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A New Method for the Synthesis of Nonsymmetric Dinucleating Ligands by Aminomethylation of Phenols and Salicylaldehydes[1]

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Monoaminomethylated phenols **5–7** and symmetrically diaminomethylated phenols **8** and **9** were prepared in a one-step procedure from *p*-cresol, formaldehyde, and a variety of secondary amines by making use of the aromatic Mannich reaction. Nonsymmetric diaminomethylated phenols **10** and **11** were prepared by a sequential aromatic Mannich reaction using *p*-cresol, formaldehyde, and two different secondary amines. Alternatively, nonsymmetric diaminomethylated phenols **20–24** were prepared by aminomethylation of 5-methylsalicylaldehyde followed by (a) condensation with a primary amine and subsequent reduction or (b) reductive amination with a secondary amine. Monoaminomethylated and (non)symmetric diaminomethylated phenols are excellent ligands for the synthesis of mono- and dinuclear transition metal complexes as is illustrated by the isolation of mononuclear iron(III) complex **25** and nonsymmetric dinuclear copper(II) complex **26**.

Introduction

Aminomethylated phenols are becoming increasingly important as ligands for both mononuclear as well as dinuclear transition metal complexes. Mononuclear iron complexes with monoaminomethylated phenols as ligands have proven to be excellent mimics for the active site of iron–tyrosinate proteins.[3] On the other hand, diaminomethylated phenols have been used as templates for the formation of dinuclear iron complexes which are active site mimics of enzymes like hemerythrine,[4] methane monooxygenase,[5] or ribonucleotide reductase.[6] Furthermore a number of related dinuclear manganese[7] complexes have recently been reported. In order to mimic hemocyanin and tyrosinase activities, various dinuclear copper complexes based on diaminomethylated phenols were investigated in recent years.[8] Although in many dinuclear metalloenzymes different coordination environments are found for the two metal centers, most of the enzyme mimics reported so far are based on symmetric dinucleating ligands. These ligands generally result in the formation of dinuclear complexes with identical coordination geometries for the two metal centers. However, a limited number of nonsymmetric dinuclear complexes is known to be formed by spontaneous self-assembly in solution.[9]

In our view straightforward and flexible synthetic methodology for the preparation of nonsymmetric dinucleating ligands is highly warranted since these ligands will force the two metal ions in the resulting complex into well defined and tunable but different chemical or coordination environments. This will ultimately result in the formation of more realistic enzyme mimics.

In this paper we present new methodology for the synthesis of nonsymmetric diaminomethylated phenols *via* the aromatic Mannich reaction.[10] Moreover we will show that a variety of mononucleating and symmetrically dinucleating ligands are obtained, *via* this aromatic Mannich reaction, in a one-step procedure from commercially available phenols and synthetically easily accessible secondary amines.

The synthetic routes to diaminomethylated phenols usually involve bishydroxymethylation of a phenol,[11] subsequent substitution of the benzylic hydroxyl group for a chorine using either $SOCl_2$[12] or HCl[8a,13] and finally substitution of the benzylic chloride by an amine[8a,14] yielding the diaminomethylated phenol (Scheme 1, route a).

The sequential aromatic Mannich reaction is a major improvement of this three-step reaction sequence (Scheme 1, route b). Starting from a phenol, both mono- and diaminomethylated phenols are accessible. In the aromatic Mannich reaction a phenol, a secondary amine, and formaldehyde are reacted, usually in an alcohol or an alcohol/water mixture, to provide an aminomethylated phenol in a single step. Formaldehyde can be regarded as a one-carbon donor connecting the phenol and the

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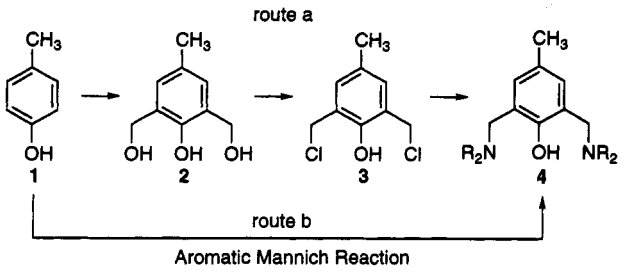
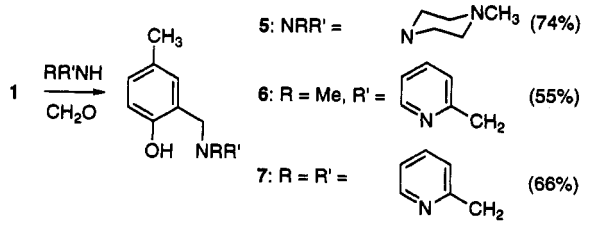
Scheme 1



Scheme 2



secondary amine. We will show that a sequential aromatic Mannich reaction, using two different secondary amines, provides nonsymmetric dinucleating ligands. In this way ligands are created that either have a different number of amine groups or amine groups which are chemically distinct on both sides of the bridging phenol moiety.

An alternative approach comprises the synthesis of monoaminomethylated salicylaldehydes. The aldehyde functional group in these molecules offers two possible pathways for transformation into nonsymmetric dinucleating ligands, i.e. either condensation with a primary amine, followed by reduction, or reductive amination with a secondary amine.

Results and Discussion

Monoaminomethylated and Symmetrically Diaminomethylated Phenols. In order to examine the feasibility to use di- and triamines with two different amine functionalities in the aromatic Mannich reaction, the monoaminomethylation of *p*-cresol was studied. Monoaminomethylated phenols **5–7** (Scheme 2) were prepared by refluxing a mixture of *p*-cresol, the appropriate secondary amine, and paraformaldehyde or formalin solution in MeOH or *i*-PrOH. Although the *p*-cresol/secondary amine/formaldehyde ratio commonly was 1/1/1, in the case of **7** the yield was improved by using an excess of *N*,*N*-bis(2-pyridylmethyl)amine (2 equiv with respect to *p*-cresol). In the case of **7** a water-rich solvent mixture was also used (EtOH/H_2O, 5/12) instead of pure MeOH or *i*-PrOH. The use of water-rich media is known to increase the rate of the aromatic Mannich reaction.[15] The reactions can easily be monitored by TLC using CH_2Cl_2/MeOH/triethylamine or EtOAc/hexane mixtures as eluent. Along with the formation of the monoaminomethylated *p*-cresol, the formation of small amounts of diaminomethylated *p*-cresol is observed. The monoaminomethylated *p*-cresols **5–7** can be isolated relatively easily from the reaction mixture containing small amounts of unreacted *p*-cresol, secondary amine, and diaminomethylated *p*-cresol. The methanol is removed in vacuo and the residue is purified by using column chromatography on silica (CH_2Cl_2/MeOH/triethylamine or EtOAc/hexane).

