New Imidazole-Based Tripodal Ligands as Cu_B Site Mimics of Cytochrome *c* Oxidase

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Introduction

Cytochrome *c* oxidase (C*c*O) is the terminal enzyme of the respiratory chains of mitochondria and aerobic bacteria.[1] Recent high-resolution X-ray diffraction analyses[2] have disclosed that the active site of C*c*O is composed of a five-coordinate myoglobin-type iron center (heme a_3) with an imidazole ligand from a histidine residue on the proximal side of the heme and a copper atom (Cu_B) coordinated to three histidine imidazoles on the distal side. Moreover, one of the Cu_B ligands, His^{240}, is cross-linked through a C−N bond to the phenol residue from Tyr^{244}, which has been postulated to serve as a hydrogen atom donor during the $4H^+$, $4e^-$ reduction of O_2 to H_2O.[3]

In the course of our long-term program on biomimetic studies of C*c*O, a series of active-site model compounds based on the $\alpha_3\beta$-5,10,15,20-tetra(2′-aminophenyl)porphyrin ($\alpha_3\beta$-TAPP) template have been designed and synthesized.[4] For example, model **1** bears a covalently linked TACN-type tridentate ligand on the distal side (Figure 1).[4c] To make these models structurally closer to the active site in C*c*O, our recent effort has been devoted to the preparation of new superstructures such as compound **2** (Figure 1)[4g] containing three individual distal imidazole ligands. However, our preliminary electrochemical studies on catalytic O_2 reduction have shown

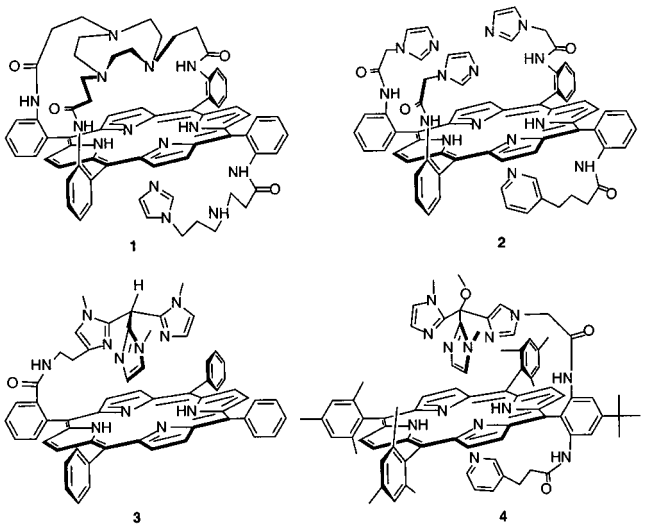

Figure 1.

that these compounds can lose copper after a few cycles on a graphite electrode, making the analyses of their electrochemical properties more difficult. Recently, models **3** and **4** (Figure 1) were reported by Naruta et al.[5] and our group.[6] Although the imidazole-based tripod in each model binds copper tightly,[7] this tripodal complex is linked to the porphyrin through a single amide bond. This single-point attachment allows free rotation of the tripod on the distal side, interfering with the formation of stable binuclear heme(Fe)/trisimidazole(Cu) oxygen adducts. Therefore, we set forth to prepare several novel model compounds containing two or three links between tripodal ligands and customized porphyrins such as $\alpha_3\beta$-TAPP and $\alpha\beta\alpha\beta$-TAPP employing Michael acceptor,[4a−e,h] chloroacetamido,[4d] or isocyanate groups[8] as links.

Although the preparation of specialized porphyrins[4] based on the $\alpha_3\beta$-TAPP and $\alpha\beta\alpha\beta$-TAPP templates and simple imidazole-based tripods[9] has been well developed, the chemistry for synthesizing trisimidazoles containing two or three functional groups is still not satisfactory. To the best of our knowledge, the −OH free precursor of compound **5** (Figure 2) synthesized from 1-methyl-1*H*-4-histamine (**9**) by Potvin et al.[9d] is the only example of this class to date. Herein, we present a practical synthesis of several new imidazole-based tridentates **6**, **7**, and **8** (Figure 2) containing −OH or $-NHCH_3$ groups as important intermediates for model studies of C*c*O.

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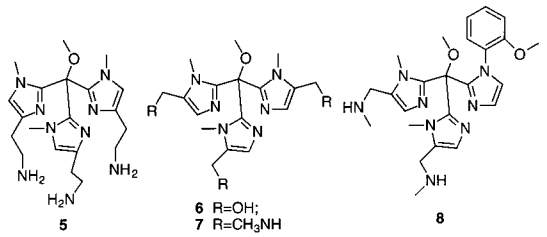
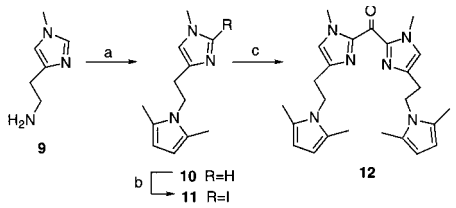


Figure 2.

