Synthesis and Coordinating Properties of Ligands Designed for Modeling of the Active Site Zinc of Liver Alcohol Dehydrogenase

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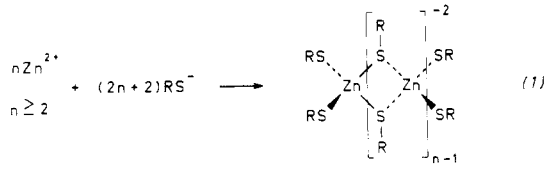
Some tridentate ligands have been prepared for coordination of zinc(II) ions (or cobalt(II), which acts as a surrogate for Zn(II) ions) in a manner analogous to the coordination found in liver alcohol dehydrogenase. This entails coordination of the metal ion to two thiolates and an imidazole. The ligands must be sufficiently sterically hindered to prevent thiolate from acting as a bridging ligand between two metal ions. For some aspects of this work pyridine was used instead of imidazole. A trisubstituted benzene derivative, 3,5-bis(3-mercaptopropoxy)-*N*-[2-(1*H*-imidazol-4-yl)ethyl]benzamide (**7**) was prepared. Zn(II) complexes with **7** could not be characterized but the Co(II) complexes showed excellent spectral correlation with liver alcohol dehydrogenase in which Zn(II) has been replaced by Co(II). Several analogues of **7** have also been synthesized. Another ligand, 2,6-bis[(9-mercaptofluoren-9-yl)methyl]pyridine (**17**), does provide a monomeric Zn(II) complex. The synthesis and coordination of various analogues of this system have been examined. The bis-alcohol, 2,6-bis(2-methyl-2-hydroxypropyl)pyridine (**24**), gives a stable pentacoordinate complex with $Zn(NO_3)_2$ and two water molecules.

Introduction

The zinc ion at the active site of horse liver alcohol dehydrogenase (HLADH) is tetrahedrally ligated by two thiolates from cysteine, an imidazole from histidine, and a water molecule.[1] A possible mechanism of action is sketched in Figure 1.[2] These ligands embedded in the peptide chain belong to the best metal complexing groups found in proteins.[3,4] However this type of coordination for the Zn(II) ion at the active site has little precedent in synthetically prepared zinc complexes. The majority of zinc thiolates described in the literature are oligomeric[5] or are found as clusters,[6] owing to the pronounced tendency of thiolate to act as a bridging ligand (eq 1).[7] Only



a few cases have been described wherein this sulfur bridging homopolymerization has been suppressed, allowing isolation of mononuclear $Zn(SR)_4^{2-}$ complexes.[8,9] The corresponding complexes with Co(II), used often as a surrogate for Zn(II), behave similarly.[7,8]

Mononuclear complexes of Zn(II) and Co(II) with imidazole ligands, in spite of the bridging ability of this ligand, are better described.[10] For the case of mixed imidazole/thiol complexes, severe steric hindrance must be present to prevent sulfur bridging. These conditions have been met in a few mononuclear Zn(II) and Co(II) complexes with N- and S-containing ligands. Schugar and co-workers[11] have described tetraligated Zn(II) and Co(II) complexes with two 1-amino-2-methylpropane-2-thiols **1**. Koch et al.[12,13] recently reported the synthesis of mixed complexes of Zn(II) and Co(II) with 1-methylimidazole and either 2,3,5,6-tetramethylbenzenethiolate (**2**) or 2,4,6-trisisopropylbenzenethiolate (**3**) that are thought[14] to model the $Zn(Cys)_2(His)_2$ center in Transcription Factor IIIA (TF IIIA).[15] A complex (**4**) with three units of **3** and one unit of 1-methylimidazole models the $Zn(Cys)_3(His)$ center in Gene 32 protein (G 32P).[16] Interest has been increasing in these proteins owing to their binding prop-

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‡ Department of Chemistry, X-Ray Service.

(1) For structural investigations, see: (a) Brändén, C.-I.; Eklund, H.; Nordström, B.; Bowe, T.; Söderlund, G.; Zeppezauer, E.; Ohlsson, I.; Åkerson, A.; *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 2439. (b) Eklund, H.; Nordström, B.; Zeppezauer, E.; Söderlund, G.; Ohlsson, I.; Bowe, T.; Brändén, C.-I. *FEBS Lett.* **1974**, *44m*, 200. (c) Eklund, H.; Nordström, B.; Zeppezauer, E.; Söderlund, G.; Ohlsson, I.; Bowe, T.; Söderberg, B.-O.; Tapia, O.; Brändén, C.-I. *J. Mol. Biol.* **1976**, *102*, 27. (d) Samama, J.-P.; Wrixon, A. D.; Biellman, J.-F. *Eur. J. Biochem.* **1981**, *118*, 479. (e) Schneider, G.; Eklund, H.; Cedergren-Zeppezauer, E.; Zeppezauer, M. *EMBO J.* **1983**, *2*, 685. (f) Boiwe, T.; Brändén, C.-I. *Eur. J. Biochem.* **1977**, *77*, 173. (g) Cedergren-Zeppezauer, E. *Biochemistry* **1983**, *22*, 5761. (h) Eklund, H.; Samama, J.-P.; Wallén, L. *Biochemistry* **1982**, *21*, 4856. (i) Plapp, B. V.; Eklund, H.; Brändén, C.-I. *J. Mol. Biol.* **1978**, *122*, 23. (j) Bignetti, E.; Rossi, G. L.; Zeppezauer, E. *FEBS Lett.* **1979**, *100*, 17. (k) Eklund, H.; Samama, J.-P.; Wallén, L.; Brändén, C.-I. *J. Mol. Biol.* **1981**, *146*, 561. (l) Eklund, H.; Plapp, B. V.; Samama, J.-P.; Brändén, C.-I. *J. Biol. Chem.* **1982**, *257*, 14349. (m) Eklund, H.; Samama, J.-P.; Jones, T. A. *Biochemistry* **1984**, *23*, 5982.

(2) Representative mechanistic discussions of the reaction that occurs at the active site are provided by the following: (a) Westheimer, F. H. In *Coenzymes and Cofactors*, Vol. II, Pyridine Nucleotide Coenzymes, part A; Dolphin, D., Poulson, R., Avramovic, O., Eds.; J. Wiley and Sons: New York, 1987; pp 253-322. (b) Brändén, C.-I. In *The Pyridine Nucleotide-Dependent Dehydrogenases*; Sund, H., Ed.; W. de Gruiter: Berlin, 1977; pp 325-338. (c) Ohno, A.; Ushio, K., in ref 2a, Part B, pp 276-331. (d) Dowarschack, R. T.; Plapp, B. V. *Biochemistry* **1977**, *16*, 2716. (e) Makinen, M. W.; Yim, M. B. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 6221. (f) Makinen, M. W.; Maret, W.; Yim, M. B. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2584. (g) Makinen, M. W.; Kuo, L. C.; Yim, M. B.; Wells, G. B.; Fukuyama, J. M.; Kim, J. E. *J. Am. Chem. Soc.* **1985**, *107*, 5245. (h) Dutler, H.; Ambar, A. *NATO Adv. Study Inst. Ser. C* **1983**, *100*, 135. (i) Sloan, D. L.; Young, J. M.; Mildvan, S. A. *Biochemistry* **1975**, *14*, 1998. (j) Drysdale, B.-E.; Hollis, D. P. *Arch. Biochem. Biophys.* **1980**, *205*, 267. (k) Dutler, H.; Brändén, C.-I. *Bioorg. Chem.* **1981**, *10*, 1. (l) Callender, R.; Chen, D.; Lugtenburg, J.; Martin, C.; Rhee, K. W.; Sloan, D.; Verdersteen, R.; Yue, K. T. *Biochemistry* **1988**, *27*, 3672. (m) Hansch, C.; Klein, T.; McClarin, J.; Landridge, R.; Cornell, N. W. *J. Med. Chem.* **1986**, *29*, 615. (n) Hansch, C.; Klein, T. *Acc. Chem. Res.* **1986**, *19*, 392. (o) Eklund, H.; Brändén, C.-I., in ref 2a, pp 52-98. (p) Sekhar, V. C.; Plapp, B. V. *Biochemistry* **1988**, *27*, 5082. (q) Sartorius, C.; Gerber, M.; Zeppezauer, M.; Dunn, M. P. *Biochemistry* **1987**, *26*, 871. (r) Laurie, D.; Lucas, E.; Nonhebel, D. C.; Suckling, C. J. *Tetrahedron* **1986**, *42*, 1035. (s) Verhoeven, J. W.; Van Gerresheim, W.; Martens, F. M.; Van der Kerk, S. M. *Tetrahedron* **1986**, *42*, 975. (t) Tanner, D. D.; Stein, A. R. *J. Org. Chem.* **1988**, *53*, 1642, 1646.

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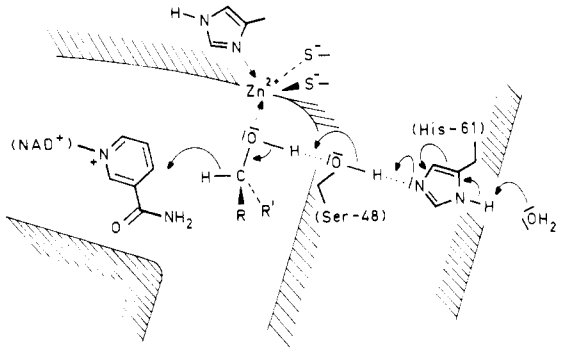


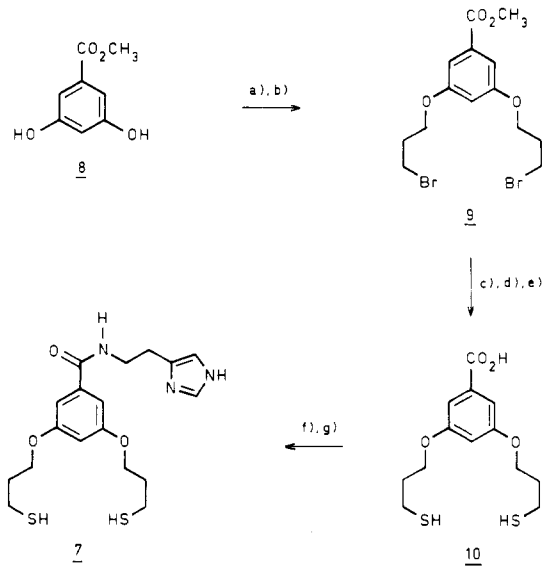
Figure 1. Coordination and presumed major interactions of the substrate at the active site of HLADH.

erties with DNA. TF IIIA contains tandem repeats of sequences of about 30 amino acids that form a structural domain around the Zn(II) ions known as "zinc fingers". These zinc fingers are thought to bind at the major groove of DNA. The gene 32 product of bacteriophage T4 belongs to a class of proteins that bind at single stranded DNA (or RNA). The zinc ions in these domains provide the structural rigidity of the DNA-binding domains.

Similar mononuclear complexes with pyridine,[12] bipyridyl,[13] and acetonitrile[17,18] as nitrogen ligands have also been prepared. In all these complexes Zn(II) and Co(II) have a strong tendency for tetrahedral coordination, as a result of the small ionic radius of these ions. In complexes with bidendate ligands with small binding angles pentacoordination is sometimes observed.[19]

These complexes have complete coordination spheres. We desired, if possible, an incomplete sphere in which a solvent molecule can be exchanged for a substrate molecule. Curtis and Brown[20] have prepared 2-(2-imidazolyl)-2-hydroxy- and 2-(2-pyridyl)-2-hydroxypropane-1,3-dithiols (**5**, **6**). Some complexes of these ligands could possibly meet this criterion. However, the free thiol forms of these ligands gave uncharacterizable complexes with Zn(II) whereas the sulfides derived by methylation of the ligands at the sulfur atoms complexed only weakly, if at all, at the sulfur sites.

Scheme I[a]

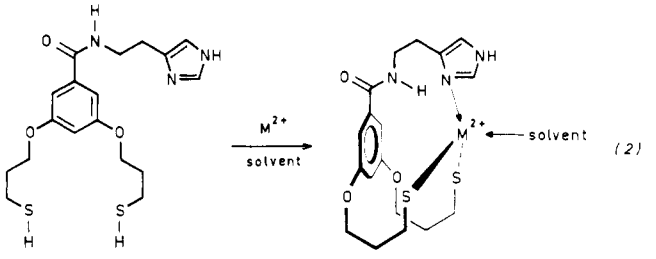


[a] (a) K_2CO_3; (b) $Br(CH_2)_3Br$ (10 equiv); (c) H_2NCSNH_2 in CH_3OH; (d) KOH/H_2O; (e) 8 N HCl; (f) CH_3OH/H_2SO_4; (g) histamine/NH_4Cl/150 °C.

