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Chemical design and synthesis of unsymmetrical diamino proligands employing a flexible route

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ABSTRACT

Three new unsymmetrical diamino proligands with a central alcohol group and four different pendant arms were obtained, employing a five step synthesis. The synthesis of these compounds involves inexpensive and commercially available reagents. The versatility of the synthetic route allows accessing to compartmental diamines with two chemically different adjacent coordination chambers.

Numerous examples of active site of binuclear metalloenzymes show that each metal atom may have chemically different environments, with coordination number asymmetry (dissimilar number of donor atoms) and/or donor asymmetry (different types of donor atoms), even in homodinuclear species.[1–3] The coordination asymmetry around the two metal ions often leaves vacant coordination sites and facilitates the interaction of the metal center with specific substrates.

A large number of dinucleating ligands have been prepared and used to synthesize metal complexes that mimic binuclear metalloproteins.[4] However, the limited number of model systems that employ non-symmetric ligands reveals the need of developing efficient routes toward this class of ligands.[4–6]

With the goal of obtaining dimanganese complexes as models of manganese catalases (MnCAT), we and others have found that polydentate ligands with a central bridging alkoxide can be used to emulate some key features of the active site of these enzymes.[7–11] In particular, symmetrical ligands derived from 1,3-diaminopropan-2-ol afford dimanganese complexes that reproduce the intermetallic distance of the enzyme (Fig. 1a).[7,8] However, while in MnCAT the two metal ions differ in the number of exchangeable solvent ligands (only one of the manganese ions is bound to a labile water molecule), symmetrical alkoxo-bridging ligands afford synthetic models with identical environment around the two metal centers, leading to a less efficient catalytic reaction. Two types of unsymmetrical phenoxo-bridged dimanganese complexes have also been studied as MnCAT mimics (Fig. 1b) [12,13]; but in these compounds, the phenoxide bridge leads to Mn···Mn separation longer than found in the enzyme and, thus, these complexes are less relevant as MnCAT models. Therefore, the chemical design of novel unsymmetrical ligands with a central alkoxide group turns out to be essential for improving the efficiency of analogues of these metalloenzymes.

As a part of our synthetic effort toward preparing proligands for obtaining mimics of dinuclear metalloproteins, we report here on the synthesis of three novel unsymmetrical ligands with N_3O_3-donor set: 1-[*N*-(2-pyridylmethyl),*N*-(2-hydroxybenzyl)amino]-3-[*N*′-(2-hydroxybenzyl),*N*′-(benzyl)amino]propan-2-ol (**H_3L^1**), 1-[*N*-(2-pyridylmethyl),*N*-(2-hydroxybenzyl)amino]-3-[*N*′-(2-hydroxybenzyl),*N*′-(4-methyl-benzyl)amino]propan-2-ol (**H_3L^2**), and 1-[*N*-(2-pyridylmethyl),*N*-(2-hydroxybenzyl)amino]-3-[*N*′-(2-hydroxy-5-chloro-benzyl),*N*′-(benzyl)amino]propan-2-ol (**H_3L^3**), depicted in Scheme 1.

The retrosynthetic analysis of the **H_3L^n** family yielded two different approaches that share the same initial steps. As shown in Scheme 1, the proligands can be accessed through two key disconnections: the reaction of a chlorohydrin and a secondary amine involving a nucleophilic displacement (***path A***); and the reductive amination of salicylaldehyde (properly substituted) with the secondary amine derived from coupling between an epoxide and picolylamine (***path B***).

The synthesis of the polypodal ligands was first attempted employing ***path A***. The reductive amination of salicylaldehyde **1** with commercially available amines (benzylamine, *p*-toluidine, and 2-picolylamine), rendered the secondary amines **2a–c** in

