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Synthesis of Unsymmetrical Dinucleating Ligands Bearing Nitrogen and Oxygen Donor Atoms

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Abstract: The synthesis of unsymmetrical dinucleating ligands bearing nitrogen and oxygen donor atoms is described. The Schiff-base condensation of functionalised salicylaldehyde derivatives with primary amines gave rise to unsymmetrical unsaturated ligands, whereas condensation with secondary amines followed by *in situ* reduction of the iminium species with sodium borohydride, led to the formation of unsymmetrical saturated ligands. The latter were also prepared by tandem Mannich reactions of 4-chlororesorcinol. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

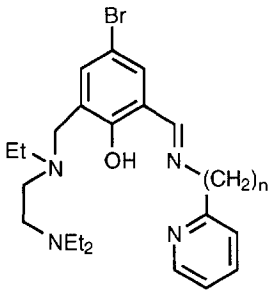
Dinucleating ligands, which can bind two metal ions within their perimeter, have been synthesised for their potential application as models of dinuclear metallobiosites.[2,3] In the majority of such ligands the donor sets that these systems present to each metal ion are identical. In dinuclear transition-metal biosites, however, the metal ions are found in chemically or geometrically distinct environments. For example, the unsymmetrical nature of the dicopper site in haemocyanin was demonstrated by the X-ray structure of deoxyhaemocyanin[4] and sequence homology studies on tyrosinases have shown that the copper sites are not always identical.[5] This observation led to the suggestion that unsymmetrical dinucleating ligands should be suitable targets for modelling studies.[3] It has recently been noted, however, that such polydentate systems which could give rise to asymmetric dinuclear complexes are still rare.[6]

The majority of symmetrical dinucleating ligands, derived from 2,6-diformylphenols by Schiff-base condensation with primary amines, readily form dinuclear transition-metal complexes that can co-ordinate either one or two exogenous bridging groups.[7-10] The formation of such dimetallic species is enforced by the ideal distance between the donor sets and the endogenous bridge provided by the phenolate group. It is anticipated that non-symmetrical substitution of salicylaldehydes would give rise to unsymmetrical ligands which may serve as first generation models for the unsymmetrical site purported to exist in tyrosinase.[5] The phenolate oxygen atom may be regarded as providing a suppositional model for one oxygen atom of the anticipated dioxygen interaction by maintaining the copper atoms at an appropriate distance apart. At this juncture these ligands and their complexes are considered to be unique and so the study of their properties could shed some light on the likely behaviour of the two copper atoms held in close proximity in dissimilar environments.

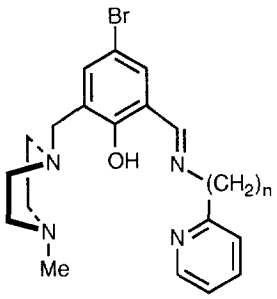
In a previous report[11] the introduction of a single pendant arm into 5-bromosalicylaldehyde by the Mannich reaction and subsequent condensation of the Mannich bases with primary amines afforded unsymmetrical dinucleating Schiff-base ligands, which were complexed *in situ* with copper (II) salts. This gave rise, for example to dinucleating ligands **HL[1]** - **HL[4]**, having one donor set comprised of saturated nitrogen atoms with the second donor set comprised of unsaturated nitrogen atoms. A similar synthetic route was later employed by Lubben and Feringa[12] in which unsymmetrical Schiff-base ligands, derived from 5-methylsalicylaldehyde, were reduced *in situ* to the corresponding secondary amines. They also reported the formation of unsymmetrical dinucleating ligands, possessing only nitrogen donor atoms, by sequential Mannich reactions of *p*-cresol with two different secondary amines in rather moderate yields.

It is envisaged that unsymmetrical dinucleating ligands should give more realistic models for the active sites of enzymes if the two metal ions in the resulting complex are forced into different chemical and co-ordination

environments. As part of a program we presented a preliminary report describing the design and synthesis of unsymmetrical dinucleating ligands containing both nitrogen and oxygen donor atoms.[13] The present paper provides a full account of our new methodology for the synthesis, isolation and characterisation of a series of compartmental ligands in which the donor sets of the adjacent compartments vary considerably. On complexing these ligands with copper(II) information can be retrieved on the nature of the interaction with the metal and on the optimum ligand(s) required for the efficient synthesis of homodinuclear complexes.



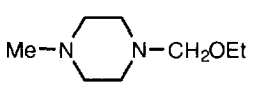
HL[1], n = 1; **HL**[2], n = 2



HL[3], n = 1; **HL**[4], n = 2

RESULTS AND DISCUSSION

As an extension to previous work[11] our aim was to synthesise unsymmetrical dinucleating ligands from the functionalised Mannich bases of salicylaldehyde derivatives. Earlier experience in the development of new methodologies for the Mannich reaction suggested that it would be more profitable to prepare Mannich bases under non-aqueous aprotic conditions.[14-17] Our synthetic strategy required the preparation of suitable Mannich reagents with residual nitrogen or oxygen atoms which could act as donor atoms in the target ligands. Therefore, the aminol ethers **1**, **2** and **3** were prepared in good yields, by condensation of the appropriate secondary amine with paraformaldehyde and ethanol in the presence of potassium carbonate. Similarly the oxazolidines **4** and **5** were obtained in excellent yield from the corresponding ethanolamine derivative and paraformaldehyde.



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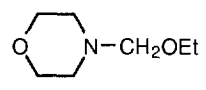

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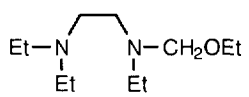

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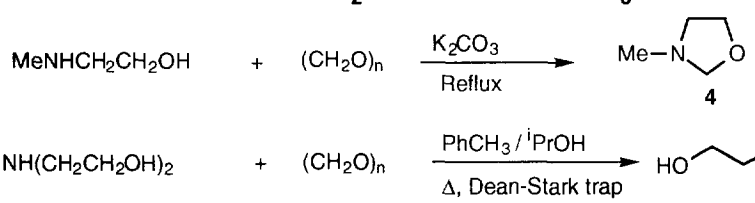
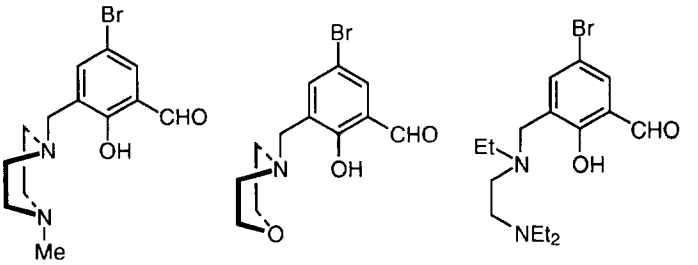


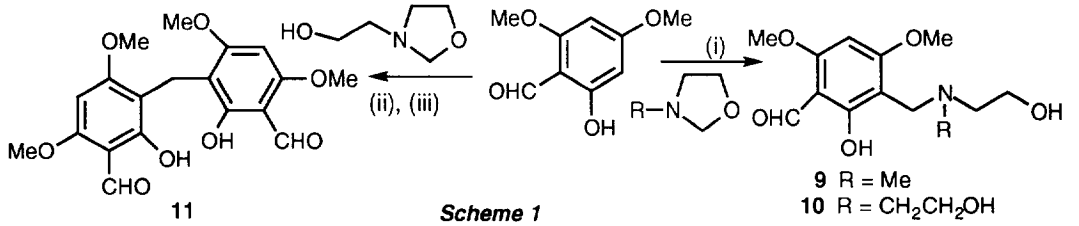
In order to examine the new methodology[18] we began the investigation by the reaction of 5-bromosalicylaldehyde with the preformed aminol ethers **1**, **2**, and **3** in dried acetonitrile under reflux. The functionalised Mannich bases **6**, **7**, and **8** respectively were obtained, as crystalline solids in high yields, which was a considerable improvement compared to the classical method reported previously[11]. It was then considered worthy of investigation the introduction of aminoethanolic moieties at the 3-position of 5-bromosalicylaldehyde which could provide a new type of a pendant side arm. Some reactions of oxazolidines with aromatic substrates including nucleophilic phenols have been reported.[19] A series of attempts, however, to react the oxazolidines **4** and **5** with 5-bromosalicylaldehyde proved fruitless even in the presence of a variety of Lewis acids such as $TiCl_4$, $ZnCl_2$, and $AlCl_3$. Generation of the iminium salts beforehand, by treatment of the oxazolidines with

chlorotrimethylsilane or methyltrichlorosilane, followed by reaction with 5-bromosalicylaldehyde was also unsuccessful. This suggests that the iminium species involved are weaker electrophiles than the *N,N*-dialkyl analogues, generated from aminol ethers, possibly due to hydroxy Schiff-base-oxazolidine tautomerism.[20] In addition the low nucleophilicity of 5-bromosalicylaldehyde towards oxazolidines can be attributed to electron withdrawing effect of the bromide and formyl groups.



6 **7** **8**

Due to the apparent inertness of 5-bromosalicylaldehyde towards oxazolidines a more nucleophilic salicylaldehyde was sought. Rather surprisingly 5-methoxysalicylaldehyde showed very little or no reactivity towards oxazolidines. 4,6-Dimethoxysalicylaldehyde, possessing two extra electron donating substituents, proved to be more reactive towards the oxazolidines **4** and **5** and the corresponding Mannich bases **9** and **10** were isolated, as crystalline solids, in moderate yields. In the effort to increase the yield of these reactions the activation of the phenolic functionality with sulphur dioxide[18] did not exhibit a substantial improvement. Furthermore, the formation of iminium trifluoroacetates,[21] before the addition of 4,6-dimethoxysalicylaldehyde showed no significant advantage. In fact the presence of trifluoroacetic acid in the reaction mixtures caused cleavage of the aminoethanolic moiety resulting in the capture of the methylenequinonium intermediate by another molecule of the phenolic derivative. This led to the formation the diaryl methane **11** in variable amounts which may have caused some reduction in the yields of the desired products. This by-product was exclusively isolated in a reaction when an excess of trifluoroacetic acid was used, as depicted in ***Scheme 1***. Deamination of Mannich bases is not unprecedented; deamination of β-aminoketones in suitably modified conditions has been employed by Danishefsky's group[22] for the synthesis of tumour inhibiting agents. Furthermore, in a kinetic study[23] of the hydrolysis of labile quaternary ammonium salts of *para*-aminomethylphenols, it was found that the intermediate methylenequinones react with water forming hydroxymethylphenols.

