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Two new ligands for carbonic anhydrase mimicry

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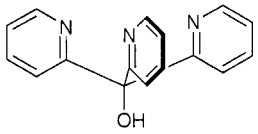
Abstract—The syntheses of tris(2-nicotinic acid)methanol methyl ether **5** and tris(2-picolinic acid)methanol methyl ether **6**, two tridentate ligands designed to also act as scaffolds for constructing chiral environments around their metal binding sites, is described. Improved yields for the essential lithiation–alkylation reactions that generate the trispyridyl core of these types of ligands are reported.

1. Introduction

The synthesis and analysis of small molecules designed to mimic enzymatic catalysts is an increasingly popular approach to both improving our understanding of enzymes, and developing novel catalysts of synthetic utility.[1] Although this approach often entails a gross oversimplification of the system in question the opportunity to glean valuable information from a relatively straightforward system, and the potential of providing ready access to broad-spectrum catalytic species, are strong driving forces for this field. Consequently, a considerable amount of research effort has been expended in the investigations of metallo-enzyme mimics.[2] With these investigations, considerable progress has been made. However, as Benner has recently pointed out,[3] we are some way from understanding the subtleties of structure–activity relationships which can result in well-meaning changes in the chemical architecture of a catalyst, inadvertently converting it to an anti-catalyst.

One of the thrusts of our research group is the development of novel mimics of the Carbonic Anhydrase enzyme family. Human Carbonic Anhydrase II (HCAII), being one of the most explored and best understood enzymes,[4] sets an excellent reference point for the examination of how changes to an enzyme mimic influences its physicochemical properties. In the enzyme, the primary "ingredient" of the active-site is a catalytically essential zinc ion tetrahedrally coordinated to three histidine side-chains (H94, H96 and H119), and a highly acidic water molecule (pK_a approximately 7).[5] Thus at physiological pH this site is occupied by a hydroxide ion, the nucleophilic species responsible for the properties of the enzyme which include the reversible hydration of carbon dioxide (its principal function in eukaryotes), as well as the hydrolysis of esters.[6] Consequently, a variety of tridentate (as well as tetradentate) ligands has been synthesized to garner information pertinent to the catalytic mechanism of the enzyme. A consideration of these ligands suggests that success at modeling the active-site of CA requires a combination of a highly Lewis acidic metal ion, and sufficient steric bulk to ensure that the deleterious formation of ZnL_2 sandwich complexes cannot occur. The latter steric bulk must of course still allow the expected CA-type chemistry; a problem that the enzyme avoids by ensuring that its active site is at the bottom of a 15 Å deep cavity. Thus, without this degree of steric bulk ligands **1** and **2**, which closely replicate the three imidazole groups in CA, form catalytically inactive sandwich complexes with metal ions.[7] Likewise, zinc complexes of the hydroborato compounds **3** developed by Parkin and Vahrenkamp also exhibit this chemistry unless the R group is sufficiently large, e.g. R_1 and R_2=*i*-Pr. If this is the case CA-type chemistries have been observed.[8] Structurally similar, phosphorus-based ligands have also been investigated and have demostrated some CA-type properties.[9] Alternatively, increasing the number and Lewis basicity of the donating groups reduces the necessity for steric bulk. Thus, [12]aneN_3 **4** (R=H or CH_2CH_2OH) and [12]aneN_4 ligands[10] as well as TREN[11] have been investigated as CA mimics.



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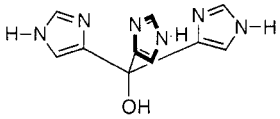

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Keywords: pyridine; ligands; biomimetic.

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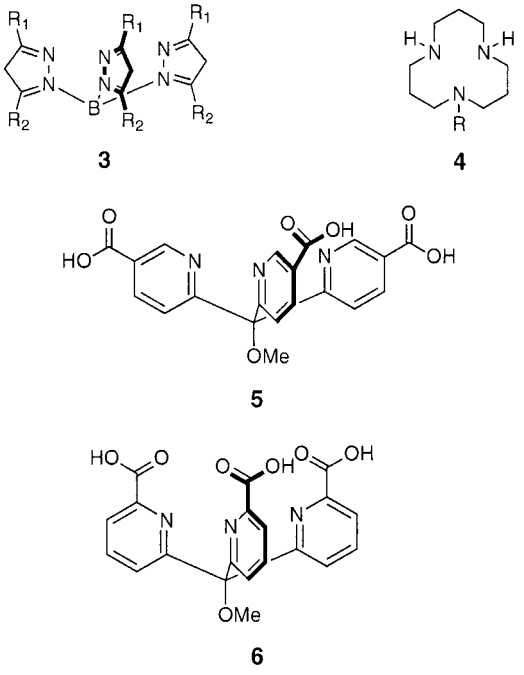
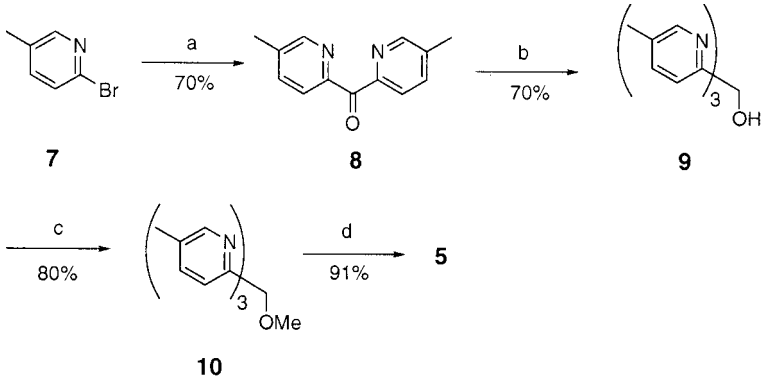