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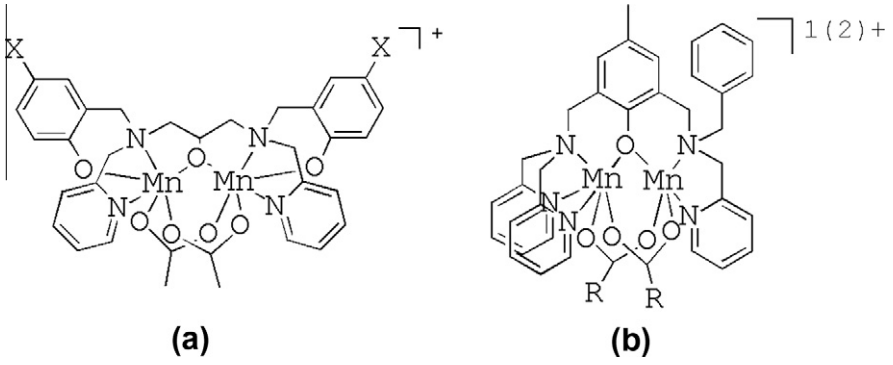
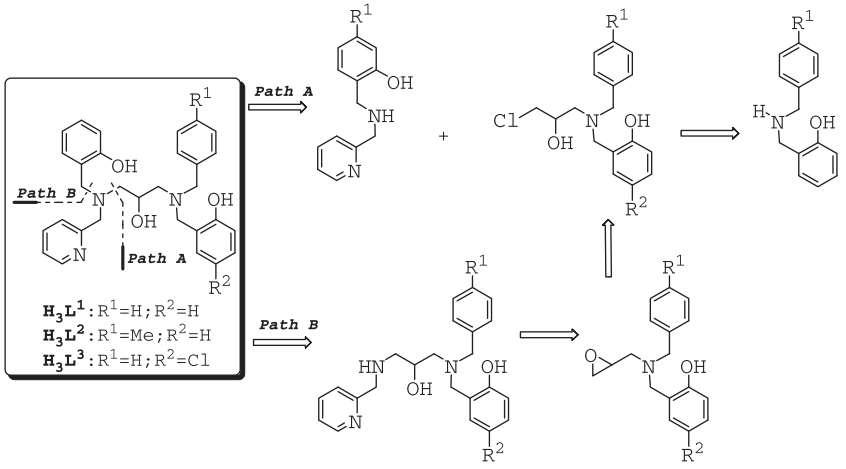


Figure 1. Dimanganese complexes with symmetrical (a) and unsymmetrical (b) ligands.

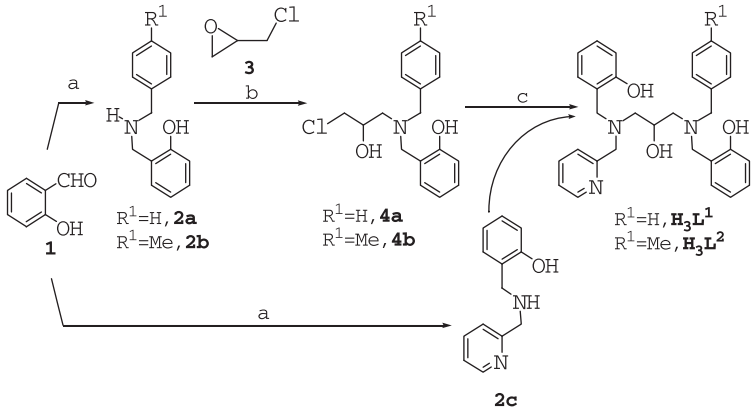


Scheme 1. Retrosynthesis of proligands H_3L^n.

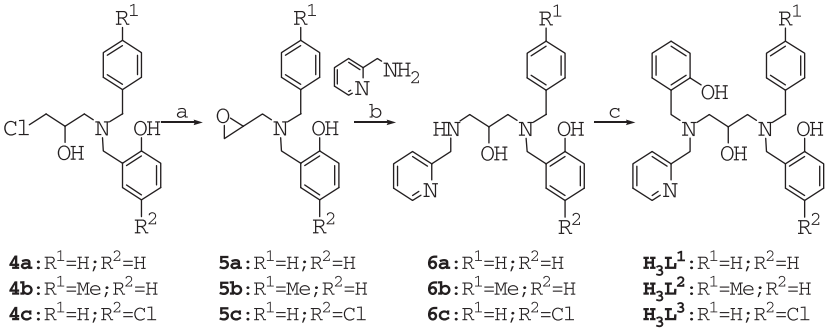
excellent yield. The subsequent condensation of **2a,b** with epichlorohydrin (**3**) gave chlorohydrins **4a,b** almost quantitatively. The reaction of **4a,b** with **2c** introduced two new potential donor sites (N,O), leading to the desired proligands $\mathbf{H_3L^1}$ and $\mathbf{H_3L^2}$ in moderate yield ($\mathbf{H_3L^1}$: 41% from **4a**, $\mathbf{H_3L^2}$: 44% from **4b**), by using conditions of nucleophilic displacement (Scheme 2).