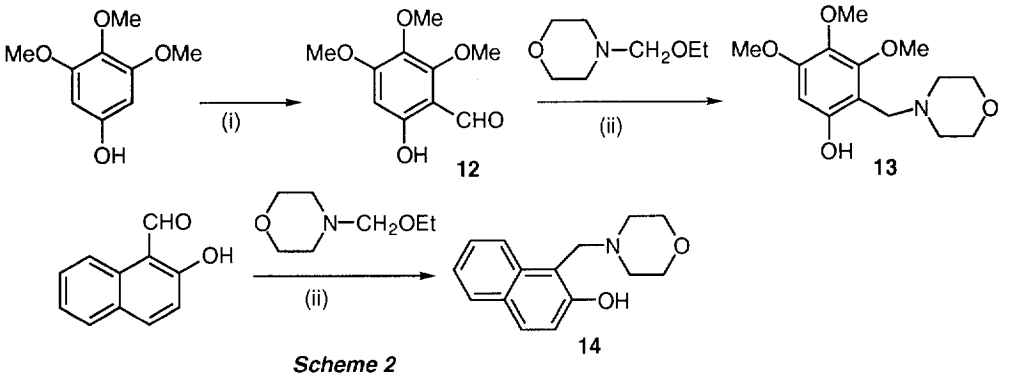


Scheme 1

(i) MeCN, Reflux, N_2; (ii) SO_2, MeCN, RT; (iii) CF_3CO_2OH, Reflux

An investigation of the suitability of more reactive salicylaldehydes towards the Mannich reagents was also undertaken. It was anticipated that antiarolaldehyde **12**, having three electron-donating groups, would be a more reactive substrate and it was therefore prepared by Vilsmeier formylation of 3,4,5-trimethoxyphenol.[24] It is of interest to note, however, that deformylation of the salicylaldehyde derivative and isolation of the Mannich base **13** took place when antiarolaldehyde **12** and ethoxy-*N*-morpholinylmethane **2** were heated in acetonitrile under reflux. Deformylation also occurred in the reaction of 2-hydroxy-1-naphthaldehyde with the aminol ether **2** under the same conditions, affording the Mannich base **14**, as shown in ***Scheme 2***. Although deformylation of

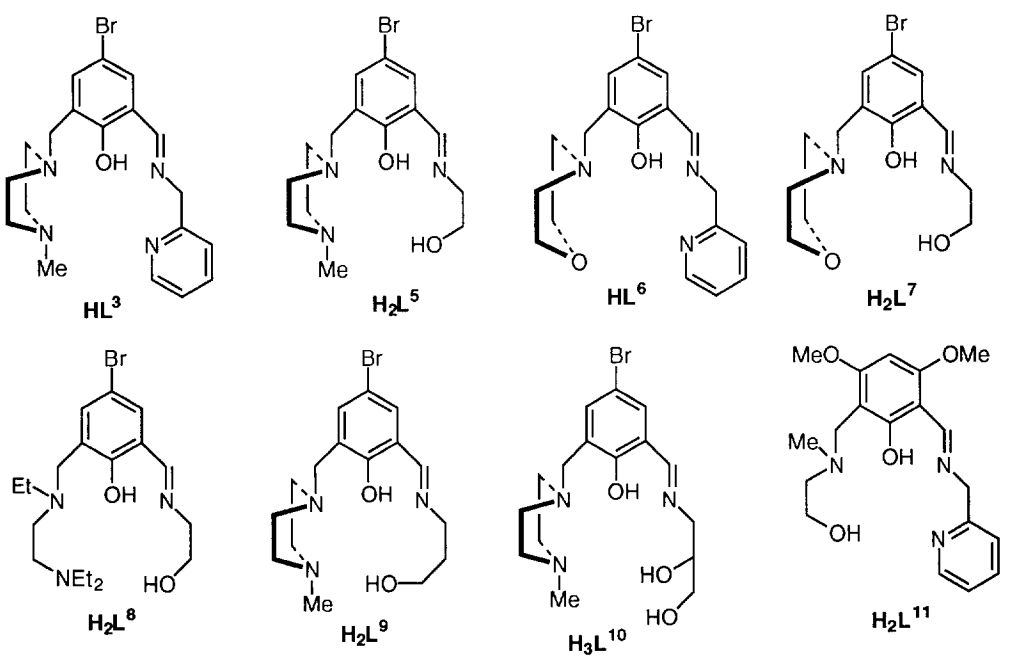
trialkyl- and trialkoxybenzaldehydes is reported to take place in 50% sulphuric acid[25] it was rather unexpected to observe this phenomenon in such mild conditions.

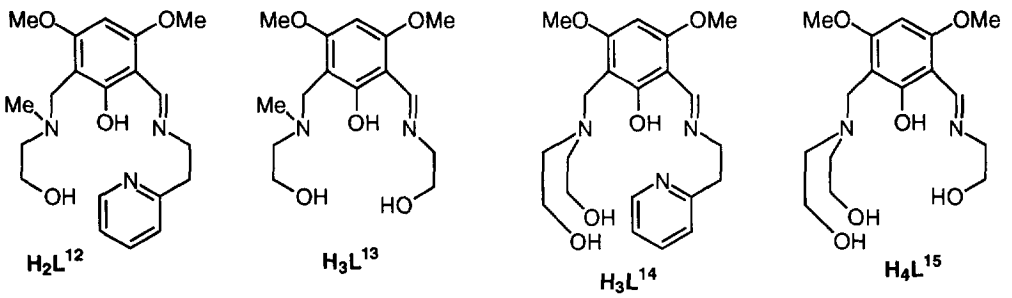


Scheme 2

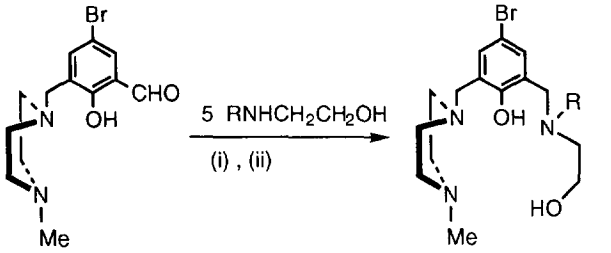
(i) *N*-methylformanilide, $POCl_3$, 1,2-dichloroethane, Reflux; (ii) MeCN, N_2, Reflux

The functionalised Mannich bases, bearing a formyl group, were successfully converted to the corresponding Schiff bases by condensation with a variety of primary amines. This gave rise to a series of unsymmetrical unsaturated ligands, bearing both nitrogen and oxygen atoms, as shown below, which were isolated in high yields and characterised by spectroscopic and analytical means. It was established that such transformations can be best achieved by heating the Mannich base and a primary amine in a mixture of toluene and ethanol under Dean-Stark conditions. It was found that the products must be handled under non-aqueous conditions during work-up. A number of ligands were isolated as crystalline solids and the X-Ray crystal structure of $\mathbf{H_2L^5}$ has been solved.[13] The isolation in high yield of unsymmetrical ligand $\mathbf{HL^3}$, bearing only nitrogen donor atoms, demonstrated the advantage of the new methodology over the traditional approach reported previously.[11,12]





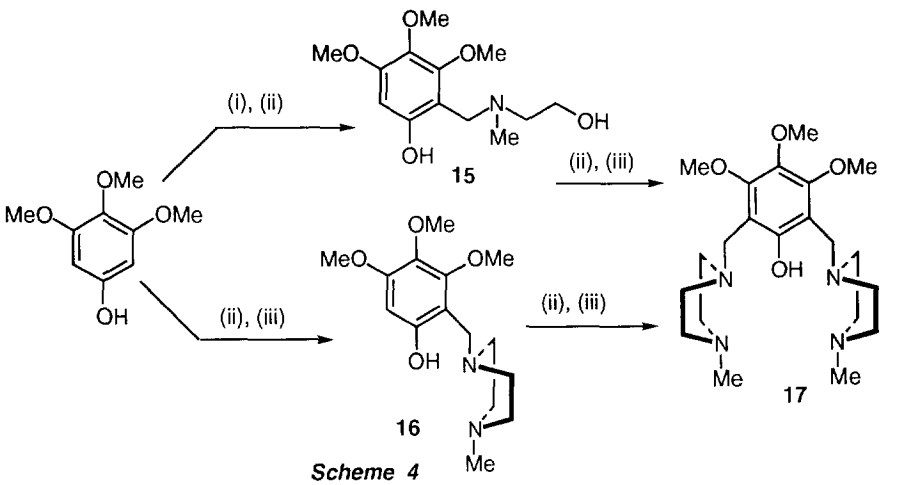
As it was not possible to introduce aminoethanolic residues on the 5-bromosalicylaldehyde ring via a direct Mannich reaction, due to its weak nucleophilicity, the formyl substituent was employed as an electrophile. Thus, condensation of the Mannich base **6** with a large excess of *N*-methylethanolamine or diethanolamine, followed by *in situ* reduction of the resulting iminium species with sodium borohydride, gave access to unsymmetrical saturated ligands, H_2L^{16} and H_3L^{17}, which were isolated as crystalline white solids in high yields, ***Scheme 3***. These fully saturated compounds could serve as an additional type of ligand having both pendant side arms free from the locking in position exhibited by the double bond in the unsaturated analogues.



Scheme 3

(i) $PhCH_3$ / EtOH, Reflux, N_2 , Dean-Stark trap; (ii) $NaBH_4$, N_2

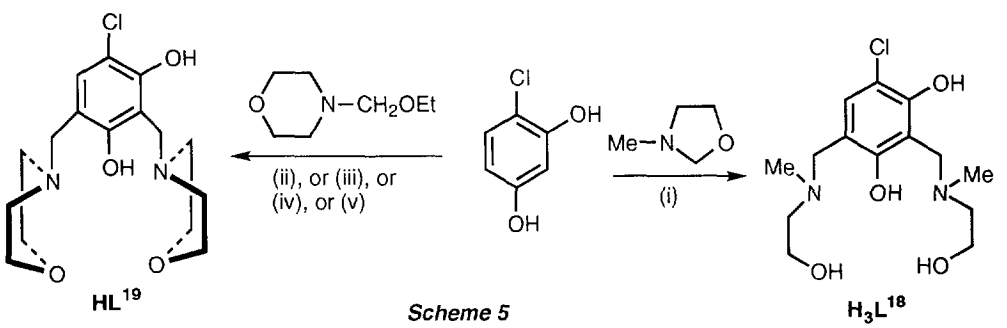
In the effort to synthesise more saturated unsymmetrical ligands we turned our attention to the tandem Mannich reactions of strongly nucleophilic phenols. Although *N*-methyloxazolidine **4** and 3,4,5-trimethoxyphenol gave the Mannich base **15** in excellent yield, further aminoalkylation at the free position did not take place in the presence of a large excess of *N*-methyloxazolidine **4** under prolonged heating in acetonitrile. The monoaminoalkylated phenol **16**, obtained by stoichiometric reaction of aminol ether **1**, produced the fully substituted phenol **17** when an excess of the Mannich reagent was used. However, when the Mannich base **15** was allowed to react with the aminol ether **1**, the symmetrical ligand **17** was isolated as depicted in ***Scheme 4***. An amine exchange took place indicating that deaminomethylation,[26] (a *retro* Mannich reaction) had taken place. Deaminomethylation of Mannich bases is important because it determines their stability in acidic conditions. It has also been linked to *trans*-aminomethylation which has pharmacological interest in some amidic Mannich bases which may yield useful pro-drugs.[27] In the alternative approach the monoalkylated phenol **16** failed to react with an excess of *N*-methyloxazolidine **4** preventing, therefore, the sequential introduction of different aminoalkyl residues into 3,4,5-trimethoxyphenol.



