated and dried with anhydrous $MgSO_4$, the dried CH_2Cl_2 solution was then concentrated to dryness in a rotary evaporator yielding a yellow glass which was recrystallized from a CH_2Cl_2/*n*-hexane solution (1:3) to yield colorless block crystals of the **5** (of crystallographic quality); these were collected, washed with *n*-hexane (5 mL) and dried in vacuo. Yield: 0.12−0.14 g (60−70%) per batch. ^{1}H NMR (400 MHz, $CDCl_3$): Table 1. IR (KBr disk): $\tilde{\nu}$ = 3434 w, 3103 w, 2960 m, 2926 m, 1680v s, 1587 w, 1515 w, 1449 m, 1432 m, 1393 s, 1355 s, 1305 m, 1259 s, 1167 w, 1085 s, 1040 s, 980 w, 958 w, 919 m, 831 w, 809 s, 798 w, 765 s, 743 s, 704 m, 685 m, 657 m, 616 w, 553 w cm^{-1}.

(f) 2-[Bis(pyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylbenzenethiol (6): **5** (0.50 g, 1.26×10^{-3} mol) and KOH (0.71 g, 25.2×10^{-3} mol) were dissolved together in MeOH (30 mL), in a 100-mL round-bottom flask fitted for reflux, forming a deep yellow solution. The apparatus was purge-filled with Ar(g) three times and then the reaction mixture brought to reflux for 18 h. The reaction mixture was then allowed to cool to room temp. and was halved in volume using a rotary evaporator. Distilled water (80 mL) was then added to the remaining methanolic solution, and this mixture was carefully acidified to pH = 6 using 6 M HCl(aq) causing the solution color to fade from deep yellow to colorless and for a white solid to precipitate. The resulting suspension was extracted into CH_2Cl_2 (30 mL) and this layer was washed with distilled water (100 mL). The organic layer was separated and dried with anhydrous $MgSO_4$ and then this CH_2Cl_2 solution concentrated to dryness in a rotary evaporator yielding a pale yellow, slightly oily "foam". This was triturated with *n*-hexane (10−15 mL) to yield a very pale yellow microcrystalline solid which was collected by filtration, washed with *n*-hexane (5 mL) and dried in vacuo. Yield: 0.30 g (73%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 1. IR (KBr disk): $\tilde{\nu}$ = 3406 w, 3108 m, 2959 s, 2919 s, 2870 s, 2562 w, 2235 w, 1770 w, 1716 w, 1602 m,

Table 4. Proposed ^{1}H NMR assignments for **23**, **24**, **25**, **26**, **27**, **28**; chemical shifts δ in ppm; all spectra were run in $CDCl_3$; ambiguous assignments are represented by merging the cells of the possible contributors; for overlapping peaks the individual components are deconvoluted in the table (sp: septuplet; dd: doublet of doublets; td: triplet of doublets; bs: broad singlet; qd: quadruplet of doublets; cm: complex multiplet)

	23	24	25[a]	26	27	28
						
A	7.19, d, 2 H	7.58, d, 1 H	7.37, dd, 1 H	7.51, d, 1 H	7.02, d, 1 H	ca. 7.25, cm, 3 H (+ see N)
B	7.45, t, 1 H	7.40, m, 2 H	7.23, td, 1 H	7.35, t, 1 H	7.06, t, 1 H (+ see N)	
C	7.26, t, 1 H		7.17, td, 1 H	7.27, t, 1 H		
D	6.85, d, 1 H	6.75, d, 1 H	6.57, dd, 1 H	6.72, d, 1 H	6.55, d, 1 H	6.57, d, 2 H
E	7.76, s, 1 H	7.99, s, 1 H	7.76, s, 1 H	8.03, s, 1 H	7.88, s, 1 H	7.94, s, 1 H
F	7.30, d, 2 H	7.03, d, 2 H	7.10, d, 2 H	7.11, d, 2 H	7.00, d, 2 H	7.02, d, 2 H
G	6,14, d, 2 H	6.07, d, 2 H	6.13, d, 2 H	6.12, d, 2 H	6.08, d, 2 H	6.09, d, 2 H
H	3.03, sp, 2 H	2.97, m, 2 H (+ see J/K)	3.01, sp, 2 H	2.99, m, 2 H (+ see L)	3.00, m, 2 H (+ see M)	3.00, sp, 2 H
I	1.28, d, 12 H	1.24, d, 12 H	1.25, d, 12 H	1.23, d, 12 H	1.24, d, 12 H	1.24, d, 12 H
J	3.38, s, 3 H	2.97, bs, 3 H				
K	3.09, s, 3 H	2.85, bs, 3 H				
L				2.95, t, 2 H	2.53, qd, 2 H	2.69, cm, 4 H
M				3.22, t, 2 H	3.00, m, 1 H[b] 2.88, td, 1 H[b]	
N					7.14–7.40, m, 10 H (+ see B/C)	7.19–7.35, cm, 10 H (+ see A/B/C)
O					4.06, m, 1 H	
P					1.32–1.83, cm, 6 H	
Q					3.84, m, 1 H[b] 3.20, m, 1 H[b]	
R						2.17, s, 1 H

