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Efficient Synthesis of a Porphyrin–N-Tripod Conjugate with Covalently Linked Proximal Ligand: Toward New-Generation Active-Site Models of Cytochrome *c* Oxidase

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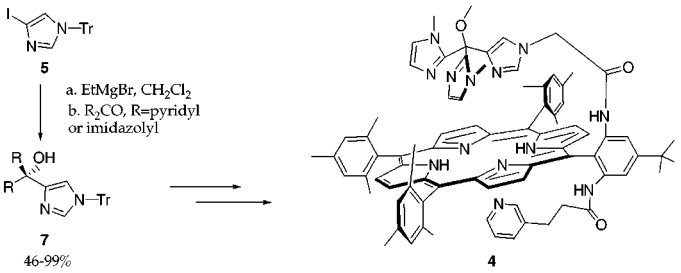
ABSTRACT



A new-generation cytochrome *c* oxidase active-site model compound (4) featuring both a trisimidazolyl moiety and a proximal base has been designed and efficiently synthesized. During this study, a facile method based on the chemistry of a 4-magnesioimidazole derivative to synthesize 4-imidazolyl-containing tripodal ligands (7) has been developed.

Cytochrome *c* oxidase (C*c*O), the terminal enzyme of the respiratory chains of mitochondria and aerobic bacteria, catalyzes the $4e^-$, $4H^+$ reduction of O_2 to H_2O.[1] The active sites of cytochrome *c* oxidase in bovine heart[2] and *Paracoccus denitrificans*[3] have recently been structurally characterized by X-ray diffraction. These structures demonstrate that, as previously surmised from indirect evidence, the O_2-binding/activating site in C*c*O is composed of a myoglobin-type iron center (heme a_3) and a copper atom (Cu_B) coordinated with three imidazoles from histidine residues on the "distal" side. Significant progress has been made in the construction of covalently linked model compounds which closely resemble the heme a_3/Cu_B active site to elucidate the mechanism of O_2 reduction. Those previous active-site models usually contain an *ortho*-substituted *meso*-phenylporphyrin connected with imidazolyl,[4] pyrazolyl,[5] or multipyridyl moieties[6] or triazacyclononane-type protocols[4c,7] through a linker on the "distal" side and/or a proximal base, such as model compounds **1** and **2** (Figure 1). Both **1** with Co(II) and Cu(I) inside[7c] and **2** with Fe(II) and Cu(I) inside[4f] showed

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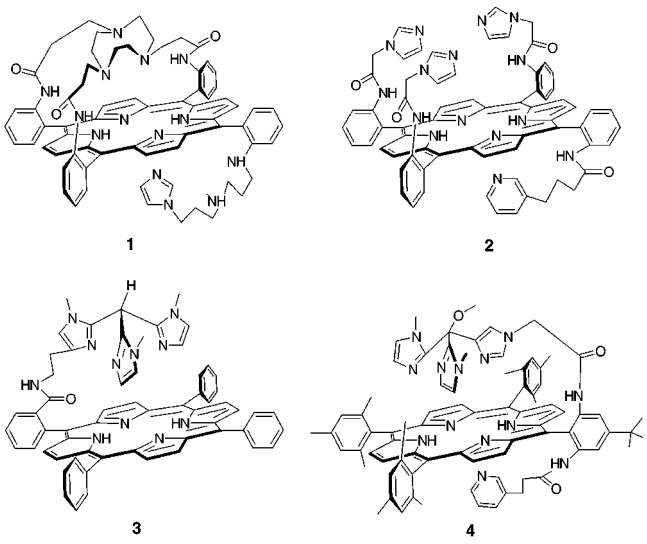
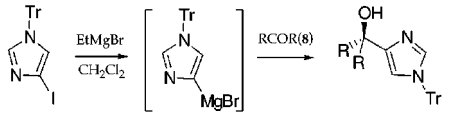


Figure 1.

clean electroreduction of O_2 to H_2O. Recently, Naruta et al.[8] reported a new active-site model compound (**3**) in which a trisimidazolylmethane known to give stable complexes with copper(I) ions[9] was combined with a porphyrin through an amide linkage. However, the synthesis of trisimidazolylmethane was inefficient because a tedious protection and a low-yield $Pd(PPh_3)_4$-catalyzed coupling reaction were employed. Furthermore, there was no built-in proximal base as in C*c*O. In our continuing efforts to design and synthesize more congruent structural models of the C*c*O active site, we have focused on developing efficient strategies to construct fully covalently linked model compounds with both a distal trisimidazolyl Cu-binding site and a promixal base. Herein we report a facile method to synthesize mono-4-imidazolyl-containing tridentate ligands, and its application in the synthesis of a new-generation model compound (**4**).