In considering ligand candidates for our research program, we prioritized three specific criteria. First, to closely replicate the zinc binding site of CA, the ligands should consist of three sp^2 nitrogen donors in a trigonal planar array. Second, the ligands should share a common functionality that allows the tailoring of a chiral environment around the metal center. Finally, the ligands should be sufficiently robust to allow full evaluation of their physicochemical properties. With these criteria in mind, we describe here the synthesis of the trisnicotinic acid and trispicolinic acid ligands **5** and **6**. We anticipate that with the aid of standard peptide coupling technologies these ligands will provide ready access to a range of chiral ligands which will engender structure–activity information pertinent to both CA and metallo-enzyme mimics in general.

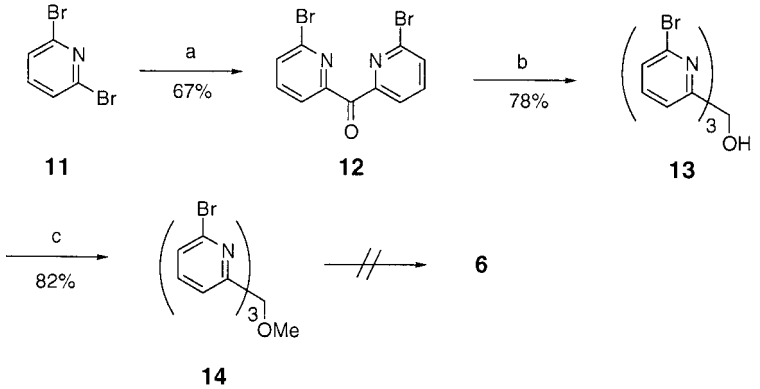
2. Results and discussion

Although tris(2-pyridyl)methanol **1** was first reported almost 50 years ago,[12] work relating to the synthesis of tri-substituted derivatives is rare;[13] a rather surprising finding considering their potential application and the commercial availability of many dipyridyl-based ligands. This can at least in part be attributed to the complexity of the pyridyllithium chemistry[14] used to form the ligands. As a consequence of these points, we include here a brief summary of our observations in forming four distinct tris(2-pyridyl)methanol derivatives.

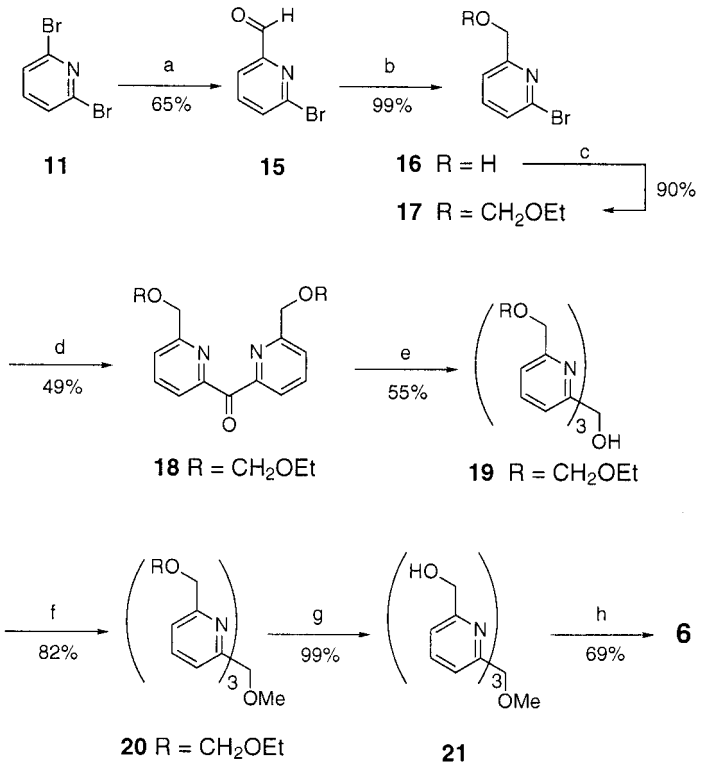
The starting material for the synthesis of trisnicotinic acid ligand **5** was 2-bromo-5-methyl pyridine **7** (Scheme 1). Thus, formation of the corresponding lithiate via metal–halogen exchange with *n*-BuLi followed by the slow addition of a solution of diethyl carbonate, gave the expected ketone **8**[13b] in reasonable yield. Ketone **8** was then itself treated with the aforementioned lithiate to generate the tris-picoline ligand **9**. Alkylation of the hydroxy group of



Scheme 1. Key: (a) (i) *n*-BuLi, (ii) $(EtO)_2CO$. (b) 2-lithio-5-methylpyridine. (c) NaH, MeI. (d) $KMnO_4$.



Scheme 2. Key: (a) (i) *n*-BuLi, (ii) $(EtO)_2CO$. (b) 2-bromo-6-lithiopyridine. (c) NaH, MeI.