[a] **25** thiol, −SH, singlet at δ = 3.195 ppm. [b] Carbon atom possesses diastereotopic protons.

1512 s, 1477 m, 1428 s, 1388 s, 1363 m, 1320 s, 1254 s, 1214 m, 1195 m, 1165 m, 1088 s, 1046 s, 971 m, 917 s, 823 s, 807 s, 748 s, 698 s, 654 s, 614 m cm^{-1}.

(2) 2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylbenzenethiol

(a) Bis(3-isopropylpyrazol-1-yl) Ketone (7): This synthesis has been previously described by this group.[72]

(b) 2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenol (8): 1 (24.0 g, 0.125 mol), **7** (30.5 g, 0.125 mol), and $CoCl_2$ (anhydrous, ca. 0.50 g) were mixed together in a 150-mL round-bottom flask fitted with a reflux condenser and for magnetic stirring. This reaction mixture was brought to a temperature of 120 °C for 96 h [during which time a dark green-blue "melt" formed from which very slow evolution of $CO_2(g)$ was observed]. The course of the reaction was monitored by taking small aliquots (ca. 0.10 g) of the reaction mixture out at 24-h intervals and elucidating its contents by ^{1}H NMR ($CDCl_3$). After 96 h, the reaction was considered to have proceeded to a satisfactory point (90+% conversion), and the mixture was allowed to cool to room temp. The "melt" was then dissolved in CH_2Cl_2 (200 mL) and this solution extracted with distilled water (2 × 300 mL). The CH_2Cl_2 layer was separated, dried with anhydrous $MgSO_4$, and then concentrated to dryness in a rotary evaporator yielding a viscous yellow oil. This oil was dissolved in *n*-hexane (100 mL) and this too was then concentrated to dryness under a reduced pressure (to remove off any residual CH_2Cl_2 azeotropically). The resultant yellow oil was dissolved in pentane (100−150 mL) and this placed in a freezer for several days at −30 °C during which time a microcrystalline very pale yellow solid precipitated. This solid was collected on a cold sinter and washed with cold (−30 °C) pentane (2 × 20 mL) and then dried in vacuo. Further batches of material could be obtained by sequentially reducing the volume of the pentane solution and cooling it to −30 °C to effect crystallization of the product. Yield: 24.0 g (49%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 2.