Various attempts to synthesize and study the coordination properties of complexes that model the active site zinc ion in HLADH are described here. The question of catalytic activity as a mimic of the zinc center of HLADH will be deferred to subsequent publications.[21]

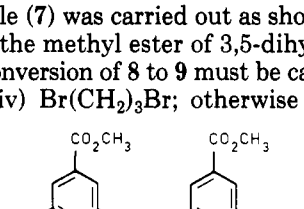
Results and Discussion

We first considered the synthesis of a "wrap-around" ligand (**7**), wherein a benzene ring could act as the "roof" to shield one side of the metal (eq 2). Synthesis of the



(2)

simplest example (**7**) was carried out as shown in Scheme I starting from the methyl ester of 3,5-dihydroxybenzoic acid (**8**). The conversion of **8** to **9** must be carried out with excess (10 equiv) $Br(CH_2)_3Br$; otherwise **11** is formed



nearly quantitatively. The conversion of **10** (the free acid is formed during hydrolysis of the isothiuronium salt to free the thiol) to **7** was difficult. Reconversion to the ester was necessary. Many fruitless attempts were made to couple **10** with histamine.[22] A rather unusual method

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(14) Berg, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 99.
(15) Corwin, D. T.; Gruff, E. S.; Koch, S. A. *Inorg. Chim. Acta* **1988**, *151*, 5.
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(17) Koch, S. A.; Fikar, R.; Corwin, D. T.; Millar, M. *Rev. Port. Quim.* **1985**, *27*, 194.
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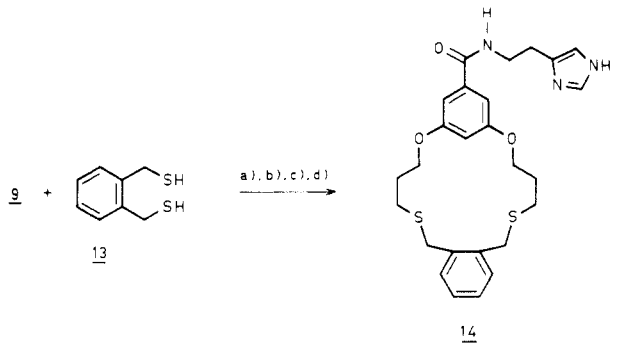
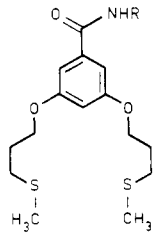
(21) A portion of these results has been described in preliminary form: Kaptein, B.; Wang-Griffin, L.; Barf, G.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1457.

Scheme II[a]



[a] (a) Cs_2CO_3 in DMF; (b) $NaOH/H_2O/CH_3OH$; (c) $SOCl_2$ in DMF; (d) histamine/$(C_2H_5)_3N$.

finally led to success. Histamine free of HCl was heated with **10** as a melt at 150 °C under reduced pressure in the presence of a catalytic quantity of NH_4Cl. Methanol was removed under these circumstances. Compound **7** has the physical characteristics of a detergent probably because of the presence of polar and apolar segments in the same molecule. In a similar fashion **12a,b** were also prepared



12

a) R = CH_2CH_2-(4,5)-imidazole

b) R = $CH_2C_6H_5$

(Experimental Section). The NH_4Cl-catalyzed coupling with histamine proceeded in 62% yield although the reactants do not mix well.

Macrocycle **14** was synthesized by the route illustrated in Scheme II. The cyclization step wherein **13** is coupled with **10** was accomplished with the aid of Cs_2CO_3,[23] but only in 23% yield, however. Histamine was introduced in modest (39%) yield through reaction with the acid chloride (the NH_4Cl-catalyzed procedure failed).

Some complexation reactions of these materials were examined. Ligand **7** as HCl salt shows titration breaks in 50% C_2H_5OH/H_2O) at pK_a values of 6.4 (imid-H^+) and 9.7 and 10.4 (thiol groups). In the presence of $Zn(NO_3)_2$ a single break on addition of 3 equiv of KOH is seen (Figure 2), indicative of the formation of a neutral complex. In HLADH both cysteines at the active site are also deprotonated.[24] All attempts to obtain monomeric, characterizable zinc complexes of **7** were to no avail, however. Nor could a complex with **14** be obtained. These experiences parallel those of Curtis and Brown.[20]

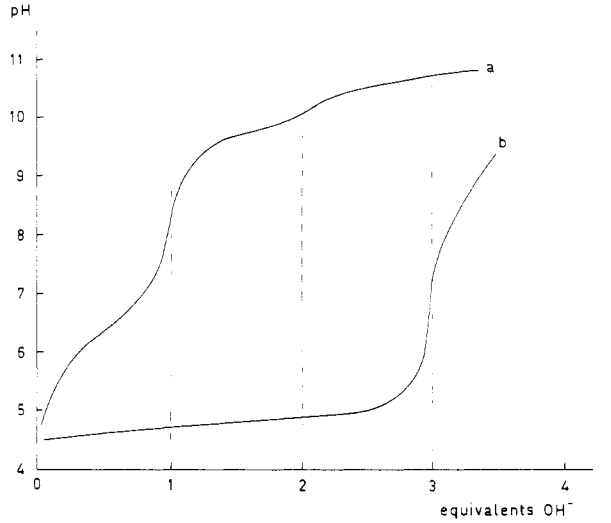


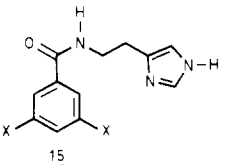
Figure 2. Titration curves of **7**·HCl (curve a) and its Zn^{2+} complex (curve b) in 50% ethanol/water (titrated with 10^{-2} M KOH solution).

Table I. Visible Absorption Spectra of Co^{2+} Complexes with Various Ligands and HLADH[a]

ligand	solvent	λ_{max} in nm (ϵ)
7	CH_3CN	599 (sh), 608 (600), 632 (sh), 667 (800)
Co-HLADH[b]	H_2O	650 (1100)
12a	CH_3OH	321 (250), 510 (25)
14a	CH_3OH	512 (12)
	$CHCl_3$	542 (50)
15a	CH_3OH	321 (108), 516 (12)
15b	CH_3OH	321 (103), 517 (7)

[a] Spectra obtained from ultraviolet concentration of the appropriate ligand in the solvent given with sufficient $Co(NO_3)_2$ to give maximum absorption (1 equiv for **7**, ca. 3 equiv for **12a**, **14a**, **15a,b**). [b] Literature spectrum of liver alcohol dehydrogenase wherein Zn^{2+} at the active center has been replaced by Co^{2+}.

Co(II) has been used with much success as a probe of the active center of HLADH. The catalytically active Zn(II) can be replaced selectively with Co(II) whereupon characteristic visible absorptions appear.[25] The complexation of ligands (**7**, **12**, **14**) and comparison compounds **15a,b** with $Co(NO_3)_2$ in CH_3CN (**7**) or CH_3OH (**12**, **14**, **15a,b** for reasons of solubility) was examined; the visible spectra are tabulated in Table I. Again no crystalline complexes amenable for X-ray diffraction studies were obtained.



15

a) X = H

b) X = $OCH_2CH_2CH_3$

Despite the difference in solvents there is good correspondence between the Co(II) complex of **7** and that of

(22) Peptide coupling methods using dicyclohexylcarbodiimide (DCC) [Klauser, Y. S.; Bodansky, M. *Synthesis* **1972**, 453] or $POCl_3$ [Klosa, J. *J. Prakt. Chem.* **1963**, *19*, 45] with histamine·2HCl/$(C_2H_5)_3N$ or with free histamine failed. The preparation of histamine free of HCl is also a problem because of its solubility in water and insolubility in most organic solvents [Pyman, F. L. *J. Chem. Soc.* **1912**, *101*, 543]. We found a reasonably successful procedure to be the Soxhlet extraction with $CHCl_3$ of the dried residue of a neutralized aqueous solution of histamine·2HCl with 2 equiv of NaOH.

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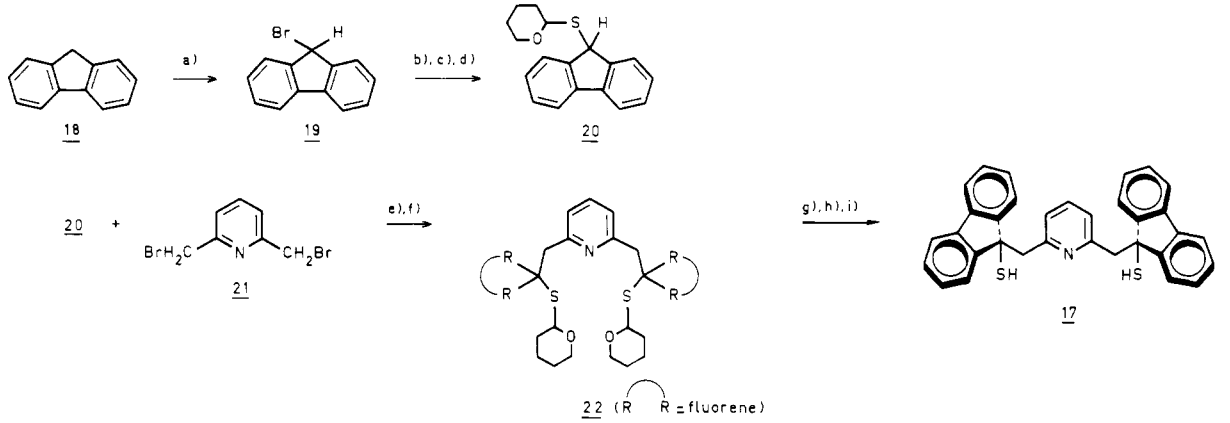
(24) Schneider, G.; Eklund, H.; Cedergen-Zeppezauer, E.; Zeppezauer, M. *EMBO J.* **1983**, *2*, 685.

(25) (a) Drum, D. E.; Vallee, B. L. *Biochem. Biophys. Res. Commun.* **1970**, *41*, 33. (b) Maret, W.; Andersson, I.; Dietrich, H.; Schneider-Bernlöhr, H.; Einarsson, R.; Zeppezauer, M. *Eur. J. Biochem.* **1979**, *98*, 501. (c) Zeppezauer, M.; Andersson, I.; Dietrich, H.; Gerber, M.; Maret, W.; Schneider, G.; Schneider-Bernlöhr, H. *J. Mol. Catal.* **1984**, *23*, 377.

Scheme III[a]

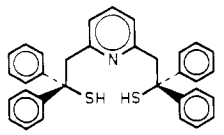


[a] (a) NBS/CCl_4/$(C_6H_5CO_2)_2$/*hv*; (b) H_2NCSNH_2 in C_2H_5OH; (c) NaOH; (d) 2,3-dihydropyran/C_5H_5NH, $SO_3C_6H_4$-4-CH_3 in CH_2Cl_2; (e) *n*-C_4H_9Li/$(C_2H_5)_2O$/0 °C; (f) **21** (0.5 equiv)/−80 °C; (g) $AgNO_3/C_5H_5N$; (h) H_2O; (i) pH 7/extraction.

HLADH substituted by Co(II) at the active site. HLADH has a second, noncatalytic, Zn(II) surrounded by four thiolates from cysteines; replacement by Co(II) leads to an UV absorption at 740 nm, which is characteristic for Co(II) complexed by four negatively charged thiolates. When only the catalytic Zn(II) is replaced by Co(II), the characteristic 650-nm absorption is observed. The long wavelength band envelope of the complex of **7** lies in the diagnostic 650-nm range. Other Co(II) complexes containing thiol and imidazole or pyridine-containing ligands have similar visible spectra.[11a,12,15,18]

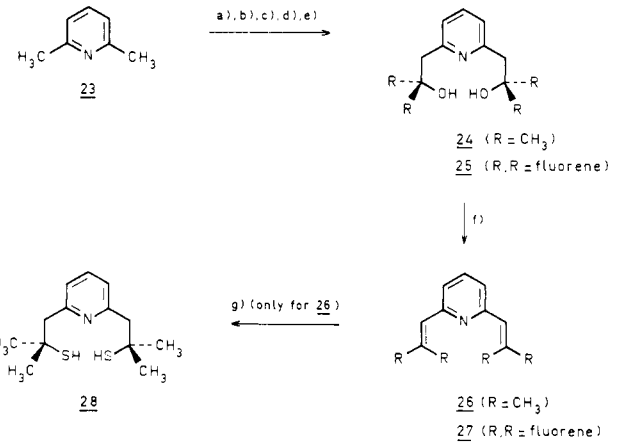
The sulfide-containing ligands **12a** and **14** clearly do not complex via these linkages. The close resemblance to the spectra of complexes of **15a,b** suggests that in all cases characteristic Co(II)–imidazole complexes are being formed.[26]

Another approach to monomeric Zn(II) or Co(II) complexes is offered via tridentate ligand **16**, the synthesis of which has been described by Holm and Berg.[27-29] This



ligand has been used as a sterically hindered component of a model for the active site of molyboenzymes. The bulky substituents shield the metal center from attack by an additional thiolate. We felt that gradation of the degree of steric shielding in the form of substituents other than phenyl would give broader possibilities. To this end **17** was prepared as illustrated in Scheme III, which is analogous to the Holm procedure for the preparation of **16** save for some modifications in synthetic details. The symmetrical dibromide of lutidine (**21**) was prepared both via bromination of lutidine as well as from the commercially available 2,6-bis(hydroxymethylene)pyridine via treatment

Scheme IV[a]



[a] (a) *n*-C_4H_9Li/$(C_2H_5)_2O$/0 °C; (b) R_2CO/−78 °C; (c) *n*-C_4H_9Li/$(C_2H_5)_2O$/20 °C; (d) R_2CO/−78 °C; (e) H_2O; (f) H_3PO_4/heat; (g) CH_3COSH/4-$CH_3C_6H_4SO_3H$/CH_3OH.

with 48% HBr.[30] The latter procedure is preferable in our opinion. The other synthetic steps in Scheme III are straightforward but laborious. Much care must be taken to prevent oxidation of the thiol once it is freed from the tetrahydropyran protecting groups, which were introduced under mildy acidic conditions as described by Grieco et al.[31]

Because of the length and complexity of this approach, an alternate synthetic route was investigated (Scheme IV). This led to the synthesis of tetramethyl ligand **28** as well as the diols **24** and **25**. Lutidine (**23**) is readily converted to the carbanion by treatment with *n*-butyllithium.[32] In a one-pot reaction in two successive steps 2 equiv of ketone, acetone or fluorenone,[28,32,33] were added. The yields of **24** and **25** are low, 34% and 13%, respectively. No attempts have been made to raise the yields. Both **24** and **25** crystallize readily and are easily isolated from solution.

