5′-Substituted-6-carboxylic-2,2′-bipyridine Acid: A Pivotal Architecton for Building Preorganized Ligands

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Abstract: A set of ligands bearing 6-bromo-2,2′-bipyridine pendant arms attached in the 5′-position are described. Transformation of the bromo to an ester was performed by a carboethoxylation reaction promoted by low-valent Pd(0), while saponification followed by acidification gave the acids. The introduction of an appended function 3-nitrobenzyl, benzamidomethyl, and *tert*-butylacetyl opens the way to further functionalize these scaffolds for potential labeling of biological material. The synthetic protocols represent a valuable approach to the rational design of ligands bearing oxophilic and anionic sidearms.

In the past few decades, important advances in the development of optical microscopy and image analysis[1] rendered possible the observation of small objects at the nanometric scale.[2] In the field of luminescence microscopy,[3] a large amount of fluorescent probes are now commercially available that can easily be bioconjugated onto biological material. A further step toward the improvement of sensitivity should be reached by the use of time-resolved luminescence microscopy.[4,5] For such an application, new luminescent tags have to be created and the main interests are actually centered around the synthesis of coordination complexes such as Pt−porphine[6] or lanthanide complexes.[7] Although lanthanide tags have long been postulated as good candidates for time-resolved fluoroimmunoassays[8] and thereby for time-resolved luminescence microscopy, the numerous requirements that have to be fulfilled by a probe to be efficient[9] drastically reduce the number of potential candidates.

As part of a research program aimed at the design and synthesis of anionic and tridentate ligands and in order to obtain compounds that fulfill as much as possible the different requirements for obtaining good probes, we have been interested in the synthesis of ligands based on preorganized scaffoldings containing 2,2′-bipyridine-6-carboxylic acid arms.[10] The bipyridine moiety is known to be very efficient for photon collection and transfer to lanthanide cations.[11] The ionizable 6-carboxylic acid function affords an anionic function at neutral pH, which strongly favors the coordination to the metal atom by purely electrostatic interactions.[12] Furthermore, grafting this carboxylate function at the 6 position further stabilizes the coordination by formation of a second five-membered ring. All efforts toward the stabilization of the complex are of particular importance to avoid the release of the toxic free lanthanide cations, a *sine qua non* condition for potential use in biological media. Finally, assuming a coordination number of nine, a situation commonly encountered for trivalent lanthanide cations,[13] the coordination of three tridentate arms allows for charge compensation and completion of the first coordination sphere, thus relegating solvent molecules to the second sphere and thereby avoiding the nonradiative deactivation pathways.

From a chemical point of view, the construction of bipyridine platforms seems to be a worthy task.[14] However, the chemistry of bipyridine bearing potentially ionizable groups (e.g., carboxylate, phosphonate, sulfate, etc.) is significantly underdeveloped due to the lack of general synthetic methods. Furthermore, the rare existing ligands bearing such fragments are symmetrically substituted and offer no synthetic means for attachment to shaping units.[15,16] Here, we partially fill the gap and describe a general procedure for the synthesis of asymmetric 5′,6-disubstituted-2,2′-bipyridine architectons, using an optimized access to the key 5′-bromomethyl-6-bromo-2,2′-bipyridine building block. We will see in detail how three tridentate units should be brought together on acyclic or macrocyclic platforms, some of them offering potentialities for further grafting on biological compounds. The development of these novel ligands would expand opportunities for applications of emergent lanthanide complexes in the field of time-resolved luminescence microscopy.