(c) *O*-{2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenyl}-*N*,*N*-dimethylthiocarbamate (9): NaH (0.66 g, 0.027 mol) was placed in a 3-necked 500-mL round-bottom flask, under Ar(g), which was fitted with both a 250-mL pressure-equalising addition funnel and a reflux condenser. In a separate 250-mL round-bottom flask, **8** (5.42 g, 13.7×10^{-3} mol) was dissolved in THF (150 mL) under Ar(g). The **8**$_{\mathrm{THF}}$ solution was then cannulated into the addition funnel and then added dropwise to the NaH [***Caution:*** $H_2(g)$ evolution as **Na[20]** formed]. Separately, in a 150-mL round-bottom flask, dimethylthiocarbamoyl chloride (1.87 g, 15.1×10^{-3} mol) was dissolved in THF (40 mL). This solution was cannulated into the addition funnel of the above apparatus. The dimethylthiocarbamoyl chloride/THF solution was then added dropwise to the **Na[8]**$_{\text{THF}}$ solution over a period of 15 min, the reaction mixture was then refluxed for 3 h, during which time the mixture turned green and an NaCl precipitate formed. The reaction mixture was allowed to cool to room temp. before the NaCl/excess NaH collected by filtration in air and washed with THF (20 mL). The yellow filtrate was concentrated to dryness in a rotary evaporator yielding a yellow oil which was dissolved in CH_2Cl_2 (65 mL). This CH_2Cl_2 solution was extracted with two portions of saturated brine (2×150 mL) and the organic layer then separated and dried with anhydrous $MgSO_4$. The CH_2Cl_2 solution was then concentrated in a rotary evaporator leaving a thick yellow oil which was dried in vacuo. This oil was dissolved in a minimum volume of *n*-hexane (10 mL) and purified by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), fractions monitored by ^{1}H NMR]. The pure fractions were combined and the solvents evaporated to dryness yielding a colorless viscous oil. Yield: 5.1 g (77%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 2.

(d) *S*-{2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylphenyl}-*N*,*N*-dimethylthiocarbamate (10): **9** (≤ 1.00 g, 2.09×10^{-3} mol) was converted into **10** by DIVPFVP at a furnace temperature of 570 °C (0.10 Torr), smaller batches of material than usual (2.00 g) were allowed to react to limit thermal decomposition. The product condensed on the far side of the furnace as a black tar [further along the quartz tube, a yellow oil condensed which was predominantly 3-isopropylpyrazole (3-*i*Prpz)]. The condensate was removed from the quartz glass tube by solvation with CH_2Cl_2 (100 mL), this solution was then concentrated to dryness in a rotary evaporator. After ten pyrolysis runs of **9**, the batches of crude product were then combined and most of the 3-*i*Prpz contamination distilled off in vacuo (0.1 Torr) using a kugelrohr over a temperature range of 100−120 °C. The residual black tar was dissolved in MeOH (150 mL) and this solution decolorized using activated charcoal. The solution was then concentrated to dryness in a rotary evaporator yielding a brown oil, this was then dried in vacuo. This material was then dissolved in a minimum volume of *n*-hexane (10 mL) and purified by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), fractions monitored by ^{1}H NMR], the fractions containing pure **10** were combined and dried in vacuo yielding a pale yellow oil. Yields: 0.40−0.60 g (40−60%) per batch. ^{1}H NMR (400 MHz, $CDCl_3$): Table 2.

(e) 2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]-6-*tert*-butyl-4-methylbenzenethiol (11): **10** (2.00 g, 4.17×10^{-3} mol) was dissolved in THF (50 mL) in a 150-mL round-bottom flask. Separately, 1.0 M $LiAlH_4$ (7.00 mL, 7.00×10^{-3} mol) was transferred via gastight syringe into a 500-mL 3-necked round-bottom flask, fitted with both a water condenser and a 150-mL pressure-equalising addition funnel. The **10**$_{\text{THF}}$ solution was then cannulated into the addition funnel and its flask washed out with a further portion of THF (50 mL) into the addition funnel. The **10**$_{\text{THF}}$ solution was then added dropwise to the 1.0 M $LiAlH_4$ solution over a period of 20 min during which time the reaction mixture turned to a deep yellow color. Following the addition, the reaction mixture was refluxed for 3 h before being allowed to cool to room temp. The reaction mixture at this point contained a large excess of $LiAlH_4$, this was destroyed by careful dropwise addition of first a 10% NaOH(aq) solution (1 mL), then distilled water (1 mL; ***Caution:*** foaming due to H_2 evolution!). The $\{Al(OH)_3\}_n$ that precipitated from the reaction mixture after quenching was collected by filtration through Celite and washed with THF (30 mL), then water (2×30 mL). These filtrates were combined and concentrated to a volume of about 60 mL thus removing most of the THF and causing a yellow oil to deposit. The solution was then acidified to pH = 5.5 by dropwise addition of 6 M HCl(aq) before being extracted with CH_2Cl_2 (2×50 mL). The CH_2Cl_2 extracts were combined and dried with anhydrous $MgSO_4$. The CH_2Cl_2 solution was then concentrated to dryness in a rotary evaporator yielding a yellow oil which was dissolved in a minimum volume of *n*-hexane (5 mL) and then purified by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), fractions monitored by ^{1}H NMR]. The fractions containing pure **11** were combined and dried in vacuo. Appearance: very viscous pale yellow oil. Yield: 1.4 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 2.