Scheme 1[a]



[a] Reagents and conditions: (a) acetonylacetone, AcOH, benzene, reflux, overnight, 81%; (b) *n*-BuLi, I_2, −78 → 0 °C, 51%; (c) *n*-BuLi, $(EtO)_2CO$, −78 → room temperature, overnight, 68%.

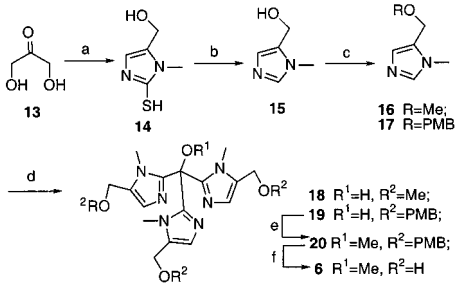
Results and Discussion

Initially, we planned to use Potvin's procedure[9d] to prepare compound **5** and then condense it with $\alpha_3\beta$-TAPP through urea-type links. 1-Methyl-1*H*-4-histamine (**9**) can be selectively prepared from histamine in high yield following a modified procedure;[10] however, it was reported that the silylation of the amino group in compound **9** with Me_3SiCl gives a low yield (37%) of the corresponding protected intermediate.[9d] Moreover, this trimethylsilyl protective group is very labile in hydroxylic media[11] and the corresponding intermediate is hard to purify by ordinary chromatography. Hence, after some trials using the trimethylsilyl group, we focused our effort on finding other suitable protective groups for the free $-NH_2$ in compound **9**.

As shown in Scheme 1, the $-NH_2$ group in compound **9** is readily converted to its 2,5-dimethyl pyrrole[11] derivative (**10**), which is stable and can be easily obtained in a much higher yield (81%) compared with the trimethylsilyl-protected form of compound **9**. However, treatment of compound **10** with *n*-BuLi, followed by the addition of methyl chloroformate, only generates the bidentate ligand **12**. None of the desired tripodal ligand is formed by treating compound **12** with either the 2-imidazolyl anion of compound **10** or the Grignard reagent of compound **11** or by treating the latter with diethyl carbonate, presumably due to the steric hindrance of the two 2,5-dimethyl pyrrole moieties.

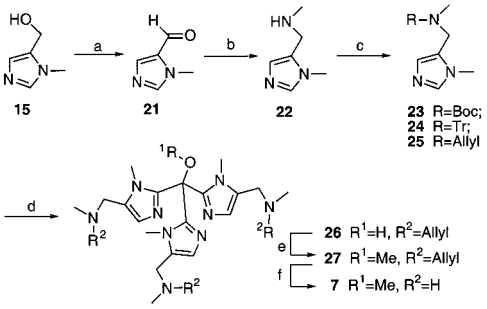
The tridentate ligand **6** having one carbon less in the side chains compared to compound **5** was then prepared. As shown in Scheme 2, the imidazole alcohol **15** is prepared in 46% yield in two steps from 1,3-dihydroxyacetone (**13**) following Rapoport's procedure[12] with some modifications. Compound **15** was then converted to its corresponding methyl ether **16** in order to test the feasibility of the condensation for preparing a tripodal

Scheme 2[a]



[a] Reagents and conditions: (a) KSCN, CH_3NH_2, acetic acid, *n*-butanol, 3 days, 62%; (b) HNO_3, catalytic $NaNO_2$, 75%; (c) NaH, CH_3I, DMF, 60% (for **16**) or NaH, *p*-methoxybenzylic bromide, DMF, 61% (for **17**); (d) *n*-BuLi, methyl chloroformate, THF, −78 → room temperature, 24 h, 92% (from **16** to **18**) and 77% (from **17** to **19**); (e) NaH, CH_3I, THF, 73%; (f) CAN, 9/1 (*v*/*v*) CH_2Cl_2/H_2O, room temperature, overnight, 62%.

Scheme 3[a]



[a] Reagents and conditions: (a) MnO_2, $CHCl_3$, reflux, 48 h, 71%. (b) 40% aqueous CH_3NH_2, CH_3OH, room temperature, overnight; $NaBH_4$, reflux, overnight, 93%. (c) $(Boc)_2O$, $NaHCO_3$, 2/1 (v/v) $CHCl_3/H_2O$, 72% (for **23**); triphenylmethyl bromide, Et_3N, DMF, 75% (for **24**); allyl bromide, Cs_2CO_3, DMF, 82% (for **25**). (d) *n*-BuLi, $(EtO)_2CO$, −78 → room temperature, 24 h, 35% (from **25** to **26**). (e) NaH, CH_3I, THF, 51%. (f) Catalytic $Pd(PPh_3)_4$, *p*-tolylsulfinic acid, CH_2Cl_2, 85%.

ligand. When compound **16** is treated with *n*-BuLi, followed by the addition of methyl chloroformate, the tripodal ligand **18** is formed in 92% yield. Encouraged by this result, we then transformed compound **15** to its corresponding *p*-methoxybenzyl (PMB) ether in order to differentiate the three primary alcohols from the tertiary alcohol in the following steps. When 3 equiv of the 2-imidazolyl anion of compound **17** react with 1 equiv of methyl chloroformate, a 77% yield of tripod **19** is formed. The tridentate **6** is produced in 45% yield by methylation of compound **19** and oxidative deprotection of the PMB groups in compound **20** with ammonium cerium nitrate (CAN).[13]