Scheme 3. Key: (a) (i) *n*-BuLi, (ii) DMF, (iii) H_3O^+. (b) $NaBH_4$. (c) $EtOCH_2Cl$, DIPEA. (d) (i) *n*-BuLi, (ii) $(EtO)_2CO$. (e) lithiate derived from **17**+*n*-BuLi. (f) NaH, MeI. (g) $MeOH/H_3O^+$. (h) $KMnO_4$.

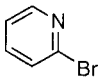
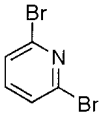
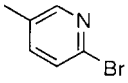
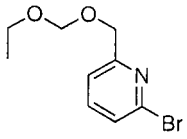
9 was then readily accomplished with a combination of sodium hydride and methyl iodide. Although the ligand contains three nitrogen atoms which could potentially undergo alkylation, the 80% yield for ether **10** indicated that despite being relatively hindered, attack by the alkoxide was the kinetically favored reaction. Finally, oxidation of the methyl groups of **10** with potassium permanganate[15] afforded ligand **5** in good yield.

The synthesis of the trispicolinic isomer **6** proved more problematic. We chose not to investigate an analogous process to that shown in Scheme 1 for the formation of **6**, primarily because the greater acidity of the methyl group of 2-bromo-6-methyl pyridine was expected to interfere with the two lithiation steps. Consequently, our first approach centered around tribromide **14** (Scheme 2). Thus, mono-lithiation of 2,6-dibromopyridine **11**,[14c] and quenching with diethyl carbonate gave the known ketone **12**.[16] Subsequently, using ketone **12** to quench the mono-lithiate of 2,6-dibromopyridine resulted in the isolation of the trispyridyl methanol **13**. Again, protection of the hydroxy group as its methyl ether was relatively straightforward and afforded the ether **14** in ca. 80% yield. Unfortunately, although we have had considerable success in performing multiple metal/halogen exchange reactions in deep-cavity cavitand systems,[17] we were unsuccessful in a number of similar approaches using **14**. Thus, attempts at forming the corresponding tris-lithiated species and quenching with DMF or CO_2 were unsuccessful over a range of reactions that considered solvent, concentration, temperature, or additives to break up the anticipated lithiate aggregates. Instead, mono and bis-substituted species predominated. In addition, attempts to directly form the tris-carboxylic acid by quenching with CO_2 resulted in further complications with apparent alkylation of the newly formed carboxy groups.

A successful alternative route to ligand **6** was devised and is shown in Scheme 3. Thus, mono-lithiation of 2,6-dibromopyridine **11** and quenching with DMF afforded known aldehyde **15**.[18a] The carbonyl group of this compound was then reduced, and the alcohol group of **16**[18b] protected as the ethoxymethyl ether (**17**). Bromide **17** then served as the building block for the construction of the trispyridyl framework. Thus, formation of the corresponding lithiate of **17** and quenching with diethyl carbonate resulted in the expected ketone **18**. Correspondingly, quenching the aforementioned lithiate with ketone **18** gave the anticipated alcohol **19**. As was observed in the previous cases, protection of the alcohol functionality of **20** as its methyl ether proceeded smoothly. Finally, removal of the ethoxymethyl ether protecting groups with dilute acid, and oxidation of the resulting triol **21** with $KMnO_4$, gave the desired ligand **6**.

These three syntheses, along with a reinvestigation of the synthesis of the unsubstituted ligand **1**,[12] allows a comparison of the one- or two-step approach to trispyridyl ligands. Previously, Hannon et al.,[13b] observed that the direct (one pot) formation of tris-pyridylmethanol derivatives from the constituent pyridine derivatives was a rather inefficient process. Thus, yields of the tris(2-pyridyl) ligands ranged from 12% to 24%. In most cases, the major side product (20–61%) was noted to be the corresponding bis(2-pyridyl ketone). Our results (Table 1) indicate that a two-step process, which also opens the way to non-C_{3v}

Table 1. Formation of C_{2v} bis-pyridylketones and C_{3v} tris-pyridylmethanols

Pyridine building block	Yield of ketone[a] (%)	Solvent system	Yield of alcohol[b] (%)	Solvent system
	—[c]		78 (38)[d]	Et_2O
	85	Et_2O	78	Et_2O/THF
	70	THF	70 (24)[d]	THF
	49	THF	55	Et_2O

[a] By formation of lithiate (−78°C) and reaction with diethyl carbonate.
[b] By formation of pyridyl-lithiate (−78°C) and reaction with the corresponding ketone.
[c] Commercially available ketone was used for the second lithiation.
[d] See Ref. 13b. [A 41% yield of the parent ligand was reported by Wibaut (Ref. 12).]

ligands, is a much more successful strategy to tris(2-pyridyl) ligands.