Although the route outlined in Scheme 2 yielded the desired $\mathbf{H_3L^1}$ and $\mathbf{H_3L^2}$, the final step generates a mixture of products difficult to separate through column chromatography and the yield of this step was quite low. Tilmans et al. devised a similar approach to synthesize a phos-tag ligand with two bis(pyridylmethyl)amino units.[14] However, when Tilmans' conditions were employed for the nucleophilic substitution (DIPEA, neat, 70 °C), instead of those of step c in Scheme 2, $\mathbf{H_3L^1}$ and $\mathbf{H_3L^2}$ were not achieved, probably because phenols strongly modify the reactivity of the system.

In order to circumvent the previous drawbacks, the alternative strategy of ***path B*** was explored. In this approach, epoxides were chosen as the activated form of the electrophiles. Nucleophilic opening of oxiranes is a powerful and effective tool for obtaining new carbon-heteroatom bonds with a carbinol in adjacent position. This highly flexible route to polypodal ligands starts from chlorohydrins **4a–c**, which upon reaction with potassium



Scheme 2. Synthesis of unsymmetrical ligands—***Path A***. Reagents and conditions: (a) (i) benzylamine/*p*-toluidine/picolylamine, EtOH, reflux for 2 h; (ii) $NaBH_4$, EtOH 0 °C→80 °C, 2 h (**2a**:87%; **2b**:90%; **2c**:82%), (b) **3**, MeOH, rt, 48 h (**4a**:95%; **4b**:99%), (c) **2c**, THF, TEA, KI, reflux for 3 d ($\mathbf{H_3L^1}$: 41% from **4a**; $\mathbf{H_3L^2}$: 44% from **4b**).



Scheme 3. Synthesis of unsymmetrical ligands—***Path B***. Reagents and conditions: (a) ^{t}BuOK, dioxane, rt, 3 h (**5a**:98%; **5b**:98%; **5c**:99%); (b) 2-picolylamine, rt, 24 h (**6a**:88%; **6b**:78%; **6c**:70%); (c) (i) salicylaldehyde, MeOH, reflux for 18 h; (ii) $NaBH(OAc)_3$, CH_2Cl_2, rt, 24 h ($\mathbf{H_3L^1}$:52% from **6a**; $\mathbf{H_3L^2}$:66% from **6b**; $\mathbf{H_3L^3}$:52% from **6c**).

Table 1
Rates of H_2O_2 disproportionation catalyzed by alkoxo-bridged dimanganese complexes[a]

Catalyst	Rate (mmol H_2O_2 mmol cat^{-1} s^{-1})	Solvent, T (°C)	Reference
$\mathbf{H_3L^1}$ + $Mn(OAc)_3$	3.3	CH_3CN, 20	This work
$[Mn_2(\mu\text{-OAc})(\mu\text{-OMe})(hppnO)]^+$	3.0	DMF, 25	9
$[Mn_2(\mu\text{-O})(OAc)(OH)(benzimpnO)]^+$	2.6	MeOH:H_2O, 25	16
$[Mn_2(\mu\text{-OMe})(OAc)(hppentO)]^+$	0.95	DMF, 10	8
$[Mn_2(\mu\text{-OMe})(\mu\text{-OAc})(salpentO)]^+$	0.89	MeOH, 25	17

[a] $[H_2O_2]_0$ = 140 mM. hppnOH = 1,3-bis[(2-hydroxybenzyl)(2-pyridylmethyl)amino]propan-2-ol; hppentOH = 1,5-bis[(2-hydroxybenzyl)(2-pyridylmethyl)amino]pentan-3-ol; benzimpnOH = N,N,N′,N′-tetrakis(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol; salpentOH = 1,5-bis(salicylidenamino)pentan-3-ol.