Subsequently, $-NHCH_3$-functionalized tridentates **7** and **8** were also prepared. As shown in Scheme 3, aldehyde **21**, obtained by oxidizing compound **15** with activated MnO_2, is readily converted to the secondary amine **22** by condensation with methylamine and reduction of the corresponding imine intermediate with $NaBH_4$. Whereas *tert*-butoxylcarbonyl (Boc)- or trityl (Tr)-protected intermediates **23** and **24** cannot generate the corresponding tripod by treatment with *n*-BuLi and diethyl carbonate, the intermediate **25**, filled with the

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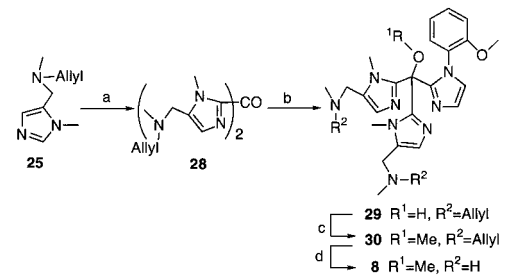
Scheme 4[a]



[a] Reagents and conditions: (a) *n*-BuLi, $(EtO)_2CO$, −78 → room temperature, 24 h, 55%. (b) *n*-BuLi, 1-(2′-methoxyphenyl)-1*H*-imidazole, THF, −78 °C, 1 h; **28**, THF, −78 → room temperature, 24 h, 55%. (c) NaH, CH_3I, THF, 51%. (d) Catalytic $Pd(PPh_3)_4$, *p*-tolylsulfinic acid, CH_2Cl_2, 83%.

less sterically hindered allylic protective group, gives a 35% yield of tripod **26**. No improved yield of the tripodal ligand **26** was obtained either by increasing the ratio of **25**/carbonyl substrate, by changing the reaction temperature, by adding *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), or by replacing *n*-BuLi with a milder lithiation reagent such as lithium *N*,*N*-di-*iso*-propylamine (LDA). Presumably, the interaction of the two sp^3 N atoms in compound **25** with lithium ion in the presence of *n*-BuLi or LDA reduces the reactivity of the corresponding substrate, resulting in a lower yield of the tripodal ligand **26** compared to that of compounds **18** and **19**. Methylation of compound **26** gives compound **27** in 51% yield. Only a 20% yield of tripod **7** is generated when a $Pd_2(dba)_3$/dppb/*o*-thiolbenzoic acid/THF system[14a] is used to remove all of the allylic groups in compound **27**, but the yield increases to 85% when a $Pd(PPh_3)_4$/*p*-tolylsulfinic acid/CH_2Cl_2 system is employed.[14b]

When 2 equiv of the 2-imidazolyl anion of compound **25** react with 1 equiv of diethyl carbonate, a 55% yield of bidentate **28** is formed (Scheme 4). The treatment of compound **28** with 1 equiv of 1-(2′-methoxyphenyl)-1*H*-2-imidazolyl anion generates the tripodal ligand **29** in 55% yield. Methylation of compound **29** and the subsequent deprotection of the allylic groups in compound **30** yield the tripodal ligand **8**, which contains a functionalized phenol moiety as a projected Tyr^{244} mimic.

In summary, we have prepared three new functionalized tripodal ligands **6**, **7**, and **8** as Cu_B site mimics of C*c*O using the readily available imidazole alcohol **15** as a starting material. It should be noted that all these tripodal ligands could serve as active-site mimics of other metalloenzymes such as zinc enzymes.[9a−c] The condensation of these ligands with specialized porphyrins as well as the metalation, coordination, and electrochemical properties of the model compounds is currently being investigated, and the results will be reported in due course.

Experimental Section

All reagents were used as supplied commercially without further purification unless otherwise noted. Melting points are uncorrected. ^1H NMR spectra were recorded at 400 and 500 MHz; ^{13}C NMR spectra were recorded at 100 and 125 MHz. Mass spectra were measured by the Mass Spectrometry Facility at the University of California, San Francisco.

4-[2′-(2″,5″-Dimethyl-1″-pyrrolyl)ethyl]-1-methyl-1*H*-imidazole (10). A mixture of 1-methyl-1*H*-4-histamine (**9**) (2.00 g, 16.0 mmol), acetonylacetone (1.86 g, 16.3 mmol), and acetic acid (0.40 g, 6.7 mmol) in benzene (40 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and then stirred with K_2CO_3 for 30 min, and the solid was filtered off. The filtrate was concentrated, and the residue was purified by preparative silica gel thin-layer chromatography using 1/3 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 2.63 g of compound **10** as a pale yellow liquid in 81% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 6.54 (s, 1H), 5.76 (s, 2H), 4.02 (t, J = 7.9 Hz, 2H), 3.63 (s, 3H), 2.83 (t, J = 7.9 Hz, 2H), 2.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.40, 137.33, 127.48, 117.19, 104.88, 43.69, 33.23, 29.92, 12.36. MS (*m*/*z*): 203(M^+), 188, 108(100), 95, 83, 67. HRMS: calcd for $C_{12}H_{17}N_3$ (M^+), 203.142; found, 203.142.