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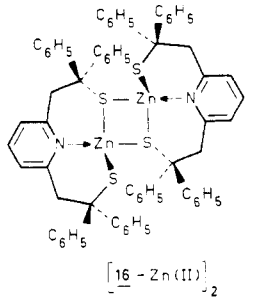
Treatment of the diols with H_3PO_4 leads to the alkenes **26** and **27**.[34,35] Treatment of the former with thiolacetic acid under acidic conditions in CH_3OH leads in one step to **28** in 96% yield. Apparently the pyridine is protonated by thiolacetic acid, thereby aiding Michael addition of thiolacetate.[35-37] Partial deacylation was observed during addition. We assumed that this meant that thiolacetic acid was not acidic enough to catalyze the transacylation effectively, and that inclusion of an extra and stronger acid would allow combination of the two steps. The addition and deacylation steps could indeed be carried out simultaneously on addition of *p*-toluenesulfonic acid and use of CH_3OH as solvent. This is the method of choice for the conversion of **26** to **28**. Unfortunately **27** failed to react under these or any other conditions tried.

Complexations with the ligands **16**, **17**, and **28** were carried out by adding to a $CHCl_3$ solution of the ligand an equimolar quantity of $Zn(NO_3)_2 \cdot 4H_2O$ dissolved in CH_3OH. The Zn(II) complex of **16** crystallized spontaneously. The complexes derived from **17** and **28** were isolated on concentration of the solutions and addition of extra CH_3OH. The solubilities of **16**·Zn(II) and **28**·Zn(II) are low. The former is sparingly soluble, <1 mg/mL in most solvents save dimethylformamide (DMF) in which the solubility is about 5 mg/mL. Complex **28**·Zn(II) dissolves somewhat better, about 5 mg/mL in most organic solvents. Only the complex from **16**·Zn(II) was suitable for X-ray crystallographic determination. The crystallographic data have



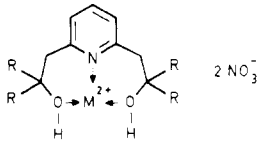
been described previously and are not reproduced here.[21] A *neutral* dimer is formed, the structure of which is illustrated schematically. Despite the steric shielding afforded by the phenyl groups, the thiolates still act as bridging ligands.

The dimeric structure is also present in solution. Despite the low solubility, an NMR spectrum of **16**·Zn(II) in $CDCl_3$ could be obtained. Complex **28**·Zn(II) is somewhat more soluble and provided a better resolved spectrum. In both complexes the plane of symmetry that prevails in the free ligands is clearly absent. The methylene groups become nonequivalent, the aromatic protons separate, and in **28**·Zn(II) the eight methyl groups are seen as four pairs. These observations are consistent with dimeric structures, which could have, in principle, C_2 symmetry if the pyridines are cisoid on the zinc thiolate four-membered ring or point symmetry if transoid. In the crystal structure the cisoid structure is obtained and CPK models suggest that this has a greater stability relative to the transoid structure.

Complex **17**·Zn(II) behaved much differently. From the crystal structure of **16**·Zn(II), we predicted greater steric hindrance on incorporation of a fluorene ring instead of phenyl groups. This complex, the crystals of which so far have not proved suitable for X-ray analysis, is readily soluble in $CHCl_3$. The stability is quite limited, however, and it decomposes to unidentified products on standing. The NMR spectrum in this case clearly indicates maintenance of a plane of symmetry through the ligand on complexation fully consistent with a monomeric formulation. We suggest that the 2,2′ bonds in the fluorene substituents in **17** and **17**·Zn(II) force these groups into a perpendicular arrangement, causing maximal shielding of the zinc center, thereby inhibiting dimerization. The zinc ion is probably coordinated by only three ligating atoms in a flat arrangement. This also explains why the hydrogens of the methylene groups in the complex were not observed as being diastereotopic. Tricoordination of Zn(II) ions by pyridine-containing complexes has been reported.[38,39]

The Co(II) complexes of **16**, **17**, and **28** were not stable enough to allow isolation. Apparently redox chemistry with the thiol groups takes place.[40]

Although the diol-containing ligands **24** and **25** are deficient models for the zinc binding site in HLADH, owing to the absence of thiol groups, complexation reactions with Zn(II) and Co(II) were nevertheless performed for comparison purposes. The molecules are expected to act as tridentate ligands, the coordination sphere being completed with solvent molecules. Complexations with somewhat analogous ligands have been reported.[41] The complexations of $Zn(NO_3)_2 \cdot 6H_2O$ and $Co(NO_3)_2 \cdot 6H_2O$ with **24** and **25** were performed in a mixture of $CHCl_3$ and CH_3OH. After recrystallization the complexes illustrated



24, **25** M(II)$(NO_3)_2$

	R	M	
		Co	Zn
24	CH_3	82%	79%
25		100%	75%

were isolated as colorless (Zn(II)) or as purple (Co(II)) crystalline compounds. The compounds formed 1:1 complexes containing two (Zn(II) complexes) or three (Co(II) complexes) additional solvent molecules (H_2O). These are easily lost on drying. The X-ray structure of the **24**·Zn(II) complex (see below) showed that in the crystalline form the solvent water molecules are complexed to Zn(II) and hydrogen bonded to nitrate. In a CH_3OH solution these water ligands are readily exchanged by methanol. Unlike thiolate- or alkoxide-containing ligands, hydroxy ligands do not bridge readily.[38,41,42]

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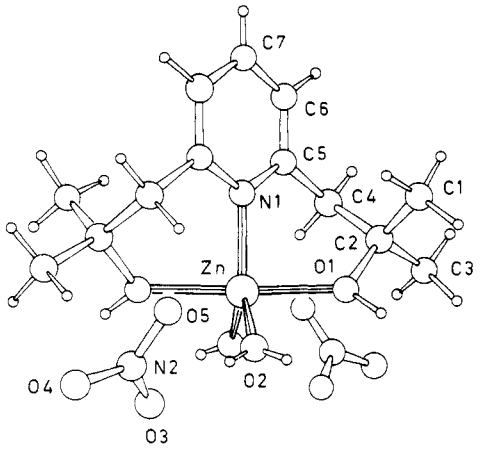

Figure 3. Structure of $[24{\cdot}Zn(II)(H_2O)_2](NO_3)_2$.

The complexation of Zn(II) with the ligands, especially with **24**, can be observed from the chemical shift changes in the ^1H NMR spectra. In this complex the signals for the CH_3 and CH_2 groups are shifted 0.10 and 0.28 ppm, respectively, downfield. The signals for the pyridine hydrogens are also shifted downfield (0.30 ppm for the 3- and 5-hydrogens and 0.34 ppm for the 4-hydrogen) as a result of complexation with the pyridine nitrogen. In $CDCl_3$ solution with various amounts of CH_3OH the signals for the CH_3OH shift gradually upfield to their normal positions as saturation is reached. The CH_3 signals shifted from δ 3.45 (with 2 equiv of CH_3OH) to δ 3.35 (large excess of CH_3OH); the OH signal shifted under identical conditions from δ 6.2 to δ 3.2. No distinct signals for free and complexed CH_3OH were observed, consistent with fast exchange.

The solubility behavior of complexes of **24** is remarkable. From a saturated solution in a mixture of $CHCl_3$ and CH_3OH the complexes *crystallized on heating* and *redissolved on cooling*. This phenomenon can be explained thermodynamically in terms of an entropy-driven process. On complexation of the metal ions in solution, ligated CH_3OH molecules are liberated, making the complexation a process with a positive entropy effect ($\Delta S > 0$). On heating, the equilibrium is shifted to the right, for $\Delta G = \Delta H - T\Delta S$ with $\Delta S > 0$. The complexes formed, however, are poorly soluble in the solvent and crystallize. The complexes can even be purified by this method of "recrystallization".

Applications of these complexes as possible enzyme model compounds have not been made. The coordination sphere of the metal ions in the complexes resembles the active site of the zinc-containing enzymes carboxypeptidase A[42] and thermolysin.[43] The complexes might be able to model the hydrolytic reactions performed by these enzymes.[44]

In general Zn(II) and Co(II) complexes tend to tetrahedral coordination, although penta-, hexa-, and heptacoordinated complexes have been described.[45] To establish an exact structure an X-ray crystallographic determination was carried out. The crystal structure of the complex $[24{\cdot}Zn(II)(H_2O)_2](NO_3)_2$ is depicted in Figure 3. Important bond distances and bond angles are listed in Tables II and III. In contrast to the thiolate complexes, the oxygens are protonated. The complex bears nitrate as a counterion. In the complex the Zn(II) ion is pentacoordinated by three atoms of the ligand and by two water molecules. The coordination sphere forms an almost idealized trigonal bipyramid, with the two hydroxy groups of the ligand in the axial positions. The structure contains a 2-fold axis of symmetry, which passes through the nitrogen–zinc bond. The pyridine ring makes an angle of 38.7° with the plane that contains O1, O1′, N1, and Zn. In the crystal structure the hydrogen atoms of the complexed water molecules form hydrogen bonds with the NO_3^- counterions (the O···H distance is about 1.7 Å, comparable with 1.79 Å for the hydrogen bridge distance in ice.[46]

Table II. Important Bond Distances (in Angstroms)

atom 1–atom 2	distance	atom 1–atom 2	distance
Zn–O1	2.104 (2)	C2–C4	1.540 (4)
Zn–O2	1.977 (3)	C4–C5	1.508 (5)
Zn–N1	2.023 (4)	C5–C6	1.382 (4)
O1–C2	1.459 (4)	C6–C7	1.389 (4)
N1–C5	1.360 (4)	N2–O3	1.276 (4)
C1–C2	1.524 (4)	N2–O4	1.253 (4)
C2–C3	1.528 (5)	N2–O2	1.231 (3)

Table III. Important Bond Angles (in Degrees)[a]

atom 1–atom 2–atom 3	angle	atom 1–atom 2–atom 3	angle
O1–Zn–O2	87.75 (9)	C3–C2–O4	109.3 (3)
O1–Zn–N1	88.79 (7)	C2–C4–O5	114.0 (3)
O1–Zn–O1′	177.58 (7)	N1–C5–O4	117.5 (3)
O2–Zn–N1	123.87 (7)	N1–C5–O4	121.2 (3)
O2–Zn–O2′	112.26 (7)	C4–C5–O6	121.3 (3)
O1–C2–C1	109.0 (3)	C5–C6–O7	119.4 (3)
O1–C2–C3	108.8 (3)		
O1–C2–C4	105.7 (2)	O3–N2–O4	118.8 (3)
C1–C2–C3	110.8 (2)	O3–N2–O4	119.8 (3)
C1–C2–C4	113.2 (3)	O4–N2–O5	121.4 (3)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

The pentacoordinated Zn(II) complex exhibits some resemblance to the structure of Zn(II) complexes reported in the literature.[47] Whether the Co(II) complex of **24** has an analogous structure is unfortunately not entirely certain, although this seems likely in view of the chemical similarity between the Zn(II) and Co(II) complexes. In the complexes derived from the fluorene-containing ligand **25**, two or three water molecules seem to be coordinated as judged from the elementary analyses, resulting also in penta- or hexacoordination.

As a final topic, a brief discussion is given some 2,-(4,5)-dialkylated imidazole derivatives that were prepared in the course of this work. The hope was that via two "arms" on imidazole thiol groups could be attached at desired distances for tridentate coordination with Zn(II) or Co(II). A condensation approach for synthesis of the

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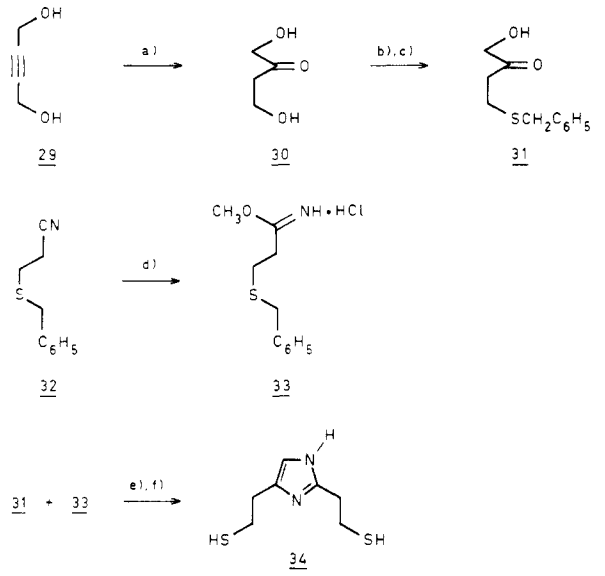
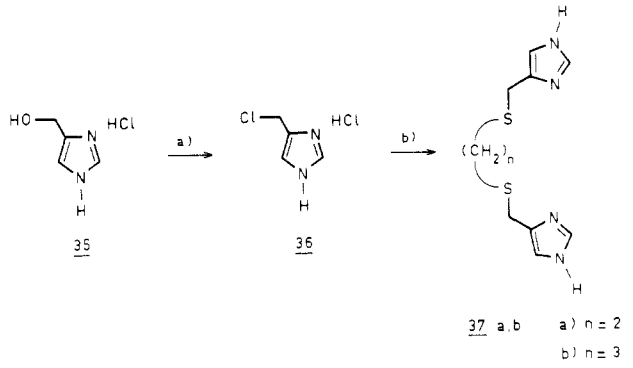
Scheme V[a]



[a] (a) $HgSO_4/H_2SO_4/H_2O/20$ °C; (b) heat; (c) $C_6H_5CH_2SH/NaOH/H_2O$; (d) CH_3OH/HCl; (e) $NH_3(l)/20$–60 °C; (f) $Na/NH_3(l)$.