Having examined these reactions in detail we can offer the following observations which may explain the low yields often obtained in these types of reaction. In the first instance, for both the ketone and (more so) the tris synthesis reactions investigated, we noted a significant interdependency between scale and yield. Thus, on the small scale yields were poor unless an excess of lithiate was used. In these cases we also noted considerable difficulty in controlling the reaction temperature. As the pyridyl-lithiates were noted to rapidly decompose at −10°C, we presume that an excess of lithiate was required to compensate for a decomposition process arising from the poor temperature control. On the larger scale, where temperature control was straightforward, the equivalents of lithiate could be kept to a minimum. Indeed, this was essential in large-scale ketone syntheses where an excess of lithiate resulted in the alkylation of the ketone to give (poor yields of) tris-pyridyl and bispyridylbutyl alcohols side products. Likewise, although for less obvious reasons, the use of excess lithiate in the formation of the tris-ligands also resulted in reduced yields. Consequently, both ketone and trispyridyl-methanol formation were undertaken on the large scale with careful control of the reagent stoichiometry. We also examined the effects of adding specific additives known to break up lithiate aggregates, and considered how reaction temperature might influence reaction outcome. Briefly, we did not observe any improvement in yields if TMEDA or HMPA were added to the lithiation reactions, while with respect to reaction temperature, −78°C seemed to strike a fine balance between lithiate stability and the solubility of the various species. Finally, it should be noted that there was no clear choice in whether to use diethyl ether or THF as solvent. Thus, bearing in mind the previously noted preference for performing the mono-lithiation of 2,6-dibromopyridine in diethyl ether,[14c] solvent choice was dictated by solubility concerns.

3. Conclusions

We have detailed here the synthesis of two new trispyridylmethane ligands. With each pyridine ring of these isomers functionalized with a carboxylic acid group, standard peptide coupling technologies should provide access to a range of chiral ligands. We anticipate that by judicious choice of amino acid or short peptide arms appended to these ligands, the corresponding zinc complexes will provide valuable information concerning how altering the environment around the metal center adjusts their physicochemical properties. Investigations following this line of reasoning are currently underway.

4. Experimental

4.1. General

The starting materials were purchased from Aldrich Chemical Company. Diethyl carbonate was purified by washing with 10% aqueous Na_2CO_3, saturated aqueous $CaCl_2$, and distilled water, before drying over anhydrous $CaCl_2$ and subsequent distillation. Dimethylformamide (DMF) was dried by stirring over BaO for 24 h followed by distillation under reduced pressure. It was stored over molecular sieves (3 Å) and degassed prior to use. *n*-BuLi

was titrated with diphenylacetic acid prior to use. Other reagents were used as received. Tetrahydrofuran (THF) or diethylether were dried by distillation from sodium benzophenone ketyl. All reactions were run under a nitrogen atmosphere.

Flash chromatography (Silica gel 60 Å, 200–400 mesh; Natland International) was used for product purification. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$. MS analysis of the products was performed with either electron impact, or electron spray techniques. Elemental analysis was performed by Atlantic Microlab Inc. Melting points are uncorrected.

4.2. Synthesis of tris nicotinic acid ligand 5

4.2.1. Bis(2-(5-methylpyridyl)ketone 8. 5 g (29 mmol) of 2-bromo-5-methylpyridine **7** was dissolved in 100 mL of THF and the resulting solution cooled to −78°C. A solution of *n*-BuLi in hexanes (29 mmol, 19.6 mL of a 1.2 M solution) was added dropwise to the cooled solution. After stirring for 5 min, a solution of diethyl carbonate (13.8 mmol, 1.66 mL in 20 mL THF) was slowly added to the solution of the lithiate. After stirring for 2 h at −78°C, the reaction was allowed to warm to ca. 0°C, and quenched with 10% HCl until acidic. The resulting mixture was basified with 10% aqueous K_2CO_3, and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, and the organic layers combined, and dried with anhydrous $MgSO_4$. The resulting brown solution was decolorized with activated carbon, and the solvent of the resulting filtrate removed under reduced pressure. Three crystallizations from acetone, and drying (0.1 mmHg, 25°C, 2 h) afforded the ketone **8**[13b] as a white solid in 70% yield: mp 132–134°C; ^{1}H NMR (400 MHz) δ 2.43 (s, 6H), 7.68 (pseudo d, 2H, J=7.6 Hz), 8.01 (d, 2H, J=8.0 Hz), 8.58 (s, 2H); MS m/z $(M+H^+)^+$ 212.9. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.55; H, 5.71. Found: C, 73.53; H, 5.75.

4.2.2. Tris(2-(5-methylpyridyl)methanol 9. 1.34 g (7.7 mmol) of 2-bromo-5-methylpyridine **7** was dissolved in 70 mL of THF and the resulting solution cooled to −78°C. A solution of *n*-BuLi in hexanes (7.7 mmol, 6.5 mL of a 1.2 M solution) was added dropwise to the cooled solution. After stirring for 5 min, a solution of ketone **8** (7.1 mmol, 1.5 g in 20 mL THF) was slowly added to the solution of the lithiate. After stirring for 2 h at −78°C, the reaction was allowed to warm to ca. 0°C, and quench with 10% HCl until acidic. The resulting mixture was basified with 10% aqueous K_2CO_3, and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, and the organic layers combined and dried with anhydrous $MgSO_4$. The resulting brown solution was decolorized with activated carbon, and the solvent of the resulting filtrate removed under reduced pressure. Flash chromatography (mobile phase 8% acetone and 2% diethylamine in hexane), removal of the solvent under reduced pressure and drying (0.1 mmHg, 25°C, 16 h) afforded the product **9**[13b] as a white solid. Yield=70%. Mp 125–127°C; ^{1}H NMR (400 MHz) δ 2.29 (s, 9H), 7.11 (s, 1H), 7.46 (pseudo d, 3H, J=8.4 Hz), 7.58 (d, 3H, J=8.0 Hz), 8.35 (pseudo s, 3H); MS m/z $(M+H^+)^+$ 305.9, $(2M+H^+)^+$ 611.2. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.72; H, 6.28. Found: C, 74.66; H, 6.29.