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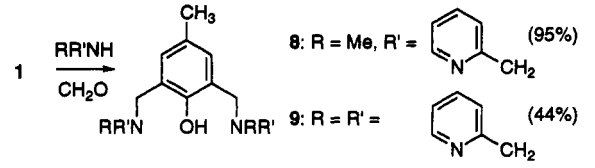
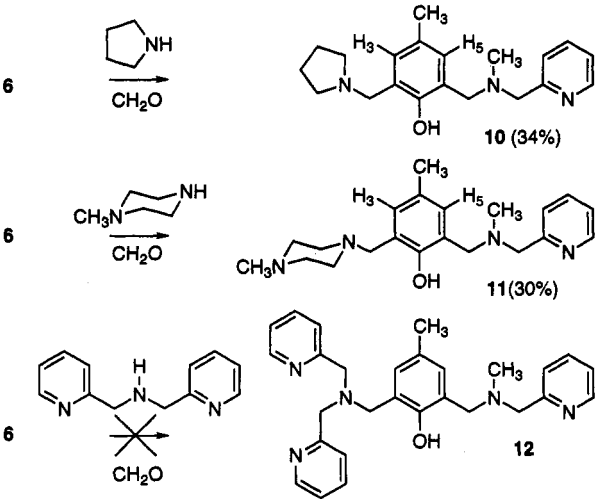
Scheme 3



Scheme 4



Monoaminomethylated phenols **5** and **6** are low-melting solids whereas **7** exists as an oil (see Experimental Section).

The attachment of a secondary amine to *p*-cresol *via* a methylenic carbon atom, which originates from formaldehyde, resulting in the formation of monoaminomethylated *p*-cresols **5–7**, can easily be proven from NMR spectral data. Both the ^1H NMR as well as the ^{13}C NMR spectra are very indicative of the presence of the methylenic CH_2 group in the aminomethylated *p*-cresol. The methylenic H-atoms of **5–7** all give a single resonance in the 3.6–3.8 ppm region. In the ^{13}C NMR spectra the methylenic carbon resonances of **5–7** are in the 56– 63 ppm region.

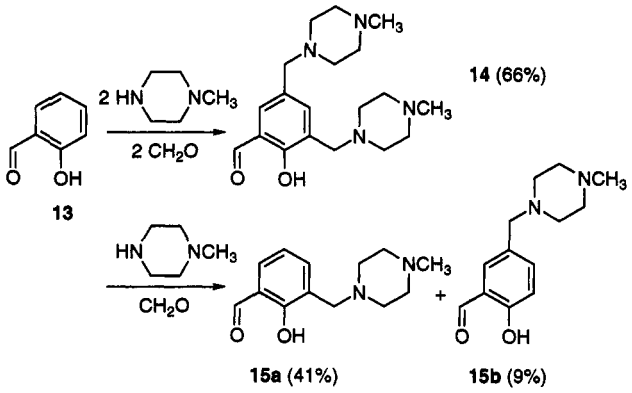
Symmetrically diaminomethylated phenols **8** and **9**,[14b] with two diamine ligating groups and two triamine units respectively (Scheme 3), were obtained by refluxing 1 equiv of *p*-cresol, 3.6 equiv of secondary amine, and 3.6 equiv of formaldehyde (either paraformaldehyde or formaldehyde in water) in ethanol/water mixtures. The reactions could easily be monitored by TLC. Compound **8** was readily purified by column chromatography and was obtained as a viscous oil in excellent yield. Compound **9** was also obtained as a viscous oil after chromatographic separation although some difficulties were encountered in separating **9** from *N*,*N*-bis(2-pyridylmethyl)amine (see Experimental Section).

Nonsymmetric Diaminomethylated Phenols by a Sequential Aromatic Mannich Reaction. Having demonstrated that both monoaminomethylated and symmetrically diaminomethylated phenols with two or three amine-containing chelating units are readily accessible, we turned to the synthesis of nonsymmetric dinucleating ligands.

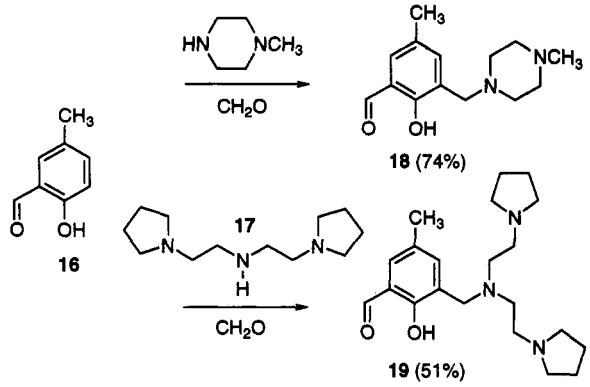
Starting from monoaminomethylated phenol **6** with a free ortho-position, the synthesis of nonsymmetric diaminomethylated phenols via an additional Mannich reaction was examined (Scheme 4).

The Mannich reaction with **6** was performed with pyrrolidine, *N*-methylpiperazine, and *N*,*N*-bis(2-pyridyl-

Scheme 5



Scheme 6



methyl)amine. Nonsymmetric diaminomethylated phenols **10** and **11** could indeed be prepared *via* this route although isolated in rather moderate yields. Both pure **10** and **11** were obtained as viscous oils after chromatographic separation but attempts to crystallize these compounds from ether/hexane mixtures were unsuccessful.

Both the ^{1}H NMR as well as the ^{13}C NMR spectra are very informative with regard to the nonsymmetric nature of these ligands and are very distinct from the NMR spectra of their symmetric analogues. In the ^{1}H NMR spectra two distinct resonances for the H^3 and H^5 aromatic protons were observed. Moreover different resonances for the two sets of protons at the benzylic positions in compounds **10** and **11** are observed. In the ^{13}C NMR spectra the resonances of the various benzylic and the phenyl carbon atoms are also well separated.

Unfortunately, aminomethylation of **6** with *N,N*-bis(2-pyridylmethyl)amine did not yield the desired nonsymmetric ligand **12**. The only product isolated was monoaminomethylated phenol **7**. An explanation for this behavior might be the fact that the aromatic Mannich reaction is a reversible reaction,[10] leading to an exchange of *N*-methyl-*N*-(2-pyridylmethyl)amine for *N,N*-bis(2-pyridylmethyl)amine in **6**. This exchange reaction of secondary amines could also be responsible for the rather moderate yields of **10** and **11**.