tert-butoxide in dioxane gave **5a–c** in almost quantitative yield, without the necessity of further purification. Nucleophilic opening of **5a–c** with neat 2-picolylamine led to diamines **6a–c**. After the reaction was completed, the extra amount of amine was removed under reduced pressure, recovering the excess of reagent for further use, and the residue was purified by column chromatography, to afford **6a–c** as pure oils. Finally, the three N_3O_3-donor ligands $\mathbf{H_3L^1}$, $\mathbf{H_3L^2}$, and $\mathbf{H_3L^3}$ were obtained by a one pot-two step reductive amination of salicylaldehyde with **6a–c** (Scheme 3).

The structure of all compounds presented in this study was confirmed by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectra (see Supplementary data).[15]

Several improvements can be highlighted for ***path B*** over ***path A*** and Tilman's approach: the two first steps of this novel route (*a* and *b*) do not require chromatographic purification and the total yield is higher than the synthetic route described in ***path A***. These facts make this approach the method of choice to obtain unsymmetrical polypodal diamines. Because this route avoids the use of protective groups, it enables incorporation of broad chemofunctional diversity.

The coordinating ability of $\mathbf{H_3L^1}$ was explored by reacting 1.4 mM $\mathbf{H_3L^1}$ with 2 equiv of manganese(III) acetate in acetonitrile, and the catalase-like activity of the complex formed in situ was tested by measuring the O_2 evolved after addition of 100 equiv of H_2O_2 to the complex solution (see Supplementary data). The catalyst was able to dismutate all H_2O_2 within 7 min with retention of activity after successive additions of H_2O_2, and the measured rate of H_2O_2 disproportionation is similar or higher than reported for Mn complexes of symmetrical alkoxide bridging ligands (Table 1). This result exemplifies the capacity of the present ligands to form efficient biomimetic catalysts.

In conclusion, we provided a versatile and flexible route, leading to new diamino proligands with a central alcohol group and unsymmetrical pendant binding sites. This is a general synthetic strategy that may allow the design of a number of dinucleating ligands with two chemically different coordination environments. These unsymmetrical polypodal proligands are of great interest, since they can be used to mimic a large number of binuclear metallobiosites where the two metal ions possess chemically distinct surroundings. Reproduction of these features is essential for obtaining efficient biomimetic compounds.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, analytical data, spectra and catalase-like activity) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.057.