4-[2′-(2″,5″-Dimethyl-1″-pyrrolyl)ethyl]-2-iodo-1-methyl-1*H*-imidazole (11). To a solution of compound **10** (814 mg, 4.0 mmol) in dry THF (80 mL) was added *n*-BuLi (1.6 mL, 2.5 M in hexanes, 4.0 mmol) at −78 °C under an atmosphere of N_2, and the solution was stirred at this temperature for 30 min. Then, a solution of I_2 (1.07 g, 4.2 mmol) in dry THF (10 mL) was added and the resulting mixture was allowed to warm to 0 °C and stirred for 30 min. The reaction was quenched by adding several drops of a saturated aqueous solution of NH_4Cl. The solvent was removed, and the residue was purified by preparative silica gel thin-layer chromatography using 1/3 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 671 mg of compound **11** as a pale yellow liquid in 51% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 6.66 (s, 1H), 5.74 (s, 2H), 3.99 (t, J = 7.7 Hz, 2H), 3.55 (s, 3H), 2.81 (t, J = 7.7 Hz, 2H), 2.17 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.52, 127.50, 121.49, 104.98, 43.49, 36.56, 30.04, 12.41. MS (FAB, *m*/*z*): 342 (M^+ + Na), 331 (M^+ + 2), 330 (M^+ + 1, 100), 328 (M^+ − 1), 235, 202.

Bis{4-[2′-(2″,5″-dimethyl-1″-pyrrolyl)ethyl]-1-methyl-1*H*-2-imidazolyl}ketone (12). To a solution of compound **10** (370 mg, 1.82 mmol) in dry THF (20 mL) was added *n*-BuLi (0.76 mL, 2.5 M in hexanes, 1.91 mmol) at −78 °C, and the solution was stirred at this temperature for 30 min. Then, $(EtO)_2CO$ (65 mg, 0.55 mmol) was added to the solution and the resulting mixture was allowed to warm to room temperature and stirred at room temperature for 24 h. The reaction was quenched by the addition of several drops of a saturated aqueous solution of NH_4Cl. The solvent was removed, and the residue was purified by preparative silica gel thin-layer chromatography using 1/3 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 162 mg of compound **12** as a pale yellow liquid in 68% yield based on the amount of the carbonyl substrate. ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 2H), 5.76 (s, 4H), 4.06 (t, J = 7.8 Hz, 4H), 3.93 (s, 6H), 2.96 (t, J = 7.8 Hz, 4H), 2.17 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.94, 142.52, 139.98, 127.53, 124.72, 105.09, 43.16, 35.68, 29.97, 12.49. MS (*m*/*z*): 432(M^+), 338, 243, 203, 149, 108(100), 71, 57. HRMS: calcd for $C_{25}H_{32}N_6O$ (M^+), 432.264; found, 432.264.

5-Hydroxymethyl-2-mercapto-1-methyl-1*H*-imidazole (14). This compound was prepared following Rapoport's procedure[12] with some modifications. A mixture of 1,3-dihydroxyacetone dimer (72.0 g, 0.8 mol), KSCN (116.6 g, 1.2 mol), and methylamine hydrochloride (67.5 g, 1.0 mol) in acetic acid (90 mL) and *n*-butanol (600 mL) was mechanically stirred in an ultrasonic bath for 3 days. The resulting suspension was diluted with water and washed with $CHCl_3$ several times in a separatory funnel. The aqueous layer was filtered, and the solid was washed with $CHCl_3$ and dried over P_2O_5 in vacuo to give 72 g of compound **14** as a pale yellow solid in 62% yield. Mp: 200−202 °C dec. ^1H NMR (400 MHz, d^6-DMSO): δ 11.99 (s, 1H), 6.80 (s, 1H), 5.19 (s, 1H), 4.31 (s, 2H), 3.43 (s, 3H).

5-Hydroxymethyl-1-methyl-1*H*-imidazole (15). This compound was prepared following Rapoport's procedure[12] with some modifications. To a vigorously stirred solution of $NaNO_2$ (100 mg, 1.45 mmol) in aqueous nitric acid (30 mL, 2.4 M in water) was added compound **14** (5.1 g, 35.4 mmol) in small portions over a 2 h period at 0 °C. After the addition was complete, the yellow solution was stirred at room temperature overnight. The reaction mixture was adjusted to pH 9.0 by adding solid $NaHCO_3$

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and evaporated to dryness in vacuo. The residue was extracted with hot $CHCl_3$, and the extract was dried over Na_2SO_4. The solvent was removed, and the residue was dried over P_2O_5 in vacuo to give 3.0 g of compound **15** as a pale yellow solid in 75% yield. Mp: 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 1H), 6.77 (s, 1H), 4.56 (s, 2H), 3.66 (s, 3H). ^{1}H NMR (400 MHz, d^6-DMSO): δ 7.53 (s, 1H), 6.77 (s, 1H), 4.42 (s, 2H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.42, 131.71, 127.52, 53.50, 31.51. ^{13}C NMR (100 MHz, d^6-DMSO): δ 138.55, 131.97, 127.13, 52.54, 31.00.