Aminomethylation of Salicylaldehydes. In order to improve the flexibility (and yields) in particular with respect to nonsymmetric diaminomethylated phenols containing triamine units, an alternative route, involving the Mannich reaction on salicylaldehydes, was studied. Recently it was shown that aminomethylation of 5-bromosalicylaldehyde was possible without affecting the aldehyde functional group.[16] Encouraged by this finding we expected that aminomethylated salicylaldehydes could easily be condensed with a variety of primary amines affording aminomethylated arylimines which are nonsymmetric dinucleating ligands and precursors to diaminomethylated dinucleating ligands.

In initial experiments it was shown that aminomethylation of salicylaldehyde **13** with two equivalents of 1-methylpiperazine afforded 3,5-diaminomethylated salicylaldehyde **14** (Scheme 5). When 1 equiv of 1-methylpiperazine was used, mixtures of 3- and 5-aminomethylated salicylaldehyde **15a** and **15b** were obtained (Scheme 5). Although the desired 3-aminomethylated salicylaldehyde **15a** could be separated from the 5-aminomethylated salicylaldehyde **15b** by column chromatography, a more selective reaction was required.

To prevent the undesired aminomethylation at the 5-position, an obvious choice is the use of 5-methylsalicylaldehyde (**16**). Aminomethylation of **16** with diamines and triamines is a very facile reaction affording 3-aminomethylated 5-methylsalicylaldehydes in good yields. The aminomethylation of **16** with 1-methylpiperazine to yield **18** and the aminomethylation of **16** with bis[2-(pyrrolidin-1-yl)ethyl]amine (**17**)[17] to afford **19** illustrate this new route (Scheme 6). Both **18** and **19** are precursors for nonsymmetric dinucleating ligands. All monoaminomethylated salicylaldehydes (**15a**, **15b**, **18**, and **19**) are solids and can be crystallized from ether/hexane mixtures.

The conversion of **18** and **19** into nonsymmetric dinucleating ligands can be accomplished in two ways: (a) the aminomethylated salicylaldehydes can be condensed with primary amines affording aminomethylated imines. Subsequently these imines can be reduced to the corresponding amines; (b) alternatively, the aminomethylated salicylaldehydes can be converted to a nonsymmetric dinucleating ligand by reductive amination with a secondary amine.

Condensation of Aminomethylated Salicylaldehydes with Primary Amines. Condensations of **18** (Scheme 7) with the primary amines 2-(aminomethyl)pyridine and bis(2-pyridyl)methylamine proceed readily when the reactions are performed in MeOH yielding the corresponding imines. Upon addition of the primary amine to the aminomethylated aldehyde, an intense yellow color is developed. The conversions can be monitored by TLC and are usually completed within 1 h. It is not necessesary to isolate the imines[18] prior to conversion into amines **20** and **21**. Hydrogenation using H_2, Pd/C or reduction with $NaBH_4$ followed by chromatographic purification affords the corresponding amines **20** and **21**

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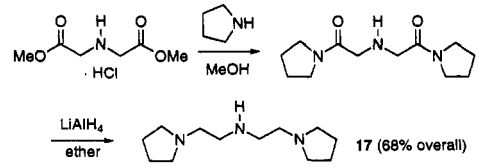
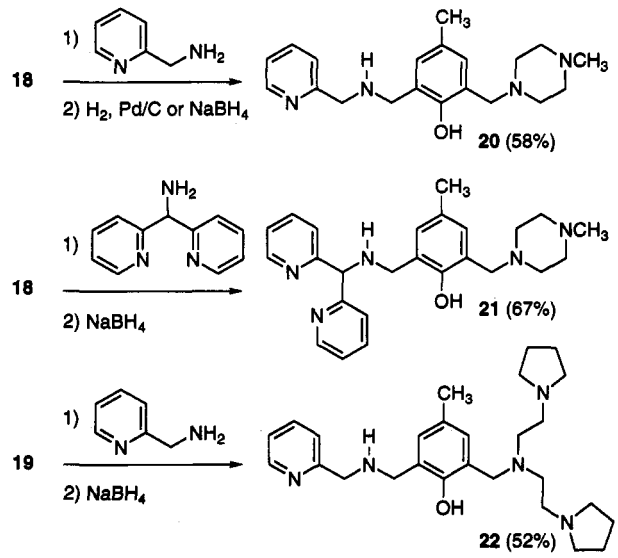
(17) A new synthesis of bis[2-(pyrrolidin-1-yl)ethyl]amine (**17**) was developed.



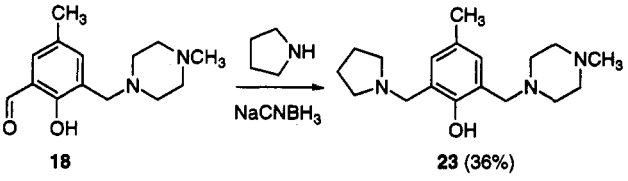
The dimethyl ester of iminoacetic acid was converted into the corresponding dipyrrolidyl diamide by reaction with pyrrolidine. Subsequent reduction of the diamide with $LiAlH_4$ afforded bis[2-(pyrrolidin-1-yl)-ethyl]amine (**17**) in 68% overall yield.

(18) The 2-(aminomethyl)-6-imino-substituted phenols are excellent multidentate ligands themselves; a typical example is shown in Scheme 9.

Scheme 7



Scheme 8

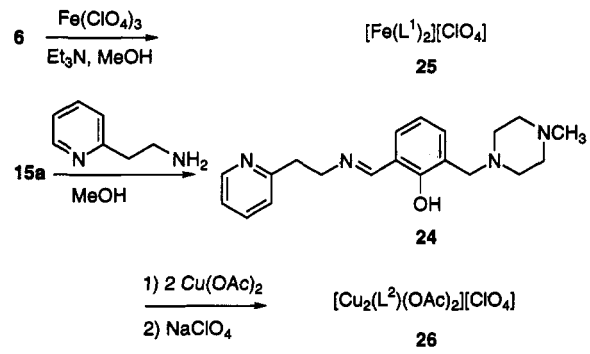


(Scheme 7). In this way both diamine and triamine ligating units can be attached to the monoaminomethylated salicylaldehyde 18 (containing a bisamine ligating unit). The flexibility toward a variety of multidentate ligands is illustrated in Scheme 7. In a reverse sequence starting with monoaminomethylated salicylaldehyde **19**, containing a triamine unit, a diamine unit can be attached. Thus condensation of **19** with 2-(aminomethyl)pyridine followed by $NaBH_4$ reduction of the *in situ* formed imine affords nonsymmetric dinucleating ligand **22**.