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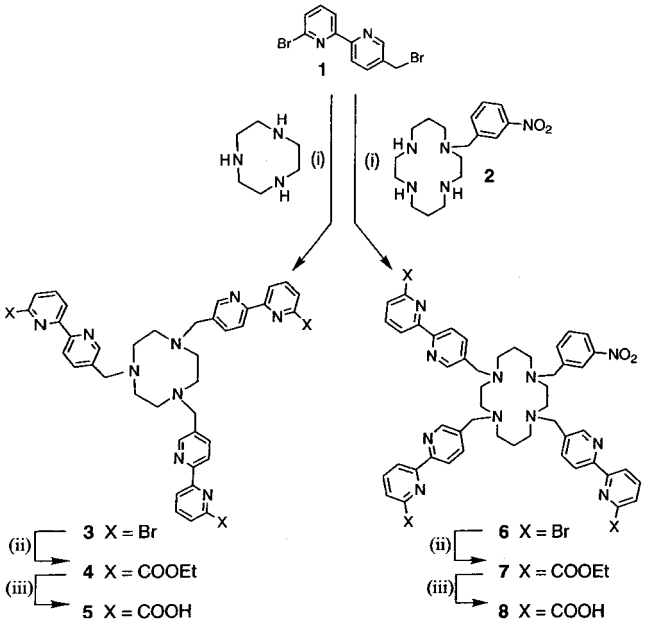
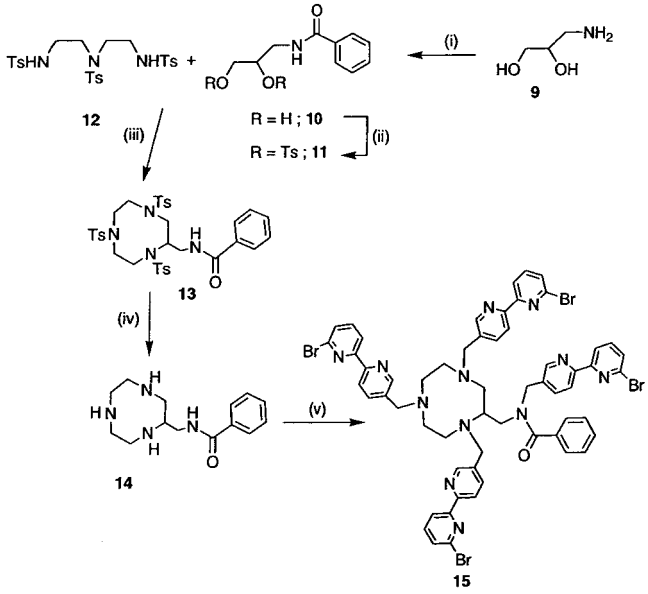
Scheme 1[a]



[a]Reaction conditions: (i) CH_3CN, Na_2CO_3, 80 °C, 96% for **3** and 63% for **6**. (ii) $[Pd(PPh_3)_2Cl_2]$ (6.8 mol % per Br atom), EtOH, Et_3N, CO (1 atm), 80 °C, 83% for **4** and 76% for **7**. (iii) MeOH, H_2O, NaOH, 80 °C; dil HCl, 78% for **5** and 83% for **8**.

Scheme 2[a]



[a]Reaction conditions: (i) C_6H_5COCl, DMF, Et_3N, 5 °C, 72%. (ii) *p*-TsCl, pyridine, 0 °C, 69%. (iii) Cs_2CO_3, DMF, 90 °C, 37%. (iv) Concd H_2SO_4, 120 °C, 50%. (v) CH_3CN, Na_2CO_3, 3.3 equiv of **1**, 80 °C, 30%.

The pivotal 5′-bromomethyl-6-bromo-2,2′-bipyridine building block **1**[10] required the synthesis of 5′-methyl-6-bromo-2,2′-bipyridine itself prepared in two steps from 2-acetyl-6-bromopyridine[17] according to the methodology of Kröhnke.[18] Activation of the 5′-methyl position was a key step in the development of our envisaged preorganized bipyridine-containing architectures. The target was reached by the use of a conventional radical bromination with NBS in refluxing CCl_4, using AIBN as an initiator. The highest yield (69% after purification) was provided with 1.25 equiv of NBS and 0.05 equiv of AIBN, in hot CCl_4, with irradiation to initiate the reaction.

The first ligand bearing three potentially anionic arms was prepared by alkylation of the 1,4,7-triazacyclononane macrocycle followed by a carboethoxylation reaction catalyzed by low-valent palladium(0)[19] to give the corresponding triester **4** in 83% yield (Scheme 1). Upon saponification with aqueous NaOH in MeOH, followed by acidification, the triply branched acid **5** was obtained, which as shown previously is ideally suited for the formation of mononuclear lanthanide complexes.[5] However, to anchor it onto biomaterials, a functional sidearm is required. For this purpose, the monoalkylation of cyclam with 3-nitrobenzylbromide was investigated (81% yield for **2**), according to methods currently used for monofunctionalization of tetraazamacrocycles consisting of the use of a large excess of the macrocycle compared to the alkylating agent.[20] The choice of a *m*-nitrobenzylbromide as the alkylating agent arose from the possibility of reducing the nitro into the corresponding amino function, which then can be converted into an isothiocyanate function.[21] This residue is a good candidate for coupling to terminal amino residues of proteins or antibodies. Furthermore, reaction of **2** with excess **1** gave the intermediate **6** in excellent yield, which can be easily converted to the ethyl ester **7** by carboalkoxylation. Subsequent saponification and acidification afforded the triacid **8**, which is an adequate target for further complexation with lanthanide cations.