5-Methoxymethyl-1-methyl-1*H*-imidazole (16). To a solution of compound **15** (1.0 g, 8.9 mmol) in dry DMF (25 mL) was added NaH (392 mg, 9.8 mmol, 60% in paraoil), and the resulting mixture was stirred at room temperature for 1 h. Subsequently, CH_3I (0.61 mL, 9.8 mmol) was added to the solution and the mixture was stirred at room temperature overnight. The solvent was removed, and the residue was purified by silica gel column chromatography using 1/1 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3) as the eluent to give 675 mg of compound **16** as a yellow liquid in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.01 (s, 1H), 4.41 (s, 2H), 3.65 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.19, 130.03, 127.78, 63.34, 57.11, 31.36. MS (*m*/*z*): 126 (M^+), 111, 95 (100), 83, 77, 57. HRMS: calcd for $C_6H_{10}N_2O$ (M^+), 126.079; found, 126.079.

5-[(4′-Methoxyphenyl)methoxymethyl]-1-methyl-1*H*-imidazole (17). This compound was obtained as a yellow liquid in 61% yield following the procedure for preparing compound **16** using *p*-methoxybenzylic bromide[15] instead of CH_3I as the electrophile. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.00 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.17 (s, 1H), 4.47 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.46, 139.38, 130.21, 129.84, 129.77, 128.14, 114.00, 71.14, 60.72, 55.42, 31.69. MS (*m*/*z*): 232 (M^+), 202, 138, 121 (100), 109, 95, 82, 77. HRMS: calcd for $C_{13}H_{16}N_2O_2$ (M^+), 232.121; found, 232.122.

Tris(5-methoxymethyl-1-methyl-1*H*-2-imidazolyl)methyl Alcohol (18). To a solution of compound **16** (180 mg, 1.4 mmol) in dry THF (7 mL) was added *n*-BuLi (0.57 mL, 1.4 mmol, 2.5 M in hexanes) at −78 °C under an atmosphere of N_2, and the solution was warmed to −40 °C and stirred for 1 h. The solution was cooled to −78 °C again, and methyl chloroformate (34 mg, 0.35 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by adding several drops of a saturated aqueous solution of NH_4Cl; the solvent was removed, and the residue was purified by preparative silica gel thin-layer chromatography using 4/1 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 131 mg of compound **18** as a white semisolid in 92% yield based on the amount of the carbonyl substrate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 3H), 4.40 (s, 6H), 3.38 (s, 9H), 3.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.40, 130.35, 127.23, 71.99, 63.73, 57.19, 31.35. MS (*m*/*z*): 404 (M^+), 279, 231, 153, 126, 95 (100), 83, 57. HRMS: calcd for $C_{19}H_{29}N_6O_4$ (M^+ + 1), 405.225; found, 405.225.

Tris{5-[(4′-methoxyphenyl)methoxymethyl]-1-methyl-1*H*-2-imidazolyl}methyl Alcohol (19). This compound was obtained as a white semisolid in 77% yield following the procedure for preparing compound **18** using compound **17** instead of compound **16** as the substrate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.6 Hz, 6H), 6.90 (s, 3H), 6.86 (d, J = 8.6 Hz, 6H), 6.09 (s, 1H), 4.44 (s, 6H), 4.39 (s, 6H), 3.78 (s, 9H), 3.40 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.50, 147.60, 130.82, 129.88, 129.85, 127.65, 114.04, 72.14, 71.20, 61.07, 55.45, 31.77. MS (ESI, *m*/*z*): 723 (M^+ + 1), 705, 490 (100), 353, 258, 224.

Tris{5-[(4′-methoxyphenyl)methoxymethyl]-1-methyl-1*H*-2-imidazolyl}methyl Methyl Ether (20). To a solution of compound **19** (175 mg, 0.24 mmol) in dry THF (5 mL) was added NaH (11 mg, 0.27 mmol, 60% in paraoil), and the resulting mixture was stirred at room temperature for 1 h. Subsequently, CH_3I (38 mg, 0.27 mml) was added and the mixture was stirred at room temperature overnight. The reaction was quenched by adding several drops of a saturated aqueous solution of NH_4Cl. The solvent was removed, and the residue was purified by preparative silica gel thin-layer chromatography using 3/1 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 130 mg of compound **20** as a yellow liquid in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 8.6 Hz, 6H), 6.98 (s, 3H), 6.84 (d, J = 8.6 Hz, 6H), 4.43 (s, 6H), 4.38 (s, 6H), 3.78 (s, 9H), 3.48 (s, 3H), 3.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.23, 145.36, 130.40, 129.62, 129.54, 127.71, 113.75, 78.79, 71.00, 60.81, 55.17, 54.54, 31.80. MS (ESI, *m*/*z*): 737 (M^+ + 1), 736 (M^+, 100), 704, 567, 505, 233, 120.