Scheme 4

(i) compound (**4**) [5 mol equiv.]; (ii) MeCN, N_2, Reflux; (iii) compound (**1**)

As the tandem aminoalkylation of 3,4,5-trimethoxyphenol was not feasible, due to *retro* Mannich reaction, it was considered worthy to investigate the suitability of 4-chlororesorcinol in these reactions. Treatment of 4-chlororesorcinol with an excess of two mole equivalents of *N*-methyloxazolidine **4** in acetonitrile at room temperature led to the formation of the saturated ligand $\mathbf{H_3L}$[18] in high yield. It can therefore be concluded that the apparent reactivity of 4-chlororesorcinol towards the oxazolidine **4** can neither be due to increased nucleophilicity of the substrate nor due to steric relief but due to the fact that the second aminoalkylation takes place on position-2, *ortho* to both hydroxy groups. A quasi six-membered hydrogen-bonded transition state has been suggested as a plausible mechanism for the preferred *ortho* aminoalkylation of phenols.[28] Furthermore it has been indicated that the *ortho* substitution of phenols may be comparable to Claisen rearrangement of allyl ethers, rather than a normal electrophilic substitution.[29] In addition, 4-chlororesorcinol under the same conditions reacted with the aminol ether **2** forming the saturated ligand $\mathbf{HL}$[19] as a white crystalline solid. Stoichiometric amounts of the latter reaction at lower temperature and shorter reaction time failed to intercept the reaction preventing the isolation of the monosubstituted 4-chlororesorcinol, as shown in ***Scheme 5***.



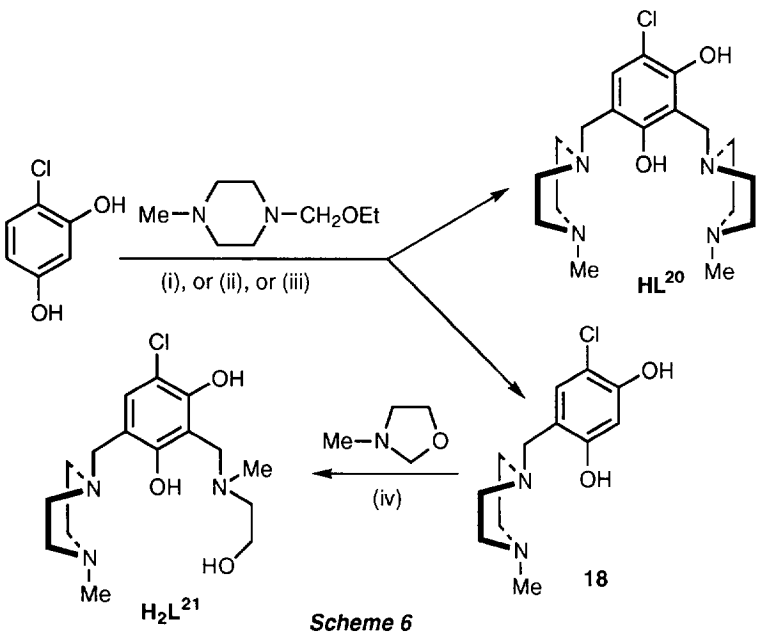
$\mathbf{HL}$[19] ***Scheme 5*** $\mathbf{H_3L}$[18]

(i) 2.5 mol equiv., MeCN, RT, N_2, 24h, 90%; (ii) 2.5 mol equiv., MeCN, RT, N_2, 16h , 90 %; (iii) 1 mol. equiv., MeCN, RT, N_2, 48h, 52%; (iv) 1 mol. equiv., MeCN, -10 °C to RT, N_2, 4h, 50%; (v) 1 mol. equiv., CH_2Cl_2, -78 °C, N_2, 2h, 63%

As expected from the above results, 4-chlororesorcinol when treated with more than two mole equivalents of the aminol ether **1** at room temperature also formed the saturated ligand $\mathbf{HL}$[20] in good yield. However, when equimolar amounts of reagents were used, at room temperature over 16 hours, both the monosubstituted base **18**

and the ligand **HL^{20}** were isolated in reasonable yields. The Mannich base **18** was exclusively formed when the latter reaction was performed at -15 to -5 °C for only 1 h. This compound proved to be a useful intermediate for our synthetic strategy, since its reaction with an excess of *N*-methyloxazolidine **4**, afforded the formation of the saturated ligand **H$_2$L^{21}**, ***Scheme 6*** in good yield. More importantly it was shown that tandem Mannich reactions could be carried out on an appropriately substituted substrate by employing two different Mannich reagents. Therefore, this methodology resulted in the preparation of an additional type of saturated dinucleating ligand possessing two different pendant side arms. Despite the fact that the saturated ligands **H$_3$L^{18}**, **HL^{19}**, and **HL^{20}** possess identical pendant side arms at the 2- and 6- positions, ^{1}H and ^{13}C nmr spectroscopic data indicate that they occupied distinct chemical environments and hence can be considered as unsymmetrical.

Although the complexation of unsymmetrical ligands is beyond the scope of this paper it is of interest to note that we have recently reported[30] that the ligand **H$_2$L^7** on treatment with copper (II) chloride formed the dinuclear complex $[Cu_2L^7]Cl_2$, but in the presence of copper (II) perchlorate hexahydrate gave only the mononuclear complex, $[Cu(H_2L^7)][ClO_4]_2{\cdot}H_2O{\cdot}MeOH$, whose X-ray crystal structure has been solved.



Scheme 6

(i) 2.2 mol. equiv., MeCN, RT, 44 h, **HL^{20}** (66%); (ii) 1 mol. equiv., MeCN, RT, 16 h, **HL^{20}** (49%); and **18** (34%); 1 mol. equiv., MeCN, -15 to -5 °C, 1 h, **18** (57%); (iv) 2.5 mol equiv., MeCN, RT, 48 h (49%)

ACKNOWLEDGEMENTS

We thank the SERC and the Royal Society for support.

EXPERIMENTAL

Solvents were dried by conventional methods and solutions of products were dried over anhydrous magnesium sulphate. Elemental analyses were carried out by the University of Sheffield Microanalytical Service. Infrared spectra were recorded on a Perkin-Elmer 1710 IR Fourier-transform spectrophotometer. ^{1}H Nmr spectra (250 MHz) and ^{13}C nmr spectra (62.9 MHz) were recorded on Bruker AM-250 spectrometer and referenced to residual solvent peak. *J* -Values are given in Hz. Electron impact (EI) and chemical impact (CI, ammonia) mass spectra were recorded using a Kratos MS 25 spectrometer and positive-ion fast atom

bombardment (FAB) mass spectra were recorded on a Kratos MS 80 spectrometer using a 3-nitrobenzyl alcohol (noba) matrix. Melting Points were recorded using a Kofler hot stage apparatus and are uncorrected. Ethoxy-*N*-morpholinylmethane **2**, 4-bromo-2-formyl-6-(morpholin-4-ylmethyl)phenol **7**, and 4-bromo-2-(2-hydroxyethyl-iminomethyl)-6-(morpholin-4-ylmethyl)phenol $\mathbf{H_2L^7}$ were prepared as we reported recently.[30] The ^1H and ^{13}C nmr data of ligand $\mathbf{H_2L^7}$ were recorded[30] incorrectly and the corrected assignments are reported in the experimental section. 1-Methyl-1,3-oxazolidine **4** was obtained in 93% yield by heating *N*-methylethanolamine, paraformaldehyde, and potassium carbonate in the absence of a solvent by an improved published procedure.[31]

Ethoxy-(4-methylpiperazin-1-yl)methane, 1

N-Methylpiperazine (45.8g, 0.67 mol) was added dropwise to a suspension of paraformaldehyde (20.3g, 0.67 mol) and anhydrous potassium carbonate (138.21g, 1 mol) in ethanol (350 ml) at 0°C. The mixture was then stirred vigorously at room temperature with an overhead mechanical stirrer for 67 h. The solid was filtered, washed with dried ether (2 x 50 ml) and the filtrate was then concentrated *in vacuo* to a brown oil and fractionally distilled. First fraction was the *title compound* (57.10g, 80%), b.p. 52 °C / 0.95 mm Hg; δ_H ($CDCl_3$) 1.10 (3H, t, *J* 6.2, OCH_2CH_3), 2.20 (3H, s, NMe), 2.25-2.50 (4H, m, $N[CH_2]_2$), 2.50-2.70 (4H, m, $N[CH_2]_2$), 3.42 (2H, q, *J* 6.2, OCH_2CH_3), and 3.95 (2H, s, NCH_2O); δ_C ($CDCl_3$) 15.14 (OCH_2CH_3), 46.00 (NCH_3), 49.29 (C-3 and C-5) 54.99 (C-2 and C-6), 64.19 (OCH_2CH_3), and 88.09 (NCH_2O); m/z (EI) 158 (M^+, 22%), 129 (21), 113 ($[MeN(CH_2CH_2)_2NCH_2]^+$, 82%), 70 (100), M^+ measured 158.1397; $C_8H_{18}N_2O$; requires 158.1419. Second fraction *bis-(4-methylpiperazin-1-yl)methane* (5.46g, 9%), b.p. 94 °C / 0.85 mm Hg; δ_H ($CDCl_3$) 2.12 (6H, s, 2xNMe), 2.64 (16H, m, $2x[CH_2CH_2]_2$), and 2.85 (2H, s, NCH_2); δ_C ($CDCl_3$) 45.99 ($2xNCH_3$), 51.29 (2xC-3 and C-5), 55.01 (2xC-2 and C-6), and 80.75 (NCH_2); m/z (EI) 212 (M^+, 0.25%), 113 ($[MeN(CH_2CH_2)_2NCH_2]^+$, 100%), 70 (85).