Scheme VI[a]



[a] (a) $SOCl_2/C_6H_6/90$ °C; (b) $HS(CH_2)_nSH/KOH/C_2H_5OH$.

imidazole ring was followed.[48] Components **31** and **33** were assembled and condensed to give **34** as illustrated in Scheme V. The bisthiol is extremely sensitive to air.

The syntheses of **37a,b** are shown in Scheme VI. Chloride **36** was obtained readily.[49] Compounds analogous to **37** have been synthesized by reaction of **35** with dithiols;[50] we had no success in preparing **37a,b** via this direct route and had to proceed via **36**. Compounds **37a,b** differ enormously in their physical properties; **37a** melts 70 °C lower, it runs far faster on TLC plates, and it dissolves in nonpolar solvents whereas **37b** dissolves only in methanol. This may be an expression of an "odd-even" effect. Metal complexes obtained from **32–34** were unfortunately too unstable to be characterized.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at 60, 200, or 300 MHz. ^{13}C NMR spectra were recorded at 25.16, 50.32, or 75.43 MHz. ^{13}C NMR spectra were recorded proton-noise decoupled and proton coupled, and the proton coupled spectra were recorded in the gyrogate mode. Mass spectra were recorded at a direct inlet temperature of ±110 °C and an accelerating voltage of 70 eV. All reagents and solvents were purified and dried where necessary, following standard procedures. All organometallic procedures were carried out under oxygen-free, nitrogen, or argon atmosphere. The solvents were distilled before use and were stored on molecular sieves, 3 or 4 Å. Silica gel 60, 230–400 mesh (Merck), was used for column chromatography. The purity of title compounds not supported by combustion analyses was judged to be ≥90% by chromatography and/or NMR criteria. Representative NMR spectra have been submitted as supplementary material.

Methyl 3,5-Dihydroxybenzoate (8). Starting with 50 g of 3,5-dihydroxybenzoic acid, the ester was prepared by a literature method[52] in 93% yield, mp 165–166.5 °C (lit.[52] mp 165 °C): ^1H NMR ($CDCl_3$) δ 3.78 (s, 3 H, CH_3), 6.41 (t, 1 H, ^4J = 2 Hz, 4-*H*), 6.79 (d, 2 H, ^4J = 2 Hz, 2,6-H_2), and 8.0 (br, 2 H, O*H*).

Methyl 3,5-Bis(3-bromopropoxy)benzoate (9). To a mixture of methyl ester **8** (8.3 g, 50 mmol) and K_2CO_3 (20.9 g, 150 mmol) in 100 mL of acetone was added 1,3-dibromopropane (50 mL, 0.5 mol). The mixture was refluxed for $4^1/_2$ hours with vigorous stirring. After cooling, the solid was filtered off and was washed with acetone. The filtrate was concentrated with a rotoevaporator first at 50 °C (12 Torr) to remove the acetone and then at 50 °C (0.1 Torr) to remove the excess dibromopropane. The residue was purified by distillation. The yield of **9** was 14.0 g (34 mmol, 68%), obtained as a slightly yellow oil, bp 115 °C (0.1 Torr): IR (film) 1725 and 778 cm^{-1}, no OH absorption; ^1H NMR ($CDCl_3$) δ 2.28 (quintet, 4 H, $CH_2CH_2CH_2$), 3.54 (t, 4 H, CH_2Br), 3.85 (s, 3 H, OCH_3), 4.08 (t, 4 H, OCH_2CH_2), 6.62 (t, 1 H, 4-H), 7.14 (d, 2 H, 2,6-H); ^{13}C NMR ($CDCl_3$) δ 29.50 (t), 31.74 (t), 51.79 (q), 65.17 (t), 106.01 (d), 107.42 (d), 131.50 (s), 159.22 (s), and 166.08 (s); exact mass *m/e* calculated for $C_{14}H_{18}Br_2O_4$ 407.957, found 407.955. When 2 equiv of 1,3-dibromopropane was used, variable amounts of **11**, identified by a peak at *m/e* 618, were obtained.

3,5-Bis(3-mercaptopropoxy)benzoic Acid (10). The dibromide **9** (7.8 g, 19 mmol) and thiourea (3.5 g, 46 mmol) in 60 mL of dry methanol were refluxed under a nitrogen atmosphere for 15 h. After cooling, the methanol was removed on the rotaevaporator and the yellow tarry residue was dissolved in 100 mL of 3 M aqueous KOH. The solution was cooled in ice and acidified with 8 M HCl solution to pH 1, to yield a white, waxy precipitate that slowly crystallized. The aqueous solution was decanted and the residue was recrystallized from 1:1 ethanol/water. Compound **10** was obtained as white crystals (4.5 g, 15 mmol, 78% yield), mp 78 °C: IR (KBr) 3000 (br), 2640 (br), and 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, 2 H, S*H*), 2.07 (quintet, 4 H, $CH_2CH_2CH_2$), 2.67 (q, 4 H, CH_2CH_2SH), 4.10 (t, 4 H, OCH_2CH_2), 6.65 (t, 1 H, 4-H), 7.20 (d, 2 H, 2,6-H), and 11.3 (br, 1 H, CO*OH*); ^{13}C NMR ($CDCl_3$) δ 21.03 (t), 32.99 (t), 65.85 (t), 107.29 (d), 108.18 (d), 130.98 (s), 159.75 (s), and 171.87 (s); exact mass *m/e* calcd for $C_{13}H_{18}O_4S_2$ 302.0658, found 302.065. The bisthiol is air sensitive, and slowly oxidizes, but is stable under a nitrogen atmosphere.

Methyl 3,5-Bis(3-mercaptopropoxy)benzoate. A solution of 3.0 g (10 mmol) of **10** and 0.2 mL of concentrated H_2SO_4 in 50 mL of dry methanol was refluxed under a nitrogen atmosphere for 20 h. The solution was cooled and concentrated. The dilute $NaHCO_3$ solution was added and the product was extracted with chloroform (3 × 150 mL). The collected organic layers were dried ($MgSO_4$) and the solvent was removed, giving a quantitative yield of ester (3.14 g, 10 mmol) as a colorless oil, bp > 200 °C/0.3 Torr, mp ± 10 °C: R_f = 0.55 (hexane/ethyl acetate 3/1); IR (film) 1715 and 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, 2 H, S*H*, with traces of methanol singlet), 2.04 (quintet, 4 H, $CH_2CH_2CH_2$), 2.71 (q, 4 H, CH_2CH_2SH, with traces of methanol t), 3.84 (s, 3 H, CO_2CH_3), 4.05 (t, 4 H, OCH_2CH_2), 6.69 (t, 1 H, 4-H), and 7.12 (d, 2 H, 2,6-H); exact mass *m/e* calcd for $C_{14}H_{20}O_4S_2$ 316.080, found 316.079.

Preparation of HCl-Free Histamine. To 9.2 g (50 mmol) of histamine·2HCl was added 5.0 g (100 mmol) of NaOH dissolved in 50 mL of water. The water was evaporated and the residue was refluxed in a Soxhlet apparatus with chloroform for 18 h. The

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chloroform was evaporated, and the remaining oil slowly crystallized and could be distilled (bulb-to-bulb at 150 °C and 0.01 Torr) to give 5.3 g of histamine (47 mmol, 94% yield): ^{1}H NMR ($CD_3OD/CDCl_3$) δ 2.7 (m, 4 H, CH_2CH_2), 6.74 (s, 1 H, 5(4)-H), and 7.48 (s, 1 H, 2-H); ^{13}C NMR (CD_3OD) δ 31.26 (t), 42.54 (t), 118.26 (d), and 136.24 (d + s).

***N*-[2-(1*H*-Imidazol-4-yl)ethyl]-3,5-bis(3-mercaptopropoxy)benzamide (7).** In a bulb-to-bulb distillation apparatus the methyl ester of **10** (750 mg, 2.4 mmol), histamine (750 mg, 6.7 mmol) purified as described above, and NH_4Cl (20 mg, 0.4 mmol) were suspended in 1 mL of chloroform. The chloroform was distilled off at 20 °C/60 mm, and the reaction mixture was heated to 130 °C/60 Torr till evolution of methanol ceased. Excess histamine was then distilled off at 150 °C/0.1 Torr. The remaining yellow oil (1.1 g) was purified by flash chromatography on silica gel with 3:2:1 ethyl acetate/methanol/hexane as eluent. The product was obtained as an oil that crystallized slowly. For further purification the compound was dissolved in 30 mL of $CHCl_3$, and 4 mL of a 0.75 M HCl solution in ether was added. The precipitate was centrifuged off, washed with a little $CHCl_3$, dissolved in a saturated $NaHCO_3$ solution, and extracted with chloroform (4 × 50 mL). After drying over $MgSO_4$ and removal of the solvent, the product was obtained as a colorless oil that crystallized slowly. The yield of **7** was 850 mg (2.15 mmol, 89% yield), mp 100–102 °C: R_f = 0.60 (ethyl acetate/methanol/hexane 3/2/1); ^{1}H NMR (CD_3OD) δ 2.07 (quintet, $^3J \sim 6.5$ Hz, $CH_2CH_2CH_2$), 2.71 (t, ^3J = 6.7 Hz, 4 H, CH_2CH_2S), 2.93 (t, ^3J = 7.2 Hz, 2 H, CH_2CH_2Im), 3.64 (t, ^3J = 7.2 Hz, 2 H, $CONDCH_2CH_2$), 4.12 (t, ^3J = 6.2 Hz, 4 H, OCH_2CH_2), 5.0 (br, 4 H, NH, SH, and CD_3OH), 6.67 (t, ^4J = 2.2 Hz, 1 H, 4-H), 6.92 (d, ^4J = 1.0 Hz, 1 H, 5′(4′)-H), 6.99 (d, ^4J = 2.2 Hz, 2 H, 2,6-H), and 7.66 (d, ^4J = 1.0 Hz, 1 H, 2′-H); ^{13}C NMR (CD_3OD) δ 21.58 (t), 27.58 (t), 34.48 (t), 40.94 (t), 67.27 (t), 105.58 (d), 106.87 (d), 117.90 (d), 135.86 (s), 135.94 (d), 137.71 (s), 161.54 (s), and 169.84 (s); IR (KBr disc) 3175, 1630, 1590, 1550, and 1175 cm^{-1}; exact mass *m/e* calcd for $C_{18}H_{25}N_3O_3S_2$ 395.134, found 395.133.

Methyl 3,5-Bis[3-(methylthio)propoxy]benzoate. To an ice-cooled solution of 9.74 g (0.174 mol) of KOH in 200 mL of methanol was added 7.65 g (0.16 mol) of methyl mercaptan. Next 32.6 g (79 mmol) of **9** in 50 mL of methanol was added slowly, and the solution was refluxed for 14 h under a nitrogen atmosphere. The reaction mixture was concentrated in vacuum; to the residue was added a solution of 100 mL 0.5 M NaOH. The resulting mixture was extracted with chloroform (3 × 75 mL). The combined chloroform layers were washed with a dilute NaOH solution and water. After drying over $MgSO_4$ and evaporation of the solvent the residue, containing about 10% elimination products, was purified by bulb-to-bulb distillation. The benzoate was obtained as a colorless oil (16.6 g, 48 mmol, 61% yield), bp 200 °C (0.02 Torr): ^{1}H NMR ($CDCl_3$) δ 2.1 (s + quintet, 10 H, SCH_3 and $CH_2CH_2CH_2$), 2.73 (t, 4 H, CH_2CH_2S), 3.84 (s, 3 H, OCH_3), 4.12 (t, 4 H, OCH_2CH_2), 6.70 (t, 1 H, 4-*H*), and 7.12 (d, 2 H, 2,6-*H*); ^{13}C NMR ($CDCl_3$) δ 14.79 (q), 27.96 (t), 29.92 (t), 51.49 (q), 65.81 (t), 105.75 (d), 107.08 (d), 131.21 (s), 159.22 (s), and 165.97 (s); exact mass *m/e* calcd for $C_{16}H_{24}O_4S_2$ 344.112, found 344.111.

The following alternate procedure was also followed. To a solution of 304 mg (13.2 mmol) of sodium in 50 mL of methanol under nitrogen was added 1.90 g (6.0 mmol) of the methyl ester of **10**, prepared as described above. The solution was heated for a few minutes, and after cooling, 1.98 g (15 mmol) of CH_3I in 10 mL of methanol was added slowly. The mixture was refluxed for 3 h. The methanol was evaporated in vacuum and water was added, and the mixture was extracted with chloroform. After drying over $MgSO_4$ and evaporation of the solvent, the residue was chromatographed on silica gel (eluent: hexane/ethyl acetate 3/1) to yield 1.05 g (3.0 mmol, 50% yield) of benzoate.