Another way to reach the goal of bioconjugation to protein plants is to envisage a 1,4,7-triazacyclononane macrocycle carrying a benzamide function with the viewpoint of releasing the primary amine in strongly acidic conditions after the alkylation process. Construction of the modified 1,4,7-triazacyclononane derivative was carried out as sketched in Scheme 2.

At first, the aminodiol **9** was acylated selectively at the primary amine using stoichiometric amounts of benzoyl chloride, followed by an activation of both alcohol functions with *p*-toluenesulfonic acid chloride in basic conditions leading to compound **11**. Afterward, cyclization between **11** and the tritosylate of diethylenetriamine **12**[22] was carried out in the presence of Cs_2CO_3 as previously described.[23] Detosylation of compound **13** is effective in concentrated sulfuric acid and provides the macrocycle **14** in 50% yield. When the alkylation reaction is carried out with a slight excess of derivative **1**, the target ligand bearing only three bipy frameworks could not be isolated, despite the fact that various experimental conditions were tested. It appears that the alkylation of the secondary amide function takes place readily even in the absence of added mineral base and provides the tetrasubstituted derivatives **15** in fair yield. Such an undesired side compound was observed even in the early stage

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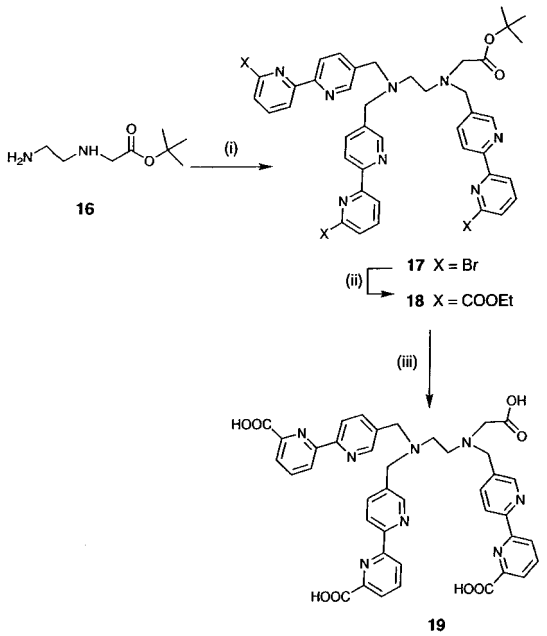
Scheme 3[a]



[a] (i) CH_3CN, Na_2CO_3, 80 °C, 3.3 equiv of **1**, 85%. (ii) [$Pd(PPh_3)_2Cl_2$] (5.0 mol % per Br atom), EtOH, Et_3N, CO (1 atm), 80 °C, 80%. (iii) MeOH, H_2O, NaOH, 80 °C; dil HCl, 57%.

of the reaction and would give disappointingly low yields of the target tris-substituted derivatives under typical reaction conditions. This is a rather surprising result because it was previously shown that alkylation of similar compounds does not occur even in the presence of a large excess of alkylating agent.[23] From these observations, it appears that the use of a short methylene linker between the amide nitrogen and the macrocycle might favor intramolecular hydrogen bonding between the amide proton and the endocyclic NH fragments leading to six- or five-membered rings and also to an indirect increase of the nucleophilicity of the amide nitrogen atom. Such an unexpected alkylation reaction on the amide function will be detrimental for the selective formation of lanthanide complexes and brings us to consider other ways to introduce the branching sidearm.

To induce more flexibility and solubility within the central polyamine frame but also introduce an additional pendant arm that could ultimately be functionalized to a targeted anchoring point, we have protected one nitrogen atom of ethylenediamine with a *tert*-butylbromoacetate[24] affording the product **16** as outlined in Scheme 3. Further alkylation of the remaining three positions with **1** afforded ligand **17** in 85% isolated yield. This tribromo-substituted derivative was esterified under smooth conditions as described above to afford the tetraester **18** in 80% yield. Saponification of this compound under basic conditions and subsequent acidification provide the tetraacid **19**.