Ethoxy-(2-N,N-diethylaminoethyl)-N´-ethylaminomethane, 3

N,N,N´-Triethyl-1,2-diaminoethane (28.85g, 0.2 mol), paraformaldehyde (12.01g, 0.4 mol) and anhydrous potassium carbonate (55.22g, 0.4 mol) in ethanol (100 ml) were treated as described for compound (**1**) affording the *title compound* (28.35g, 70%), b.p. 47 °C / 0.4 mm Hg; δ_H ($CDCl_3$) 1.02 (6H, t, *J* 7.5, $2xCH_2CH_3$), 1.11 (3H, t, *J* 7.5, CH_2CH_3), 1.18 (3H, t, *J* 7.5, OCH_2CH_3), 2.51 (4H, q, *J* 7.5, $2xCH_2CH_3$), 2.54 (2H, q, *J* 7.5, CH_2CH_3), 2.75 (2H, t, *J* 7.5, NCH_2) 2.78 (2H, t, *J* 7.5, NCH_2), 3.50 (2H, q, *J* 7.5, OCH_2CH_3), and 4.19 (2H, s, NCH_2O); δ_C ($CDCl_3$) 11.67 ($2xCH_2CH_3$), 13.28 (CH_2CH_3), 15.21 (OCH_2CH_3), 46.06 (CH_3CH_2N), 47.34 ($2xCH_3CH_2N$), 49.61 (NCH_2), 51.51(NCH_2), 63.06 (OCH_2), and 85.11 (NCH_2O),; m/z (EI), 202 (M^+, not detected), 173 ($Et_2NCH_2CH_2N(Et)CH_2O^+$, 5%), M^+ measured 173.1658; $C_9H_{21}N_2O$ requires 173.1638; 157 ($Et_2NCH_2CH_2N(Et)CH_2^+$, 9%), M^+ measured 157.1690; $C_9H_{21}N_2$ requires 157.1705, 86 (100).

3-(2-Hydroxyethyl)-1,3-oxazolidine , 5

A solution of diethanolamine (210.28g, 2 mol) in isopropanol (400 ml) was added to a suspension of paraformaldehyde (60.06g, 2 mol) in toluene (400 ml) and the mixture was then heated under reflux for 18 h using a Dean-Stark trap. The solvents were removed by distillation and the residue was fractionally distilled under reduced pressure to give the *title compound* as a colourless oil (218.8g, 93%), b.p. 62-67 °C / 0.3 mm Hg; ν_{max} (film)/cm^{-1} 3404 (OH), 2941, 2880, 1355, 1308, 1158, 1056, 1011, 893; δ_H ($CDCl_3$) 2.72 (2H, t, *J* 7.5, 4-H_2), 3.15 (2H, t, *J* 7.5, NCH_2), 3.66 (2H, t, *J* 7.5, 5-H_2), 3.81 (2H, t, *J* 7.5, OCH_2), 3.51-4.00 (1H, br. s, D_2O ex. OH), and 4.33 (2H, s, 2-H_2); δ_C ($CDCl_3$) 52.22 (C-4), 56.31 (NCH_2), 60.58 (C-5), 63.13 ($HOCH_2$), and 86.13 (C-2); m/z (EI) 117 (M^+, 5%), 86 (100), (CI) 118 (M+ H^+, 100%), 86 (37).

Preparation of Mannich Bases— General Method (A)

The phenolic derivative and the Mannich reagent in acetonitrile were heated under reflux in a nitrogen atmosphere for a specified length of time. The solvent was removed *in vacuo* and the residue dissolved in diethyl ether and washed with 2M HCl, water, dried and concentrated *in vacuo* to give in some cases the

unreacted phenolic derivative. The acid phase was then basified to pH 9 by careful addition of $NaHCO_3$ and washed with dichloromethane. The combined dichloromethane layers were washed with water, dried and concentrated *in vacuo* to give the Mannich base.

4-Bromo-2-formyl-6-(4-methylpiperazin-1-ylmethyl)phenol, 6

5-Bromosalicylaldehyde (30.46g, 0.15 mol) and ethoxy-(4-methylpiperazin-1-yl)methane (**1**) (25.32g, 0.16 mol) in acetonitrile (300 ml) were treated for 16 h as described in General Method (A) to give unreacted 5-bromosalicylaldehyde (2.62g, 9%) and the *title compound* as pale yellow crystals (40.68g, 87%), m.p. 83-84 °C (from *n*-hexane), (lit.,[11] m.p. 83-84 °C).

4-Bromo-2-[(2-diethylaminoethyl)ethylaminomethyl]-6-formylphenol, 8

5-Bromosalicylaldehyde (2.01g, 10 mol) and ethoxy-(2-*N,N*-diethylaminoethyl-*N'*-ethylamino)methane (**2**) (2.23g, 11 mmol) in acetonitrile (60 ml) were treated for 20 h as described in General Method (A) affording unreacted 5-bromosalicylaldehyde (0.20g, 10%) and the *title compound* as large yellow crystals (2.90g, 81%), m.p. 82-84 °C (from *n*-hexane), (lit.,[11] m.p. 81-82 °C).

3,5-Dimethoxy-2-formyl-6-[(2-hydroxyethyl)methylaminomethyl]phenol, 9

4,6-Dimethoxysalicylaldehyde (3.64g, 20 mmol) and 3-methyl-1,3-oxazolidine (**4**) (1.92g, 22 mmol) in acetonitrile (80 ml) were treated for 48 h as described in General Method (A) to give unreacted 4,6-dimethoxy-salicylaldehyde (1.16g, 32%) and the *title compound* as a brown crystalline solid (3.50g, 65%), m.p. 96-98 °C; (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 3215 (OH), 1670 (CHO), 1617 (aromatic ring), 1273, 1216, 1118, 996, 837, 782; δ_H ($CDCl_3$) 2.27 (3H, s, NMe), 2.66 (2H, t, *J* 7.5, NCH_2), 3.57 (2H, s, $ArCH_2$), 3.68 (2H, t, *J* 7.5, CH_2 OH), 3.91 (3H, s, OMe), 3.93 (3H, s, OMe), 5.98 (1H, s, 4-H), and 10.15 (1H, s, CHO); δ_C ($CDCl_3$) 42.03 (NCH_3), 46.97 (NCH_2), 55.72 (OCH_3), 55.87 (OCH_3), 58.35 ($ArCH_2$), 58.50 (CH_2OH), 85.84 (C-4), 105.61 (C-6), 105.73 (C-2), 163.57 (C-1), 163.90 (C-3), 166.46 (C-5), and 192.02 (CHO); m/z (EI) 269 (M^+, 0.7%), 238 (16), 195 (100); (CI) 270 ($M+H^+$, 21%), 238 (13), 195 (100).

2-[(Bis-2-hydroxyethyl)aminomethyl)]-3,5-dimethoxy-6-formylphenol, 10

4,6-Dimethoxysalicylaldehyde (3.64g, 20 mmol) and 3-(2-hydroxyethyl)-1,3-oxazolidine (**5**) (3.51g, 30 mmol) in acetonitrile (80 ml) were treated for 48 h as described in General Method (A) giving unreacted 4,6-dimethoxysalicylaldehyde (1.94g, 53%) and the *title compound* as a light brown crystalline solid (2.40g, 40%), m.p. 123-124 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 3424 (OH), 2954, 2816, 1634 (CHO), 1617 (aromatic ring) 1308, 1214, 1118, 789; δ_H ($CDCl_3$) 2.72 (4H, t, *J* 7.5, 2xNCH_2), 3.63 (4H, t, *J* 7.5, 2xCH_2 OH), 3.69 (2H, s, $ArCH_2$), 3.93 (3H, s, OMe), 3.96 (3H, s, OMe), 6.00 (1H, s, 4-H), and 10.15 (1H, s, CHO); δ_C ($CDCl_3$) 44.49 ($ArCH_2$) 55.51 (2xNCH_2), 55.76 (OCH_3), 56.00 (OCH_3), 59.01 (2xCH_2OH), 86.11 (C-4), 105.64 (C-6), 105.86 (C-2), 163.39 (C-1), 163.95 (C-3), 166.20 (C-5), and 192.23 (CHO); m/z (EI) 299 (M^+, not detected), 268 (19%), 195 (100); (CI) 300 ($M+H^+$, 7.5%), 268 (3), 195 (38) 106 (100).

Reaction of 4,6-Dimethoxysalicylaldehyde and 3-(2-Hydroxyethyl)-1,3-oxazolidine (**5**) *in the Presence of Sulphur Dioxide and an Excess of Trifluoroacetic Acid*

4,6-Dimethoxysalicylaldehyde (3.64g, 20 mmol) in acetonitrile (50 ml) was treated with a 20% solution of sulphur dioxide in acetonitrile (5 ml, 22.4 mmol) and the mixture was allowed to stand at room temperature for 1h. In a separate flask 3-(2-hydroxyethyl)-1,3-oxazolidine (**5**) (2.93g, 25 mmol) in acetonitrile (50 ml) was treated with trifluoroacetic acid (5.70g, 50 mmol, 3.85 ml) and the mixture was stirred at room temperature for 30 minutes before the 4, 6-dimethoxysalicylaldehyde solution was added. The resulted mixture was treated for 48 h as described in General Method (A) to give bis-*(4,6-dimethoxy-3-formyl-2-hydroxyphenyl)methane* (**11**) as a pale yellow solid (3.14g, 83%); m.p. 218-220 °C (from ethanol); δ_H ($CDCl_3$) 3.81 (2H, s, $ArCH_2Ar$), 3.84 (6H, s, 2xOMe), 3.87 (6H, s, 2xOMe), 5.89 (2H, s, 5-H and 5'-H), 10.13 (2H, s, 2xCHO), and 12.50 (2H, s, 2xOH); δ_C ($CDCl_3$) 14.92 (Ar*C* H_2Ar), 55.51 (2xOCH_3), 55.76 (2xOCH_3), 85.72 (C-5 and C-5'), 105.71 (C-

3 and C-3′), 108.49 (C-1 and C-1′), 162.51 (C-2 and C-2′), 162.89 (C-4 and C-4′), 165.97 (C-6 and C-6′), and 191.91 (2xCHO); m/z (EI) 376 (M^+, 31%), 343 (17), 195 (100), (CI) 376 (M^+, 20%), 344(5), 195 (100).

Reaction of Antiarolaldehyde (**12**) *with ethoxy-N-morpholinylmethane* (**2**)

Antiarolaldehyde (1.06g, 5 mmol) and ethoxy-*N*-morpholinylmethane (**2**) (0.80g, 5.5 mol) in acetonitrile (80 ml) were treated for 18 h as described in General Method (A) to give *2-(N-morpholinylmethyl)-3,4,5-trimethoxyphenol* (**13**) as white crystals (0.75g, 53%), m.p. 74-76 °C (from diethyl ether). Found: C, 59.28; H, 7.53; N, 4.88. $C_{14}H_{21}NO_5$ requires C, 59.35; H, 7.47; N, 4.94%; ν_{max} (KBr)/cm^{-1} 3427 (OH), 2969, 2849, 1616 (aromatic ring), 1503, 1391, 1297, 1198, 1116, 1082, 1038, 910, 854; δ_H ($CDCl_3$) 2.35-2.70 (4H, m, $N[CH_2]_2$), 3.72 (2H, s, $ArCH_2$), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 3.81 (3H, s, OMe), 3.62-3.82 (4H, m, $O[CH_2]_2$), and 6.22 (1H, s, 6-H); δ_C ($CDCl_3$) 52.90 (C-3′and C-5′), 54.56 ($ArCH_2$), 55.80 (OCH_3), 61.07 (2xOCH_3), 66.82 (C-2′ and C-6′), 96.29 (C-6), 105.51 (C-2), 135.06 (C-4), 151.82 (C-3), 153.46 (C-1), and 154.17 (C-5); m/z (EI) 283 (M^+, 60%), 268 (15), 196 (100), 181(36), 153 (24), M^+ measured 283.1428; $C_{14}H_{21}NO_5$ requires 283.1420.