(3) 3-{2′-[Bis(3′′,5′′-dimethylpyrazol-1′′-yl)methyl]phenylsulfanyl}-1,1-diphenylpropane-1-thiol

(a) Bis(3,5-dimethylpyrazol-1-yl) Ketone (12): This synthesis has been previously described by this group.[72]

(b) 2-[Bis(3′,5′-dimethylpyrazol-1′-yl)methyl)]phenol (13): The procedure for this synthesis has been described by this group in a previous publication.[72]

(c) *O*-{2-[Bis(3′,5′-dimethylpyrazol-1′-yl)methyl]phenyl}-*N*,*N*-dimethylthiocarbamate (14): The same procedure as used to synthesise **9** was applied using **13** (20.0 g, 0.0676 mol), NaH (1.95 g, 81.1×10^{-3} mol), dimethylthiocarbamoyl chloride (8.77 g, 70.9×10^{-3} mol). The final product was triturated with Et_2O to yield a pale yellow solid. Yield: 18.6 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 3.

(d) *S*-{2-[Bis(3′,5′-dimethylpyrazol-1′-yl)methyl]phenyl}-*N*,*N*-dimethylthiocarbamate (15): **14** (2.00 g, 5.22×10^{-3} mol) was converted into **15** by DIVPFVP at 520 °C (0.1 Torr). Ten batches of **5** were subjected to DIVPFVP, the batches of crude **15** were combined and distilled under vacuum (0.10 Torr) using a kugelrohr, to remove the 3,5-dimethylpyrazole contamination, over a temperature range of 60−120 °C, the 3,5-dimethylpyrazole distillate condensing as dendritic clumps of white crystals. The dark brown oily residue from the distillation was dissolved in MeOH (150 mL) and decolorized with activated charcoal. After removal of the charcoal, the solution was concentrated to dryness in a rotary evaporator yielding a light yellow-orange oil was dried in vacuo. This material was used in the next step of the synthesis without further purification. Yield: 1.2−1.4 g (60−70%) per batch. ^{1}H NMR (400 MHz, $CDCl_3$): Table 3.

(e) Lithium 2-[Bis(3′,5′-dimethylpyrazol-1′-yl)methyl]benzenethiolate−THF Solvate {Li[16]·THF}: **15** (12.2 g, 31.9×10^{-3} mol) was placed into a 250-mL round-bottom flask under Ar(g). THF (100 mL) was added, and the flask was shaken until **15** had dissolved. Separately, 1.0 M $LiAlH_4$ (32.0 mL, 31.9×10^{-3} mol) was transferred (using a gas-tight 50-mL syringe) into a 1-L 3-necked round-bottom flask fitted with both a water condenser and a 250-mL pressure-equalising addition funnel. The **6**$_{\text{THF}}$ solution was cannulated into the addition funnel and the flask was washed out with a further portion of THF (50 mL) into the addition funnel. The **15**$_{\text{THF}}$ solution was then added dropwise to the 1.0 M $LiAlH_4$ solution over a period of 20 min. As the addition of **15**$_{\text{THF}}$ proceeded the reaction mixture turned deep orange in color and started refluxing due to the highly exothermic reduction reaction. After several minutes, a white microcrystalline solid started to precipitate from the reaction mixture (**Li[16]·THF**). After completion of the addition, the reaction mixture was refluxed for a further 90 min before being allowed to cool to room temp. The white solid was collected by filtration under Ar(g), using standard Schlenk line techniques, washed with THF (2 × 30 mL), and dried in vacuo. The THF filtrate containing the excess $LiAlH_4$ was then destroyed by careful dropwise addition of H_2O (***Caution:*** foaming due to H_2 evolution!). Yield: 7.3 g (59%). ^1H NMR (400 MHz, CD_3OD): Table 3.