Reductive Amination of Aminomethylated Salicylaldehydes. A second route to nonsymmetric diaminomethylated phenols involves reductive amination of 3-aminomethylated salicylaldehydes. A typical example is given in Scheme 8. Aminomethylated salicylaldehyde **18** could be reductively aminated with pyrrolidine in MeOH using $NaCNBH_3$ as the reducing agent affording the nonsymmetric dinucleating ligand **23**. This one-pot procedure allows rapid access to multidentate ligands although yields of this route need to be optimized and the scope with respect to a variety of mono-, di-, and triamines will be examined in due course.

Preparation of a Mononuclear Iron(III) and a Nonsymmetric Dinuclear Copper(II) Complex.[19] As expected several of these new compounds are excellent multidentate ligands for the binding of transition metal ions. Mononuclear iron(III) complex **25** was synthesized by reaction of 2 equiv of monoaminomethylated phenol **6** with 1 equiv of $Fe(ClO_4)_3 \cdot 10\ H_2O$ in methanol in the presence of triethylamine (Scheme 9). Elemental analysis was in accordance with the stoichiometry $[Fe(L^1)_2][ClO_4]$ (L^1 is the phenolate anion of **6**). In addition a dinuclear copper(II) complex based on an *in situ* prepared non-

Scheme 9



symmetric dinucleating ligand was prepared as shown in Scheme 9. Aminomethylated salicylaldehyde **15a** was condensed with 2-(aminoethyl)pyridine in methanol to afford imine **24**. Without isolation 2 equiv of $Cu(OAc)_2 \cdot H_2O$ were directly added to the solution of **24** in methanol to afford the dinuclear copper(II) complex **26** in good yield which was crystallized as its perchlorate salt. Elemental analysis and spectroscopic data were in accordance with the stoichiometry $[Cu_2(L^2)(OAc)_2][ClO_4]$ where L^2 is the phenolate anion of **24**.

Concluding Remarks

The aromatic Mannich reaction has proven to be a very useful tool in the synthesis of monoaminomethylated phenols **5–7** (mononucleating ligands) and symmetrically diaminomethylated phenols **8** and **9** (dinucleating ligands). The aromatic Mannich route is a very short and straightforward approach compared to the usual synthetic strategies for aminomethylated phenols. Yields are good and the reaction is attractive from the point of view of flexibility and atom economy as only water is formed as a byproduct circumventing halogenated intermediates.

A sequential aromatic Mannich reaction on *p*-cresol using two different secondary amines allows the formation of nonsymmetric dinucleating ligands **10** and **11** in moderate yields. These moderate yields are probably caused by the reversibility of the aromatic Mannich reaction. Despite this drawback the route allows rapid access to multidentate ligands to study complexation behavior.

A high yield and synthetically very facile alternative was developed along two lines. Aminomethylation of 5-methylsalicylaldehyde (**16**) with the secondary amines 1-methylpiperazine and bis[2-(pyrrolidin-1-yl)ethyl]amine yields **18** and **19** being precursors for nonsymmetric dinucleating ligands. These can be converted to nonsymmetric dinucleating ligands **20–22** by condensation with primary amines followed by reduction or by reductive amination with secondary amines such as pyrrolidine to yield **23**.

The ligating capability of these new nonsymmetric dinucleating ligands is illustrated by the isolation of iron(III) complex **25** and dicopper(II) complex **26**.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were obtained at 200 MHz. ^{13}C NMR spectra were obtained at 50.32 MHz. The NMR spectra were recorded in $CDCl_3$ unless stated otherwise. Elemental analyses were performed in the Microanalytical Department of this laboratory. Mass spectra (HRMS) were obtained on an AEI-MS-902 mass spectrometer.

(19) The *X*-ray structure of nonsymmetric dicopper(II) complex **26** and details about the nonequivalent coordination of the two copper(II) ions will be published elsewhere.

MeOH and EtOH were distilled from magnesium and stored over 3-Å sieves. CH_2Cl_2, ether, and hexane were distilled from P_2O_5 and stored over 4-Å sieves. Triethylamine was stored over solid KOH. All other reagents and solvents were of commercial grade and used without further purification. *N*-Methyl-*N*-(2-pyridylmethyl)amine,[20] *N,N*-bis(2-pyridylmethyl)amine,[21] bis-(2-pyridyl)methylamine,[22] 5-methylsalicylaldehyde,[23] and dimethyl iminodiacetate hydrochloride[24] were prepared according to literature procedures.

4-Methyl-2-[(4-methylpiperazin-1-yl)methyl]phenol (5). To 1-methylpiperazine (1.01 g, 10.1 mmol) was added paraformaldehyde (0.30 g, 10.0 mmol). After the mixture was stirred for 1 h at 80 °C, *p*-cresol (1.08 g, 10.0 mmol) dissolved in methanol (10 mL) was added. The mixture was refluxed for 20 h. The methanol was evaporated to give a yellow oil which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/triethylamine, 50/5/1) to afford **5** (1.63 g, 74% yield) as a colorless oil. Crystallization from *n*-hexane afforded **5** as white crystals: mp 61.3–62.3 °C; ^{1}H NMR (200 MHz) δ 2.23 (s, 3 H), 2.29 (s, 3 H), 2.54 (br, 8 H), 3.66 (s, 2 H), 6.71 (d, 1 H, *J* = 8.1 Hz), 6.78 (br s, 1 H), 6.96 (dd, 1 H, *J* = 8.1, 2.0 Hz); ^{13}C NMR (50 MHz) δ 20.4 (q), 45.9 (q), 52.5 (t), 54.9 (t), 61.3 (t), 115.7 (d), 120.8 (s), 128.1 (s), 129.2 (d), 155.3 (s); HRMS calcd for $C_{13}H_{20}N_2O$ 220.158, found 220.158. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.97; H, 9.11; N, 12.42.

