Synthesis of Flexible Polydendate Ligands Bearing 5′-Substituted-6-carboxylic-2,2′-bipyridine Subunits

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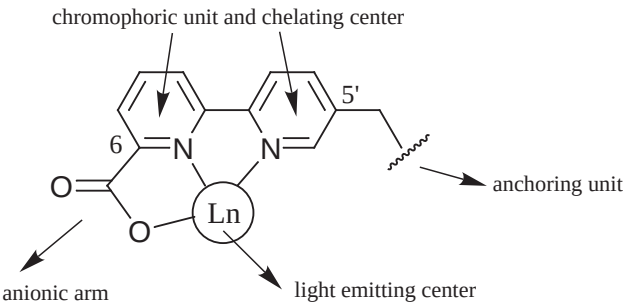
Abstract: The synthetic scope of asymmetric 5′,6-disubstituted-2,2′-bipyridines in the preparation of flexible multitopic ligands has been investigated. The preparation of the pivotal 6-bromo-5′-bromomethyl-2,2′-bipyridine building block involved a Kröhnke protocol followed by a radical bromination reaction which has been optimized. Functionalization of 6-bromo-5′-bromomethyl-2,2′-bipyridine has been realized by both a Delepine and a Gabriel reaction, providing after hydrolysis the corresponding amino compound, whereas a nucleophilic attack of acetate followed by a saponification reaction provided the corresponding alcohol. Multifunctionalized bipyridine ligands have been prepared in one step from 6-bromo-5′-bromomethyl-2,2′-bipyridine and acyclic amines or primary alcohol via base-assisted nucleophilic substitutions. In all cases, transformation of the bromo-function to the corresponding ethyl esters has been made possible under mild conditions using a palladium promoted carboethoxylation reaction, while saponification under basic conditions provided the corresponding acids after protonation. The utility of the herein reported protocols has been extended to the synthesis of an ethylenediamine platform bearing an appended 4-nitrobenzyl group for potential linking to other molecules.

Key words: bromination, pyridines, bipyridines, ligands, radical reaction, nucleophilic additions

Transition metal and lanthanide complexes involving 2,2′-bipyridine (bpy) or its derivatives have been used in a wide variety of applications ranging from catalytic mediated reactions[1] to amperomeric[2] and luminophoric sensors[3] and more recently as thin films in electroluminescent devices.[4,5] The remarkable intrinsic properties of these complexes such as intense absorption bands in the near ultraviolet or visible region, long-lived metal-to-ligand charge transfer or lanthanide centered excited states and modest to high quantum yields make possible the labelling of biological material for quantitative analytical purposes.[6,7] Such highly desirable features have stimulated a wealth of synthetic efforts to promote tailor-made ligands in order to provide stable complexes with outstanding optical properties. In this context, the coordination of lanthanide centres allow the production of very good labels which have been used in fluoroimmunoassays.[8,9] In comparison with other ligands with nitrogen donors, in particular with the strictly related bpy platforms, the use of anionic derivatives as auxiliaries in the field of luminophoric labels is less extensive than one might expect.[10] This shortcoming is due largely to difficulties in preparing the prerequisite starting building blocks.[11,12] A notable advance was reported with pyridine and bpy ligands bearing flexible polyacetate arms.[13,14] However, the direct connection of a carboxylate function in the 6-substitution position of a bpy framework provide an ideal anionic tridendate pocket for lanthanide complexation and many different preorganized platforms have recently been engineered (Figure).[15]



Figure

The objective of this study was to investigate the scope and limitations of a methodology applied to the synthesis of asymmetric 5′,6-disubstituted-2,2′-bipyridine *bausteine*, using an optimized access to the key 5′-bromomethyl-6-bromo-2,2′-bipyridine compounds. Three such tridentate units were brought together on acyclic platforms, one of them offering potentialities for further grafting on biological compounds.

The synthetic strategy for the 5′,6-disubstituted-2,2′-bipyridine compounds is sketched in Scheme 1 and the objective of this study was to develop a concise and practical synthesis of 5′-bromomethyl-6-bromo-2,2′-bipyridine (**5**), a pivotal synthon for the targeted ligands. This has led us to devise a flexible synthetic protocol, which employs 2-acetyl-6-bromopyridine **1**[16] as a template. The preparation of 5′-methyl-6-bromo-bipyridine (**2**) was achieved in a two steps procedure via the formation of the acetylpyridinium according to the method developed by King[17] followed by condensation with a mixture of methacrolein and $(NH_4)OAc$ according to the methodology of Kröhnke.[18] From this building block **2**, further derivatization can be achieved orthogonally either at the 5′-methyl or at the 6-bromo positions. For example activation at the