(f) 1-{2′-[Bis(3′′,5′′-dimethylpyrazol-1′′-yl)methyl]phenylsulfanyl}-2-bromoethane (17): Li[16]·THF (0.50 g, 1.28×10^{-3} mol) was dissolved in 1,2-dibromoethane (21.0 g, 0.11 mol)/MeOH (10 mL) in a 100-mL round-bottom flask fitted with a reflux condenser, this mixture was brought to reflux for 15 min. After cooling to room temp., the MeOH component of the reaction solvents was evaporated under a reduced pressure, this resulted in the precipitation of LiBr as a white microcrystalline solid. CH_2Cl_2 (20 mL) was added and the mixture extracted with distilled water (2 × 100 mL) to remove the LiBr. The organic layer was separated and dried with anhydrous $MgSO_4$. The solvents (CH_2Cl_2, $BrCH_2CH_2Br$) were then distilled off under vacuum yielding a pale yellow solid in the distillation flask. This solid was recrystallised from CH_2Cl_2/*n*-hexane, crystallising as small pale yellow blocks. Yield: 0.47 g (87%). ^1H NMR (400 MHz, $CDCl_3$): Table 3.

(g) Diphenylmethanethiol (18). This synthesis of this compound was achieved by the published procedure of Archer et al.[82]

(h) 2-[(Diphenylmethyl)thio]tetrahydropyran (19): The method of Berg and Holm was utilized to effect synthesis of this compound.[83]

(i) 2-(3′-{2′′-[Bis(3′′′,5′′′-dimethylpyrazol-1′′′-yl)methyl]phenylsulfanyl}-1′,1′-diphenylpropyl-1′-sulfanyl)tetrahydropyran (20): 19 (2.00 g, 7.04×10^{-3} mol) was dissolved in THF (100 mL) in a 1-L 2-necked round-bottom flask fitted with a 250-mL pressure-equalising addition funnel. The solution was then cooled to −78 °C using a dry-ice/acetone bath and 1.6 M *n*BuLi in *n*-hexane (4.40 mL, 7.04×10^{-3} mol) was added using a Hamilton 5.0-mL gas-tight syringe. Upon addition of the *n*BuLi the color of the solution changed from colorless to deep orange. The solution was stirred at −78 °C for 30 min during which time a microcrystalline solid precipitated from the solution (presumably **Li[19]**). The mixture was then allowed to warm to room temp. over a period of about 1 h, as the mixture neared room temp. the solid re-dissolved once again forming a deep orange solution. Separately, **17** (1.48 g, 3.52×10^{-3} mol) was dissolved in THF (50 mL) in a 100-mL round-bottom flask and this solution was cannulated into the addition funnel of the above apparatus. This $\mathbf{8}_{THF}$ solution was then added dropwise to the $\mathbf{Li[19]}_{THF}$ solution (at room temp.) over a period of 1 h. During the addition the color of the reaction mixture darkened to a brown color. After completion of the addition, the reaction mixture was stirred at room temp. for a further 30 min before being quenched with distilled water (5 mL) which caused the color of the solution to change to yellow. The solution was then concentrated to dryness in a rotary evaporator yielding a yellow oil, this was dissolved in CH_2Cl_2 (60 mL) and extracted with distilled water (2 × 150 mL). The CH_2Cl_2 layer was separated and dried with anhydrous $MgSO_4$, then concentrated to dryness. The residual yellow oil was dissolved in a minimum amount of *n*-hexane (20−30 mL) and then purified by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), fractions monitored by ^1H NMR]. The fractions containing the desired product were combined and the solvents evaporated to dryness yielding a "foam" which was broken up to give a white solid. Yield: 2.0 g (92%). ^1H NMR (400 MHz, $CDCl_3$): Table 3.