In summary, we have presented a logical and expedient protocol for the synthesis of different 2,2′-bipyridyl derivatives asymmetrically substituted at the 5′ and 6 positions with various functions. The engineering of a reactive bromomethyl group in the 5′ position allowed nucleophilic substitution by primary or secondary amines. The presence of a bromine atom at the 6 position facilitates a Pd-assisted carboethoxylation reaction leading to esters and carboxylic acids and potentially to amide functions. In addition, the optimized synthesis of 5′-bromomethyl-6-bromo-2,2′-bipyridine makes this compound an attractive and more available template for ligand synthesis. We succeeded in preparing a large variety of preorganized platforms spanning from triazacyclononane to tetraazacyclotetradecane, all of them carrying polytridentate subunits. The chosen protocols allow an amalgamation of several distinct functionalities and properties. The basic architecture of the target molecules is the presence of three anionic N,N,O donor fragments, which is an ideal situation for the complexation of tricationic cations. The complexation of lanthanide(III) cations with these 6-carboxylic-2,2′-bipyridyl acid functionalized ligands is currently in progress in our laboratory and has already shown remarkable photophysical properties for the europium and terbium complexes generated with ligand **5**.[5] Finally, in some cases, the presence of an additional pendant arm carrying a potential activated function is auspicious for bioconjugation to proteins and biological analogues.

Experimental Section

Materials. 6-Bromo-2-acetylpyridine,[17] bis[2-(tosylamino)-ethyl]tosylamine **12**,[22] (2-amino-ethylamino)acetic acid-*tert*-butylester **16**,[24] and 6-bromo-5′-methyl-2,2′-bipyridine[10,25] were prepared according to literature procedures. All other reagents were used as commercially supplied.

6-Bromo-5′-bromomethyl-2,2′-bipyridine (1). 69%; TLC: $R_f = 0.38$, SiO_2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 4.53 (s, 2H), 7.50 (dd, 1H, $^3J = 8.0$ Hz, $^4J = 1.0$ Hz), 7.67 (t, 1H, $^3J = 8.0$ Hz), 7.85 (dd, 1H, $^3J = 8.0$ Hz, $^4J = 2.4$ Hz), 8.37 (dd, 1H, $^3J = 7.5$ Hz, $^4J = 1.0$ Hz), 8.40 (d, 1H, $^3J = 8.5$ Hz), 8.67 (d, 1H, $^4J = 2.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 29.5, 119.9, 121.4, 128.3, 134.3, 137.7, 139.3, 141.7, 149.5, 154.5, 156.8. FT-IR (KBr, cm^{-1}): 1541 (s), 1430 (s), 1391 (m), 1156 (m). Anal. Calcd for $C_{11}H_8Br_2N_2$: C, 40.30; H, 2.46; N, 8.54. Found: C, 39.91; H, 2.14; N, 8.22. Mp: 166−167 °C. ESI-ToF/MS *m/z*: 326.902 ([M + H]$^+$, 30%), 328.901 ([M + H]$^+$, 83%), 330.980 ([M + H]$^+$, 24%), 348.874 ([M + Na]$^+$, 45%), 350.876 ([M + Na]$^+$, 83%), 352.874 ([M + Na]$^+$, 32%).

1-(3-Nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane (2). 81%. ^{1}H NMR ($CDCl_3$): δ 1.56−1.90 (m, 4H), 2.36−2.88 (m, 16H), 3.58 (s, 2H), 7.37 (t, 1H, $^3J = 7.5$ Hz), 7.52 (d, 1H, $^3J = 7.5$ Hz), 8.02 (d, br, 1H, $^3J = 8.5$ Hz), 8.34 (s, br, 1H). ^{13}C NMR ($CDCl_3$): δ 26.1, 28.8, 47.2, 47.9, 48.8, 49.3, 49.9, 51.9, 53.3, 55.2, 57.5, 122.1, 123.2, 128.9, 134.7, 135.0, 141.8. $R_f = 0.51$, deactivated SiO_2, CH_2Cl_2/MeOH, 90/10. FT-IR (KBr, cm^{-1}): 3293 (m), 2806 (s), 1527 (s), 1463 (m), 1352 (m). Anal. Calcd for $C_{17}H_{29}N_5O_2$: C, 60.85; H, 8.71; N, 20.88. Found: C, 60.41; H, 8.46; N, 20.37. Mp: 58−59 °C. FAB$^+$/MS: 336.4 ([M + H]$^+$, 100%).