Reaction of 2-Hydroxy-1-naphthaldehyde with Ethoxy-N-morpholinylmethane (**2**)

2-Hydroxy-1-naphthaldehyde (3.44g, 20 mmol) and ethoxy-*N*-morpholinylmethane (**2**) (3.19g, 22 mmol) in acetonitrile (100 ml) were treated for 16 h as described in General Method (A) affording *1-(N-morpholinylmethyl)-2-naphthol* (**14**) as a white solid (3.02g, 62%), m.p. 108-110 °C (from ethanol). Found: C, 73.81; H, 7.02; N, 5.71. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%; ν_{max} (KBr) 3410 (OH), 2971, 2849, 1622 (aromatic ring), 1586, 1522, 1415, 1361, 1323, 1268, 1231, 1164, 1115, 989, 901, 867, 813, 740; δ_H ($CDCl_3$) 2.52-2.82 (4H, m, $N[CH_2]_2$), 3.67-3.92 (4H, m, $O[CH_2]_2$), 4.17 (2H, s, $ArCH_2$), 7.10 (1H, d, *J* 9.3, 4-H), 7.25-7.37 (1H, m, 6-H), 7.39-7.51 (1H, m, 7-H), 7.70 (1H, d, *J* 9.3, 5-H), 7.77 (1H, d, *J* 9.3, 8-H), and 7.84 (1H, d, *J* 9.3, 3-H); δ_C ($CDCl_3$) 53.14 (C-3′ and C-5′), 56.74 ($ArCH_2$), 66.81 (C-2′ and C-6′), 110.38 (C-1), 119.08 (C-3), 121.00 (C-6), 122.61 (C-8), 126.48 (C-7), 128.62 (C-4a), 128.94 (C-5), 129.45 (C-4), 132.74 (C-8a), and 156.19 (C-2); m/z (EI) 243 (M^+, 100%), 157 (50), 128 (98) 86 (60), M^+ measured 243.1252; $C_{15}H_{17}NO_2$ requires 243.1259.

2-[(2-Hydroxyethyl)methylaminomethyl)]-3,4,5-trimethoxyphenol, ***15***

3,4,5-Trimethoxyphenol (1.93g, 10.5 mmol) and 3-methyl-1,3-oxazolidine (**4**) (0.87g, 0.87 mmol) in acetonitrile (50 ml) were treated for 3.5 h as described in General Method (A) giving unreacted 3,4,5-trimethoxyphenol (0.43g, 22%) and the *title compound* as a brown viscous oil (1.76g, 65%) which was converted to the hydrochloride salt and recrystallised from acetone-ethyl acetate to a white solid (1.90g, 95%), m.p. 134-136 °C; ν_{max} (KBr)/cm^{-1} 3146 (OH), 1608 (aromatic ring), 1473, 1418, 1353, 1246, 1200, 1132, 1881, 1012, 824; δ_H (D_2O) 2.79 (3H, s, NMe), 3.32 (2H, t, NCH_2), 3.74 (3H, s, OMe), 3.79 (3H, s, OMe), 3.91 (3H, s, OMe), 3.94 (2H, t, CH_2OH), 4.33 (2H, s, $ArCH_2$), and 6.38 (1H, s, 6-H); δ_C (D_2O) 40.23 (NCH_3), 50.03 (NCH_2), 55.37 ($ArCH_2$), 55.93 (4-OCH_3), 57.28 (CH_2OH), 61.10 (5-OCH_3), 61.43 (3-OCH_3), 92.82 (C-6), 101.86 (C-2), 134.20 (C-4), 152.46 (C-5), 152.60 (C-3), and 155.16 (C-1); m/z (FAB) 272 (M^++1, 37%), 197 (100), (EI) 271 (M^+, 19%), 197 (72), 44 (100), (CI) 272 (M+H^+, 81%), 197 (100).

2-(4-Methylpiperazin-1-ylmethyl)-3,4,5-trimethoxyphenol, ***16***

3, 4, 5-Trimethoxyphenol (1.93g, 10.5 mmol) and ethoxy-(4-methylpiperazin-1-yl)methane (**1**) (1.58g, 10 mmol) in acetonitrile (80 ml) were treated for 20 h as described in General Method (A) giving unreacted 3,4,5-trimethoxyphenol (0.20g, 10%) and the *title compound* as a brown viscous oil (2.55g, 86%) which was converted to the dihydrochloride salt and recrystallised from ethanol to a white solid (2.80g, 79%), m.p. 198-204 °C; ν_{max} (KBr)/cm^{-1} 3395, 3126, 2992, 2542, 2441, 1610, 1364, 1238, 1195, 1133, 1094, 987, 947; δ_H (D_2O) 3.03 (3H, s, NMe), 3.18-3.70 (8H, m, $[CH_2CH_2]_2$), 3.70 (3H, s, OMe), 3.79 (3H, s, OMe), 3.93 (3H, s, OMe), 4.39 (2H, s, $ArCH_2$), and 6.39 (1H, s, 6-H); δ_C (D_2O) 42.87 (NCH_3), 48.08 (C-3′ and C-5′), 49.99 (C-2′ and C-6′) 50.24 ($ArCH_2$), 55.14 (4-OCH_3), 61.14 (5-OCH_3), 61.46 (3-OCH_3), 95.77 (C-6), 101.26 (C-

2), 134.11 (C-4), 152.70 (C-5), 153.05 (C-3), and 155.67 (C-1); m/z (EI) 296 (M^+, 9%), 196 (23), 100 (38), 58 (100).

2,6-Bis-(4-methylpiperazin-1-ylmethyl)-3,4,5-trimethoxyphenol, 17

3,4,5-Trimethoxyphenol (0.92g, 5 mmol) and ethoxy-(4-methylpiperazin-1-yl)methane (**1**) (3.16g, 20 mmol) in acetonitrile (100 ml) were treated for 20 h as described in General Method (A) to give the *title compound* as a brown viscous oil (2.04g, 100%) which was converted to the tetrahydrochloride salt and recrystallised from ethyl acetate-methanol to a white solid (1.80g, 65%), m.p. 222-224 °C; ν_{max} (KBr)/cm^{-1} 3410, 3001, 2637, 2438, 1654, 1591, 1197, 1123, 1066, 1016, 976, 896; δ_H (D_2O) 3.00 (6H, s, 2xNMe), 3.12-3.87 (16H, m, 2x[CH_2CH_2]$_2$), 3.87 (3H, s, OMe), 3.96 (6H, s, 2xOMe), and 4.48 (4H, s, 2x$ArCH_2$); δ_C (D_2O) 42.85 (2xNCH_3), 48.41 (2x[C-3′and C-5′]), 50.21 (2x[C-2′ and C-6′]), 50.51 (2x$ArCH_2$), 61.16 (4-OCH_3), 61.56 (3-OCH_3 and 5-OCH_3), 106.94 (C-2 and C-6), 139.10 (C-4), 152.27 (C-1) and 155.42 (C-3 and C-5); m/z (FAB) 409 (M^++1, 13%), 309 (28), 209 (100).

Reaction of 2-[(2-Hydroxyethyl)methylaminomethyl)]-3,4,5-trimethoxyphenol (**15**) *with Ethoxy-(4-methylpiperazin-1-yl)methane* (**1**)

2-(2-Hydroxyethyl-*N*-methylaminomethyl)-3,4,5-trimethoxyphenol (**9**) (1.20g, 4.4 mmol) and ethoxy-(4-methylpiperazin-1-yl)methane (**1**) (1.90g, 12.0 mmol) in acetonitrile (50 ml) were treated for 73 h as described in General Method (A) to give *2,6-bis-(4-methylpiperazin-1-ylmethyl)-3,4,5-trimethoxyphenol* (**12**) (1.55g, 86%). The product was converted to the tetrahydrochloride salt (1.60g, 76%), m.p. 222-224°C (from ethanol), identical to the material prepared above.

Preparation of Schiff Base Ligands from Mannich Bases – General Method (B)

A solution of the Mannich base in toluene or ethanol was treated with the appropriate primary amine in ethanol or toluene and the mixture was heated under reflux using a Dean-Stark trap to remove the water formed as an azeotropic mixture of ethanol-toluene-water. After cooling to room temperature the solvents were removed *in vacuo* and the residue was dissolved diethyl ether, dried and concentrated *in vacuo* to give either a yellow solid or an oil which, upon trituration in some cases, gave also crystalline products.

4-Bromo-2-(4-methylpiperazin-1-ylmethyl)-6-(2-pyridylmethyliminomethyl)phenol, ***HL^3***

4-Bromo-2-formyl-6-(4-methylpiperazin-1-ylmethyl)phenol (**6**) (1.57g, 5 mmol) in ethanol (50 ml) and 2-aminomethylpyridine (0.60g, 5.5 mmol) in toluene (50 ml) were treated for 2.5 h as described in General Method (B) affording the *title compound* as a yellow-brown viscous oil (186g, 92%); δ_H ($CDCl_3$) 2.30 (3H, s, NMe), 2.37-2.67 (8H, m, [CH_2CH_2]$_2$), 3.60 (2H, s, $ArCH_2$), 4.92 (2H, s, CH_2Py), 7.15-7.23 (1H, m, 5′-H), 7.35 (1H, d, *J* 3.12, 3′-H), 7.40 (1H, d, *J* 3.12, 5-H), 7.47 (1H, d, *J* 3.12, 3-H), 7.65-7.72 (1H, m, 4′-H), 8.50 (1H, s, ArCH=N), and 8.55-8.60 (1H, m, 6′-H); m/z (FAB) 402 (M^+, 63%), 354 (66), 313 (67), 303 (100).