4.2.3. Tris(2-(5-methylpyridyl)methanol methyl ether 10. 0.65 g (16.4 mmol) of a 60% oil dispersion of NaH was washed twice with pentane and added to 80 mL THF. To this stirring mixture was added 1.00 g (3.27 mmol) of alcohol **9**, and 1.03 mL (16.4 mmol) of MeI. The reaction was stirred at 60°C for 16 h. After cooling to room temperature, the mixture was quenched with 10% HCl until acidic, and then basified with 10% aqueous K_2CO_3. The crude product was then partitioned between $CHCl_3$ and water, the aqueous layer washed twice with $CHCl_3$. The organic layers were combined, dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Flash chromatography (mobile phase 20% acetone and 2% diethylamine in hexane), removal of the solvent under reduced pressure and drying (0.1 mmHg, 25°C, 16 h) afforded an 80% yield of **10** as a white solid. Mp 117–119°C; ^{1}H NMR (400 MHz) δ 2.28 (s, 9H), 3.24 (s, 3H), 7.45 (pseudo d, 3H, J=7.9 Hz), 7.56 (d, 3H, J=8.0 Hz), 8.39 (pseudo s, 3H); ^{13}C NMR (75 MHz) δ 18.3, 53.0, 88.2, 123.6, 131.6, 136.8, 149.0, 159.0; IR (film) cm^{-1} 3017, 2947, 2887, 1616, 1586, 1492, 1391, 1103, 1048, 849, 819, 769, 594; MS m/z $(M+H^+)^+$ 320.2, $(2M+H^+)^+$ 639.0. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 75.19; H, 6.64. Found: C, 75.12; H, 6.69.

4.2.4. Tris(2-(nicotinic acid)methanol methyl ether 5. 250 mg (0.78 mmol) of **10**, 1.24 g (7.8 mmol) of $KMnO_4$ and 315 mg (7.8 mmol) of NaOH were added to 35 mL of distilled H_2O. The reaction mixture was stirred at 60°C for 16 h and quenched with methanol. The brown MnO_2 precipitate was filtered off, washed with water and the aqueous phases combined. Removal of the water under reduced pressure gave a brown solid which was taken up in isopropanol, sonicated, and the crude product filtered off. The off-white mixture was then added to methanol, sonicated, and the resulting inorganic salts filtered off. The solvent was then removed under reduced pressure, and the crude product dried (0.1 mmHg, 25°C, 16 h). The crude triacid was dry-loaded on a silica column and isolated with flash chromatography (mobile phase 2:1 methanol/$CHCl_3$). Removal of the solvent under reduced pressure gave a 91% yield of the triacid **5** as a white solid. Mp 264–266°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.17 (s, 3H), 7.71 (d, 3H, J=8.0 Hz), 8.26 (dd, 3H, J=2.2, 8.0 Hz), 8.96 (d, 3H, J=2.0 Hz), 13.38 (broad s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 54.4, 89.6, 125.6, 132.9, 139.8, 150.3, 162.4, 173.0; IR (paraffin oil) cm^{-1} 3046 (broad), 2937, 2867, 1616, 1472, 1392, 1038, 734; MS m/z $(M+H^+)^+$ 410.2, $(M+Na^+)^+$ 432.2, $(2M+Na^+)^+$ 841.2. Anal. Calcd for $C_{20}H_{15}N_3O_7$: C, 58.67; H, 3.70; N, 10.27. Found: C, 58.42; H, 3.84; N, 10.14.

4.3. Synthesis of trispicolinic ligand 6

4.3.1. Bis(2-(6-bromopyridyl)ketone 12. 5 g (21 mmol) of 2,6-dibromopyridine **11** was dissolved in 150 mL of diethyl ether and the resulting solution cooled to −78°C. A solution of *n*-BuLi in hexanes (23 mmol, 19.2 mL of a 1.2 M solution) was added dropwise to the cooled solution. After a period of 5 min, a solution of diethyl carbonate (9.5 mmol,

1.15 mL in 20 mL diethyl ether) was slowly added to the solution of the lithiate. After stirring for 2 h at −78°C, the reaction was allowed to warm to ca. 0°C, and quenched with 10% HCl until acidic. The resulting mixture was basified with 10% aqueous K_2CO_3, and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, and the organic layers combined and dried with anhydrous $MgSO_4$. The resulting brown solution was decolorized with activated carbon, and the solvent removed under reduced pressure. Crystallization from acetone/hexane, and drying (0.1 mmHg, 25°C, 4 h), afforded ketone **12** as white needles in 67% yield. Mp 155–156°C (lit. 155–156.5°C)[15]; ^{1}H NMR (400 MHz) δ 7.70 (dd, 2H, J=8.0 Hz, 0.8 Hz), 7.76 (pseudo t, 2H, J=8.0 Hz), 8.09 (dd, 2H, J=8.0 Hz, 0.8 Hz).