1,4,7-Tris[(6-bromo-2,2′-bipyridine-5′-yl)methyl]-1,4,7-triazacyclononane (3). 96%. ^{1}H NMR ($CDCl_3$): δ 2.81 (s, 12H, br), 3.68 (s, 6H, br), 7.48 (dd, 3H, $^3J = 7.8$ Hz, $^4J = 1.0$ Hz), 7.67 (t, 3H, $^3J = 8.0$ Hz), 7.78 (dd, 3H, $^3J = 8.0$ Hz, $^4J = 2.0$ Hz), 8.35 (d, 3H, $^3J = 8.0$ Hz), 8.37 (dd, 3H, $^3J = 8.0$ Hz, $^4J = 1.0$ Hz), 8.60 (s, 3H, br). ^{13}C NMR ($CDCl_3$): δ 55.5, 60.2, 119.6, 121.0, 127.7, 136.3, 137.7, 139.2, 141.5, 149.8, 153.3, 157.3. $R_f = 0.44$, deactivated SiO_2, CH_2Cl_2. FT-IR (KBr, cm^{-1}): 1647 (s), 1541 (m), 1430 (s). Anal. Calcd for $C_{39}H_{36}N_9Br_3$: C, 53.81; H, 4.17; N, 14.48. Found: C, 53.62; H, 3.91; N, 14.24. Mp: 150−151 °C. FAB$^+$/MS: 870.3 ([M + H]$^+$, 96%), 872.3 ([M + H]$^+$, 100%), 620.2 ([M − CH_2bipyBr)], 20%), 622.2 ([M − CH_2bipyBr)], 50%), 624.2 ([M − CH_2bipyBr)], 28%).

1,4,7-Tris[(6-carboethoxy-2,2′-bipyridine-5′-yl)methyl]-1,4,7-triazacyclononane (4). 83%. ^{1}H NMR ($CDCl_3$): δ 1.46 (t, 9H, $^3J = 7.0$ Hz), 2.93 (s, 12H, br), 3.77 (s, 6H, br), 4.49 (qd, 6H, $^3J = 7.5$ Hz), 7.89−8.02 (m, 6H), 8.11 (dd, 3H, $^3J = 7.5$ Hz, $^4J = 1.0$ Hz), 8.51−8.64 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 14.6, 55.8, 60.5,

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62.0, 121.5, 124.3, 125.0, 132.2, 136.5, 138.0, 148.0, 150.0, 154.4, 156.6, 165.5. R_f = 0.66, deactivated SiO_2, CH_2Cl_2/MeOH, 99.5/0.5. FT-IR (KBr, cm^{-1}): 2929 (m), 1732 (s), 1719 (s), 1450 (m), 1240 (s), 1139 (s). Anal. Calcd for $C_{48}H_{51}N_9O_6$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.67; H, 5.81; N, 14.66. Mp: >150 °C dec. FAB$^+$/MS: 850.7 ([M + H]$^+$, 100%).

1,4,7-Tris[(6-carboxy-2,2′-bipyridine-5′-yl)methyl]-1,4,7-triazacyclononane (5). 78%. ^{1}H NMR (DMSO-d_6): δ 3.99 (s, 12H, br), 4.04 (s, 6H, br), 7.83 (d, 3H, br, ^3J = 8.0 Hz), 8.05−8.10 (m, 6H), 8.53−8.56 (m, 6H), 8.59 (s, 3H, br). ^{13}C NMR (D_2O/NaOD): δ 55.7, 60.4, 123.8, 124.7, 125.8, 137.0, 140.5, 140.9, 151.3, 155.3, 155.6, 156.0, 174.4. FT-IR (KBr, cm^{-1}): 1720 (s), 1630 (s), 1460 (m), 1352 (s), 1262 (m). Mp: >220 °C dec. Anal. Calcd for $C_{42}H_{39}N_9O_6 \cdot H_2O$: C, 64.36; H, 5.27; N, 16.08. Found: C, 64.26; H, 5.15; N, 16.14. FAB+/MS: 766.5 ([M + H]$^+$, 30%).

1-(3-Nitrobenzyl)-4,8,11-tris[(6-bromo-2,2′-bipyridine-5′-yl)methyl]-1,4,8,11-tetraazacyclotetradecane (6). 63%. ^{1}H NMR ($CDCl_3$): δ 1.66−1.86 (m, 4H), 2.40−2.72 (m, 16H), 3.43 (s, br, 8H), 7.31−7.48 (m, 4H), 7.52−7.80 (m, 7H), 8.05 (d, br, 1H, ^3J = 8.0 Hz), 8.16−8.35 (m, 7H), 8.47−8.58 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 24.7, 29.8, 50.5, 50.6, 50.7, 50.9, 51.4, 51.6, 56.1, 56.3, 56.4, 58.0, 119.7 (2C), 121.0, 121.1, 122.1, 123.7, 127.9, 129.0, 134.8, 136.2, 136.3, 137.6, 139.3, 141.6, 142.7, 148.3, 149.8, 153.4, 157.4, 157.5. R_f = 0.26, SiO_2, CH_2Cl_2/MeOH, 95/5. Mp: >200 °C dec. FT-IR (KBr, cm^{-1}): 2936 (m), 2800 (m), 1544 (s), 1526 (s), 1384 (m), 1347 (m). Anal. Calcd for $C_{50}H_{50}N_{11}O_2Br_3$: C, 55.78; H, 4.68; N, 14.31. Found: C, 55.41; H, 4.32; N, 13.92. FAB$^+$/MS: 1076.3 ([M + H]$^+$, 100%), 1078.3 ([M + H]$^+$, 100%), 940.5 ([M − CH_2PhNO_2 + H]$^+$, 30%), 942.5 ([M − CH_2PhNO_2 + H]$^+$, 10%).