(j) 3-{2′-[Bis(3′′,5′′-dimethylpyrazol-1′′-yl)methyl]phenylsulfanyl}-1,1-diphenylpropane-1-thiol (21): 20 (2.75 g, 4.41×10^{-3} mol) was dissolved in MeOH (40 mL). Separately, $AgNO_3$ (1.65 g, 9.70×10^{-3} mol) was dissolved in MeOH (100 mL)/pyridine (10 mL). The flask containing the $\mathbf{20}_{MeOH}$ solution was wrapped with Al foil to completely eliminate all light and the $AgNO_{3(MeOH/pyridine)}$ solution was added. The reaction mixture was stirred for 24 h at room temp. in the dark. After 24 h, a white microcrystalline solid had precipitated from the solution, it was collected by filtration, washed with MeOH (2 × 10 mL) and air-dried on the sinter to give approximately 3.0 g of material. This solid was dissolved in pyridine (5 mL), then diluted with CH_2Cl_2 (100 mL) to give a brown solution, and H_2S [generated by dropwise addition of 6 M HCl(aq) to pellets of K_2S] bubbled through this solution for 20 min causing the dense precipitation of black $[Ag_2S]_n$. The $[Ag_2S]_n$ was then removed by filtration, and the filtrate concentrated to dryness using a kugelrohr. This yielded a viscous yellow oil which was dissolved in CH_2Cl_2 (40 mL), then extracted with distilled water (3 × 100 mL). The CH_2Cl_2 layer was separated, dried with anhydrous $MgSO_4$ and then concentrated in a rotary evaporator to yield a pale yellow oil which was triturated to a white microcrystalline solid with *n*-hexane/diethyl ether. Yield: 1.7 g (73%). ^1H NMR (400 MHz, $CDCl_3$): Table 3.

(4) 3-{2′-[Bis(3′′-isopropylpyrazol-1′′-yl)methyl]phenylsulfanyl}-1,1-diphenylpropane-1-thiol

(a) 2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]phenol (22): The procedure for this synthesis has been described by this group in a previous publication.[72]

(b) *O*-{2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]phenyl}-*N*,*N*-dimethylthiocarbamate (23): The same procedure as used to synthesise **9** was applied using **22** (20.0 g, 61.7×10^{-3} mol), NaH (1.93 g, 0.080 mol), dimethylthiocarbamoyl chloride (8.77 g, 0.0709 mol). The final product was triturated with *n*-hexane to yield a slightly "sticky" yellow solid. Yield: 19.3 g (76%). ^1H NMR (400 MHz, $CDCl_3$): Table 4.

(c) *S*-{2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]phenyl}-*N*,*N*-dimethylthiocarbamate (24): 23 (2.00 g, 4.86×10^{-3} mol) was converted into **24** by DIVPFVP at a furnace temperature of 580 °C (0.10 Torr). The product condensed on the far side of the furnace as a very dark brown oil (further along the quartz tube, a yellow oil condensed which was predominantly 3-*i*Prpz). The condensate was removed from the quartz glass tube by solvating it with CH_2Cl_2 (150 mL), and this solution was concentrated to dryness in a rotary evaporator. Ten batches of **23** were subjected to DIVPFVP. The batches of crude product were then combined and distilled under vacuum (0.10 Torr) using a kugelrohr, to remove most of the 3-*i*Prpz contamination, over a temperature range of 100−120 °C, the 3-*i*Prpz distillate condensing as a yellow oil. The residual dark brown oil from the distillation was dissolved in MeOH (150 mL) and decolorized with activated charcoal. The solution was then concentrated yielding a pale brown oil which was then dried in vacuo. This material was then purified further by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), fractions monitored by ^1H NMR]. The pure fractions were combined, and concentrated yielding a viscous yellow oil. Yield: 1.0−1.4 g (50−70%) per batch. ^1H NMR (400 MHz, $CDCl_3$): Table 4.

(d) 2-[Bis(3′-isopropylpyrazol-1′-yl)methyl]benzenethiol (25): The same $LiAlH_4$ reduction procedure as used to synthesise **10** was applied using **24** (12.5 g, 0.030 mol) and $LiAlH_4$ (1.0 M in THF, 30.4 mL, 0.026 mol). The crude product, a yellow oil, was purified by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), fractions monitored by ^{1}H NMR]. The fractions containing pure **25** were combined and dried in vacuo. Appearance: viscous pale yellow oil. Yield: 8.3 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 4.