4.3.2. Tris(2-(6-bromopyridyl)methanol 13. 1.09 g (4.60 mmol) 2,6-dibromopyridine **11** was dissolved in 46 mL of diethyl ether. With vigorous stirring, the temperature was lowered to −78°C and a solution of *n*-BuLi in hexanes (5.06 mmol, 4.2 mL of a 1.2 M solution) added dropwise. After stirring for 5 min, a solution of ketone **12** (4.20 mmol, 1.44 g in 14 mL THF) was slowly added to the solution of the lithiate. After stirring for 2 h at −78°C, the reaction was allowed to warm to ca. 0°C, and quenched with 10% HCl until acidic. The resulting mixture was basified with 10% aqueous K_2CO_3, and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, the organic layers combined, dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. Column chromatography (mobile phase 1% acetone in hexane), removal of the solvent under reduced pressure, and drying (0.1 mmHg, 25°C, 16 h), gave a 78% yield of the product as a white solid: mp 146–147°C; ^{1}H NMR (400 MHz) δ 6.59 (s, 1H), 7.39 (d, 3H, J=7.3 Hz), 7.56 (pseudo t, 3H, J=7.7 Hz), 7.71 (d, 3H, J=8.1 Hz); ^{13}C NMR (75 MHz) δ 80.4, 122.2, 127.4, 139.1, 140.3, 162.9; IR (film) cm^{-1} 3406, 1591, 1566, 1436, 1412, 1168, 1143, 993, 808, 759, 709; MS m/z 500 (M^+), 422 $(M-Br^-)^+$. Anal. Calcd for $C_{16}H_{10}N_3Br_3O$: C, 38.44; H, 2.02. Found: C, 38.70; H, 2.01.

4.3.3. Tris(2-(6-bromopyridyl)methanol methyl ether 14. 622 mg (15.55 mmol) of a 60% oil dispersion of NaH was washed twice with pentane and added to 104 mL THF. To this stirring mixture was added 1.56 g (3.11 mmol) of alcohol **13**, and 970 μL (15.55 mmol) of MeI. The reaction was stirred at 60°C for 16 h. After cooling to room temperature, the mixture was quenched with 10% aqueous HCl until acidic, and then basified with 10% aqueous K_2CO_3. The crude product was then partitioned between $CHCl_3$ and water and the aqueous layer was washed twice with $CHCl_3$. The organic layers were combined, dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. Flash chromatography (mobile phase 10% acetone in hexane), removal of the solvent under reduced pressure and drying (0.1 mmHg, 25°C, 16 h), afforded the product as a white solid in 82% yield. Mp 133–134°C; ^{1}H NMR (400 MHz) δ 3.31 (s, 3H), 7.37 (d, 3H, J=7.3 Hz), 7.54 (pseudo t, 3H, J=7.3 Hz), 7.61 (d, 3H, J=7.3 Hz); ^{13}C NMR (75 MHz) δ 53.5, 87.4, 123.6, 127.2, 138.6, 140.5, 161.8; IR (film) cm^{-1} 2957, 2837, 1601, 1576, 1437, 1412, 1168, 1143, 998, 804, 759, 709; MS m/z 514 (M^+), 436 $(M-Br^-)^+$. Anal. Calcd for $C_{17}H_{12}N_3Br_3O$: C, 39.72; H, 2.35. Found: C, 39.92; H, 2.37.

4.3.4. 2-Bromo-6-pyridinecarboxaldehyde 15. 10 g (42.2 mmol) of 2,6-dibromopyridine **11** was dissolved in 200 mL of diethyl ether and the resulting solution cooled to −78°C. A solution of *n*-BuLi in hexanes (42.2 mmol, 16.9 mL of a 2.5 M solution) was added dropwise to the cooled solution. After a period of 5 min, a solution of DMF (51.6 mmol, 4.00 mL in 20 mL diethyl ether) was slowly added to the solution of the lithiate. The reaction was then allowed to warm to ca. −10°C, and quenched with 10% HCl until acidic. The resulting mixture was stirred for 10 min, then basified with 10% aqueous K_2CO_3, and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, and the organic layers combined and dried with anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product as an oil. Column chromatography (mobile phase 2% acetone in hexane) removal of the solvent under reduced pressure and drying (0.1 mmHg, 25°C, 1 h) gave the desired product as a white solid in 65% yield: mp 78.5–79°C (lit. 77–78°C).[18a] ^{1}H NMR (400 MHz) δ 7.72–7.78 (m, 2H), 7.93 (dd, 1H, J=6.4 Hz, 2.4 Hz), 10.0 (s, 1H).

4.3.5. 2-Bromo-6-pyridylcarbinol 16. 6.55 g (34.2 mmol) of aldehyde **15** was dissolved in 150 mL of methanol. To this stirring solution was added 1.29 g (34.2 mmol) of sodium borohydride. The reaction was stirred for 1 h at room temperature. After this period, the reaction was quenched with 10% aqueous HCl and concentrated under reduced pressure. The solution was then basified with 5% aqueous potassium carbonate and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, and the organic layers combined and dried with anhydrous $MgSO_4$. Column chromatography (mobile phase 8% ethyl acetate in chloroform) and removal of the solvent under reduced pressure gave the alcohol **16** in 99% yield as a viscous oil which solidified as a wax on standing. Mp 36–37°C (lit. 32–33°C);[17] ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 3.53 (t, 1H, J=5.8 Hz), 4.61 (d, 2H, J=5.9 Hz), 7.41–7.42 (m, 1H), 7.44–7.46 (m, 1H), 7.66 (dd, 1H, J=7.7 Hz, 7.7 Hz).