1-(3-Nitrobenzyl)-4,8,11-tris[(6-carbethoxy-2,2′-bipyridine-5′-yl)methyl]-1,4,8,11-tetraazacyclotetradecane (7). 76%. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, br, 9H, ^3J = 7.0 Hz), 1.79 (m, 4H), 2.32−2.75 (m, 16H), 3.40 (s, br, 8H), 4.44 (q, 6H, ^3J = 7.0 Hz), 7.10−8.58 (m, 22H). ^{13}C NMR ($CDCl_3$): δ 14.4, 24.6, 50.5 (2C), 50.8, 51.3, 51.4, 51.5, 56.2, 56.3, 56.4, 58.0, 61.9, 119.7, 121.2, 121.3, 122.0, 123.7, 124.1, 124.8, 127.8, 128.4, 128.7, 129.0, 132.0 (2C), 132.2, 134.8, 136.0, 136.2, 137.6 (2C), 137.8, 139.3, 141.6, 142.7, 147.8, 148.3, 149.8, 154.2, 156.4, 156.5 (2C), 165.4. R_f = 0.35, deactivated SiO_2, CH_2Cl_2/hexane, 70/30. FT-IR (KBr, cm^{-1}): 2939 (m), 2793 (m), 1717 (s), 1527 (m), 1348 (m). Anal. Calcd for $C_{59}H_{65}N_{11}O_8$: C, 67.08; H, 6.20; N, 14.59. Found: C, 66.74; H, 5.94; N, 14.38. Mp: 51−52 °C. FAB$^+$/MS: 1056.2 ([M + H]$^+$, 100%), 814.2 ([M − (CH_2bipyCO_2Et)], 47%).

1-(3-Nitrobenzyl)-4,8,11-tris[(6-carboxy-2,2′-bipyridine-5′-yl)methyl]-1,4,8,11-tetraazacyclotetradecane (8). 83%. ^{1}H NMR (DMSO-d_6): δ 1.90−2.25 (m, br, 4H), 2.60−3.50 (m, 16H), 3.70−4.30 (m, br, 8H), 7.50−8.80 (m, 22H). FT-IR (KBr, cm^{-1}): 2980 (m), 1637 (s), 1384 (m). Anal. Calcd for $C_{53}H_{53}N_{11}O_8 \cdot H_2O$: C, 64.30; H, 5.60; N, 15.56. Found: C, 64.20; H, 5.76; N, 15.48. Mp >190 °C dec. FAB$^+$/MS: 972.3 ([M + H]$^+$, 23%), 759.3 ([M − (CH_2bipyCO_2H) + H]$^+$, 100%).

***N*-(2,3-Dihydroxypropyl)benzamide (10).** 72%. ^{1}H NMR ($CDCl_3$): δ 3.35−3.61 (m, 4H), 3.83 (m, 1H), 4.82 (s, br, 2H), 7.20−7.42 (m, 3H), 7.60 (t, 1H, br, ^3J = 5.5 Hz), 7.70 (d, 2H, ^3J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 42.8, 64.0, 71.1, 127.2, 128.6, 131.8, 133.7, 169.3. R_f = 0.34, SiO_2, CH_2Cl_2/MeOH, 95/5. FT-IR (KBr, cm^{-1}): 2933 (s), 2878 (m), 1637 (s), 1541 (s), 1310 (m). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.50; H, 6.51; N, 6.84. FAB+/MS: 196.3 ([M + H]$^+$, 100%).