4-Bromo-2-(2-hydroxyethyliminomethyl)-6-(4-methylpiperazin-1-ylmethyl)phenol, ***H_2L^5***

4-Bromo-2-formyl-6-(4-methylpiperazin-1-ylmethyl)phenol (**6**) (9.40g, 30 mmol) in toluene (150 ml) and 2-aminoethanol (2.02g, 33 mmol) in ethanol (150 ml) were treated for 4 h as described in General Method (B) affording the *title compound* as a yellow crystals (10.05g, 94%), m.p. 101-103 °C (from diethyl ether). Found: C, 50.71; H, 6.20; Br, 22.48; N, 11.63. $C_{15}H_{22}BrN_3O_2$ requires C, 50.57; H, 6.22; Br, 22.43, N, 11.79%; ν_{max} (KBr)/cm^{-1} 3162 (OH), 2939, 2842, 2801, 1632 (CH=N), 1601 (aromatic ring), 1349, 1288, 1240, 1165, 1150, 1065, 1004, 871; δ_H ($CDCl_3$) 2.26 (3H, s, NMe), 2.30-2.69 (8H, m, [CH_2CH_2]$_2$), 3.54 (2H, s, $ArCH_2$), 3.72 (2H, t, *J* 7.5, NCH_2), 3.87 (2H, t, *J* 7.5, CH_2 OH), 7.32 (1H, d, *J* 3.75, 3-H), 7.42 (1H, d, *J* 3.75, 5-H), and 8.30 (1H, s, ArCH=N); δ_C ($CDCl_3$) 45.92 (NCH_3), 52.90 (C-3′ and C-5′), 54.92 (C-2′ and C-6′), 55.68 ($ArCH_2$), 61.50 (NCH_2), 61.70 (CH_2OH) 109.79 (C-4), 119.97 (C-2), 127.76 (C-6), 132.08 (C-5), 135.57 (C-3), 158.91 (C-1), and 164.88 (ArCH=N); m/z (EI) 355 (M^+, 14%), 285 (23), 258 (100), (CI) 356 ($M+H^+$, 51%), 285 (53), 258 (100).

4-Bromo-2-(N-morpholinylmethyl)-6-(2-pyridylmethyliminomethyl)phenol, ***HL***[6]

4-Bromo-2-formyl-6-(*N*-morpholinylmethyl)phenol (**7**) (1.50g, 5 mmol) in ethanol (50 ml) and 2-aminomethylpyridine (0.61g, 5.5 mmol) in toluene (50 ml) were treated for 4 h as described in General Method (B) affording the *title compound* as a yellow/brown oil (1.95g, 100%); ν_{max} (film)/cm^{-1} 3425 (OH), 2940, 2593, 1648 ArCH=N), 1596, 1388, 1214, 1123, 1979, 996, 963, 878, 824; δ_H ($CDCl_3$) 2.50 (4H, t, *J* 6.2, N[CH_2]$_2$), 3.55 (2H, s, ArCH_2), 3.70 (4H, t, *J* 6.2, O[CH_2]$_2$), 4.93 (2H, s, CH_2Py), 7.12-7.25 (1H, m, 5′-H), 7.35 (1H, d, *J* 9.37, 3′-H), 7.37 (1H, d, *J* 3.12, 5-H), 7.50 (1H, d, *J* 3.12, 3-H), 7.65-7.72 (1H, m, 4′-H), 8.48 (1H, s, ArCH=N), 8.53-8.60 (1H, m, 6′-H), and 13.30-13.80 (1H, br.s, ArOH).

4-Bromo-2-(2-hydroxyethyliminomethyl)-6-(morpholin-4-ylmethyl)phenol, ***H_2L***[7]

δ_H ($CDCl_3$) 2.55 (4H, t, *J* 6.2, N[CH_2]$_2$), 3.55 (2H, s, ArCH_2), 3.70 (4H, t, *J* 6.2, O[CH_2]$_2$), 3.76 (3H, t, *J* 3.2, NCH_2), 3.93 (3H, t, *J* 3.2, C*H*$_2$ OH), 7.33 (1H, d, *J* 3 Hz, 3-H), 7.47 (1H, d, *J* 3, 5-H), and 8.33 (1H, s, ArCH=N); δ_C ($CDCl_3$) 53.59 (C-3′and C-5′), 56.07 (ArCH_2), 61.53 (NCH_2), 61.08 (CH_2OH), 66.90 (C-2′and C-6′), 109.82 (C-4), 119.86 (C-2), 127.59 (C-6), 132.36 (C-5), 135.75 (C-3), 158.98 (C-1), and 165.27 (ArCH=N).

4-Bromo-2-[(2-diethylaminoethyl)ethylaminomethyl]-6-(2-hydroxyethyliminomethyl)phenol, ***H_2L***[8]

4-Bromo-2-[(2-diethylaminoethyl)ethylaminomethyl]-6-formylphenol (**8**) (1.02g, 2.8 mmol) in toluene (30 ml) and 2-aminoethanol (0.19g, 3.1 mmol) in ethanol (30 ml) were treated for 4 h as described in General Method (B) affording the *title compound* as a yellow/brown viscous oil (1.11g, 100%), ν_{max} (film)/cm^{-1} 3353 (OH), 2964, 2820, 1631 (ArCH=N), 1600 (aromatic ring), 1369, 1282, 1061, 867; δ_H ($CDCl_3$) 1.02 (3H, t, *J* 6.2, NCH$_2$C*H*$_3$), 1.07 (6H, t, *J* 6.2, 2xCH$_2$C*H*$_3$), 2.50 (2H, q, *J* 6.2, C*H*$_2$ CH$_3$), 2.52 (4H, q *J* 6.2, 2xC*H*$_2$ CH$_3$), 2.60-2.65 (4H, m, CH_2CH_2), 3.60 (2H, s, ArCH_2), 3.73 (3H, t, *J* 6.2, NCH_2), 3.86 (3H, t, *J* 6.2, C*H*$_2$ OH), 7.45 (2H, dd, *J* 3.1, 5-H and 3-H), and 8.40 (1H, s, ArCH=N); δ_C ($CDCl_3$) 11.39 (2xCH$_2$*C* H$_3$), 11.61 (CH$_2$*C* H$_3$), 47.13 (2x*C* H$_2$CH$_3$), 48.12 (*C* H$_2$CH$_3$) 50.55 (N*C* H$_2$CH$_2$), 51.08 (NCH$_2$*C* H$_2$), 52.21 (ArCH_2), 61.59 (*C* H$_2$CH$_2$OH), 61.79 (CH$_2$*C* H$_2$OH), 109.93 (C-4), 120.51, 119.86 (C-6), 129.29 (C-2), 131.18 (C-3), 134.90 (C-5), 158.68 (C-1), and 163.99 (ArCH=N).

4-Bromo-2-(3-hydroxypropyliminomethyl)-6-(4-methylpiperazin-1-ylmethyl)phenol, ***H_2L***[9]

4-Bromo-2-formyl-6-(4-methylpiperazin-1-ylmethyl)phenol (**6**) (3.13g, 10 mmol), in toluene (80 ml) and 3-aminopropanol (0.83g, 11 mmol) in ethanol (80 ml) were treated for 3 h as described in General Method (B) affording the *title compound* as a yellow/orange viscous oil (3.67g, 99%); δ_H ($CDCl_3$) 0.90 (2H, quintet, *J* 3.2, CH$_2$C*H*$_2$ CH$_2$OH), 2.27 (3H, s, NMe), 2.32-2.72 (8H, m, [CH_2CH_2]$_2$), 3.55 (2H, s, ArCH_2), 3..65 (2H, t, *J* 6.2, NCH_2), 3.68 (2H, t, *J* 6.2, C*H*$_2$ OH), 7.27 (1H, d, *J* 3.1, 3-H), 7.42 (1H, d, *J* 3.1, 5-H), and 8.27 (1H, s, ArCH=N).

4-Bromo-2-(2,3-dihydroxypropyliminomethyl)-6-(4-methylpiperazin-1-ylmethyl)phenol, ***H_3L***[10]

4-Bromo-2-formyl-6-(4-methylpiperazin-1-ylmethyl)phenol (**6**) (1.57g, 5 mmol) in toluene (50 ml) and (±)-3-amino-1,2-propanediol (0.52g, 5.5 mmol) in ethanol (50 ml) were treated for 18 h as described in General Method (B) to give a viscous oil (1.96g) which after trituration with ether gave the *title compound* as a yellow solid (1.70g, 88%) , m.p. 183-185 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 3357 (OH), 2934, 2802, 1634 (CH=N), 1605 (aromatic ring), 1353, 1289, 1237, 1147, 1044, 1012, 875; δ_H ($CDCl_3$) 2.23 (3H, s, NMe), 2.30-2.70 (8H, m, [CH_2CH_2]$_2$), 3.50 (2H, s, ArCH_2), 3.55 -3.76 (4H, m, C*H*$_2$ CH(OH)) and CH(OH)C*H*$_2$ OH), 3.90-4.00 (1H, m, C*H* (OH), 7.25 (1H, d, *J* 3.1, 3-H), 7.38 (1H, d, *J* 3.1, 5-H), and 8.25 (1H, s, ArCH=N); δ_C ($CDCl_3$) 45.77 (NCH_3), 52.72 (C-3′ and C-5′), 54.72 (C-2′ and C-6′), 55.77 (ArCH_2), 61.66 (*C* H$_2$CH(OH)), 64.32 (CH(OH)*C* H$_2$OH), 70.96 (CH$_2$*C* H(OH), 109.56 (C-4), 119.86 (C-2), 127.58 (C-6), 132.03 (C-5), 135.71 (C-3), 159.31 (C-1), and 164.81 (ArCH=N); m/z (EI) 385 (M^+, 5%), 285 (28), 99 (57), 58 (100), (CI) 386 ($M+H^+$, 3%), 288 (7), 101 (28), 58 (100).