4.3.6. 2-Bromo-6-pyridylcarbinol ethoxymethyl ether 17. 9 g (48.19 mmol) of alcohol **16** was dissolved in 35 mL of DMF. To this stirring solution was added 15.57 g of diisopropylethyl amine (120.48 mmol, 8.39 mL), followed by 6.84 g chloromethyl ethyl ether (72.29 mmol). After stirring at room temperature for 16 h, the solvent was removed under reduced pressure. The crude product was partitioned between $CHCl_3$ and water, the aqueous layer washed twice with $CHCl_3$, and the organic layers combined and dried with anhydrous $MgSO_4$. Removal of the solvent under reduced pressure and distillation of the crude product gave the desired ether as a colorless liquid in 90% yield: bp 113°C (0.6 mmHg); ^{1}H NMR (400 MHz) δ 1.22 (t, 3H, J=7.3 Hz), 3.65 (q, 2H, J=7.3 Hz), 4.70 (s, 2H), 4.82 (s, 2H), 7.38 (d, 1H, J=7.3 Hz), 7.42 (d, 1H, J=8.0 Hz), 7.56 (pseudo t, 1H, J=7.6 Hz); ^{13}C NMR (75 MHz) δ 15.27, 63.77, 69.62, 95.21, 120.09, 126.77, 139.09, 141.48, 160.21; IR (film) cm^{-1} 2937, 2851, 1601, 1576, 1451, 1422, 1133, 1053,

799; MS *m/z* 247 $(M+H^+)^+$. Anal. Calcd for $C_9H_{12}NBrO_2$: C, 43.92; H, 4.91. Found: C, 44.04; H, 4.90.

4.3.7. Bis(2-(6-pyridylcarbinol ethoxymethyl ether)ketone 18. 2.35 g (9.55 mmol) of **17** was dissolved in 40 mL of THF and the resulting solution cooled to −78°C. A solution of *n*-BuLi in hexanes (10.5 mmol, 8.75 mL of a 1.2 M solution) was added dropwise to the cooled solution. After a period of 5 min, a solution of diethyl carbonate (4.78 mmol, 580 μL in 16 mL diethyl ether) was slowly added to the solution of the lithiate. After stirring for 2 h at −78°C, the reaction was allowed to warm to ca. 0°C, and quenched with water. The resulting mixture was basified with 10% aqueous K_2CO_3, and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, and the organic layers combined, dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. Column chromatography (mobile phase 4% acetone in hexane), and removal of the solvent under reduced pressure gave the product as a pale yellow oil in 49% yield: ^{1}H NMR (400 MHz) δ 1.22 (t, 6H, *J*=7.0 Hz), 3.65 (q, 4H, *J*=7.0 Hz), 4.79 (s, 4H), 4.84 (s, 4H), 7.66 (d, 2H, *J*=7.8 Hz) 7.87 (pseudo t, 2H, *J*=7.8 Hz), 8.00 (d, 2H, *J*=7.8 Hz); ^{13}C NMR (75 MHz) δ 15.1, 63.6, 70.1, 95.1, 123.9, 124.3, 137.1, 153.4, 158.4, 192.6; IR (film) cm^{-1} 2997, 2947, 2897, 1696, 1596, 1457, 1402, 1372, 1337, 1237, 1197, 1168, 1128, 1058, 854, 814, 764; MS *m/z* 361 $(M+H^+)^+$. Anal. Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71. Found: C, 63.30; H, 6.77.

4.3.8. Tris(2-(6-pyridylcarbinol ethoxymethyl ether)-methanol 19. 0.26 g (1.07 mmol) of **17** was dissolved in 10 mL diethyl ether and the resulting solution cooled to −78°C. A solution of *n*-BuLi in hexanes (1.18 mmol, 0.98 mL of a 1.2 M solution) was then added dropwise to the cooled solution. After a period of 5 min, a solution of **18** (0.95 mmol, 340 mg in 5 mL) in ether was slowly added to the lithiate solution. After stirring for 2 h at −78°C, the reaction was allowed to warm to ca. 0°C, and quenched with water. The resulting mixture was basified with 10% aqueous K_2CO_3, and the crude product partitioned between $CHCl_3$ and water. The aqueous layer was washed twice with $CHCl_3$, the organic layers combined and dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. Flash chromatography (mobile phase, hexane to chloroform gradient), and removal of the solvent under reduced pressure gave the product as colorless oil in 55% yield: ^{1}H NMR (400 MHz, CD_3CN) δ 1.11 (t, 9H, *J*=7.0 Hz) 3.55 (q, 6H, *J*=7.0 Hz) 4.55 (s, 6H) 4.71 (s, 6H) 7.08 (s, 1H) 7.33 (d, 3H, *J*=7.3 Hz) 7.54 (d, 3H, *J*=7.3 Hz) 7.72 (pseudo t, 3H, *J*=7.3 Hz); ^{13}C NMR (75 MHz) δ 15.4, 63.7, 70.3, 81.1, 95.1, 119.8, 122.0, 137.0, 156.4, 162.2; IR (film) cm^{-1} 3326, 3007, 2947, 2907, 1606, 1586, 1472, 1407, 1377, 1197, 1163, 1113, 1058, 794, 769; MS *m/z* 528 $(M+H^+)^+$. Anal. Calcd for $C_{28}H_{37}N_3O_7$: C, 63.74; H, 7.07. Found: C, 63.46; H, 7.10.