4-Methyl-2-[[*N*-methyl-*N*-(2-pyridylmethyl)amino]methyl]phenol (6). Following the procedure for **5**, reaction of *N*-methyl-*N*-(2-pyridylmethyl)amine (2.40 g, 19.7 mmol), paraformaldehyde (0.60 g, 20.0 mmol), and *p*-cresol (2.16 g, 20.0 mmol) in *i*-PrOH (10 mL) after a reaction time of 2 d, workup, and chromatography on silica gel (ethyl acetate/hexane, 1/1) afforded **6** (2.54 g, 55% yield) as a slightly yellow oil. Crystallization from ether/hexane afforded **6** as white crystals: mp 52.9–53.5 °C; ^{1}H NMR (200 MHz) δ 2.25 (s, 3 H), 2.32 (s, 3 H), 3.74 (s, 2 H), 3.79 (s, 2 H), 6.77 (d, 1 H, *J* = 8.1 Hz), 6.83 (s, 1 H), 6.99 (dd, 1 H, *J* = 8.1, 1.7 Hz), 7.21 (m, 1 H), 7.36 (d, 1 H, *J* = 8.1 Hz), 7.70 (m, 1 H), 8.59 (m, 1 H), 10.80 (br, 1 H); ^{13}C NMR (50 MHz) δ 20.4 (q), 41.7 (q), 60.7 (t), 62.8 (t), 115.9 (d), 121.7 (s), 122.4 (d), 123.2 (d), 128.1 (s), 129.2 (d), 129.4 (d), 136.8 (d), 149.2 (d), 155.3 (s), 157.4 (s); HRMS calcd for $C_{15}H_{18}N_2O$ 242.142, found 242.142. Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.34; H, 7.56; N, 11.45.

2-[[*N,N*-Bis(2-pyridylmethyl)amino]methyl]-4-methylphenol (7). To *N,N*-bis(2-pyridylmethyl)amine (1.75 g, 8.8 mmol) in EtOH/H_2O (5 mL/12 mL) was added *p*-cresol (0.486 g, 4.5 mmol) and formaline solution (0.7 mL, 37% in H_2O). The two-phase reaction mixture was refluxed for 3 d and allowed to cool to rt. The reaction mixture was partioned between CH_2Cl_2 (100 mL) and H_2O (50 mL), and the H_2O layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to leave a crude oil. Chromatography on silica gel (CH_2Cl_2/MeOH/triethylamine, 95/5/1) afforded **7** (0.954 g, 66% yield) as a slightly yellow oil: ^{1}H NMR (200 MHz) δ 2.23 (s, 3 H), 3.75 (s, 2 H), 3.86 (s, 4 H), 6.82 (d, 1 H, *J* = 8.1 Hz), 6.87 (br s, 1 H), 6.98 (dd, 1 H, *J* = 8.1, 1.8 Hz), 7.14 (m, 2 H), 7.34 (d, 2 H, *J* = 7.7 Hz), 7.61 (ddd, 2 H, *J* = 7.7, 7.7, 1.8 Hz), 8.55 (m, 2 H); ^{13}C NMR (50 MHz) δ 20.4 (q), 57.0 (t), 59.1 (t), 116.2 (d), 122.2 (d), 122.5 (s), 123.2 (d), 127.8 (s), 129.5 (d), 130.7 (d), 136.8 (d), 148.9 (d), 155.1 (s), 158.3 (s); HRMS calcd for $C_{20}H_{21}N_3O$ 319.168, found 319.168.

2,6-Bis[[(*N*-methyl-*N*-(2-pyridylmethyl)amino]methyl]-4-methylphenol (8). Following the procedure for **7**, reaction of *p*-cresol (0.119 g, 1.10 mmol), *N*-methyl-*N*-(2-pyridylmethyl)-amine (0.503 g, 4.12 mmol), and paraformaldehyde (0.126 g, 4.20 mmol) in H_2O/EtOH (5 mL/2 mL) after a reaction time of 3.5 d, workup, and chromatography on silica gel (CH_2Cl_2/MeOH, 19/1) afforded **8** (0.392 g, 95% yield) as a slightly yellow oil: ^{1}H NMR (200 MHz) δ 2.25 (s, 3 H), 2.29 (s, 6 H), 3.71 (s, 4 H), 3.77 (s, 4 H), 6.94 (s, 2 H), 7.16 (m, 2 H), 7.45 (d, *J* = 7.7 Hz, 2 H), 7.66 (m, 2 H), 8.55 (m, 2 H); ^{13}C NMR (50 MHz) δ 20.5 (q), 42.1 (q), 58.6 (t), 63.3 (t), 122.1 (d), 123.1 (s), 123.2 (d), 127.6 (s), 129.4 (d), 136.5 (d), 149.0 (d), 153.7 (s), 158.6 (s); HRMS calcd for $C_{23}H_{28}N_4O$ 376.226, found 376.226.

2,6-Bis[[*N,N*-bis(2-pyridylmethyl)amino]methyl]-4-methylphenol (9). Following the procedure for **7**, reaction of *p*-cresol (0.252 g, 2.33 mmol), *N,N*-bis(2-pyridylmethyl)amine (1.755 g, 8.82 mmol), and paraformaldehyde (0.272 g, 9.07 mmol) in H_2O/EtOH (12 mL/5 mL) after a reaction time of 2.5 d, workup, and three successive column chromatographic separations on silica gel (CH_2Cl_2/MeOH, 19/1; CH_2Cl_2/MeOH, 4/1; CH_2Cl_2/MeOH, 9/1) afforded **9** (0.539 g, 44% yield)[25] as a slightly yellow oil: ^{1}H NMR (200 MHz) δ 2.23 (s, 3 H), 3.78 (s, 4 H), 3.87 (s, 8 H), 6.99 (s, 2 H), 7.10 (m, 4 H), 7.56 (m, 8 H), 8.50 (m, 4 H); ^{13}C NMR (50 MHz) 20.6 (q), 54.8 (t), 59.7 (t), 121.9 (d), 122.9 (d), 123.7 (s), 127.3 (s), 129.7 (d), 136.5 (d), 148.8 (d), 153.6 (s), 159.2 (s).

4-Methyl-2-[[(*N*-methyl-*N*-(2-pyridylmethyl)amino]-methyl]-6-(pyrrolidin-1-ylmethyl)phenol (10). Following the procedure for **5**, reaction of pyrrolidine (0.278 g, 3.92 mmol), paraformaldehyde (0.12 g, 4.0 mmol), and **6** (0.93 g, 3.86 mmol) in *i*-PrOH (10 mL) after a reaction time of 20 h and column chromatography on silica gel (CH_2Cl_2/MeOH, 4/1) afforded **10** (0.43 g, 34% yield) as a colorless oil: ^{1}H NMR (200 MHz) δ 1.82 (m, 4 H), 2.24 (s, 3 H), 2.28 (s, 3 H), 2.63 (m, 4 H), 3.67 (s, 2 H), 3.75 (s, 4 H), 6.85 (d, *J* = 1.8 Hz, 1 H), 6.96 (d, *J* = 1.8 Hz, 1 H), 7.15 (m, 1 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 7.66 (m, 1 H), 8.55 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H); ^{13}C NMR (50 MHz) δ 20.5 (q), 23.6 (t), 42.2 (q), 53.6 (t), 56.7 (t), 57.8 (t), 63.3 (t), 122.0 (d), 122.9 (s), 123.1 (d), 123.3 (s), 127.4 (s), 128.6 (d), 129.4 (d), 136.5 (d), 149.0 (d), 153.8 (s), 158.9 (s); HRMS calcd for $C_{20}H_{27}N_3O$ 325.215, found : 325.215.