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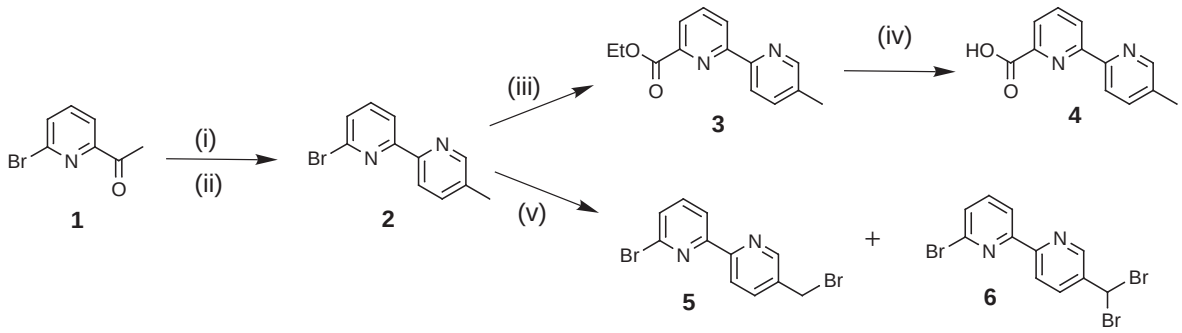


Scheme 1 *Reagents and conditions:* (i) I_2, pyridine, 115 °C; (ii) $HC(O)NH_2$, NH_4OAc, methacrolein, 90 °C, 68% for the two steps; (iii) $Pd(PPh_3)_2Cl_2$ (3.5 mol%), EtOH, Et_3N, CO (1 atm), 80 °C, 98%; (iv) EtOH, HCl, H_2O, 100 °C, 89%; (v) NBS, AIBN, CCl_4, 80 °C, 69% of **5**, 28% of **6**.

6-bromo position is made feasible by a carboalkoxylation reaction,[19] using a stream of CO in a hot mixture of EtOH/Et_3N containing catalytic amounts of $Pd(PPh_3)_2Cl_2$, affording the ethyl ester **3** which upon aqueous acidic treatment was converted to the tridentate ligand **4**.

Activation of the 5′-methyl position was a key step in the development of our strategy, as it afforded the milestones for grafting on preorganized architectures. At first, preparation of **5** was attempted using the method developed by Fraser et al.[20] in which methyl substituted bipyridines are first transformed into trimethylsilane derivatives by deprotonation with LDA at low temperature followed by reaction with TMSCl. When the silane reacted with CsF in the presence of $C_2F_4Br_2$, the monobrominated compounds are usually obtained with excellent yields. Despite all synthetic efforts to extend this procedure to **2**, we have been unable to isolate the corresponding silane in reasonable amounts. It is surmized that the presence of the bromine atom in the 6 position affords competing pathways for the metallation of the pyridine rings with LDA. As part of our research program dealing with the synthesis of monobromomethyl and dibromomethyl derivatives,[21] it was soon established that the radical bromination reaction of **2** provide a non-negligible deviation from the expected statistical distribution of the products (63% of monobrominated compound **5** was obtained with one equivalent NBS, instead of the expected 50% statistical value, Table, Scheme 1). Consequently, a set of general conditions (including temperature, concentrations, irradiation) was established and the main facets are gathered in the Table. As expected, the presence of the radical initiator and light irradiation during the reaction gave the best results, although in the dark the reaction proceeded if the temperature is raised to 100 °C in a Schlenk tube. Varying the quantity of NBS leads to an optimal value of 1.25 equivalents, for which only traces of the starting material remained, an important point for the purification by column chromatography. In this latter case, the optimal yield reached 69% after isolation and appropriate purification of the product. For higher quantities of NBS, the second bromination leading to derivative **6** occured at the expense of the monobrominated compound **5**.

Table Various Experimental Conditions for Radical Bromination of **2**

Quantities (equiv)[a]			Temp (°C)[b]	hν[c]	Products (%)[d]	
2	NBS	AIBN			**5**	**6**
1.0	1.0	0	80 to 100	No	0	0
1.0	1.0	0.05	80	No	0	0
1.0	1.0	0.05	100	No	51	4
1.0	1.0	0.05	80	Yes	63	9
1.0	1.25	0.05	80	Yes	69	28
1.0	1.5	0.05	80	Yes	62	33[e]

[a] Typical conditions: **2** (50 mg) in CCl_4 (10 mL).
[b] For T > 80 °C, the reaction was carried out in a Schlenk tube.
[c] Irradiation was performed with a conventional incandescence lamp, 60 Watts.
[d] Percentages obtained from the integral values on the ^1H NMR spectra.
[e] About 5% of a compound identified as the tribrominated compound were formed.