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15. *Typical procedure for the preparation of proligand* $\boldsymbol{H_3L^1}$ *(**Path B**)*: A mixture of **2a** (1.582 g; 7.4 mmol) and epichloro hydrin **3** (2.9 mL; 37.0 mmol) in methanol (5 mL) was stirred at room temperature for 48 h. The resulting colorless solution was evaporated under vacuum and the crude solid was purified by recrystallization from MeOH, to afford **4a** as a white solid (2.155 g; 7.0 mmol; 95% yield). Chloro hydrin **4a** (0.195 g, 0.64 mmol) and ^{t}BuOK (0.197 g, 1.75 mmol) were stirred in 5 mL of 1,4-dioxane at room temperature for 2 h and purged with dry Argon. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with AcOEt (3 × 5 mL), and dried with $MgSO_4$, filtered and concentrated under vacuum to afford **5a** (0.168 g; 0.62 mmol; yield 98%) as a colorless oil. A mixture of **5a** (0.182 g; 0.7 mmol) and 2-picolylamine (1 mL; 9.7 mmol) was stirred in a warm water bath (40 °C) overnight. After the total consumption of **5a**, the remaining 2-picolylamine was recovered by distillation at reduced pressure (50 °C; 2 mmHg). The crude product obtained was purified by column chromatography (hexane/AcOEt 100:0 to AcOEt/EtOH/TEA 90:7:3) to afford **6a** as a yellowish oil (0.233 g; 0.62 mmol; yield 88%). To a solution of **6a** (0.128 g; 0.34 mmol) in 2 mL of methanol was added salicylaldehyde (0.046 g; 0.38 mmol) and stirred at room temperature for 6 h. After removal of solvent the obtained pale orange oil was dissolved in 3 mL of dichloromethane and sodium triacetoxyborohydride (0.108 g; 0.49 mmol) was added. The mixture was stirred for 12 h and 120 μL of saturated solution of KF (0.114 g; 1.96 mmol) was added. Solvent was removed and the solid residue was extracted with AcOEt (3 × 10 mL), dried, filtered, and purified by column chromatography (AcOEt/EtOH/TEA 90:7:3) to afford $\mathbf{H_3L^1}$ as a colorless oil (0.086 g; 0.18 mmol; yield 52%). $\mathbf{H_3L^{2–3}}$ were synthesized similarly, and the selected spectroscopic data of **4a**, **5a**, **6a**, and $\mathbf{H_3L^{1–3}}$ are as follows.
Compound ***4a***: white solid; mp: 94–96 °C; ^{1}H NMR (δ): 7.35–7.25 (m, 5H), 7.17 (dt, *J* = 7.6, 1.4, 1H), 7.01 (dd, *J* = 7.6, 1.3, 1 H), 6.86 (dd, *J* = 8.2, 0.9, 1 H), 6.79 (dt, *J* = 7.5, 1.2, 1 H), 4.07–4.00 (m, 1H), 3.93 (d, *J* = 13.9, 1 H), 3.76 (d, *J* = 13.7, 2 H), 3.63 (d, *J* = 13.2 Hz, 1 H), 3.50–3.33 (m, 2H), 2.73–2.59 (m, 2H); ^{13}C (δ): 157.3, 136.5, 129.6, 129.1, 129.0, 128.7, 127.8, 122.0, 119.5, 116.3, 69.1, 58.8, 58.3, 56.5, 48.2; ESI-HRMS: calcd. for $[C_{17}H_{20}ClNO_2+H]^+$ = 306.1261, found 306.1255.
Compound ***5a***: colorless oil; ^{1}H NMR (δ): 7.38–7.28 (m, 5 H), 7.17 (dt, *J* = 7.7, 1.5, 1 H), 7.00 (dd, *J* = 7.4, 1.3, 1 H), 6.86 (dd, *J* = 8.1, 1.0, 1 H), 6.78 (dt, *J* = 7.4, 1.2, 1 H), 4.09–3.90 (m, 2 H), 3.73–3.62 (m, 2 H), 3.17–3.11 (m, 1 H), 2.92 (dd, *J* = 13.9, 3.4, 1 H), 2.75–2.72 (m, 1 H), 2.44–2.37 (m, 2H); ^{13}C NMR (δ): 157.6, 136.5, 129.6, 129.0, 128.9, 128.7, 127.8, 121.7, 119.4, 116.2, 58.8, 58.0, 55.3, 49.8, 44.9; ESI-HRMS: calcd. for $[C_{17}H_{19}NO_2+H]^+$ = 270.1494, found 270.1491.