4-Methyl-6-[(4-methylpiperazin-1-yl)methyl]-2-[[(*N*-methyl-*N*-(2-pyridylmethyl)amino]methyl]phenol (11). Following the procedure for **7**, reaction of **6** (0.241 g, 1.00 mmol), formaline solution (0.15 mL, 37% in H_2O), and 1-methylpiperazine (0.20 g, 2.0 mmol) in EtOH/H_2O (2 mL/5 mL) after a reaction time of 19 h, workup, and chromatography on silica gel (CH_2Cl_2/MeOH, 9/1) afforded **11** (0.107 g, 30% yield) as a colorless oil: ^{1}H NMR (200 MHz) δ 2.17 (s, 3 H), 2.22 (s, 3 H), 2.24 (s, 3 H), 2.49 (br, 8 H), 3.58 (s, 2 H), 3.62 (s, 2 H), 3.69 (s, 2 H), 6.77 (s, 1 H), 6.90 (s, 1 H), 7.09 (m, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 7.60 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1 H), 8.48 (d, *J* = 4.7 Hz, 1 H), 8.90 (br, 1 H); ^{13}C NMR (50 MHz) δ 20.5 (q), 42.1 (q), 45.8 (q), 52.4 (t), 54.8 (t), 57.8 (t), 59.1 (t), 63.1 (t), 121.6 (s), 122.0 (d), 123.1 (d), 123.3 (s), 127.5 (s), 129.2 (d), 129.6 (d), 136.4 (d), 148.9 (d), 153.8 (s), 158.7 (s); HRMS calcd for $C_{21}H_{30}N_4O$ 354.242, found 354.242.

4,6-Bis[(4-methylpiperazin-1-yl)methyl]-2-formylphenol (14). Following the procedure for **7**, reaction of salicylaldehyde **13** (1.22 g, 10.0 mmol), 1-methylpiperazine (3.60 g, 36.0 mmol), and formaline solution (2.75 mL, 37% in H_2O) in EtOH/H_2O (2 mL/5 mL) after a reaction time of 16 h, workup, and chromatography on silica gel (CH_2Cl_2/MeOH, 4/1) afforded **14** (2.27 g, 66% yield) as a bright yellow oil: ^{1}H NMR (200 MHz) δ 2.20 (s, 3 H), 2.24 (s, 3 H), 2.36 (br, 8 H), 2.53 (br, 8 H), 3.39 (s, 2 H), 3.66 (s, 2 H), 7.21 (d, 1 H, *J* = 1.7 Hz), 7.46 (d, 1H, *J* = 1.7 Hz), 9.80 (br, 1 H), 10.24 (s, 1 H); ^{13}C NMR (50 MHz) δ 45.8 (q), 45.9 (q), 52.4 (t), 52.7 (t), 54.6 (t), 54.9 (t), 59.3 (t), 61.8 (t), 122.1 (s), 123.1 (s), 128.5 (s), 128.9 (d), 136.2 (d), 160.4 (s), 191.3 (d); HRMS calcd for $C_{19}H_{30}N_4O_2$ 346.237, found 346.237.

2-Formyl-6-[(4-methylpiperazin-1-yl)methyl]phenol (15a) and 2-Formyl-4-[(4-methylpiperazin-1-yl)methyl]phenol (15b). Following the procedure for **5**, reaction of 1-methylpiperazine (2.01 g, 20.1 mmol), paraformaldehyde (0.60 g, 20.0 mmol),

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(25) The conversion of *p*-cresol **1** to the diaminomethylated phenol **9** is complete since no *p*-cresol or monoaminomethylated phenol **7** could be observed on TLC. However, the yield is rather low because **9** is difficult to separate from *N,N*-bis(2-pyridylmethyl)amine by column chromatography.

and salicylaldehyde **13** (2.45 g, 20.1 mmol) in methanol (10 mL) after a reaction time of 30 h and column chromatography on silica gel (CH_2Cl_2/MeOH, 9/1) afforded a fraction of pure **15a** (1.21 g, 26% yield), a fraction (0.664 g, 14% yield) consisting of a mixture of **15a** and **15b** (**15a**/**15b**, 7.1/1), and a fraction (0.56 g, 12% yield) consisting of a mixture of of **15a** and **15b** (**15a**/**15b**, 1/3.4). All fractions were solids. Crystallization from hexane/ether gave **15a** as slightly yellow crystals: mp 86.0–87.0 °C; ^{1}H NMR (200 MHz) δ 2.28 (s, 3 H), 2.49–2.61 (br, 8 H), 3.70 (s, 2 H), 6.83 (dd, J = 7.7, 7.7 Hz, 1 H), 7.26 (m, 1 H), 7.60 (dd, J = 7.7, 1.7 Hz, 1 H), 10.30 (s, 1 H), 11.05 (br, 1 H); ^{13}C NMR (50 MHz) δ 45.8 (q), 55.5 (t), 54.8 (t), 59.4 (t), 119.0 (d), 122.7 (s), 123.4 (s), 128.7 (d), 135.3 (d), 161.3 (s), 191.6 (d); HRMS calcd for $C_{13}H_{18}N_2O_2$ 234.137, found 234.137. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.35; H, 7.80; N, 11.70. **15b**: ^{1}H NMR (200 MHz) δ 2.31 (s, 3 H), 2.48 (br, 8 H), 3.47 (s, 2 H), 6.94 (d, J = 9.0 Hz, 1 H), 7.46–7.51 (m, 2 H), 9.88 (s, 1 H); ^{13}C NMR (50 MHz) δ 45.9 (q), 52.8 (t), 55.0 (t), 61.8 (t), 117.5 (d), 120.3 (s), 129.8 (s), 133.9 (d), 138.0 (d), 160.8 (s), 196.5 (d); HRMS calcd for $C_{13}H_{18}N_2O_2$ 234.137, found 234.137.