***N*-[2,3-(Bis-toluene-*p*-sulfonato)propyl]benzamide (11).** 69%. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.43 (s, 3H), 3.45−3.85 (m, 2H), 4.10−4.25 (m, 2H), 4.83 (sx, 1H, ^3J = 8.0 Hz), 6.70 (t, br, 1H, ^3J = 6.0 Hz), 7.18−7.51 (m, 7H), 7.65−7.73 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 21.6 (2C), 40.3, 68.3, 77.1, 127.0, 127.9, 128.0, 128.5, 129.9, 130.0, 131.8, 131.9, 132.4, 133.2, 145.3, 145.4, 167.5. R_f = 0.14, SiO_2, CH_2Cl_2/MeOH, 99/1. FT-IR (KBr, cm^{-1}): 3428 (s), 1663 (s), 1537 (s), 1347 (s), 1192 (s), 1176 (s). Anal. Calcd for $C_{24}H_{25}NO_7S_2$: C, 57.20; H, 5.00; N, 2.78. Found: C, 57.11; H, 4.92; N, 2.63. FAB$^+$/MS: 504.6 ([M + H]$^+$, 100%).

***N*-(Benzamidomethyl)-1,4,7-tris(toluene-*p*-sulfonyl)-1,4,7-triazacyclononane (13).** 37%. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.37 (s, 3H), 2.40 (s, 3H), 3.00−3.50 (m, 10H), 3.67−4.18 (m, 2H), 4.80−5.00 (m, 1H), 5.19 (t, 1H, ^3J = 5.5 Hz), 7.18−7.50 (m, 9H), 7.56 (d, 2H, ^3J = 8.5 Hz), 7.68 (d, 2H, ^3J = 8.0 Hz), 7.72 (d, 2H, ^3J = 8.5 Hz), 7.86 (d, 2H, ^3J = 8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 21.4 (3C), 29.6, 42.3, 49.6, 49.8, 49.9, 57.9, 78.4, 127.0, 127.1, 127.2 (2C), 128.1, 128.3, 129.6, 129.8, 129.9, 131.4, 134.7, 135.0, 136.5, 143.3, 143.8, 143.9, 163.5. R_f = 0.31, SiO_2, CH_2Cl_2/MeOH, 96/4. FT-IR (KBr, cm^{-1}): 2921 (m), 2873 (w), 1651 (m), 1343 (s), 1155 (s). Anal. Calcd for $C_{35}H_{40}N_4O_7S_3$: C, 58.00; H, 5.56; N, 7.73. Found: C, 57.78; H, 5.25; N, 7.46. ESI-ToF/MS: 725.311 ([M + H]$^+$, 100%), 747.282 ([M + Na]$^+$, 50%).

2-(Benzamidomethyl)-1,4,7-triazacyclononane (14). 50%. ^{1}H NMR ($CDCl_3$): δ 2.58−2.85 (m, 10H), 3.65−4.15 (m, 2H), 4.81 (m, 1H), 7.25−7.48 (m, 4H), 7.90 (d, 2H, ^3J = 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 29.8, 41.9, 49.3, 49.6, 52.6, 58.4, 79.6, 127.9, 128.2, 128.4, 131.4. FT-IR (KBr, cm^{-1}): 2925 (m), 1645 (s), 1538 (m), 1308 (m). HRMS (ES): calcd for $C_{14}H_{22}N_4O$, 263.1871 (MH); found, 263.1875.

2-[*N*-((6-Bromo-2,2′-bipyridine-5′-yl)methyl)benzamidomethyl)-1,4,7-tris-[(6-bromo-2,2′-bipyridine-5′-yl)methyl]-1,4,7-triazacyclononane (15). 30%. ^{1}H NMR ($CDCl_3$): δ 2.40−2.79 (m, 10H), 3.43−3.65 (m, 9H), 3.93−4.05 (m, 1H), 4.62−4.78 (m, 1H), 7.28−7.70 (m, 15H), 7.84 (d, br, 2H, ^3J = 7.5 Hz), 8.15−8.58 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 51.7, 52.6, 52.8, 53.0, 56.0 (br), 56.7, 56.9, 58.3, 58.5, 78.6, 119.5, 120.9, 121.0, 127.6, 127.7, 127.8, 128.0, 128.3, 128.6, 131.3, 135.0, 135.1, 135.4 (br), 137.1, 137.2, 137.3, 139.1, 141.5 (br), 149.4, 149.5, 153.4, 153.5 (br), 157.0, 157.1, 163.6. R_f = 0.49, SiO_2, CH_2Cl_2/MeOH, 90/10. FT-IR (KBr, cm^{-1}): 2927 (m), 2817 (m), 1647 (s), 1543 (m), 1430 (s), 1124 (m). Mp: >220 °C dec. Anal. Calcd for $C_{58}H_{50}N_{12}OBr_4$: C, 53.46; H, 4.23; N, 14.12. Found: C, 55.42; H, 3.74; N, 13.15. ESI-ToF/MS: 1273.035 ([M + Na]$^+$, 100%).