***N*-[2-(1*H*-Imidazol-4-yl)ethyl]-3,5-bis[3-(methylthio)propoxy]benzamide (12a) by Amidation of Methyl 3,5-Bis[3-(methylthio)propoxy]benzoate.** The preparation of **12a** was analogous to that described for the synthesis of **7**. Starting with methyl 3,5-bis[3-(methylthio)propoxy]benzoate and 0.88 g (8.0 mmol) of histamine, there was obtained 837 mg of **12a** as a slightly yellow oil (1.97 mmol, 62% yield): R_f 0.59 (ethyl acetate/methanol/hexane 6/3/2); IR (film) 3220, 1640, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 2.13 (quintet + s, 10 H, $CH_2CH_2CH_2$ + SCH_3), 2.4–3.05 (m, 6 H, CH_2CH_2S + CH_2CH_2Im), 3.65 (t (br), $CONHCH_2CH_2$), 4.10 (t, 4 H, OCH_2CH_2), 6.62 (t, 1 H, 4-H), 6.85 (s, 1 H, 5′(4′)-H), 6.98 (d, 2 H, 2,6-H), and 7.76 (s, 1 H, 2′-H); ^{13}C NMR (CD_3OD) δ 15.37 (q), 27.69 (t), 29.81 (t), 31.41 (t), 41.00 (t), 67.72 (t), 105.51 (d), 106.81 (d), 117.94 (d), 136.04 (d), 137.69 (s), 161.58 (s), and 169.84 (s); exact mass *m/e* calcd for $C_{20}H_{29}N_3O_3S_2$ 423.165, found 423.166.

3,5-Bis[3-(methylthio)propoxy]-*N*-benzylbenzamide (12b). A mixture of 3,5-bis[3-(methylthio)propoxy]benzoic acid (660 g, 2.0 mmol), and $SOCl_2$ (425 mg, 3.6 mmol), and 1 drop of DMF were refluxed in 50 mL of benzene for 2.5 h. After removal of the solvent and excess $SOCl_2$, 850 mg (122% crude yield!) of a yellowish oil was obtained: ^{1}H NMR ($CDCl_3$) δ 1.8–2.3 (s (br) + m, 10 H, $CH_2CH_2CH_2$ + SCH_3), 2.71 (br t, 4 H, CH_2CH_2S), 4.10 (t, 4 H, OCH_2CH_2), 6.75 (t, 1 H, 4-H), and 7.18 (d, 2 H, 2,6-H); mass spectrum *m/e* (rel intensity) 348 (parent peak), 89 (100). The acid chloride, still containing some $SOCl_2$, was not purified but used directly in the next step. A solution of 415 mg (1.0 mmol) of the acid chloride in chloroform was added slowly to a solution of 275 mg of benzylamine (110 mg, 1 mmol) and triethylamine (250 mg, 2.5 mmol) in 25 mL of chloroform. After the addition was complete the mixture was stirred for 16 h at room temperature. Water was added to the reaction mixture. After washing, the water layer was extracted with chloroform (2 × 50 mL). After drying over $MgSO_4$ and evaporation of the solvent, the crude product was purified by chromatography on silica gel (eluent: ethyl acetate/methanol/hexane 6/3/2). There was obtained 294 mg (0.70 mmol, 70% yield) of **12b** as a slightly yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.95 (s + m, 10 H, SCH_3 + $CH_2CH_2CH_2$), 2.55 (t, 4 H, CH_2CH_2S), 3.89 (t, 4 H, OCH_2CH_2), 4.40 (d, 2 H, $NHCH_2Ph$), 6.48 (t, 1 H, 4-H), 6.85 (d, 2 H, 2,6-H), and 7.15 (s, 5 H, Ph-H). Compound **12a** was also prepared by this route in 42% yield.

1,2-Bis(mercaptomethyl)benzene (13). The compound was prepared according to the procedure described in the literature[53] from 1,2-bis(bromomethyl)benzene (26.4 g, 0.10 mol). The yield of **13** was 16.2 g (95 mmol, 95% yield), mp 41–45 °C (lit.[53] mp 41–44 °C): ^{1}H NMR ($CDCl_3$) δ 1.80 (t, 2 H, CH_2SH), 3.79 (d, 4 H, CH_2SH), and 7.17 (s, 4 H, Ph-H).

8,9-Benzo-18-(methoxycarbonyl)-6,11-dithia-2,15-dioxabicyclo[14.3.1]eicosa-1(20),16,18-triene. To a solution of 3.26 g (10 mmol) of Cs_2CO_3 in 250 mL of dry DMF at 55–60 °C under a nitrogen atmosphere was slowly added half of a solution of 1.70 g (10 mmol) of **13** and 4.10 g (10 mmol) of **9** in 250 mL of DMF during 32 h. An additional 3.26 g (10 mmol) of Cs_2CO_3 was added and the second half of the DMF solution was added over 38 h. The DMF was distilled off on the rota-evaporator, and the tarry residue was dissolved in 250 mL of CH_2Cl_2 and washed with water and a saturated NaCl solution. After drying of the organic layer over $MgSO_4$ and removal of the solvent, 3.47 g of a brown oil remained, to which 50 mL of methanol was added. The mixture was refluxed for 5 min and the methanol was decanted. This procedure was repeated twice with 50 mL of methanol. On standing the product crystallized from the combined methanol layers, yielding 637 mg of colorless crystals. The filtrate and the methanol-insoluble residue were combined and were subjected to column chromatography (eluent: $CHCl_3$), to yield an additional 311 mg of product. The total yield of the title compound was 948 mg (2.27 mmol, 23% yield) as colorless crystals, mp 90.4–93.7 °C: R_f 0.48 ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.00 (quintet, 4 H, $CH_2CH_2CH_2$), 2.72 (t, 4 H, CH_2CH_2S), 3.77 (s, 3 H, OCH_3), 3.88 (s, 4 H, SCH_2Ar), 4.22 (t, 4 H, OCH_2CH_2), 6.93 (t, 1 H, 20-H), 7.18 (m, 6 H, 17,19-H and Ar-H); ^{13}C NMR ($CDCl_3$) δ 28.40 (t), 29.45 (t), 34.68 (t), 51.98 (q), 66.52 (t), 106.33 (d), 110.25 (d), 127.31 (d), 129.77 (d), 132.06 (s), 135.59 (s), 159.38 (s), and 166.39 (s); exact mass *m/e* calcd for $C_{22}H_{26}O_4S_2$ 418.127, found 418.126.

8,9-Benzo-18-carboxy-6,11-dithia-2,15-dioxabicyclo-[14.3.1]eicosa-1(20),16,18-triene. The above methyl ester (100 mg, 0.239 mmol) was dissolved in 12 mL of methanol. To this solution was added 6 mL of a 5 N NaOH solution. The clear solution was refluxed for 42 h and then concentrated to 10 mL. The solution was acidified with a 4 N HCl solution and extracted with chloroform (4 × 30 mL). After drying over $MgSO_4$ and evaporation of the solvent, 90 mg of free acid (0.223 mmol, 93%

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yield) was isolated as a white solid, mp 197–199 °C (sublimes slowly): ^{1}H NMR ($CDCl_3/CD_3OD$) δ 2.03 (quintet, 4 H, $CH_2CH_2CH_2$), 2.86 (t, 4 H, CH_2CH_2S), 3.76 (s, 4 H, SCH_2Ar), 4.22 (t, 4 H, OCH_2CH_2), 4.4 (br, ~1 H, COOH/CD_3OH), 6.90 (t, 1 H, 20-H), and 7.15 (m, 6 H, 17,19-H and Ar-H); exact mass *m/e* calcd for $C_{21}H_{24}O_4S_2$ 404.112, found 404.113.

8,9-Benzo-18-[[[2-(1*H*-imidazol-4-yl)ethyl]amino]carbonyl]-6,11-dithia-2,15-dioxabicyclo[14.3.1]eicosa-1(20),16,18-triene (14). To 90 mg (0.22 mol) of the above carboxylic acid in 20 mL of benzene and 1 drop of DMF was added 150 mg (1.26 mmol) of $SOCl_2$. The solution was refluxed for 1 h under a nitrogen atmosphere. After cooling, the solution was concentrated under vacuum, leaving 110 mg of a pale yellow oil. This oil was dissolved in 10 mL of hot chloroform containing completely dissolved histamine (25 mg, 0.22 mmol). The solution was stirred for 4 h at room temperature. Next, 15 mL of a 1 N NaOH solution and additional chloroform were added. The aqueous layer was extracted with chloroform (4 × 20 mL). The combined chloroform layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed on silica gel (eluent: ethyl acetate/hexane/methanol 2/2/1). The yield of **14** was 43 mg (87 mmol, 39% yield) as a white solid, mp 214–217 °C: R_f 0.50 (ethyl acetate/hexane/methanol 3/3/2); IR (KBr) 3220, 2940, 1640, and 1580 cm^{-1}; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 2.05 (quintet, 4 H, $CH_2CH_2CH_2$), 2.78 (t, 4 H, CH_2CH_2S), 2.88 (t, 2 H, CH_2CH_2Im), 3.60 (t, 2 H, $CONHCH_2CH_2$), 3.83 (s, 4 H, SCH_2Ar), 4.29 (t, 4 H, OCH_2CH_2), 6.84 (br s, 1 H, 20-H), 6.94 (br s, 3 H, 17,19-H and Im-5(4)-H), 7.20 (m, 2 H, benzo-H), 7.35 (m, 2 H, benzo-H), and 7.57 (s, 1 H, Im-2-H); exact mass *m/e* calcd for $C_{26}H_{31}N_3O_3S_2$ 497.181, found 497.180.

***N*-[2-(1*H*-Imidazol-4-yl)ethyl]benzamide (15a).** This compound was prepared by a literature method[54] starting with 1.84 g (10 mmol) of histamine·2HCl. Compound **15a** was obtained (1.26 g, 5.8 mmol; 58% yield) as a colorless oil that crystallized slowly, mp 145–148 °C (lit.[54] mp 148 °C): ^{1}H NMR ($CDCl_3$) δ 2.84 (t, 2 H, CH_2CH_2Im), 3.65 (q (br), 2 H, $CONHCH_2CH_2$), and 7.1–8.0 (m, 8 H, Ar-H, Im-H, and NH).

***N*-[2-(1*H*-Imidazol-4-yl)ethyl]-3,5-di-*n*-propoxybenzamide (15b).** This was prepared in 23% yield as described for compound **7**: ^{1}H NMR ($CDCl_3/CD_3OD$) δ 0.99 (t, 6 H, CH_2CH_3), 1.82 (sextet, 4 H, $CH_2CH_2CH_3$), 2.87 (br t, 2 H, CH_2CH_2Im), 3.60 (br), and 3.85 (t, 6 H, $CONHCH_2CH_2$ and OCH_2CH_2), 6.50 (t, 1 H, 4-H), 6.78 (s, 1 H, 5′(4′)-H), 6.90 (d, 2 H, 2,6-H), 7.48 (s, 1 H, 2′-H), 7.80 (br t, 1 H, CONH), and 9.0 (br, 1 H, ImN-H).

General Procedure for the Preparation of the Metal Complexes of 7. Ligand **7** (370 mg, 1 mmol) was dissolved in 20 mL of methanol under a nitrogen atmosphere and was added slowly to a solution of 1 mmol of the appropriate Zn^{2+} or Co^{2+} salt ($M(NO_3)_2·6H_2O$, $M(ClO_4)_2·6H_2O$, $MCl_2·2H_2O$, or $M(CH_3CO_2)_2·2H_2O$) in 10 mL of methanol under a nitrogen atmosphere at room temperature. A white precipitate was formed immediately. The mixture was stirred for 1 h and then centrifuged off. The precipitate was washed with methanol and with 1/1 methanol/water, again centrifuged off, and dried over $MgSO_4$ under vacuum.

The yield of the zinc complex was 405 mg (0.85 mmol, 85% yield) as a white solid, mp > 300 °C dec; IR (KBr) 3300 (br), 3100 (br), 1630, 1590, and 1160 cm^{-1}. Anal. Calcd for $C_{18}H_{23}N_3O_3S_2·Zn·H_2O$: C, 45.33; H, 5.28; N, 8.81; S, 13.71; Zn, 13.71. Found: C, 43.39; H, 5.18; N, 7.82; S, 12.31; Zn, 14.20. The analysis could not be improved. A mass spectrum of the complex could not be obtained either by chemical ionization or by fast atom bombardment.

The yield of the cobalt complex was 270 mg (0.57 mmol, 57%) obtained as a green solid, mp > 300 °C: IR (KBr) 3300 (br), 3140 (br), 1630, 1580, and 1160 cm^{-1}; UV (DMF) 599 (shoulder), 608 (ε 600), 632 (shoulder), and 667 nm (800). Anal. Calcd for $C_{18}H_{23}N_3O_3S_2·Co·H_2O$: C, 45.95; H, 5.36; N, 8.93; S, 13.63; Co, 12.53. Found: C, 45.02; H, 5.03; N, 9.04; S, 13.22; Co, 10.81. A mass spectrum could not be obtained.

Complexation of $Zn(NO_3)_2·6H_2O$ or $Co(NO_3)_2·6H_2O$ with Ligands 12a, 14, 15a, and 15b. Complexation reactions were performed analogously to the complexation of **7**, except that an additional dilution by a factor of 10 was used, leading to solutions ready for UV experiments. No complexes could be isolated from the reaction mixtures. The cobalt complexes of the ligands (5 × 10^{-3} M in methanol) showed the following UV and visible absorptions in the visible region: **12a**, λ_{max} (CH_3OH) 320 (ε 250), 510 nm (24); **14**, λ_{max} 512 nm (ε 12) and λ_{max} ($CHCl_3$) 542 nm (50); **15a**, λ_{max} 321 (ε 108), 516 nm (12); **15b**, λ_{max} 321 (ε 103), 517 nm (7).