4.3.9. Tris(2-(6-pyridylcarbinol ethoxymethyl ether)-methanol methyl ether 20. 310 mg (7.80 mmol) of a 60% oil dispersion of NaH was washed twice with pentane and added to 60 mL THF. To this stirring mixture was added 0.82 g (1.56 mmol) of alcohol **19**, and 490 μL (7.80 mmol) of MeI. The reaction was stirred at 60°C for 16 h. After cooling to room temperature, the mixture was quenched with water, and then basified with 10% aqueous K_2CO_3. The crude product was then partitioned between $CHCl_3$ and water, the aqueous layer was washed twice with $CHCl_3$, and the organic layers combined and dried with anhydrous $MgSO_4$. Column chromatography (mobile phase 10% acetone in hexane), and removal of the solvent under reduced pressure, gave the desired product as colorless oil in 82% yield: ^{1}H NMR (400 MHz, CD_3CN) δ 1.10 (t, 9H, *J*=7.0 Hz) 3.17 (s, 3H) 3.53 (q, 6H, *J*=7.0 Hz) 4.50 (s, 6H) 4.69 (s, 6H) 7.29 (d, 3H, *J*=7.3 Hz) 7.49 (d, 3H, *J*=7.3 Hz) 7.69 (pseudo t, 3H, *J*=7.3 Hz); ^{13}C NMR (75 MHz) δ 15.3, 53.3, 63.6, 70.6, 88.6, 95.1, 119.4, 123.2, 136.3, 157.0, 161.0; IR (film) cm^{-1} 2997, 2947, 2887, 1606, 1581, 1462, 1407, 1372, 1193, 1158, 1118, 1068, 799, 764; MS *m/z* 542 $(M+H^+)^+$. Anal. Calcd for $C_{29}H_{39}N_3O_7$: C, 64.31; H, 7.26. Found: C, 64.28; H, 7.35.

4.3.10. Tris(2-(6-pyridylcarbinol)methanol methyl ether 21. 500 mg of ether **20** was dissolved in 30 mL of methanol containing 1 mL of 37% aqueous HCl. The reaction was warmed to 60°C for 15 min. The solvent was removed under reduced pressure and the crude product partitioned between $CHCl_3$ and 10% aqueous K_2CO_3. The aqueous layer was then washed twice with $CHCl_3$, and the organic layers combined and dried with anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave the essentially pure product as a colorless oil in 99% yield. ^{1}H NMR (400 MHz) δ 3.26 (s, 3H) δ 4.00 (broad s, 3H) 4.64 (s, 6H) 7.09 (d, 3H, *J*=7.3 Hz) 7.54 (d, 3H, *J*=7.3 Hz) 7.67 (pseudo t, 3H, *J*=7.3 Hz); ^{13}C NMR (75 MHz) δ 53.3, 63.6, 88.3, 119.0, 122.5, 136.8, 157.4, 159.7; IR (film) cm^{-1} 3356 (broad), 2927, 2857, 1606, 1581, 1462, 1227, 1093, 1008, 784; MS *m/z* 368 $(M+H^+)^+$. Anal. Calcd for $C_{20}H_{21}N_3O_4.1/2\ H_2O$: C, 63.80; H, 5.98. Found: C, 63.79; H, 5.81.

4.3.11. Tris(2-(picolinic acid)methanol methyl ether 6. To a suspension of 0.18 g (0.49 mmol) of **11** and 0.06 g of NaOH (1.47 mmol) in 20 mL H_2O, was added 0.70 g (4.41 mmol) $KMnO_4$. The mixture was stirred at room temperature for 12 h. An excess of methanol was then added to quench the reaction and the mixture was stirred for a further 10 min. The MnO_2 precipitate was filtered off, and the filtrate acidified with 10% aqueous HCl. Removal of the solvent under reduced pressure gave the crude product as a white solid. The pure triacid was isolated as a white solid in 69% yield by washing the solid with THF and recrystallization from methanol: mp >400°C, decomposition at 150°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.24 (s, 3H) 7.81 (dd, 3H, *J*=7.6 Hz, 2.0 Hz) 7.96 (m, 6H) δ 13.00 (broad s, 3H); ^{13}C NMR (75 MHz) δ 53.2, 88.2, 123.8, 127.8, 137.8, 147.2, 161.1, 166.3; IR (film) cm^{-1} 3475 (broad), 2947, 2867, 1716, 1691, 1591, 1572, 1472, 1392, 1322, 1282, 1098, 1033, 1013, 779; MS *m/z* 410 $(M+H^+)^+$, 442 $(M+Na^+)^+$, 819 $(2M+H^+)^+$. Anal. Calcd for $C_{20}H_{15}N_3O_7{\cdot}H_2O$: C, 56.21; H, 4.00. Found: C, 56.47; H, 4.13.

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