Compound ***6a***: yellowish oil; ^{1}H NMR (δ): 8.53 (d, *J* = 4.9, 1 H), 7.61 (dt, *J* = 7.7, 1.7, 1 H), 7.34–7.25 (m, 5 H), 7.21–7.13 (m, 3 H), 6.99 (dd, *J* = 7.4, 1.2, 1 H), 6.84 (dd, *J* = 8.0, 0.9, 1 H), 6.76 (dt, *J* = 7.4, 0.8, 1 H), 3.96–3.90 (m, 1 H), 3.86 (s, 2H), 3.84 (d, *J* = 5.0, 2 H), 3.69 (s, 2H), 2.73–2.42 (m, 4 H). ^{13}C NMR (δ): 159.4, 157.6, 149.2, 136.9, 136.6, 129.7, 128.9, 128.8, 128.5, 127.6, 122.33, 122.27, 122.1, 119.2, 116.2, 67.2, 58.7, 58.1, 57.1, 54.5, 53.3; ESI-HRMS: calcd. for $[C_{23}H_{27}N_3O_2+H]^+$ = 378.21815, found 378.21760.
Compound $\boldsymbol{H_3L^1}$: colorless oil; ^{1}H NMR (δ): 8.58 (d, *J* = 4.5, 1 H), 7.64 (dt, *J* = 7.7, 1.7, 1 H), 7.32–7.27 (m, 2 H), 7.23–7.18 (m, 4 H), 7.16–7.09 (m, 2 H), 6.98–6.95 (m, 2 H), 6.83 (d, *J* = 8.1, 2 H), 6.76 (t, *J* = 7.4, 2 H), 4.16–3.71 (m, 6 H), 3.67–3.59 (m, 3 H), 2.54–2.43 (m, 4 H); ^{13}C NMR (δ): 157.5, 157.4, 157.3, 148.8, 137.2, 136.8, 129.7, 129.6, 129.2, 128.9, 128.7, 128.5, 127.5, 123.1, 122.6, 122.4, 122.3, 119.2, 119.1, 116.7, 116.1, 66.6, 58.8, 58.7, 58.6, 58.5, 58.2, 57.3; IR (KBr): ν = 3058, 3028, 2830, 1614, 1588, 1488, 1374, 1255, 1183, 1151, 1035, 979, 870, 802, 754, 701, 636, 455, 405 cm^{-1}; ESI-HRMS: calcd. for $[C_{30}H_{33}N_3O_3+H]^+$ = 484.2600, found 484.2589.
Compound $\boldsymbol{H_3L^2}$: colorless oil; ^{1}H NMR (δ): 8.58 (d, *J* = 4.5, 1 H), 7.63 (dt, *J* = 7.7, 1.8, 1 H), 7.23–7.13 (m, 4 H), 7.11 (s, 4 H), 6.99–6.95 (m, 2 H), 6.84 (dd, *J* = 8.2, 0.9, 2 H), 6.79–6.73 (m, 2 H), 4.16–3.77 (m, 6 H), 3.73–3.57 (m, 3 H), 2.54–2.48 (m, 4 H), 2.31 (s, 3 H); ^{13}C NMR (δ): 157.5, 157.4, 157.3, 148,8, 137.3, 133.4, 129.74, 129.69, 129.2, 129.0, 128.8, 123.2, 122.6, 122.4, 122.2, 119.2, 119.1, 116.7, 116.2, 66.5, 58.8, 58.6, 58.5, 58.3, 57.9, 57.3, 21.1; IR (KBr): ν = 3048, 2924, 2828, 1715, 1588, 1488, 1375, 1254, 1184, 1151, 1036, 970, 871, 803, 755, 703, 636, 485, 455, 407 cm^{-1}; ESI-HRMS: calcd. for $[C_{31}H_{35}N_3O_3+H]^+$ = 498.2757, found 498.2771.
Compound $\boldsymbol{H_3L^3}$: yellow oil; ^{1}H NMR (δ): 8.58 (d, *J* = 4.9, 1 H), 7.65 (dt, *J* = 7.7, 1.8, 1 H), 7.36 (s, 3 H), 7.36–7.14 (m, 3 H), 7.10 (dd, *J* = 8.5, 2.3, 2 H), 6.98–6.93 (m, 2 H), 6.87–6.83 (m, 2 H), 6.80–6.74 (m, 2 H), 4.00–3.75 (m, 6 H), 3.69–3.59 (m, 3 H), 2.56–2.40 (m, 4 H); ^{13}C NMR (δ):157.4, 157.2, 156.3, 148.8, 137.3, 136.6, 129.7, 129.6, 129.3, 128.6, 128.5, 128.3, 127.62, 123.9, 123.6, 123.1, 122.6, 122.3, 119.2, 117.5, 116.8, 66.6, 58.8, 58.6, 58.5, 57.6, 57.1; IR (KBr): ν = 3051, 2924, 2837, 1595, 1585, 1481, 1375, 1265, 1251, 1180, 1151, 1029, 979, 908, 819, 736, 703, 669, 642 cm^{-1}; ESI-HRMS: calcd. for $[C_{30}H_{32}ClN_3O_3+H]^+$ = 518.2210, found 518.2196.
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