3,5-Dimethoxy-2-[(2-hydroxyethyl)methylaminomethyl]-6-(2-pyridylmethyliminomethyl)phenol, ***H_2L^{11}***

3,5-Dimethoxy-2-formyl-6-[(2-hydroxyethyl)methylaminomethyl)]phenol (**9**) (1.35g, 5 mmol) in ethanol (25 ml) and 2-aminomethylpyridine (0.54g, 5 mmol) in toluene (25 ml) were treated for 3 h as described in General Method (B) to give the *title compound* as a yellow-brown oil (1..60g, 89%); δ_H ($CDCl_3$) 2.30 (3H, s, NMe), 2.66 (2H, t, *J* 7.5, CH_2CH_2OH), 3.60 (2H, s, $ArCH_2$), 3.72(2H, t, *J* 7.5, CH_2OH), 3.87 (3H, s, OMe), 3.90 (3H, s, OMe), 4.84 (2H, s, CH_2Py), 5.87 (1H, s, 4-H), 7.12-7.24 (1H, m, 5′-H), 7.27-7.39 (1H, m, 3′-H), 7.57-7.72 (1H, m, 4′-H), 8.54-8.63 (1H, m, 6′-H), 8.78 (1H, s, ArCH=N), 14.69-14.96 (1H, br.s, 2-OH); δ_C ($CDCl_3$) 42.53 (NCH_3), 47.12 (NCH_2), 55.45 (OCH_3), 55.58 (OCH_3), 58.42 ($ArCH_2$), 58.65 (CH_2OH), 61.91 (CH_2Py), 84.08 (C-4), 102.62 (C-2), 106.75 (C-6), 121.87 (C-3′), 122.45 (C-5′), 136.96 (C-4′), 149.44 (C-6′), 157.52 (C-2′), 160.78 (C-1), 161.31 (ArCH=N), 163.93 (C-3), and 167.81 (C-5)

3,5-Dimethoxy-2-[(2-hydroxyethyl)methylaminomethyl]-6-(2-pyridylethyliminomethyl)phenol, ***H_2L^{12}***

3,5-Dimethoxy-2-formyl-6-[(2-hydroxyethyl)methylaminomethyl)]phenol (**9**) (0.81g, 3 mmol) in ethanol (75 ml) and 2-(2-aminoethyl)pyridine (95%) (0.39g, 3 mmol) in toluene (75 ml) were treated for 1 h as described in General Method (B) to give the *title compound* as a yellow oil (0.72g, 64%); δ_H ($CDCl_3$) 2.18 (3H, s, NMe), 2.53 (2H, t, *J* 6.2, CH_2CH_2OH), 3.05 (2H, t, *J* 6.2, CH_2CH_2Py), 3.38 (2H, s, $ArCH_2$), 3.65 (2H, t, *J* 6.2, CH_2OH), 3.73 (3H, s, OMe), 3.78 (3H, s, OMe), 3.85 (2H, t, *J* 6.2, CH_2CH_2Py), 5.68 (1H, s, 4-H), 7.02-7.15 (2H, m, 3′-H and 5′-H), 7.50-7.60 (1H, m, 4′-H), 8.30 (1H, s, ArCH=N), 8.42-8.50 (1H, m, 6′-H) and 14.45-14.87 (1H, br s, 2-OH).

3,5-Dimethoxy-2-[(2-hydroxyethyl)methylaminomethyl]-6-(2-hydroxyethyliminomethyl)phenol, ***H_3L^{13}***

3,5-dimethoxy-2-formyl-6-[(2-hydroxyethyl)methylaminomethyl)]phenol (**9**) (0.81g, 3 mmol) in toluene (75 ml) and 2-aminoethanol (0.20g, 3.3 mmol) in ethanol (75 ml) were treated for 4 h as described in General Method (B) to give the *title compound* as a yellow oil (0.81g, 86%); δ_H ($CDCl_3$) 2.19 (3H, s, NMe), 2.71 (2H, t, *J* 6.2, CH_2CH_2OH), 3.42 (2H, s, $ArCH_2$), 3.55 (2H, t, *J* 6.2, CH_2CH_2OH), 3.70 (2H, t, *J* 6.2, CH_2CH_2OH), 3.75 (2H, t, *J* 6.2, CH_2CH_2OH), 3.80 (3H, s, OMe), 3.82 (3H, s, OMe), 5.56 (1H, s, 4-H), and 8.42 (1H, s, ArCH=N).

2-[(Bis-2-hydroxyethyl)aminomethyl]-3,5-dimethoxy-6-(2-pyridylethyliminomethyl)phenol, ***H_3L^{14}***

2-[(Bis-2-hydroxyethyl)aminomethyl)]-3,5-dimethoxy-6-formylphenol (**10**) (0.60g, 2 mmol) in ethanol (50 ml) and 2-(2-aminoethyl)pyridine (95%) (0.27g, 2.1 mmol) in toluene (50 ml) were treated for 2 h as described in General Method (B) to give a yellow oil which upon trituration with ether gave the *title compound* as a yellow solid (0.76g, 94%), m.p. 72-74 °C (from diethyl ether); ν_{max} (KBr)/cm^{-1} 3384 (OH), 2941, 2842, 1624 (CH=N), 1590, 1544, 1251, 1214, 1149, 1126, 1050, 1022, 768; δ_H ($CDCl_3$) 2.65 (4H, t, *J* 6.2, 2xNCH_2), 3.15 (2H, t, *J* 6.2, CH_2CH_2Py), 3.60 (4H, t, *J* 7.2, 2xCH_2OH), 3.65 (2H, s, $ArCH_2$), 3.80 (3H, s, OMe), 3.82 (3H, s, OMe), 3.90 (2H, t, *J* 7.5, CH_2CH_2Py), 5.68 (1H, s, 4-H), 7.10-7.30 (2H, m, 3′-H and 5′-H), 7.57-7.63 (1H, m, 4′-H), 8.32 (1H, s, ArCH=N), 8.55-8.60 (1H, m, 6′-H) and 14.32-14.85 (1H, br s, 1-OH); δ_C ($CDCl_3$) 38.72 (CH_2CH_2Py), 44.72 ($ArCH_2$), 52.65 (CH_2CH_2Py), 54.94 (2xNCH_2), 55.23 (OCH_3), 55.52 (OCH_3), 59.34 (2xCH_2OH), 82.58 (C-4), 102.45 (C-6), 108.41 (C-2), 121.84 (C-3′), 123.80 (C-5′), 136.76 (C-4′), 149.61 (C-6′), 157.79 (C-2′), 159.39 (ArCH=N), 160.97 (C-1), 164.67 (C-5), and 173.62 (C-3); m/z (EI) 403 (M^+, not detected), 385 (4.4%), 358 (4.5), 299 (89), 74 (100); (CI) 403 (M^+, 1%). 385 (2.5), 358 (3), 299 (90), 106 (85), 74 (100).

2-[(Bis-2-hydroxyethyl)aminomethyl]-3,5-dimethoxy-6-(2-hydroxyethyliminomethyl)phenol, ***H_4L^{15}***

2-[(Bis-2-hydroxyethyl)aminomethyl)]-3,5-dimethoxy-6-formylphenol (**10**) (0.94g, 3.1 mmol) in toluene (50 ml) and 2-aminoethanol (95%) (0.24g, 4 mmol) in ethanol (50 ml) were treated for 4 h as described in General Method (B) to give a brown viscous oil (0.91g) which after trituration with ether-petroleum ether (40-60 °C) afforded the *title compound* as a yellow solid (0.87g, 82%) m.p. 152-153 °C (from ethyl acetate) ; ν_{max} (KBr)/cm^{-1} 3435 (OH), 3176 (OH), 2931, 2839, 2770, 1637 (CH=N), 1608 (aromatic ring), 1556, 1388, 1286,

1140, 1071, 892, 766; δ_H ($CDCl_3$) 2.67 (4H, t, *J* 6.2, 2xCH_2 CH_2OH), 3.57 (2H, t, *J* 6.2, CH_2 CH_2OH), 3.59 (4H, t, *J* 6.2, 2xCH_2 OH) 3.65 (2H, s, $ArCH_2$), 3.78 (2H, t, *J* 6.2, CH_2 OH), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 5.67 (1H, s, 4-H), and 8.4 (1H, s, ArCH=N); δ_C ($CDCl_3$) 45.04 ($ArCH_2$), 54.96 (N=*C* H_2), 55.03 (2xNCH_2), 55.25 (OCH_3), 55.54 (OCH_3), 59.30 (2x*C* H_2OH), 61.12 (*C* H_2OH), 82.47 (C-4), 102.65 (C-6), 108.45 (C-2), 160.45 (Ar*C* H=N), 161.31(C-1), 165.18 (C-5), and 1174.42 (C-3).

4-Bromo-2-[(2-hydroxyethyl)methylaminomethyl)]-6-(4-methylpiperazin-1-ylmethyl)-phenol, ***H_2L^{16}***

4-Bromo-2-formyl-6-(4-methylpiperazin-1-ylmethyl)phenol (**6**) (7.83g, 25 mmol) in toluene (150 ml) and *N*-methylethanolamine (9.39g, 125 mmol) in ethanol (150 ml) were heated under reflux in a nitrogen atmosphere for 17 h using a Dean-Stark trap. After cooling to room temperature the yellow-orange solution was cooled in ice and treated with sodium borohydride (3.78g, 0.1 mol) in small portions. The mixture was then stirred under nitrogen for 2 h until the evolution of hydrogen ceased and decolourisation occurred. Following the work-up procedure described in General Method (A) gave a light brown viscous oil (9.16g) which after trituration with ether-*n*-hexane afforded the *title compound* as a crystalline white solid (8.84g, 95%), m.p. 74-75 °C (from diethyl ether). Found: C, 51.67; H, 7.21; Br, 21.69 N, 11.27. $C_{15}H_{22}BrN_3O_2$ requires C, 51.62; H, 7.04; Br, 21.46; N, 11.29%; ν_{max} (KBr)/cm^{-1} 3182 (OH), 2939, 2797, 1608 (aromatic ring), 1578, 1348, 1297, 1219, 1146, 1081, 1011, 961, 858, 783; δ_H ($CDCl_3$) 2.20 (3H, s, NMe), 2.25 (3H, s, NMe), 2.30-2.80 (8H, m, $[CH_2CH_2]_2$), 2.58 (2H, t, *J* 6.2, NCH_2), 3.50 (2H, s, $ArCH_2$), 3.60 (2H, s, $ArCH_2$), 3.63 (2H, t, *J* 6.2, CH_2 OH), 7.03 (1H, d, *J* 3.1, 3-H), and 7.17 (1H, d, *J* 3.1, 5-H); δ_C ($CDCl_3$) 42.09 (NCH_3), 45.81 (NCH_3), 52.45 (C-3′ and C-5′), 54.73 (C-2′ and C-6′), 56.34 (NCH_2), 58.64 ($ArCH_2$), 58.34 ($ArCH_2$), 59.95 (CH_2OH) 110.39 (C-4), 123.57 (C-2), 126.97 (C-6), 130.58 (C-3), 132.09 (C-5), and 155.49 (C-1); m/z (EI) 371 (M^+, 3%), 299 (100).

4-Bromo-2-[(bis-2-hydroxyethyl)aminomethyl]-6-(4-methylpiperazin-1-ylmethyl)phenol, ***H_3L^{17}***

4-Bromo-2-formyl-6-(4-methylpiperazin-1-ylmethyl)phenol (**6**) (6.26g, 20 mmol) in toluene (150 ml) and diethanolamine (10.51g, 100 mmol) in ethanol (150 ml) were treated as described for ligand (**H_2L^{16}**) to give a light brown viscous oil (7.96g) which upon trituration with ethyl acetate afforded the *title compound* (7.41g, 92%) as a crystalline white solid, m.p. 248-250 °C [from ethyl acetate-methanol (9:1)]; ν_{max} (KBr)/cm^{-1} 3453 (OH), 2934, 2792, 1592, 1350, 1298, 1235, 1141, 1092, 1048, 997, 887, 819; δ_H ($CDCl_3$) 2.27 (3H, s, NMe), 2.32-2.72 (8H, m, $[CH_2CH_2]_2$), 3.12 (4H, dt, *J* 6.2, 2xNCH_2), 3.62 (2H, s, $ArCH_2$), 3.95 (4H, dt, *J* 6.2, 2xCH_2 OH), 4.00 (2H, s, $ArCH_2$), 7.03 (1H, d, *J* 3.1, 3-H), and 7.55 (1H, d, *J* 3.1, 5-H); δ_C ($CDCl_3$) 46.00 (NCH_3), 52.90 (C-3′ and C-5′), 54.93 ($ArCH_2$), 55.11 (C-2′ and C-6′), 56.43 ($ArCH_2$), 58.35 (2xNCH_2), 60.69 (2xCH_2OH) 112.30 (C-4), 122.57 (C-2), 128.94 (C-3), 131.46 (C-6), 133.63 (C-5), and 154.48 (C-1).