(e) 1-{2′-[Bis(3′′-isopropylpyrazol-1′′-yl)methyl]phenylsulfanyl}-2-bromoethane (26): NaH (1.27 g, 0.053 mol) was placed in a two-necked 500-mL round-bottom flask fitted with a 150-mL pressure-equalising addition funnel. Separately, **25** (12.0 g, 0.035 mol) was dissolved in THF (100 mL) in a 250-mL round-bottom flask, and this was cannulated into the addition funnel. The **25**$_{THF}$ was added dropwise to the NaH [***Caution:*** effervescence due to H_2(g) generation]. Upon completion of the addition, the mixture was stirred for a further 20 min at room temp. before the excess NaH was collected by filtration. The deep yellow filtrate was concentrated to dryness under a reduced pressure, then MeOH (5 mL)/dibromoethane (48.45 g, 0.258 mol) was added to the resulting yellow "foam". The yellow material quickly dissolved, and this reaction mixture was then refluxed for 25 min. After cooling to room temp., the MeOH was removed in a rotary evaporator, causing the precipitation of LiBr, CH_2Cl_2 (50 mL) was then added and the mixture extracted with distilled water (2×150 mL) to remove the LiBr. The organic layer was separated and dried with anhydrous $MgSO_4$ before being concentrated to dryness under vacuum to yield the crude product, a yellow oil. This material was purified by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), fractions monitored by ^{1}H NMR]. The pure fractions of **26** from the dry flash chromatography were combined, dried in vacuo and then recrystallized from *n*-hexane, pure **26** was isolated as a pale yellow solid. Yield: 7.2 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 4.

(f) 2-(3′-{2′′-[Bis(3′′′-isopropylpyrazol-1′′′-yl)methyl]phenylsulfanyl}-1′,1′-diphenylpropyl-1′-sulfanyl)tetrahydropyran (27): The synthesis of **27** (from **26** and **19**) was exactly the same as that of **20** (from **17** and **19**), substituting **26** for **17** and using the following reactant ratios: **19** (3.43 g, 0.0121 mol), 1.6 M *n*BuLi in *n*-hexane (7.55 mL, 0.0121 mol), and **26** (2.70 g, 6.04×10^{-3} mol). Yield: 1.7 g (43%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 4.

(g) 3-{2′-[Bis(3′′-isopropylpyrazol-1′′-yl)methyl]phenylsulfanyl}-1,1-diphenylpropane-1-thiol (28): The same procedure as used to synthesise **21** was applied using **27** (1.80 g, 2.77×10^{-3} mol) and $AgNO_3$ (1.04 g, 6.09×10^{-3} mol) in MeOH (60 mL)/pyridine (10 mL). The resultant Ag^I thiolate complex was again cleaved using H_2S(g) [from K_2S + 6 M HCl(aq)]. The ^{1}H NMR spectrum of the crude product indicated a 9:1 ratio of **28**/**27**. This material was purified by dry flash column chromatography [TLC-grade silica gel w/o binder, CH_2Cl_2/EtOAc (2% increments of EtOAc), **28** eluted first, fractions monitored by ^{1}H NMR]. The pure fractions were combined and the solvents evaporated to dryness yielding a very viscous pale yellow oil [***Note:*** air-sensitive material, stored under Ar(g)]. Yield: 1.1 g (71%). ^{1}H NMR (400 MHz, $CDCl_3$): Table 4.

Crystallography: Crystals of **3**, **4**, and **5** were all grown by solvent evaporation of CH_2Cl_2/*n*-hexane solutions of the respective compounds (see Exp. Sect., vide supra). For all three compounds a crystals was glued to a glass fiber with epoxy resin and mounted onto a goniometer head and this loaded into a Siemens P4 diffractometer, with a sealed-tube Mo-K_α X-ray source (λ = 0.71073 Å), under PC control with an installed Siemens XSCANS 2.1 software package. Automatic searching, centering, indexing, and least-squares routines were carried out on **3**, **4**, and **5** for at least 30 reflections in the range $24° \leq 2\theta \leq 25°$ and these subsequently used to determine unit cell parameters. During the data collection, the intensities of three representative reflections were monitored every 97 reflections for each of the three crystals, no significant decay was observed for any of the crystals. The three data sets were corrected for Lorentz and polarization effects. No semi-empirical

Table 5. Crystallographic data and data collection parameters for **3**, **4**, and **5**