***N*,*N*,*N*′-Tris[(6-bromo-2,2′-bipyridine-5′-yl)methyl]-*N*′-*t*-butylacetyl-ethylenediamine (17).** 85%. ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 9H), 2.61 (t, br, 2H, ^3J = 6.0 Hz), 2.85 (t, br, 2H, ^3J = 6.0 Hz), 3.20 (s, 2H), 3.62 (s, 4H), 3.80 (s, 2H), 7.40−7.47 (m, 3H), 7.58−7.76 (m, 6H), 8.22−8.38 (m, 6H), 8.51 (d, 1H, ^4J = 1.5 Hz), 8.56 (d, 2H, ^4J = 1.5 Hz). ^{13}C NMR ($CDCl_3$): δ 28.1, 29.6, 51.4, 51.9, 55.2, 55.8 (2C), 81.2, 119.6, 121.1, 127.8, 135.2 (2C), 137.3, 137.4, 139.1, 141.5, 149.5, 149.6, 153.6, 157.1, 157.2, 170.3. R_f = 0.80, deactivated SiO_2, CH_2Cl_2/MeOH, 98/2. FT-IR (KBr, cm^{-1}): 1731 (m), 1569 (m), 1544 (m), 1430 (s), 1153 (m), 1124 (m). Mp: >180 °C dec. Anal. Calcd for $C_{41}H_{39}N_8O_2Br_3$: C, 53.79; H, 4.29; N, 12.24. Found: C, 53.61; H, 4.02; N, 12.00. FAB$^+$/MS: 916.2, 917.2, 918.2, 919.2 (40, 100, 45, and 40%, respectively, [M + H]$^+$).

***N*,*N*,*N*′-Tris[(6-carboethoxy-2,2′-bipyridine-5′-yl)methyl]-*N*′-*t*-butylacetyl-ethylenediamine (18).** 80%. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H), 1.44 (t, br, 9H, ^3J = 7.0 Hz), 2.63 (t, br, 2H, ^3J = 6.0 Hz), 2.88 (t, br, 2H, ^3J = 6.0 Hz), 3.20 (s, 2H), 3.64 (s, 4H), 3.80 (s, 2H), 4.45 (q, 6H, ^3J = 7.5 Hz), 7.72−7.95 (m, 6H), 8.04−8.10 (m, 3H), 8.41−8.60 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 14.4, 28.24, 29.7, 45.9, 51.5, 51.9, 55.2, 55.8, 61.9 (2C), 81.2, 121.5, 124.1, 124.2, 124.8, 135.2, 137.5, 137.7, 137.8, 147.8, 149.6, 149.7, 154.5, 156.3, 156.4, 165.4, 170.5. R_f = 0.47, deactivated SiO_2, CH_2Cl_2. Mp: >200 °C dec. HRMS (ES): calcd for $C_{50}H_{54}N_8O_8$, 895.4142 (MH); found, 895.4145.

***N*,*N*,*N*′-Tris[(6-carboxy-2,2′-bipyridine-5′-yl)methyl]-*N*′-acetoxy-ethylenediamine (19).** 57%. ^{1}H NMR (DMSO-d_6): δ 3.37 (s, br, 2H), 3.58 (s, br, 2H), 3.75−3.95 (m, br, 2H), 4.35 (s, br, 2H), 4.53 (s, br, 4H), 8.05−8.20 (m, br, 6H), 8.25−9.10 (m, br, 12H). ^{13}C NMR (DMSO-d_6): δ 48.8, 53.0, 53.3, 53.8, 54.3, 121.4, 122.0, 124.1, 124.4, 125.3, 125.5, 128.1, 128.8, 129.4, 132.1, 137.2, 139.1, 139.3, 141.8, 142.3, 147.8, 149.8, 151.4, 152.7, 165.4 (2C), 169.7. FT-IR (KBr, cm^{-1}): 1736 (s), 1630 (s), 1350 (m), 1264 (m). Mp: >220 °C dec. Anal. Calcd for $C_{40}H_{34}N_8O_8$: C, 63.65; H, 4.54; N, 14.85. Found: C, 63.30; H, 4.27; N, 14.69. FAB$^+$/MS: 755.3 ([M + H]$^+$, 90%), 777.3 ([M + Na]$^+$, 100%).

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Supporting Information Available: Experimental details for the radical bromination of 6-bromo-5′-methyl-2,2′-bipyridine, synthesis and detailed characterization of analogous linear dipodal and start tripodal ligands, and experimental methods for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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