Commercially available 4-iodo-1-tritylimidazole (**5**)[10] can undergo magnesium−iodine exchange with a Grignard reagent to give selectively a 4-magnesioimidazole intermediate (**6**), which then attacks carbonyl compounds. This protocol has been used to synthesize not only monoimidazole compounds of pharmaceutical significance[11] but also a wide range of 4-imidazolyl-containing multidentate ligands for biomimetic studies.[12] To our knowledge there is no previous study using **5** as a key synthon to make mono-4-imidazolyl-containing tridentate ligands (**7**) which can be deprotected and further functionalized through the N-1 position. As a part of our active-site model studies, we set forth to study the reaction of 4-magnesio-1-tritylimidazole (**6**) with bisimidazolyl and bispyridyl ketones (**8**)[13] (Scheme 1).

Scheme 1



As shown in Table 1, 4-magnesio-1-tritylimidazole (**6**) (1.2 equiv) which was derived from **5** (1.2 equiv) and EtMgBr (1.2 equiv) in CH_2Cl_2 reacted with bis(1-methyl-2-imidazolyl)ketone (**8a**) (1.0 equiv) to give the trisimidazolylcarbinol **7a** in 67% yield. Interestingly, when the more lipophilic bisimidazolyl ketones **8b** and **8c** were used, the yield of the reaction increased to 91% and 99%, respectively. Bispyridyl ketone (**8d**) can also react with **6** to form a tridentate ligand (**7d**) featuring pyridine donors in 84% yield. However, when the C-4 or C-5 position on the pyridine rings of **8** was substituted by methyl group (**8e** or **8f**), the yield of this reaction decreased dramatically to 55% and 46%, respectively. No desired addition product was obtained when bis(3-methyl-2-pyridyl)ketone or bis(6-methyl-2-pyridyl)ketone was treated with **6**, probably because of the interference of steric hindrance or an acidic methyl group adjacent to nitrogen in the corresponding ketone. We also found that the reactivities of the bisimidazolyl ketones (**8a**−**c**) are relatively higher than those of the bispyridyl ketones (**8d**−**f**) in this reaction. All of these tripodal ligands are not only

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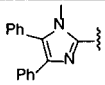
Table 1. Synthesis of 4-Imidazolyl-Containing Tripodal Ligands from **5**, EtMgBr, and R_2CO (**8**)[a]

entry	R_2CO R	**8**	product **7**	isolated yield (%)
1		**8a**	**7a**	67
2		**8b**	**7b**	91
3		**8c**	**7c**	99
4		**8d**	**7d**	84
5		**8e**	**7e**	55
6		**8f**	**7f**	46

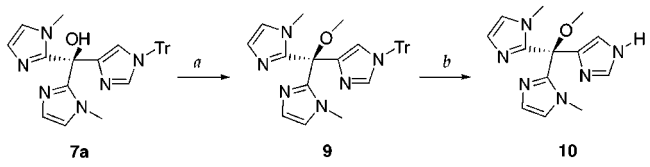
[a] Reaction conditions: **5** (1.2 equiv) reacted with EtMgBr (1.2 equiv) in CH_2Cl_2 at room temperature for 2 h; then **8** (1.0 equiv) was added and the resulting mixture was stirred at room temperature for 24−48 h.

important building blocks in C*c*O active-site model studies but are also possible carbonic anhydrase (CA) mimics.[14]

Trisimidazolylcarbinol (**7a**) was converted to the methylated tripod (**9**) in a NaH/CH_3I/THF system in 93% yield. Surprisingly, mainly decomposed compounds were obtained in a NaH/CH_3I/DMF system due to retro-aldol condensation. The trityl groups of the tripodal ligands can be easily removed in mild acidic conditions. When **9** was stirred in 85% aqueous TFA at room temperature overnight, the free NH imidazolyl tripod (**10**) was obtained in 98% yield (Scheme 2).

After the free NH imidazolyl tripod (**10**) was obtained, a customized bis-faced porphyrin synthon (**11**) which contains

Scheme 2[a]