Titration Curves of 7·HCl and the Zn(II) Complex. Titration was performed on 4 × 10^{-2} M solutions of **7**·HCl and **7**·Zn(II) in 50% C_2H_5OH/H_2O at 20 °C, using a microburet with an adjusted KOH solution (8.8 × 10^{-3} M). The pH was measured with a combined glass electrode connected with a Corning pH meter 130 and pK_a values are estimated from the titration curves.

2,6-Bis(bromomethyl)pyridine (21). This compound was first prepared according to the literature method, which involves bromination of lutidine by NBS.[30a] Crystallization of the reaction mixture from pentane and chromatography on silica (eluent: benzene) gave a 2:1 mixture of **21** and 2-(dibromomethyl)-6-methylpyridine. Recrystallization from pentane gave two different types of crystals: colorless plates, 2-(dibromomethyl)-6-methylpyridine, and large square crystals of **21**, which were separated by hand using a pair of tweezers, to yield 4.5 g (17 mmol, 18%) of **21** as colorless crystals, mp 88–89 °C (lit.[30] mp 84–89 °C): ^{1}H NMR ($CDCl_3$) δ 33.32 (t), 122.52 (d), 137.86 (d), and 156.36 (s); MS *m/e* 263, 265, and 267 (1:2:1, M$^+$). There was also isolated 2.2 g (8.3 mmol, 9% yield) of 2-(dibromomethyl)-6-methylpyridine, mp 100–105 °C: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3 H, CH_3), 6.57 (s, 1 H, $CHBr_2$), 6.90–7.75 (m, 3 H, Py-H); MS *m/e* 263, 265, and 267 (1:2:1, M$^+$). The dibromide **21** was prepared in better yield by refluxing 8.4 g (60 mmol) of 2,6-bis(hydroxymethylene)pyridine in 80 mL of 48% HBr for 17 h. After chromatography on silica gel (eluent: $CHCl_3$ + 5% CH_3OH, R_f 0.76), 6.5 g (25 mmol, 41% yield) of **21** was isolated, in addition to 5.3 g (26 mmol, 44% yield) of the monobromide (R_f 0.48).

9-Bromofluorene (19). This compound was prepared following the procedure described in the literature[55] from 50 g (0.30 mmol) of fluorene (**18**). The yield of **19** was 53 g (0.22 mmol, 72%), mp 103–104 °C (lit.[55] mp 102–103 °C): ^{1}H NMR ($CDCl_3$) δ 6.89 (s, 1 H, CHBr) and 7.1–7.7 (m, 8 H, Ar-H).

9-Mercaptofluorene. This compound was prepared according to a procedure described in the literature[56] from 24.5 g (0.10 mol) of **18**. The yield was 18.0 g (91 mmol, 91%), tan colored crystals, mp 104–106 °C (lit.[56] mp 103–106 °C): ^{1}H NMR ($CDCl_3$) δ 1.98 (d, 1 H, CHSH), 4.83 (d, 1 H, CHSH), and 7.1–7.7 (m, 8 H, Ar-H). The disulfide of 9-mercaptofluorene: mp 169–171 °C; exact mass *m/e* calcd for $C_{26}H_{16}S_2$ 394.085, found 394.086.

2-(Fluoren-9-ylthio)tetrahydropyran (20). The procedure described in the literature[29] for the synthesis of the tetraphenyl compound was used. Product **20** was purified by chromatography on silica gel (eluent: hexane/EtAC, 95:5). From 5.0 g (25 mmol) of 9-mercaptofluorene, 5.7 g (20 mmol, 81% yield) of **20** was isolated as a colorless oil that crystallized slowly, mp 40–42 °C: R_f 0.37 (hexane/EtAc 95:5); IR (film) 3055, 2965, and 2840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40–1.90 (m, 6 H, THP-H), 3.25 (m, 1 H, 6-H_{ax}), 3.98 (m, 1 H, 6-H_{eq}), 4.88 (m, 2-H), and 4.93 (s, Fl-9H, together 2 H), 7.0–7.3 (m, 4 H, Ar-H), and 7.4–7.7 (m, 4 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 21.08 (t), 25.24 (t), 30.96 (t), 47.55 (d), 63.58 (t), 81.43 (d), 119.55 (d), 124.99 (d), 125.35 (d), 126.85 (d), 127.03 (d), 127.38 (d), 127.54 (d), 139.64 (s), 140.31 (s), 144.33 (s), and 145.77 (s); MS *m/e* (rel intensity) 282 (M$^+$), 165 (100). Anal. Calcd for $C_{18}H_{18}OS$: C, 76.55; H, 6.42; S, 11.36. Found: C, 76.62; H, 6.45; S, 11.32.

2,6-Bis[[9-[(tetrahydropyran-2-yl)thio]fluoren-9-yl]methyl]pyridine (22). The synthesis was carried out analogously to the procedure described for preparation of the tetraphenyl compound.[29] Starting with 4.25 g (15 mmol) of **20**, 4.2 g of **22** (6.3 mmol, 84% yield) were isolated as colorless crystals, mp 165–166 °C: R_f 0.18 (hexane/EtAc 9:1); ^{1}H NMR ($CDCl_3$) δ 1.10–1.80 (m, 12 H, THP-H), 2.97 (2 H, m, THP-6-H_{ax}), 3.48 (s, 4 H, CH_2), 3.75 (m, 2 H, THP-6-H_{eq}), 4.36 (m, 2 H, THP-2-H), 5.98 (d, *J* = 8 Hz, Py-3,5-H), 6.62 (t, 1 H, Py-4-H), 7.1–7.6 (m,

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16 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 21.19 (t), 25.14 (t), 31.03 (t), 47.55 (t), 59.18 (s), 63.08 (t), 81.20 (d), 119.22 (d), 120.69 (d), 124.85 (d), 125.01 (d), 126.50 (d), 126.83 (d), 127.14 (d), 127.49 (d), 134.15 (d), 139.07 (s), 139.86 (s), 146.82 (s), 147.76 (s), and 154.82 (s); MS *m/e* (rel intensity) 582 (11), 433 (52), and 431 (100) (no parent peak observed). Anal. Calcd for $C_{43}H_{41}NO_2S_2$: C, 77.32; H, 6.19; N, 2.10; S, 9.60. Found: C, 77.08; H, 6.14; N, 2.15; S, 9.57.

2,6-Bis[(9-mercaptofluoren-9-yl)methyl]pyridine (17). This compound was prepared following literature precedent.[24] Starting with 1.0 g (1.5 mmol) of **22**, 710 mg of impure product was obtained, which was purified by flash chromatography on silica gel (eluent: $CHCl_3$). There was some decomposition of the product. The yield of **17** was 450 mg (0.90 mmol, 60%) as a colorless oil that crystallized slowly, mp 164–166 °C: R_f 0.15 ($CHCl_3$); IR (KBr) 3060, 2500, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 2 H, SH), 3.50 (s, 4 H, CH_2), 6.23 (d, J = 8 Hz, 2 H, Py-2,5-H), 6.91 (t, J = 8 Hz, 1 H, Py-4-H), 7.2–7.3 (m, 12 H, Ar-H), and 7.45–7.7 (m, 4 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 49.50 (t), 54.69 (s), 119.81 (d), 122.57 (d), 124.61 (d), 127.51 (d), 127.88 (d), 135.13 (d), 138.51 (s), 149.49 (s), and 155.99 (s); MS *m/e* (rel intensity) 433 (100) and 431 (78) (no parent peak could be observed). A correct analysis could not be obtained for this compound, apparently owing to its instability.

General Procedure for the Synthesis of 2,6-Bis(2-methyl-2-hydroxypropyl)pyridine (24) and 2,6-Bis[(9-hydroxyfluoren-9-yl)methyl]pyridine (25). To a solution of 5.0 g (47 mmol) of 2,6-lutidine in 120 mL of dry ether at 20 °C was added 32 mL of a 1.6 M solution of butyllithium in hexane (50 mmol) slowly over 15 min. The temperature rose to 30 °C, and the solution turned orange. After 1 h of stirring at room temperature the solution was cooled to −80 °C. Next 1 equiv of ketone was slowly added [3.5 mL (47 mmol) of pure acetone or 8.3 g (46 mmol) of fluorenone] dissolved in a minimal amount of ether. The reaction mixture was stirred for 60 min and allowed to warm to room temperature. Then another 32 mL of a 1.6 M butyllithium solution in hexane (50 mmol) was added during 15 min, followed by an additional 60 min of stirring. After cooling to −80 °C, an additional amount of the ketone was added, and the reaction mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was poured into 400 mL of NaCl solution (100 mL in case of the tetramethyl-substituted compound). The yellow organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, and concentrated at the rota-evaporator. The residue was purified by flash chromatography on silica gel (eluent: hexane/20% ethyl acetate). Compound **24** was obtained as a yellow oil that crystallized slowly and which was recrystallized from hexane. Compound **25** crystallized from the elution solvent used for chromatography. The yield of **24** was 3.6 g (16 mmol, 34%), obtained as colorless crystals, mp 79–82 °C: R_f 0.15 (hexane/20% EtAc); IR (film) 3360, 2960, 2920, 1590, and 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 12 H, CH_3), 2.89 (s, 4 H, CH_2), 4.1 (br, 2 H, OH), 7.0 (d, 2 H, 3,5-H), and 7.55 (dd, 1 H, 4-H); ^{13}C NMR (CD_3OD) δ 29.62 (q), 50.97 (t), 71.90 (s), 123.87 (d), 138.03 (d), and 159.30 (s); MS *m/e* (rel intensity) 223 (4), 165 (75), and 147 (100). Also 2.8 g (17 mmol, 36% yield) of monoalkylated product was obtained. The yield of **25** was 2.9 g (6.2 mmol, 13%), as yellow "star-shaped" crystals, mp 190–191 °C: R_f 0.18 (hexane/40% EtOAc); IR (KBr) 3340, 3050, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39 (s, 4 H, CH_2), 4.86 (br, 2 H, OH), 6.70 (d, J = 7.7 Hz, 2 H, Py-3,5-H), 7.09 (d, J = 7.6 Hz, 4 H, Fl-1-H), 7.19 (t, J = 7.7 Hz, 4 H), 7.28–7.33 (m, 5 H, Fl-2-H + Py-4-H), and 7.59 (d, J = 7.6 Hz, 4 H, Fl-4-H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 46.29 (t), 81.06 (s), 119.09 (d), 122.10 (d), 123.50 (d), 127.11 (d), 128.17 (d), 135.97 (d), 138.68 (s), 147.71 (s), and 156.19 (s). Anal. Calcd for $C_{33}H_{25}NO_2$: C, 84.77; H, 5.39; N, 3.00. Found: C, 84.37; H, 5.43; N, 3.12. Also 5.67 g (20 mmol, 42% yield) of the monoalkylated product was isolated.

2,6-Bis(2-methyl-1-propenyl)pyridine (26). Diol **24** (1.0 g, 4.5 mmol) in 20 mL of H_3PO_4 was heated at 130 °C with stirring for $2^1/_2$ hours. After cooling in ice, the reaction mixture was neutralized with 10% NaOH solution to pH 7. The aqueous solution was extracted with $CHCl_3$ (4 × 50 mL). After drying and careful evaporation of the solvent (the product is rather volatile), the residue was purified by chromatography on silica gel (eluent: hexane/20% ethyl acetate). The yield of **26** was 570 mg (3.0 mmol, 68%) as a colorless oil: R_f 0.68 (hexane/20% ethyl acetate); ^1H NMR ($CDCl_3$) δ 1.93 (d, ^4J = 1.2 Hz, 6 H, CH_3), 2.08 (d, ^4J = 1.0 Hz, 6 H, CH_3), 6.34 (septet, $^4J \approx 1$ Hz, 2 H, =C*H*—), 6.94 (d, 2 H, 3,5-H), and 7.38–7.65 (m, 1 H, 4-H).

2,6-Bis(9-fluorenylidenemethyl)pyridine (27). This compound was prepared as described for **26**, from 330 mg (0.71 mmol) of **25**. The product was isolated as an orange solid (280 mg, 0.65 mmol, 92% yield), mp 83–86 °C: R_f 0.68 (hexane/40% EtOAc); UV (hexane) 368 (log ϵ 4.12), 349 (4.16), 332 (4.16), 298 (4.5), and 259 (4.5) nm; ^1H NMR ($CDCl_3$) δ 7.01 (t, J = 7.2 Hz, 2 H), 7.22–7.47 (m, 7 H), 7.64–7.72 (m, 8 H), 7.80–7.85 (dd, J = 7.2 and 3 Hz, 2 H), 8.22 (d, J = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 119.45 (2 × d), 120.48 (d), 124.13 (d), 125.27 (d), 126.26 (d), 126.61 (d), 126.97 (d), 128.65 (d), 129.09 (d), 136.07 (s), 136.30 (d), 138.96 (s), 139.50 (s), 139.77 (s), 141.58 (s), and 155.56 (s); exact mass *m/e* calcd for $C_{25}H_{21}N$ 431.167, found 431.165.