Compound[a]	3	4	5
Empirical formula	$C_{18}H_{22}N_4O$	$C_{21}H_{27}N_5OS$	$C_{21}H_{27}N_5OS$
Bravais lattice	monoclinic	monoclinic	triclinic
Space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a [Å]	15.2701(17)	12.6279(6)	9.3154(12)
b [Å]	9.9914(12)	9.6906(8)	9.8197(17)
c [Å]	12.1924(12)	18.4360(17)	12.5959(12)
α [°]			96.050(11)
β [°]	110.786(6)	104.494(6)	100.216(11)
γ [°]			106.366(13)
V [Å^3]	1739.1(3)	2184.2(3)	1073.2(3)
ρ [g·cm^{-3}]	1.185	1.209	1.230
F(000)	664	848	424
Crystal size [mm]	0.7 × 1.2 × 1.0	0.7 × 0.7 × 0.7	0.2 × 0.2 × 0.3
Crystal color, habit	Colorless, block	Yellow, cube	Colorless, block
μ [mm^{-1}]	0.076	0.169	0.172
2θ collection range [°]	3.5−45.0	3.5−45.0	3.5−45.0
No. unique data	2256	2846	2771
No. observed data, [$\lvert F\rvert > 4\sigma(\lvert F\rvert)$]	1683	2418	1679
Data/restraints/parameters	2256/0/213	2846/0/282	2771/0/254
R_1 [$\lvert F\rvert > 4\sigma(\lvert F\rvert)$]	4.19[b]	4.49[c]	5.85[d]
wR_2	12.66	13.16	14.24
Largest difference peak [e Å^{-3}]	+0.184	+0.289	+0.226
Largest difference hole [e Å^{-3}]	−0.159	−0.239	−0.233

[a] Temp. 298 K; radiation Mo-K_α; scan type θ-2θ. [b] $w = 1/[\sigma^2(F_o^2) + (0.0673P)^2 + 0.3881P]$ where $P = (F_o^2 + 2F_c^2)/3$. [c] $w = 1/[\sigma^2(F_o^2) + (0.0683P)^2 + 1.5934P]$ where $P = (F_o^2 + 2F_c^2)/3$. [d] $w = 1/[\sigma^2(F_o^2) + (0.0457P)^2 + 0.8206P]$ where $P = (F_o^2 + 2F_c^2)/3$.

absorption corrections were applied since examination of the ψ scan data collected for each crystal indicated little anisotropic radiation absorption. The SHELXTL version 5[84] software package was used to solve all three structures by direct methods and subsequently refine them. A summary of cell parameters, data collection conditions, transmission factors, and refinement results can be found in Table 5. Details pertinent to the individual refinements are outlined below. The structure of **3** was solved by direct methods, the asymmetric unit containing a single complete molecule of **3**. All non-hydrogen atoms were refined isotropically and subsequently anisotropically. All hydrogen atoms were included in calculated positions except for H1B, which is attached to O1 and hydrogen-bonded to N2 [O1···N2; 2.64(1) Å], which was located on the E-map by difference Fourier synthesis. The structure of **4** was also solved by direct methods, with once again a single complete molecule within the asymmetric unit. The non-hydrogen atoms were first refined isotropically whereupon disorder over two positions was observed in the *tert*-butyl group (C15, C16, C17, C18) of the C7−C12 phenyl ring. The *tert*-butyl methyl groups (C16, C17, and C18) had their occupancies tied to their disordered counterparts (C16′, C17′, and C18′) to give a total of 1.0 for each pair, then these were refined to give respective occupancy values of 0.68 and 0.32. All the non-hydrogen atoms were then refined anisotropically. Hydrogen atoms were included in calculated positions (including the disordered *tert*-butyl group, the H occupancies corresponding to those of the C atom to which they were bonded) using a riding model and fixed isotropic thermal parameters. The structure of **5** was solved by direct methods with one complete molecule being contained within the asymmetric unit. All non-hydrogen atoms were refined with anisotropic thermal parameters and the hydrogen atoms subsequently included in the refinement in calculated positions using a riding model with fixed isotropic thermal parameters. CCDC-187103 (**3**), -187104 (**4**) and -187105 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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