Tris(5-hydroxymethyl-1-methyl-1*H*-2-imidazolyl)methyl Methyl Ether (6). A solution of compound **20** (130 mg, 0.18 mmol) and ammonium cerium nitrate (580 mg, 1.06 mmol) in CH_2Cl_2 (4.5 mL) and water (0.5 mL) was stirred at room temperature overnight. The solvent was removed, and the residue was diluted with water (10 mL). The aqueous solution was extracted several times with ether, and then the pH was adjusted to 9.0 by adding solid $NaHCO_3$. The solvent was removed, and the residue was extracted with a small amount of methanol. Subsequently, the organic portion was concentrated and the residue was purified by preparative silica gel thin-layer chromatography using 9/1 (*v*/*v*) $CHCl_3$/CH_3OH (saturated with NH_3 gas) as the eluent to give 41 mg of compound **6** as a white semisolid in 62% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 6.83 (s, 3H), 4.45 (s, 6H), 3.32 (s, 9H), 3.22 (s, 3H). ^{1}H NMR (400 MHz, d^5-pyridine): δ 7.17 (s, 3H), 4.80 (s, 6H), 3.80 (s, 3H), 3.76 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ 145.83, 136.28, 126.42, 79.92, 55.26, 54.45, 32.46. MS (*m*/*z*): 376 (M^+), 375 (M^+ − 1), 374 (M^+ − 2), 359, 266, 161, 130 (100), 83. HRMS: calcd for $C_{17}H_{22}N_6O_4$ (M^+ − 2), 374.1702; found, 374.1712.

1-Methyl-1*H*-imidazole-5-carboxaldehyde (21). This compound was prepared following Rapoport's procedure[12] with some modifications. A mixture of compound **15** (24.7 g, 0.22 mol) and activated MnO_2 (95.6 g, 1.1 mol) in $CHCl_3$ was refluxed for 48 h. The reaction mixture was cooled to room temperature and filtered through a Celite 545 column. The filter cake was washed with 5% CH_3OH in $CHCl_3$, and the filtrate was concentrated. The residue was purified by silica gel column chromatography using 1/19 (*v*/*v*) CH_3OH/$CHCl_3$ as the eluent to give 17.4 g of compound **21** as a pale yellow solid in 71% yield. Mp 52−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.77 (s, 1H), 7.60 (s, 1H), 3.93 (s, 3H).

***N*-Methyl-5-aminomethyl-1-methyl-1*H*-imidazole (22).** A solution of compound **21** (15.4 g, 0.14 mol) in CH_3NH_2 (36.0 mL, 0.42 mol, 40% in water) and CH_3OH (270 mL) was stirred at room temperature overnight, and then $NaBH_4$ (15.9 g, 0.42 mol) was cautiously added to the solution. The resulting mixture was stirred at room temperature for several hours and then refluxed overnight. The reaction mixture was cooled to room temperature and evaporated to dryness in vacuo. The resulting solid was extracted with hot $CHCl_3$, and the extract was dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was purified by silica gel column chromatography using 1/19 (*v*/*v*) CH_3OH/$CHCl_3$ (saturated with NH_3 gas) as the eluent to give 16.3 g of compound **22** as a pale yellow liquid in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 6.88 (s, 1H), 3.67 (s, 2H), 3.63 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.01, 129.63, 127.70, 44.63, 35.56, 30.98. MS (*m*/*z*): 125 (M^+), 95 (100), 83, 68. HRMS: calcd for $C_6H_{11}N_3$ (M^+), 125.095; found, 125.095.

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-5-aminomethyl-1-methyl-1*H*-imidazole (23).** To a mixture of compound **22** (2.0 g, 16 mmol) and $NaHCO_3$ (1.4 g, 16 mmol) in a biphasic solvent $CHCl_3$/H_2O (30 mL/15 mL) was added $(Boc)_2O$ (3.5 g, 16 mmol), and the resulting mixture was stirred at room temperature for 2 h and then refluxed for another 1 h. The reaction mixture was cooled to room temperature and extracted with $CHCl_3$. The extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was purified by preparative silica gel thin-layer chromatography using 3/1 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 2.6 g of compound **23** as a yellow oil in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 6.95 (s, 1H), 4.43 (s, 2H), 3.59 (s, 3H), 2.71 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.50, 138.99, 129.59, 127.49, 79.90, 40.73, 32.47, 31.54, 28.31. MS (*m*/*z*): 225 (M^+), 169, 124, 110, 95 (100), 83, 58. HRMS: calcd for $C_{11}H_{19}N_3O_2$ (M^+), 225.1477; found, 225.1478.

(15) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem.* **1998**, *63*, 6952−6967.

***N*-Trityl-*N*-methyl-5-aminomethyl-1-methyl-1*H*-imidazole (24).** To a solution of compound **22** (350 mg, 2.8 mmol) in dry DMF (10 mL) were added, respectively, dry Et_3N (425 mg, 4.2 mmol) and triphenylmethyl bromide (970 mg, 3.0 mmol). The resulting mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was purified by preparative silica gel thin-layer chromatography using 1/19 (*v*/*v*) CH_3OH/EtOAc as the eluent to give 770 mg of compound **24** as a yellow liquid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.5 Hz, 6H), 7.36 (s, 1H), 7.24−7.28 (m, 6H), 7.22 (s, 1H), 7.16 (t, J = 7.5 Hz, 3H), 3.47 (s, 3H), 3.30 (s, 2H), 2.03 (s, 3H). MS (*m*/*z*): 367 (M^+), 243 (100), 165, 95. HRMS: calcd for $C_{25}H_{25}N_3$ (M^+), 367.2048; found, 367.2050.