2,6-Bis[2-methyl-2-(acetylthio)propyl]pyridine. Compound **26** (270 mg, 1.44 mmol) and thiolacetic acid (530 mg, 7.0 mmol) in 10 mL of CH_3OH were refluxed for 20 h under a nitrogen atmosphere. After cooling, 30 mL of phosphate buffer (pH 7) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). After drying over $MgSO_4$ and evaporation of the solvent, the crude product was obtained containing ~10% alkene and ~20% hydrolyzed thiol ester. After chromatography on silica gel (eluent: hexane/10% EtOAc), 340 mg of product (1.0 mmol, 70%) was obtained as a colorless oil: R_f 0.31 (hexane/15% EtOAc); IR (film) 1680, 1450, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 12 H, $(CH_3)_2C$), 2.23 (s, 6 H, $SCOCH_3$), 3.25 (s, 4 H, CH_2), 7.00 (d, 2 H, 3,5-H), and 7.2–7.6 (m, 1 H, 4-H); ^{13}C NMR ($CDCl_3$) δ 27.54 (q), 48.17 (t), 51.41 (s), 122.64 (d), 135.37 (d), 156.97 (s), and 196.56 (s).

2,6-Bis(2-methyl-2-mercaptopropyl)pyridine (28). Via Hydrolysis of Thioacetate. To 300 mg (0.88 mmol) of 2,6-bis[2-methyl-2-(acetylthio)propyl]pyridine, dissolved in 15 mL of CH_3OH (under N_2), was added 300 mg (5.4 mmol) of KOH. The solution was stirred for 20 h at room temperature. Next, 50 mL of phosphate buffer (pH 7) was added, and the mixture was extracted with CH_2Cl_2 (4 × 30 mL). After drying over $MgSO_4$ and evaporation of the solvent, 230 mg (0.90 mmol, 100%) of **28** was obtained as a colorless oil that crystallized slowly.

Directly from 26. A solution of 127 mg (0.68 mmol) of **26** (4.25 mg, 5.6 mmol) of thiolacetic acid and 10 mg (50 μmol) of *p*-toluenesulfonic acid in 5 mL of CH_3OH was refluxed for 110 h (under N_2). After cooling, 20 mL of phosphate buffer (pH 7) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). After drying over $MgSO_4$ and evaporation of the solvent, 220 mg (0.65 mmol, 96% yield) of **28** was obtained as a colorless oil that slowly crystallized, mp 52–55 °C: R_f 0.44 (hexane/15% ethyl acetate); IR (film) 2530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 2 H, CH_3), 2.09 (br, 2 H, SH), 3.00 (s, 4 H, CH_2), 6.95–7.10 (m, 2 H, 3,5-H), and 7.35–7.60 (m, A_2B system, 1 H, 4-H); ^{13}C NMR ($CDCl_3$) δ 32.80 (q), 44.47 (s), 53.85 (t), 122.78 (d), 135.46 (d), and 157.70 (s). In a $CDCl_3$ solution the compound is slowly oxidized by air.

Complexation of $Zn(NO_3)_2 \cdot 6H_2O$ or $Co(NO_3)_2 \cdot 6H_2O$ with the Pyridine Diols 24 and 25. To a solution of 1.0 mmol of ligand (**24** or **25**) in 5 mL of $CHCl_3$, under nitrogen at room temperature, was added a solution of 1.0 mmol of $Zn(NO_3)_2 \cdot 6H_2O$ (or $Co(NO_3)_2 \cdot 6H_2O$) in 5 mL of CH_3OH. On the addition of the Co^{2+} solution, the purple color intensified. After being stirred for 5 h at room temperature, the clear solutions were concentrated under vacuum to yield a solid, or sometimes a tarry, compound. The tarry compounds isolated from ligand **25**, still containing CH_3OH, were suspended in hexane, and crystallized on standing. Starting from 100 mg (0.21 mmol) of **25**, there was obtained 138 mg of **25**·$Co(NO_3)_2$ (0.21 mmol, 100% yield) as a purple crystalline complex, mp 165 °C dec; IR (KBr) 3250 cm^{-1}; UV ($CHCl_3$) 520 (ϵ 30), 505 (shoulder), and 480 nm (shoulder). Anal. Calcd for $C_{33}H_{25}NO_2 \cdot Co(NO_3)_2 \cdot 3H_2O$: C, 56.25; H, 4.44; N, 5.96; Co, 8.36. Found: C, 56.61; H, 4.67; N, 5.81; Co, 8.21.

25·$Zn(NO_3)_2$. In an analogous fashion from 100 mg (0.21 mmol) of **25** with $Zn(NO_3)_2 \cdot 6H_2O$, there was obtained 104 mg of **25**·$Zn(NO_3)_2$ (0.16 mmol, 75% yield) as a white solid, mp 185 °C dec: Ir (KBr) 3250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, ~6 H, CH_3OH), 3.50 (br, ~4 H, OH + CH_3OH), 3.71 (s, ~4 H, CH_2), 7.0–7.7 (m, ~19 H, Ar-H) (complex contains 2 mol of CH_3OH, before careful

drying). Anal. Calcd for $C_{33}H_{25}NO_2{\cdot}Zn(NO_3)_2{\cdot}2H_2O$: C, 57.19; H, 4.22; N, 6.06; Zn, 9.43. Found: C, 57.36; H, 4.15; N, 5.83; Zn, 9.19.

The complexes isolated from ligand **24** were "recrystallized" from $CHCl_3$ (+ 10% CH_3OH). The complexes crystallized after slow heating to room temperature of a saturated solution initially at −40 °C! The complexes could also be recrystallized from a solution in $ClCH_2CH_2Cl$/30% CH_3OH by slow evaporation of the solvent. Starting from 140 mg (0.63 mmol) of **24**, there was obtained 210 mg of **24**·$Co(NO_3)_2$ (0.52 mmol, 82% yield) as purple crystals, mp 220 °C dec: IR (KBr) 3280 cm^{-1}; UV ($CHCl_3$) 512 nm (ϵ 25), in DMF 523 nm (ϵ 22), and in DME: 518 nm (ϵ 38). Anal. Calcd for $C_{13}H_{21}NO_2{\cdot}Co(NO_3)_2$: C, 38.43; H, 5.21; N, 10.34; Co, 14.51. Found: C, 37.66; H, 5.13; N, 10.27; Co, 14.39.

24·Zn(NO$_3$)$_2$. From 45 mg (0.20 mmol) of **24** with $Zn(NO_3)_2{\cdot}6H_2O$, there was obtained 66 mg of **24**·$Zn(NO_3)_2$ (0.16 mmol, 79% yield), as colorless crystals, mp 211–213 °C dec: IR (KBr) 3170 cm^{-1}; ^1H NMR ($CDCl_3$ + 2 equiv of CH_3OH) δ 1.30 (s, 12 H, $C(CH_3)_2$), 3.15 (s, 4 H, CH_2), 3.46 (s, 6 H, CH_3OH), 6.2 (br, ~4 H, OH), 7.27 (d, 2 H, 3,5-H), and 7.74–8.01 (m, 1 H, 4-H). Anal. Calcd for $C_{13}H_{21}NO_2{\cdot}Zn(NO_3)_2$: C, 37.83; H, 5.13; N, 10.18; Zn, 15.84. Found: C, 37.88; H, 5.22; N, 10.13; Zn, 15.85. Crystals suitable for X-ray analysis were prepared by mixing 45 mg (0.20 mmol) of **24** dissolved in 3 mL of dichloroethane with 60 mg of $Zn(NO_3)_2{\cdot}6H_2O$ dissolved in 1 mL of CH_3OH. After slow evaporation of the solvent (mainly CH_3OH), single crystals were obtained suitable for X-ray analysis.

Complexation of Zn(NO$_3$)$_2$·4H$_2$O with Dimercapto Pyridines 16, 17, and 28. To a solution of 1.0 mmol of the ligand (**16**, **17**, or **28**) in 10 mL of chloroform (with **16** an additional 5 mL of CH_3OH was added) was added 1.0 mmol of $Zn(NO_3)_2{\cdot}4H_2O$ in 10 mL of CH_3OH. The clear reaction mixtures were stirred for 2 h at room temperature and carefully stored under nitrogen.

16·Zn. In the reaction mixture a white precipitate slowly formed. After cooling the mixture at −20 °C for 4 days, the crystals were filtered off and washed with CH_3OH. This yielded 280 mg of (**16**·Zn)$_2$ (0.25 mmol, 49% yield) as a white crystalline compound, mp 232–233 °C dec: IR (KBr) 3050, 1600, 1455, 1440, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (br) and 3.95 (br, together 2 H, 1′- and 1″-H_{eq}?), 4.52 (br) and 4.60 (br, together 2 H, 1′- and 1″-H_{ax}?), 6.03 (br d, 1 H, Py-3-H), 6.32 (br d, 1 H, py-5-H), and 6.8–7.5 (m, ~21 H, Py-4-H + Ar-H). Anal. Calcd for $(C_{33}H_{27}NS_2Zn)_2$: S, 11.53; Zn, 11.31. Found: S, 11.51; Zn, 11.52.

Crystals for X-ray analysis were obtained after recrystallization from CH_3CN. The diamond-shaped crystals were kept under CH_3CN, as the crystals fell to pieces after drying, caused by the loss of solvent included in the crystal structure.

17·Zn. After the complexation reaction of **17** (308 mg, 0.62 mmol), the solution was concentrated to 5 mL, and 10 mL of CH_3OH was added. After storing at −20 °C overnight, the crystals were filtered off and washed with CH_3OH. The yield of **17**·Zn was 200 mg (0.34 mmol, 56% yield), obtained as a white crystalline compound, mp 143 °C dec; IR (KBr) 3050, 1580, 1570, 1440, 750, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.06 (s, 4 H, CH_2), 6.37 (d, J = 7.9 Hz, 2 H, Py-3,5-H), 7.30–7.38 (m, 9 H, Py-4-H and Ar-H), and 7.50–7.60 (m, 8 H, Ar-H). A correct analysis could not be obtained from the complex.

28·Zn. After the reaction of 100 mg (0.39 mmol) of **28**, the clear solution was concentrated to half of the original volume, 10 mL of CH_3OH was added, and the mixture was heated for 5 min. After crystallization overnight 98 mg of (**28**·Zn)$_2$ (0.15 mmol, 79% yield) was isolated as a white solid, mp > 295 °C: IR (KBr) 2960, 2920, 2800, 1590, 1580, and 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 3.04 (d, ^2J = 13.7 Hz, 1 H, HC*H*), 3.07 (d, ^2J = 14.5 Hz, HC*H*), 3.38 (d, ^2J = 13.7 Hz, 1 H, HC*H*), 3.49 (d, ^2J = 14.5 Hz, 1 H, HC*H*), 7.13 (d, ^3J = 7.5 Hz, 1 H, Py-3-H), 7.21 (d, ^3J = 7.5 Hz, 1 H, Py-5-H), and 7.76 (t, ^3J = 7.5 Hz, 1 H, Py-4-H); ^{13}C NMR ($CDCl_3$) δ 32.32 (q), 34.02 (q), 37.27 (q), 38.59 (q), 43.00 (s), 45.50 (s), 54.30 (t), 54.63 (t), 125.48 (d), 125.60 (d), 139.31 (d), 158.50 (s), and 160.07 (s). Anal. Calcd for $(C_{13}H_{19}NS_2Zn)_2$: C, 48.97; H, 6.00; Zn, 20.51. Found: C, 48.48; H, 5.93; Zn, 20.62.

Complexation of Co(NO$_3$)$_2$·6H$_2$O with 16. The complex of Co^{2+} with **16** was prepared as described for complex **16**·Zn. From 500 mg (1.0 mmol) of **16**, there was isolated 150 mg of **16**·Co (0.27 mmol, 27% yield) as dark red-brown crystals, mp 206–207 °C dec: IR (KBr) 3050, 1600, 1485, 745, and 700 cm^{-1}; UV (CH_2Cl_2) 349 (log ϵ 3.69), and 684 nm (2.78). In solution the complex slowly decolorized: IR (KBr) 3410, 3050, 1170, 1050, and 710 cm^{-1} (oxidized complex). Anal. Calcd for $(C_{33}H_{27}NO_6S_2){\cdot}Co{\cdot}(H_2O)_2$: C, 57.21; H, 4.51; N, 2.03; S, 9.26; Co, 8.51. Found: C, 57.97; H, 4.65; N, 2.20; S, 9.15; Co, 8.35 (after contact with air for a long time).

1,4-Dihydroxybutanone (30). This compound was prepared from 30 g (0.35 mol) of 2-butyne-1,4-diol (**29**) by a method described in the literature.[48c] The product was purified by bulb-to-bulb distillation (120 °C/1 Torr). There was obtained 13 g (0.13 mol, 37%) of **30** as a colorless oil, bp ±120 °C (1 Torr): ^1H NMR ($CDCl_3$) δ 2.57 (t, 2 H, $COCH_2CH_2$), 3.76 (t, 2 H, CH_2CH_2OH), 4.20 (s, 3 H, CH_2), and 4.4 (br, 2 H, OH). Fractional distillation resulted in elimination of water and formation of 3-oxo-1-buten-4-ol, which polymerized on standing.

3-Oxobuten-4-ol. This compound was prepared as described in the literature[48c] from 30 g (0.35 mol) of **30**, only the temperature was maintained at 40–60 °C for 2 h. After the workup procedure the aqueous solution was distilled on the rota-evaporator. The distillate consisted of a 2.5 mol/L solution of the product in water (80 mL, 200 mmol, 57% yield): ^1H NMR (H_2O) δ 4.41 (s, 2 H, CH_2), 5.6–6.0 (dd, 1 H, =CH), and 6.2–6.6 (m, 2 H, $=CH_2$).