Bis[2-(pyrrolidin-1-yl)ethyl]amine (17). To dimethyl iminodiacetate hydrochloride (5.11 g, 25.9 mmol) in methanol (100 mL) was added pyrrolidine (8.52 g, 120 mmol). After the mixture was refluxed for 2 d, the methanol was removed in vacuo. The residue was taken up in CH_2Cl_2/2 N KOH solution (100 mL/50 mL) and the layers were separated. The KOH layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to yield the crude amide (7.84 g) as a dark red oil. To this oil was added Et_2O (100 mL) and $LiAlH_4$ (5.00 g, 132 mmol). After the mixture was refluxed for 3 h, H_2O (15 mL) was added carefully in portions. The mixture was stirred for 1 h, dried over Na_2SO_4, and evaporated to leave a yellow oil. The oil was purified by bulb-to-bulb distillation (110 °C, 0.02 mmHg) (lit.[26] 145–146 °C, 12 mmHg) to afford **17** (3.74 g, 68% yield) as a colorless oil: ^{1}H NMR (200 MHz) δ 1.76 (m, 8 H), 2.36 (br, 1 H), 2.50 (m, 8 H), 2.60 (m, 4 H), 2.75 (m, 4 H); ^{13}C NMR (50 MHz) δ 23.4 (t), 48.6 (t), 54.2 (t), 55.9 (t).

2-Formyl-4-methyl-6-[(4-methylpiperazin-1-yl)methyl]-phenol (18). Following the procedure for **5**, reaction of 1-methylpiperazine (1.478 g, 14.78 mmol), paraformaldehyde (0.440 g, 14.66 mmol), and 5-methylsalicylaldehyde (1.99 g, 14.63 mmol) in methanol (10 mL) after a reaction time of 20 h and column chromatography on silica gel (ethyl acetate/hexane, 1/1) followed by (CH_2Cl_2/MeOH, 9/1) afforded **18** (2.701 g, 74% yield) as a yellow solid. Recrystallization from hexane/ether gave **18** as colorless crystals: mp 82.9–84.4 °C; ^{1}H NMR (200 MHz) δ 2.16 (s, 3 H), 2.21 (s, 3 H), 2.46 (br, 8 H), 3.59 (s, 2 H), 7.02 (d, 1 H, J = 1.7 Hz), 7.30 (d, 1 H, J = 1.7 Hz), 10.18 (s, 1 H), 10.25 (s, 1 H); ^{13}C NMR (50 MHz) δ 20.2 (q), 45.7 (q), 52.4 (t), 54.7 (t), 59.3 (t), 122.2 (s), 123.2 (s), 128.1 (s), 128.3 (d), 136.4 (d), 159.1 (s), 191.5 (d); HRMS calcd for $C_{14}H_{20}N_2O_2$ 248.152, found: 248.153. Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.32; H, 8.15; N, 11.15.

2-[[Bis[2-(pyrrolidin-1-yl)ethyl]amino]methyl]-6-formyl-4-methylphenol (19). Following the procedure for **7**, reaction of 5-methylsalicylaldehyde (0.323 g, 2.38 mmol), paraformaldehyde (97 mg, 3.17 mmol), and **17** (0.452 g, 2.14 mmol) in methanol (10 mL) after a reaction time of 26 h and chromatography on silica gel (CH_2Cl_2/MeOH/triethylamine, 32/8/1) afforded **19** (0.388 g, 51% yield) as a yellow oil. Crystallization from hexane/ether gave **19** as slightly yellow crystals: mp 49.2–50.4 °C; ^{1}H NMR (200 MHz) δ 1.77 (m, 8 H), 2.22 (s, 3 H), 2.57 (m, 8 H), 2.70 (s, 8 H), 3.60 (s, 2 H), 7.08 (d, 1 H, J = 2 Hz), 7.39 (d, 1 H, J = 2 Hz), 9.66 (br, 1 H), 10.33 (s, 1H); ^{13}C NMR (50 MHz) δ 20.2 (q), 23.3 (t), 51.8 (t), 53.1 (t), 53.9 (t), 54.2 (t), 122.8 (s), 125.3 (s), 127.5 (s), 127.8 (d), 137.4 (d), 159.8 (s), 192.0 (d); HRMS calcd for $C_{21}H_{33}N_3O_2$ 359.257, found: 359.257. Anal. Calcd for $C_{21}H_{33}N_3O_2$: C, 70.16; H, 9.25; N, 11.69. Found: C, 70.07; H, 9.05; N, 11.39.

4-Methyl-2-[(4-methylpiperazin-1-yl)methyl]-6-[[*N*-(2-pyridylmethyl)amino]methyl]phenol (20). To **18** (0.497 g, 2.00 mmol) in methanol (10 mL) was added 2-(aminomethyl)-pyridine (0.250 g, 2.32 mmol). After stirring for a few minutes a catalytic amount of Pd–C was added and the reaction mixture was hydrogenated in a Parr apparatus at 30 psi for 16 h. After filtration of the catalyst, methanol was evaporated and a slightly yellow oil was obtained. Chromatography on silica gel (CH_2Cl_2/MeOH, 9/1) afforded **20** (0.394 g, 58% yield) as a colorless oil: ^{1}H NMR (200 MHz) δ 2.18 (s, 3 H), 2.26 (s, 3 H), 2.48 (br, 8 H), 3.61 (s, 2 H), 3.82 (s, 2 H), 3.91 (s, 2 H), 6.71 (s, 1 H), 6.90 (s, 1 H), 7.11 (m, 1 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.61 (ddd, J = 7.7, 7.7, 1.7 Hz, 1 H), 8.50 (m, 1 H); ^{13}C NMR (50 MHz) δ 20.4 (q), 45.8 (q), 49.2 (t), 52.4 (t), 54.3 (t), 54.8 (t), 60.6 (t), 120.9 (s), 121.9 (d), 122.3 (d), 125.3 (s), 127.7 (s), 128.6 (d), 129.5 (d), 136.5 (d), 149.1 (d), 153.6 (s), 159.4 (s); HRMS calcd for $C_{20}H_{28}N_4O$ 340.226, found: 340.226.