***N*-Allyl-*N*-methyl-5-aminomethyl-1-methyl-1*H*-imidazole (25).** A mixture of compound **22** (6.25 g, 50.0 mmol), allyl bromide (6.65 g, 55.0 mmol), and Cs_2CO_3 (19.5 g, 60.0 mmol) in dry DMF (120 mL) was stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in $CHCl_3$. The mixture was passed through a Celite 545 column, and the filter cake was washed with $CHCl_3$. The filtrate was concentrated, and the residue was purified by silica gel column chromatography using 1/1 (*v*/*v*) $CHCl_3$/hexanes (flushed with NH_3 gas) as the eluent to give 6.77 g of compound **25** as a yellow liquid in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 6.85 (s, 1H), 5.80 (m, 1H), 5.14 (m, 2H), 3.62 (s, 3H), 3.38 (s, 2H), 2.96 (d, J = 6.4 Hz, 2H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.29, 135.21, 128.96, 128.50, 117.48, 59.96, 50.12, 41.50, 31.31. MS (*m*/*z*): 165 (M^+), 122, 95 (100), 84. HRMS: calcd for $C_9H_{15}N_3$ (M^+), 165.1266; found, 165.1261.

Tris(*N*-allyl-*N*-methyl-5-aminomethyl-1-methyl-1*H*-2-imidazolyl)methyl Alcohol (26). This compound was obtained as a white semisolid in 35% yield following the procedure for preparing compound **18** using compound **25** instead of compound **16** as the substrate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (s, 3H), 6.29 (s, 1H), 5.76 (m, 3H), 5.09 (m, 6H), 3.36 (s, 6H), 3.32 (s, 9H), 2.93 (d, J = 6.5 Hz, 3H), 2.10 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.04, 135.47, 126.81, 117.68, 71.80, 60.12, 50.81, 41.74, 31.34. MS (*m*/*z*): 521 (M^+), 452, 357, 315, 287 (100), 84. HRMS: calcd for $C_{29}H_{43}N_9O$ (M^+), 521.3590; found, 521.3593.

Tris(*N*-allyl-*N*-methyl-5-aminomethyl-1-methyl-1*H*-2-imidazolyl)methyl Methyl Ether (27). This compound was obtained as a yellow semisolid in 51% yield following the procedure for preparing compound **20** using compound **26** instead of compound **19** as the substrate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 3H), 5.76 (m, 3H), 5.09 (m, 6H), 3.49 (s, 3H), 3.36(s, 6H), 3.34 (s, 9H), 2.92 (d, J = 6.5 Hz, 3H), 2.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.15, 135.41, 130.95, 127.11, 117.69, 78.76, 60.14, 54.63, 50.73, 41.72, 31.54. MS (ESI, *m*/*z*): 536 (M^+ + 1, 100), 504, 465, 433, 311, 197, 163.

Tris(5-methylaminomethyl-1-methyl-1*H*-2-imidazolyl)-methyl Methyl Ether (7). A mixture of compound **27** (391 mg, 0.73 mmol), $Pd(PPh_3)_4$ (169 mg, 0.15 mmol), and *p*-tolylsulfinic acid (342 mg, 2.4 mmol) in dry CH_2Cl_2 (30 mL) was stirred at room temperature for 24 h under an atmosphere of N_2. To the solution was added Na_2CO_3 (500 mg, 4.7 mmol), and the mixture was stirred at room temperature for 1 h. The solid was filtered off, and the filtrate was concentrated. The residue was purified by preparative silica gel thin-layer chromatography using 1/19 (*v*/*v*) CH_3OH/$CHCl_3$ (saturated with NH_3 gas) as the eluent to give 257 mg of compound **7** as a white semisolid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 3H), 3.65 (s, 6H), 3.45(s, 3H), 3.39 (s, 9H), 2.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.65, 132.22, 125.57, 78.78, 54.31, 45.49, 35.93, 31.45. MS (ESI, *m*/*z*): 416 (M^+ + 1, 100), 401, 384, 369, 352, 316, 311, 177.

Bis(*N*-allyl-*N*-methyl-5-aminomethyl-1-methyl-1*H*-2-imidazolyl)ketone (28). To a solution of compound **25** (529 mg, 3.2 mmol) in dry THF (15 mL) was added *n*-BuLi (1.3 mL, 3.2 mmol, 2.5 M in hexanes) at −78 °C under an atmosphere of N_2, and the resulting solution was warmed to −40 °C and stirred for 1 h. The solution was cooled to −78 °C again, and diethyl carbonate (189 mg, 1.6 mmol) was added. Subsequently, the mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by adding several drops of a saturated aqueous solution of NH_4Cl. The solvent was removed, and the residue was purified by preparative silica gel thin-layer chromatography using 1/1 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 313 mg of compound **28** as a yellow semisolid in 55% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 2H), 5.84 (m, 2H), 5.19 (m, 4H), 3.98 (s, 6H), 3.49 (s, 4H), 3.02 (d, J = 6.6 Hz, 4H), 2.19 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.56, 144.56, 135.36, 134.89, 131.40, 118.38, 60.66, 50.81, 42.28, 33.15. MS (ESI, *m*/*z*): 357 (M^+ + 1, 100), 334, 317, 302, 286, 215, 202, 179, 143.