2,6-Bis-[(2-hydroxyethyl)methylaminomethyl)]-4-chlororesorcinol, ***H_3L^{18}***

A solution of 4-chlororesorcinol (98%) (2.95g, 20 mmol) and 3-methyl-1,3-oxazolidine (**4**) (4.36g, 50 mmol) in acetonitrile (100 ml) under nitrogen was stirred at room temperature for 2 days, filtered and concentrated *in vacuo* to a pink solid which was washed with cold ethanol and dried in a vacuum desiccator to give the *title compound* as light brown solid (5.74g, 90%), m.p. 104-106 °C (decomposed); ν_{max} (KBr)/cm^{-1} 3244 (OH), 2808, 1610 (aromatic ring), 1544,1370, 1247, 1196, 1021, 985, 912, 840, 806; δ_H (CD_3OD) 2.30 (2H, s, NMe), 2.45 (2H, s, NMe), 2.65 (2H, t, *J* 6.2, NCH_2), 2.80 (2H, t, *J* 6.2, NCH_2), 3.62 (2H, s, $ArCH_2$), 3.70 (2H, t, *J* 6.2, CH_2OH), 3.77 (2H, t, *J* 6.2, CH_2OH), 3.97 (2H, s, $ArCH_2$), and 6.90 (1H, s, 5-H); δ_C (CD_3OD) 41.35 (NCH_3), 41.47 (NCH_3), 54.84 ($ArCH_2$), 59.08 (NCH_2), 59.45 (NCH_2), 59.53 ($ArCH_2$), 59.66 (CH_2OH), 61.10 (CH_2OH), 110.32 (C-4), 111.89 (C-6), 113.81 (C-2), 129.66 (C-5), 156.77 (C-3), and 157.20 (C-1).

2,6-Bis-(morpholin-4-ylmethyl)-4-chlororesorcinol, ***HL[19]***

A solution of 4-chlororesorcinol (98%) (3.69g, 25 mmol) and ethoxy-*N*-morpholinylmethane (**2**) (7.99g, 55 mmol) in acetonitrile (100 ml) under nitrogen was stirred at room temperature for 16 h, filtered and concentrated *in vacuo* to a brown solid which was washed with cold ether affording the *title compound* as a white solid (7.71g, 90%), m.p. 146-148 °C (from ethyl acetate). Found: C, 55.93; H, 6.79; Cl, 10.58; N, 7.92. $C_{16}H_{23}ClN_2O_4$ requires C, 56.06; H, 6.76; Cl, 10.34; N, 8.17%; ν_{max} (KBr)/cm^{-1} 3429 (OH), 2962, 2850, 1618 (aromatic ring), 1387, 1343, 1299, 1265, 1204, 1115, 1077, 986, 907, 862, 796; δ_H ($CDCl_3$) 2.35-2.80 (8H, m, 2x[NCH_2]$_2$), 3.57 (2H, s, $ArCH_2$), 3.62-3.90 (8H, m, 2x[OCH_2]$_2$], 3.82 (2H, s, $ArCH_2$), and 6.88 (1H, s, 5-H); δ_C ($CDCl_3$) 52.74 (C-3′ and C-5′), 52.90 (C-3′ and C-5′), 54.66 ($ArCH_2$), 61.17 ($ArCH_2$), 66.69 (C-2′ and C-6′), 66.75 (C-2′ and C-6′), 108.48 (C-4), 110.57 (C-6), 111.91 (C-2), 128.19 (C-5), 154.12 (C-3), and 154.66 (C-1); m/z (EI) 342 (M^+, 7%), 255 (19), 168 (73), 140 (54), 100 (58), 87 (100), (CI) 343 (M+ H^+, 12%), 255 (24), 168 (26), 140 (30), 100 (40), 88 (100).

2,6-Bis-(4-methylpiperazin-1-ylmethyl)-4-chlororesorcinol, ***HL[20]***

A solution of 4-chlororesorcinol (98%) (2.95g, 20 mmol) and ethoxy-(4-methylpiperazin-1-yl)methane (**1**) (6.96g, 44 mmol) in acetonitrile (100 ml) under nitrogen was stirred at room temperature for 44 h, filtered and concentrated *in vacuo* to a light brown foam. Trituration with ether-petroleum ether (40-60 °C), gave the *title compound* as a white solid (4.87g, 66%), m.p. 106-108 °C (from *n*-hexane). Found: C, 58.88; H, 8.02; Cl, 9.90; N, 15.08. $C_{18}H_{29}ClN_4O_2$ requires C, 58.61; H, 7.92; Cl, 9.61; N, 15.19%; ν_{max} (KBr)/cm^{-1} 3413 (OH), 2936, 2786, 1620 (aromatic ring), 1454, 1342, 1293, 1216, 1160, 1093, 1008, 914, 815; δ_H ($CDCl_3$) 2.286 (3H, s, NMe), 2.292 (3H, s, NMe), 2.32-3.00 (16H, m, 2x[CH_2CH_2]$_2$), 3.57 (2H, s, $ArCH_2$), 3.82 (2H, s, $ArCH_2$), and 6.85 (1H, s, 5-H); δ_C ($CDCl_3$) 45.85 (NCH_3), 52.28 and 52.51 (C-3′ and C-5′), 54.25 ($ArCH_2$), 54.74 and 54.86 (C-2′ and C-6′), 108.73 (C-4), 110.30 (C-6), 112.13 (C-2), 127.78 (C-5), 154.23 (C-3), and 154.74 (C-1); m/z (EI) 368 (M^+, 0.4%), 268 (1.3), 168 (29), 140 (22), 113 (45), 100 (100), (CI) 369 (M+H^+, 1.9%), 269 (5), 168 (23), 140 (20), 100 (87), 58 (100).

4-Chloro-6-(4-methylpiperazin-1-ylmethyl)resorcinol, ***18***

A solution of 4-chlororesorcinol (98%) (5.90g, 40 mmol) in acetonitrile (80 ml) was cooled in ice-methanol (-15 °C) under nitrogen. Ethoxy-(4-methylpiperazin-1-yl)methane (**1**) (6.33g, 40 mmol) in acetonitrile (50 ml) was added dropwise over 0.5 h and the mixture was stirred for 1h keeping the temperature below -5 °C. A pink precipitate was formed, filtered and washed with ether (100 ml) and recrystallised from chloroform to give the *title compound* as a light brown solid (5.88g, 57%), m.p. 172-174 °C. Found: C, 55.63; H, 6.63; Cl, 13.94; N, 10.59. $C_{12}H_{17}ClN_2O_2$ requires C, 56.14; H, 6.67; Cl, 13.81; N, 10.91%); ν_{max} (KBr)/cm^{-1} 3420 (OH), 2946, 2829, 2363, 1618 (aromatic ring), 1584, 1504, 1463, 1412, 1333, 1278, 1240, 1172, 1002, 884, 818; δ_H (CD_3OD) 2.30 (3H, s, NMe), 2.35-2.77 (8H, m, [CH_2CH_2]$_2$), 3.57 (2H, s, $ArCH_2$), 6.35 (1H, s, 3-H), and 6.96 (1H, s, 5-H); δ_C (CD_3OD) 45.93 (NCH_3), 52.93 (C-3′ and C-5′), 55.81 (C-2′ and C-6′), 60.01 ($ArCH_2$), 104.99 (C-2), 111.72 (C-4), 115.36 (C-6), 1231.00 (C-5), 154.52 (C-3), and 158.19 (C-1); m/z (EI) 256 (M^+, 99%), 185 (55), 157 (59), 99 (100).

4-Chloro-2-[(2-hydroxyethyl)methylaminomethyl)-6-(4-methylpiperazin-1-ylmethyl)resorcinol, ***H_2L[21]***

A suspension of 4-chloro-6-(4-methylpiperazin-1-ylmethyl)resorcinol (**18**) (1.28g, 5 mmol) in acetonitrile (80 ml) was treated under nitrogen with 3-methyl-1,3-oxazolidine (**4**) (0.87g, 10 mmol) in acetonitrile (20 ml). The mixture was then stirred at room temperature for 2 days until the solid eventually dissolved and a clear light brown solution was formed. The solution was then filtered and concentrated *in vacuo* to a brown viscous oil which after trituration with ether gave the *title compound* (0.84g, 49%) as a white crystalline solid m.p. 96-98 °C (from diethyl ether). Found: C, 56.16; H, 7.41; Cl, 10.04; N, 12.38. $C_{16}H_{26}ClN_3O_3$ requires C, 55.89; H, 7.62; Cl, 10.31; N, 12.22%; ν_{max} (KBr)/cm^{-1} 3195 (OH), 2814, 1600 (aromatic ring), 1597, 1458, 1355, 1282, 1209, 1148, 1076, 1041, 1005, 919, 972, 818; δ_H ($CDCl_3$) 2.22 (3H, s, NMe), 2.30 (3H, s, NMe), 2.35-2.62 (8H, m, [CH_2CH_2]$_2$), 2.66 (2H, t, *J* 6.2, NCH_2), 3.52 (2H, s, $ArCH_2$), 3.75 (2H, t, *J* 6.2,

CH_2OH), 3.80 (2H, s, $ArCH_2$), 5.05-6.12 (2H, br.s, 2xOH), and 6.77 (1H, s, 5-H); δ_C ($CDCl_3$) 41.85 (NCH_3), 45.49 (NCH_3), 52.16 (C-3′ and C-5′), 54.23 (NCH_2), 54.83 (C-2′ and C-6′), 58.91 ($ArCH_2N$), 58.91 ($ArCH_2$), 60.59 (CH_2OH), 109.48 (C-4), 110.45 (C-6), 112.05 (C-2), 127.79 (C-5), 154.43 (C-3), and 154.61(C-1); m/z (FAB) 344 (M^++1, 100%), 269 (89), 244 (85), 169 (31), 154 (36), 136 (29), M^+ measured 344.1736; $C_{16}H_{26}ClN_3O_3$ requires 344.1741.

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