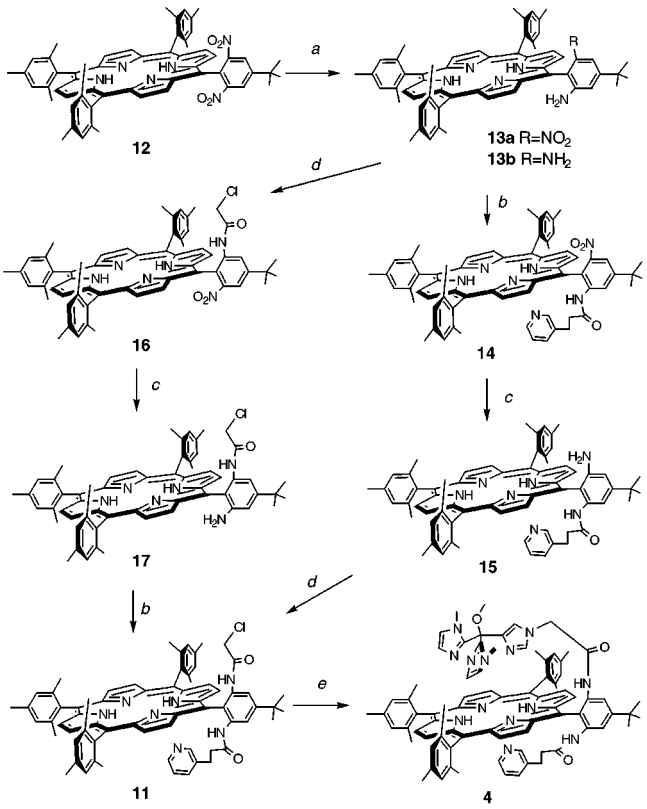


7a 9 10

[a] Reagents and conditions: (a) NaH, CH_3I, THF, rt, overnight, 93%; (b) 85% aqueous TFA, rt, overnight, 98%.

a chloroacetamide and a proximal base on two sides of the same phenyl ring was desired. In this case, not only the ^1H NMR spectra of all intermediates were simplified but also the atropisomers were minimized. The chloroacetamide functional group is a potential linker between the porphyrin and the tripod on the basis of the well-documented multiple S_N2 reactions.[7d,15] As shown in Scheme 3, the bis-faced

Scheme 3[a]



[a] Reagents and conditions: (a) $SnCl_2 \cdot 2H_2O$, concentrated HCl, CH_2Cl_2, 0 °C, 64% for **13**a, 28% for **13b**; (b) 3-(3′-pyridyl)propionyl chloride, *N*,*N*-diethylaniline, DMF, 68% for **14**, 63% for **11**; (c) $SnCl_2 \cdot 2H_2O$, concentrated HCl, CH_2Cl_2, rt, 86% for **15**, 94% for **17**; (d) chloroacetyl chloride, Et_3N, THF, 0 °C → rt, 84% for **11**, 92% for **16**; (e) **10**, Cs_2CO_3, CH_3CN, rt, 32%.

dinitroporphyrin (**12**) was prepared from the mixed condensation[16] of mesitaldehyde and 4-*tert*-butyl-2,6-dinitrobenzaldehyde[17] with pyrrole in the presence of 3 Å molecular sieves and $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 at room temperature for 1 h

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followed by oxidation of the resulting porphyrinogen with DDQ. The yield of this mixed-condensation reaction is extremely dependent on not only the ratio of the two aldehydes but also on the condensation time. The optimized ratio of mesitaldehyde/4-*tert*-butyl-2,6-dinitrobenzaldehyde was 6/1 and the condensation time was 1 h. Interestingly, compound **12** can be selectively reduced by $SnCl_2 \cdot 2H_2O$ in the presence of concentrated HCl in CH_2Cl_2 at 0 °C to give monoaminoporphyrin (**13a**) in 64% yield. Thus, selective acylation could be achieved using **13a** instead of diaminoporphyrin (**13b**) as a precursor. Acylation of **13a** with 3-(3′-pyridyl)propionyl chloride[18] using *N*,*N*-diethylaniline as a base in DMF gave **14**, followed by reduction to give **15** in 86% yield. Then **15** was acylated with chloroacetyl chloride while triethylamine served as a base. The reaction afforded **11** which contains all the functions as described above in 84% yield. Alternatively, **12** could undergo acylation with chloroacetyl chloride first to give **16**, which was reduced by $SnCl_2 \cdot 2H_2O$, and then followed by condensation with the proximal base to give **11**. The overall yield of the latter route is 54%, which is higher than the former one (49% from **13a**).

Subsequently, efforts were made to complete the synthesis of the new model compound (**4**). The tripodal ligand (**10**) was condensed with porphyrin (**11**) in the presence of Cs_2CO_3 in CH_3CN at room temperature to give **4** in 32% yield (Scheme 3). In this model compound, the distance between the center of the tripod and the core of porphyrin can be controlled by using different linkers between them. Also, the structures and properties of the building blocks "distal tridentate ligand" and "proximal base" can be readily varied. It can be foreseen that a large number of interesting model compounds of this series can be efficiently synthesized according to the present method.

In summary, we have developed a general method to synthesize tripodal ligands (**7**) containing 4-imidazolyl moieties based on the reaction of 4-magnesioimidazole derivative with bisimidazolyl and bispyridyl ketones (**8**). We have also designed and efficiently synthesized a new-generation active-site analogue (**4**) featuring both a distal trisimidazolyl moiety and a proximal base. The facile routes to the new series of tridentate ligands (**7**) and the modular approach to construct the model compound (**4**) will open up new possibilities in biomimetic heme chemistry.

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Supporting Information Available: Experimental procedures and characterizations for compounds **4**, **7a**−**f**, **8a**−**f**, **9**−**12**, **13a**−**b**, and **14**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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