Bis(*N*-allyl-*N*-methyl-5′-aminomethyl-1′-methyl-1′*H*-2′-imidazolyl)[1″-(2‴-methoxyphenyl)-1′*H*-2′-imidazolyl] Methyl Alcohol (29). To a solution of 1-(2′-methoxyphenyl)-1*H*-imidazole (278 mg, 1.6 mmol) in dry THF (16 mL) was slowly added *n*-BuLi (0.64 mL, 1.6 mmol, 2.5 M in hexanes) at −78 °C under an atmosphere of N_2, and the resulting mixture was warmed to −40 °C and stirred for 1 h. The mixture was cooled to −78 °C again, and compound **28** (517 mg, 1.45 mmol) in dry THF (4 mL) was added. Subsequently, it was warmed to room temperature and stirred at room temperature for 24 h. The reaction was quenched by adding several drops of a saturated aqueous solution of NH_4Cl. The solvent was removed, and the residue was purified by preparative silica gel thin-layer chromatography using 2/1 (*v*/*v*) $CHCl_3$/hexanes (saturated with NH_3 gas) as the eluent to give 420 mg of compound **29** as a yellow oil in 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 1.2 Hz, 1H), 7.04 (br, 1H), 6.94 (d, J = 1.2 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.75 (t, J = 8.0 Hz, 1H), 6.66 (s, 2H), 5.84 (m, 2H), 5.60 (s, 1H), 5.16 (m, 4H), 3.69 (s, 3H), 3.44 (s, 6H), 3.43 (m, 2H), 3.31 (m, 2H), 3.01 (m, 4H), 2.16 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.36, 147.18, 146.37, 135.36, 130.66, 129.83, 129.21, 126.63, 126.39, 126.13, 124.58, 119.71, 117.88, 110.90, 71.66, 60.34, 55.49, 50.61, 41.85, 31.62. MS (*m*/*z*): 530 (M^+), 461, 366, 295, 287 (100), 201, 174, 146, 95. HRMS: calcd for $C_{29}H_{38}N_8O_2$ (M^+), 530.3118; found, 530.3114.

Bis(*N*-allyl-*N*-methyl-5′-aminomethyl-1′-methyl-1′*H*-2′-imidazolyl)[1″-(2‴-methoxyphenyl)-1′*H*-2′-imidazolyl] Methyl Methyl Ether (30). This compound was obtained as a yellow oil in 51% yield following the procedure for preparing compound **20** using compound **29** instead of compound **19** as the substrate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (br, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 1.2 Hz, 1H), 6.85 (d, J = 1.2 Hz, 1H), 6.71 (t, J = 8.0 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 6.60 (br, 2H), 5.79 (m, 2H), 5.10 (m, 4H), 3.56 (s, 3H), 3.40 (s, 6H), 3.37 (s, 3H), 3.32 (m, 4H), 2.94 (m, 4H), 2.10 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.63, 145.62, 144.50, 135.13, 130.01, 129.61, 129.26, 126.76, 126.08, 125.77, 124.10, 119.44, 117.41, 110.14, 78.07, 59.97, 54.98, 54.19, 50.37, 41.57, 31.34. MS (*m*/*z*): 544 (M^+), 529, 475 (100), 444, 373, 279, 187, 84. HRMS: calcd for $C_{30}H_{40}N_8O_2$ (M^+), 544.3274; found, 544.3268.

Bis(5-methylaminomethyl-1-methyl-1*H*-2-imidazolyl)[1′-(2″-methoxyphenyl)-1′*H*-2′-imidazolyl] Methyl Methyl Ether (8). This compound was obtained as a yellow oil in 83% yield following the procedure for preparing compound **7** using compound **30** instead of compound **27** as the substrate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 1.0 Hz, 1H), 6.86 (d, J = 1.2 Hz, 1H), 6.76 (t, J = 7.5 Hz, 1H), 6.64 (d, J = 7.5 Hz, 3H), 3.61 (s, 3H), 3.55 (s, 3H), 3.42 (s, 6H), 3.39 (s, 4H), 2.41 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.90, 145.75, 144.57, 131.63, 130.17, 129.66, 126.35, 125.87, 125.60, 124.59, 119.75, 110.39, 78.30, 55.29, 54.56, 45.40, 36.01, 31.57. MS (*m*/*z*): 464 (M^+), 449 (100), 434, 418, 281, 187, 138, 57. HRMS: calcd for $C_{24}H_{32}N_8O_2$ (M^+), 464.2648; found, 464.2634.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for new compounds **6**−**8**, **16**−**20**, and **25**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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