4-[(Phenylmethyl)thio]-1-hydroxy-2-butanone (31). To a 2.5 M solution of 3-oxo-1-buten-4-ol in water (52 mL, 130 mmol) were added 10.0 g (80 mmol) of benzyl mercaptan and 0.5 g (9 mmol) of KOH. The mixture was heated at 40–50 °C for 3 h and stirred overnight at room temperature. The reaction mixture was then extracted with $CHCl_3$ (3 × 100 mL), and the combined organic layers were washed with a 2 N NaOH solution and with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica (eluent: $CHCl_3$/5% CH_3OH). This yielded 9.3 g (44 mmol, 55%) of **31** as a colorless oil: R_f 0.55 ($CHCl_3$/10% CH_3OH); IR (film) 3440, 1720, and 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.4–2.7 (m, 4 H, CH_2CH_2), 3.2 (br, 1 H, OH), 3.61 (s, 2 H, SCH_2Ar), 4.11 (br s, 2 H, CH_2OH), and 7.20 (s, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 24.88 (t), 36.61 (t), 38.13 (t), 127.03 (d), 128.44 (d), 128.63 (d), 137.86 (s), and 207.79 (s).

3-[(Phenylmethyl)thio]propionitrile (32). To a 12.5 g (0.10 mol) of benzyl mercaptan with 100 mg of $NaOC_2H_5$ was slowly added 10 g (0.19 mol) of acrylonitrile. The reaction mixture was heated to reflux and maintained at reflux for 15 min. The excess of acrylonitrile was distilled off, $CHCl_3$ (200 mL) was added, and the resulting solution was washed with a 0.1 N NaOH solution and H_2O. After drying over $MgSO_4$, followed by evaporation of the solvent under reduced pressure, 16.5 g (93 mmol, 93%) of **32** was obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.50 (m, A_2B_2 system, 4 H, CH_2CH_2), 4.73 (s 2 H, SCH_2Ar), and 7.26 (s, 5 H, C_6H_5).

Methyl 3-[(Phenylmethyl)thio]propanimidate·HCl (33). Super dry methanol (4 mL) was saturated with dry HCl gas (3.2 g). To this solution was added 5.5 g (31 mmol) of **32** slowly with a syringe. The clear solution was left at 0 °C for 19 h, 20 mL of ether was then added, and the product crystallized. The crystals were filtered off and washed with ether. After drying the yield of **33** was 7.6 g (31 mmol, 100%), mp 104.8–105.2 °C dec: IR (KBr) 2850 (br) and 1650 cm^{-1}; ^1H NMR (CD_3OD) δ 2.81 (m, A_2B_2 system, 4 H, CH_2CH_2), 3.76 (s, 2 H, SCH_2Ar), 4.08 (s, 3 H, OCH_3), 4.73 (br, ± 2 H, NH + CD_3OH), and 7.23 (s, 5 H, C_6H_5); MS m/e (rel intensity) 209 (M^+ − HCl) and 91 (100).

2,4(5)-Bis[2-[(phenylmethyl)thio]ethyl]-1*H*-imidazole. This compound was prepared from 1.10 g (5.2 mmol) of **31**, 1.50 g (6.1 mmol) of **33**, and 90 mL of liquid ammonia. The crude product was purified by column chromatography on silica (eluent: $CHCl_3$/10% CH_3OH). The yield was 1.20 g (3.3 mmol, 63%) obtained as a brown oil: R_f 0.53 ($CHCl_3$/10% CH_3OH); IR (film) 3030, 2910 (br), 1595, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55–2.75 (m, 4 H, 2-(CH_2CH_2S) and 4(5)-(CH_2CH_2S)), 2.86 (t, 2 H, 2-(CH_2CH_2)), 3.61 and 3.65 (2 × s, 4 H, $2SCH_2Ar$), 6.60 (s, 1 H, 5(4)-H), and 7.25 (m, 11 H, C_6H_5 + NH); ^{13}C NMR ($CDCl_3$, 60 °C) δ 27.0 (t), 28.3 (t), 30.0 (t), 31.1 (t), 36.20 (t), 36.27 (t), 116.8 (d (br at 30 °C)), 126.75 (d), 126.89 (d), 128.28 (d), 128.34 (d), 128.6 (d, 2 ×), 134.9 (d (br at 30 °C)), 137.9 (s), 138.2 (s), and 146.1 (s); exact mass m/e calcd for $C_{21}H_{24}N_2S_2$ 368.138, found 368.139. Notwithstanding extensive purification, the compound remained a brownish oil.

2,4(5)-Bis(2-mercaptoethyl)-1*H*-imidazole (34). To a solution of 0.99 g (2.68 mmol) of 2,4(5)-bis[2-[(phenylmethyl)thio]ethyl]-1*H*-imidazole in 50 mL of liquid ammonia was added small pieces of sodium until the blue color persisted for 45 min (±350 mg, 15 mmol). Next the solution was neutralized with 1 g (18 mmol) of NH_4Cl. The NH_3 was evaporated in a stream of N_2, and the residue was dissolved in 50 mL of $CHCl_3$ and washed with a dilute solution of $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (2 × 25 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica (eluent: $CHCl_3$/7% CH_3OH). The yield of **34** was 450 mg (2.39 mmol, 89%), obtained as a slightly yellow oil): R_f 0.25 ($CHCl_3$/7% CH_3OH); ^1H NMR ($CDCl_3/CD_3OD$) δ 2.6–3.0 (m, 8 H, 4 × CH_2), 4.5 (br, 3 H, SH + NH), and 6.74 (s, 1 H, 5(4)-H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 22.7 (t), 23.7 (t), 31.0 (t), 32.2 (t), 114.9 (d), 134.6 (s), and 145.7 (s); exact mass *m/e* calcd for $C_7H_{12}N_2S_2$ 188.044, found 188.043. On exposure to air, a precipitate formed within 15 min from a methanol solution as a result of oxidation.

4(5)-(Chloromethyl)-1*H*-imidazole (36). This compound was prepared by a method described in the literature,[57] from 6.9 g (51 mmol) of **35**. The yield of **36** was 7.65 g (50 mmol, 99%), obtained as a beige solid, mp 138–142 °C (lit.[57] mp 138–141 °C): ^1H NMR ($CDCl_3$) δ 4.88 (s, 2 H, CH_2), 5.1 (br, 2 H, NH), 7.73 (s, 1 H, 5(4)-H), and 9.90 (s, 1 H, 2-H).

1,6-Bis(imidazol-4(5)-yl)-2,5-dithiahexane (37a). To a solution of 1.17 g (12.5 mmol) of 1,2-ethanedithiol and 2.8 g (50 mmol) of KOH in 50 mL of absolute ethanol was slowly added 3.8 g (25 mmol) of **36** dissolved in 50 mL of absolute ethanol. The solution was refluxed for 3 h and left overnight at room temperature. After evaporation of the solvent, the residue was redissolved in 100 mL of a 1 N HCl solution, which was washed with $CHCl_3$ (3 × 50 mL). The aqueous solution was made alkaline (pH 9) with a NaOH solution and extracted with $CHCl_3$ (+ 10% C_2H_5OH) (6 × 50 mL). After evaporation of the solvent, the residue was chromatographed on silica (eluent: $CHCl_3$/10% CH_3OH). Recrystallization of the product from CH_3OH afforded 1.5 g (5.9 mmol, 47% yield) of **37a** as white crystals, mp 189–191 °C: R_f 0.19 ($CHCl_3$/10% CH_3OH); ^1H NMR (CD_3OD) δ 2.65 (s, 4 H, SCH_2CH_2S), 3.74 (s, 4 H, SCH_2Im), 6.93 (d, J = 1 Hz, 2 H, 5(4)-H), and 7.69 (d, J = 1 Hz, 2 H, 2-H); ^{13}C NMR (CD_3OD) δ 28.28 (t), 32.20 (t), 118.88 (d), 135.70 (s), and 136.55 (d); MS *m/e* (rel intensity) 254 (2) and 81 (100). Anal. Calcd for $C_{20}H_{14}N_4S_2$: C, 47.21; H, 5.55; N, 22.02; S, 25.22. Found: C, 46.96; H, 5.60; N, 21.75; S, 25.10.

1,7-Bis(imidazol-4(5)-yl)-2,6-dithiaheptane (37b). This compound was prepared as described for **37a**, from 1.35 g (12.5 mmol) of 1,3-propanedithiol. The yield of **37a** was 2.2 g (8.3 mmol, 66%), obtained as colorless crystals, mp 114–116 °C: R_f 0.08 ($CHCl_3$/10% CH_3OH); IR (KBr) 3500–2600 (br), 1460 and 840 cm^{-1}; ^1H NMR (CD_3OD) δ 1.81 (quintet, 2 H, $CH_2CH_2CH_2$), 2.60 (t, 4 H, SCH_2CH_2), 3.76 (s, 4 H, SCH_2Im), 6.92 (s, 2 H, 5(4)-H), and 7.75 (s, 2 H, 2-H); ^{13}C NMR (CD_3OD) δ 28.25 (t), 29.87 (t), 31.10 (t), 118.92 (d), 135.71 (s), and 136.47 (d); MS *m/e* (rel intensity) 268 (1) and 81 (100). An analysis within 0.3% could not be obtained for this compound.

Crystal Structure Determination of [24·Zn·$(H_2O)_2$]$(NO_3)_2$. Crystallographic details are available in the supplementary material.

Registry No. **7**, 111692-80-9; **7**·Zn·H_2O, 125329-57-9; **7**·Co·H_2O, 125329-58-0; **8**, 2150-44-9; **9**, 111682-05-4; **10**, 125329-36-4; **12a**, 111682-04-3; **12b**, 125329-39-7; **13**, 41383-84-0; **14**, 125329-43-3; **15a**, 29677-71-2; **15b**, 125329-44-4; (**16**·Zn)$_2$, 125329-67-1; **16**·Co, 125329-70-6; **17**, 125329-47-7; **17**·Zn, 125329-68-2; **19**, 1940-57-4; **20**, 125329-46-6; **21**, 7703-74-4; **22**, 125329-45-5; **23**, 108-48-5; **24**, 125357-28-0; **24**·Zn$(NO_3)_2$, 125329-66-0; [**24**·Zn·$(H_2O)_2$]$(NO_3)_2$, 125329-72-8; **24**·Co$(NO_3)_2$, 125329-64-8; **25**, 125329-48-8; **25**·Zn$(NO_3)_2$, 125329-62-6; **25**·Co$(NO_3)_2$, 125329-60-4; **26**, 125329-49-9; **27**, 125329-50-2; **28**, 125329-52-4; (**28**·Zn)$_2$, 125329-69-3; **29**, 110-65-6; **30**, 140-86-3; **31**, 125329-53-5; **32**, 5601-23-0; **33**, 125329-54-6; **34**, 125329-56-8; **35**, 32673-41-9; **36**, 38585-61-4; **37a**, 118090-72-5; **37b**, 119827-35-9; HLADH, 9031-72-5; $BrCH_2CH_2CH_2Br$, 109-64-8; H_2NCSNH_2, 62-56-6; CH_3SH, 74-93-1; $PhCH_2NH_2$, 100-46-9; CH_3COSH, 507-09-5; $PhCH_2SH$, 100-53-8; CH_3CN, 107-13-1; CH_3OH, 67-56-1; NH_3, 7664-41-7; $HSCH_2CH_2SH$, 540-63-6; $HSCH_2CH_2CH_2SH$, 109-80-8; methyl 3,5-bis(3-mercaptopropoxy)benzoate, 125329-37-5; histamine, 51-45-6; histamine-2HCl, 56-92-8; methyl 3,5-bis[3-(methylthio)propoxy]benzoate, 125329-38-6; 3,5-bis[3-(methylthio)propoxy]benzoic acid, 125329-40-0; 3,5-bis[3-(methylthio)propoxy]benzoyl chloride, 125357-27-9; 8,9-benzo-18-(methoxycarbonyl)-6,11-dithia-2,15-dioxabicyclo[14.3.1]eicosa-1(20),16,18-triene, 125329-41-1; 8,9-benzo-18-carboxy-6,11-dithia-2,15-dioxabicyclo[14.3.1]eicosa-1-(20),16,18-triene, 125329-42-2; 9-fluorenyl disulfide, 101796-83-2; 2,6-bis[2-methyl-2-(acetylthio)propyl]pyridine, 125329-51-3; 3-oxobuten-4-ol, 52642-66-7; 2,4(5)-bis[2-[(phenylmethyl)thio]-ethyl]-1*H*-imidazole, 125329-55-7; 9-mercaptofluorene, 19552-08-0.

Supplementary Material Available: Structural report, tables of bond distances, bond angles, root-mean-square amplitudes of thermal vibration, least-square planes, torsional angles, temperature factor expressions, positional parameters, and packing diagram from X-ray analysis of **24**·Zn·$(H_2O)_2(NO_3)_2$ and NMR (^{13}C and ^1H) spectra for **12a**, **14**, **25**, **27**, **32a,b**, and **37a** together with those for various intermediates (33 pages). Ordering information is given on any current masthead page.

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Stereoselective Intramolecular Nitrone Cycloadditions Promoted by an Allylic Stereocenter

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A series of intramolecular nitrone cycloadditions to chiral allyl ethers was studied in order to evaluate the influence on the stereochemical outcome exerted by several factors, including the nature of the substituents at the stereocenter and the steric and electronic features of the double bond. A comparison between the stereoselectivity of these reactions and that of related nitrile oxides cycloadditions suggests that they could proceed via similar transition states.

Nitrone cycloaddition to alkenes is an efficient method of constructing a variety of complex carbon frameworks.[1] In this process the stereochemical information present in the dipolarophile is completely retained in the cycloadduct,

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