4-Methyl-2-[(4-methylpiperazin-1-yl)methyl]-6-[[*N*-[bis-(2-pyridyl)methyl]amino]methyl]phenol (21). To **18** (0.602 g, 2.42 mmol) in methanol (10 mL) was added bis(2-pyridyl)-methylamine (0.452 g, 2.44 mmol). After stirring for 1.5 d at rt $NaBH_4$ (0.382 g, 10.1 mmol) was added in small portions. After stirring for 2 h at rt the reaction mixture was acidified to pH 1–2 using a 2 N HCl solution and stirred for another 0.5 h. After the solution was brought to pH 7–8 using a 2 N KOH solution, the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried over Na_2SO_4 and evaporated to leave a dark yellow oil. The oil was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 9/1) to afford **21** (0.674 g, 67% yield) as a colorless oil: ^{1}H NMR (200 MHz) δ 2.19 (s, 3 H), 2.31 (s, 3 H), 2.57 (br, 8 H), 3.64 (s, 2 H), 3.79 (s, 2 H), 5.15 (s, 1 H), 6.73 (d, J = 1.7 Hz, 1 H), 6.90 (d, J = 1.7 Hz, 1 H), 7.12 (m, 2 H), 7.47 (d, J = 7.7 Hz, 2 H), 7.62 (ddd, J = 7.7, 7.7, 1.7 Hz, 2 H), 8.55 (d, J = 4.3 Hz, 2 H); ^{13}C NMR (50 MHz) δ 20.4 (q), 45.6 (q), 47.8 (t), 52.1 (t), 54.6 (t), 60.2 (t), 68.8 (d), 120.6 (s), 122.2 (d), 122.4 (d), 125.5 (s), 127.7 (s), 128.7 (d), 129.5 (d), 136.6 (d), 149.3 (d), 153.7 (s), 161.2 (s); HRMS calcd for $C_{25}H_{31}N_5O$ 417.253, found: 417.253.

2-[[Bis[2-(pyrrolidin-1-yl)ethyl]amino]methyl]-6-[[*N*-(2-pyridylmethyl)amino]methyl]-4-methylphenol (22). To **19** (0.159 g, 0.433 mmol) in methanol (5 mL) was added 2-(aminomethyl)pyridine (49.8 mg, 0.461 mmol). After stirring for 1 h at rt, $NaBH_4$ (49.3 mg, 1.30 mmol) was added in small portions. Using the workup procedure for **21** followed by chromatography on silica gel (CH_2Cl_2/MeOH/triethylamine, 75/25/1), **22** (0.102 g, 52% yield) was obtained as a colorless oil: ^{1}H NMR (200 MHz) δ 1.87 (m, 8 H), 2.18 (s, 3 H), 2.86 (m, 16 H), 3.58 (s, 2 H), 3.90 (s, 2 H), 3.92 (s, 2 H), 6.81 (s, 2 H), 7.02 (br, 4 H), 7.16 (m, 1 H), 7.29 (d, J = 7.7 Hz, 1 H), 7.63 (ddd, J = 7.7, 7.7, 1.8 Hz, 1 H), 8.49 (m, 1 H); ^{13}C NMR (50 MHz) δ 20.3 (q), 23.2 (t), 45.9 (t), 50.5 (t), 51.0 (t), 53.2 (t), 53.9 (t), 122.3 (d), 122.5 (d), 122.8 (s), 123.4 (s), 127.6 (s), 129.6 (d), 130.4 (d), 136.7 (d), 149.2 (d), 154.1 (s), 157.7 (s).

4-Methyl-2-[(4-methylpiperazin-1-yl)methyl]-6-[(pyrrolidin-1-yl)methyl]phenol (23). To **18** (0.246 g, 0.992 mmol) in methanol (5 mL) was added pyrrolidine (0.077 g, 1.09 mmol), NaOAc (0.165 g, 2.01 mmol), and $NaBH_3CN$ (0.13 g, 2.06 mmol). The reaction mixture was stirred for 18 h at rt. Using the workup procedure of **21** followed by chromatography on silica gel (CH_2Cl_2/MeOH, 9/1), **23** (0.109 g, 36% yield) was obtained as a colorless oil: ^{1}H NMR (200 MHz) δ 2.08 (m, 4 H), 2.24 (s, 3 H), 2.62 (br, 8 H), 3.25 (m, 4 H), 3.70 (s, 2 H), 4.14 (s, 2 H), 6.87 (d, J = 1.7 Hz, 1 H), 7.05 (d, J = 1.7 Hz, 1 H), 7.52 (br, 2 H); ^{13}C NMR (50 MHz) δ 20.3 (q), 23.1 (t), 45.5 (q), 52.1 (t), 53.3 (t), 53.5 (t), 54.5 (t), 60.6 (t), 116.4 (s), 121.3 (s), 128.9 (s), 131.3 (d), 131.4 (d), 154.3 (s); HRMS calcd for $C_{18}H_{29}N_3O$ 303.231, found 303.231.

$[Fe(L^1)_2][ClO_4]$ (25). To **6** (0.234 g, 0.967 mmol) in MeOH (5 mL) was added Et_3N (0.105 g, 1.04 mmol) and $Fe(ClO_4)_3 \cdot 10\ H_2O$ (0.257 g, 0.481 mmol) dissolved in MeOH (2 mL). After stirring for 1.5 h at rt, the MeOH was removed in vacuo. The resulting oil was redissolved in MeOH (1.5 mL) and this solution was placed in an ethyl acetate bath. After 1 d the formed crystals were collected and washed with ethyl acetate to afford **25** (0.188 g, 61% yield) as dark purple crystals. Anal. Calcd for $C_{30}H_{34}ClFeN_4O_6$: C, 56.49; H, 5.37; N, 8.78. Found: C, 56.42; H, 5.41; N, 8.89.

(26) Marxer, A. *Helv. Chim. Acta* **1954**, *19*, 166.

$[Cu_2(L^2)(OAc)_2][ClO_4]$ (26). To **15a** (0.236 g, 1.01 mmol) in MeOH (50 mL) was added 2-(aminoethyl)pyridine (0.123 g, 1.01 mmol). After stirring for 1 h at rt $Cu(OAc)_2 \cdot H_2O$ (0.40 g, 2.00 mmol) was added. After the mixture was refluxed for 1.5 h, $NaClO_4 \cdot H_2O$ (0.200 g, 1.42 mmol) was added and the mixture was refluxed for another 0.5 h. The reaction mixture was filtered and the MeOH was removed in vacuo. A small amount of EtOH was added to the residue. The mixture was boiled for 5 min and filtered to afford **26** (0.43 g, 62% yield). Slow crystallization from CH_2Cl_2/EtOH afforded dark green crystals. Anal. Calcd for $C_{24}H_{31}ClCu_2N_4O_9$: C, 42.26; H, 4.58; Cu, 18.63, N, 8.21. Found: C, 41.47; H, 4.66; Cu, 18.81, N, 8.10.

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Supplementary Material Available: Copies of ^1H NMR spectra of all new compounds (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.