From the 5′-bromomethyl compound **5**, it was then possible to prepare the corresponding hydroxymethyl derivative **7**, via a nucleophilic attack of sodium acetate, followed by a subsequent saponification of the resulting ester (Scheme 2). This derivative could then be used in Williamson etherification reactions (*vide infra*). Furthermore, the amino derivative **8**, could be prepared by a straightforward manner using a Delepine reaction with hexamethylenetetramine, and a subsequent acidic hydrolysis of the resulting ammonium salt. The direct carboethoxylation of the bromine function of amino derivative such as **8**, under standard conditions [CO, EtOH, Et_3N, catalytic amounts of $Pd(PPh_3)_2Cl_2$], gave mixtures of compounds from which the expected esters were obtained only in low yields.[22] It is surmized that during the carboalkoxylation process the starting primary amine and the in situ formed secondary amide also readily reacted to form polymeric amide species.[23,24] A smarter way to obtain **11** was to prepare the amine in the form of a phthalimide group as outlined in Scheme 2. Compound **9** was

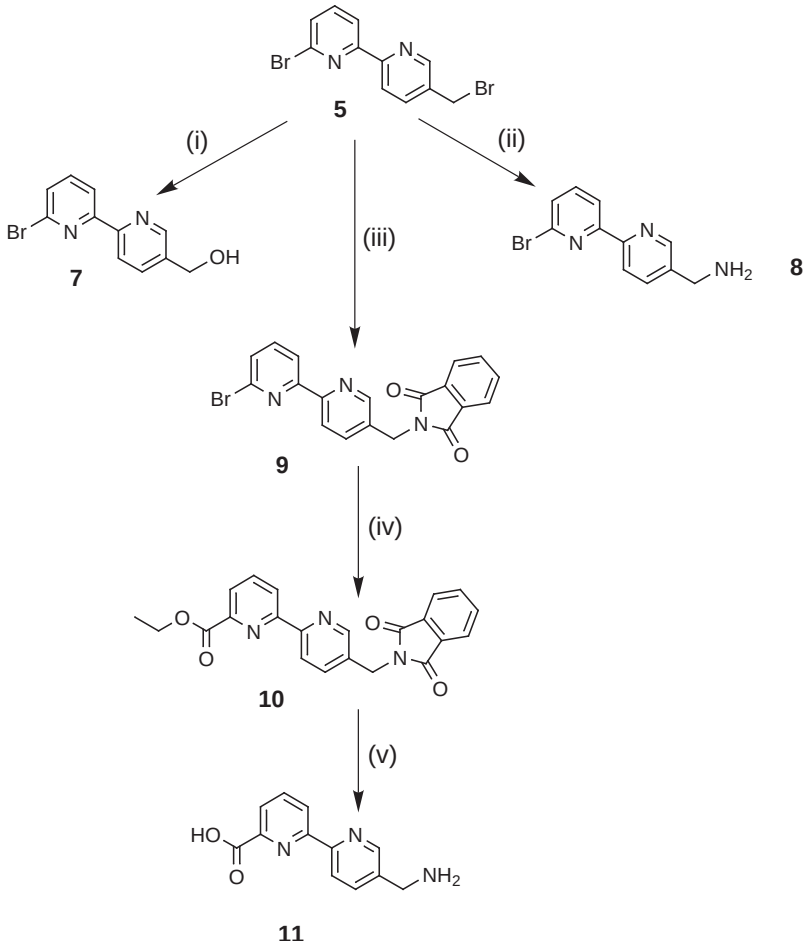
obtained by a nucleophilic substitution of the methyl bromide in **5** with potassium phthalimidate under anhydrous conditions according to the classical Gabriel synthesis methodology. Then, the carboethoxylation protocol afforded the ester **10**. Simultaneous hydrolysis of the ester and the phthalimide fragments to the target compound **11** was feasible but the final separation of the resulting phthalic acid from the acid **11** is tedious. A much better way was to perform the amine deprotection as a first step in the presence of hydrazine, allowing an easy removal of the phthalic moiety, while the ester hydrolysis was further realized under acidic conditions as depicted in Scheme 2. Stepwise conversion of **5** to **11** was made possible in four steps with a total yield of 39%.

Access to the ether-bridged ditopic ligand **12** requires deprotonation of **7** with NaH while the resulting alcoholate induced a nucleophilic substitution at the bromide in compound **5** (Scheme 3). Similarly, the carboalkoxylation sequence of reactions previously applied, was repeated with compound **12** affording the bis-tridentate ligand **13**. Hydrolysis under basic conditions and reacidification readily afforded the diacid compound **14**.

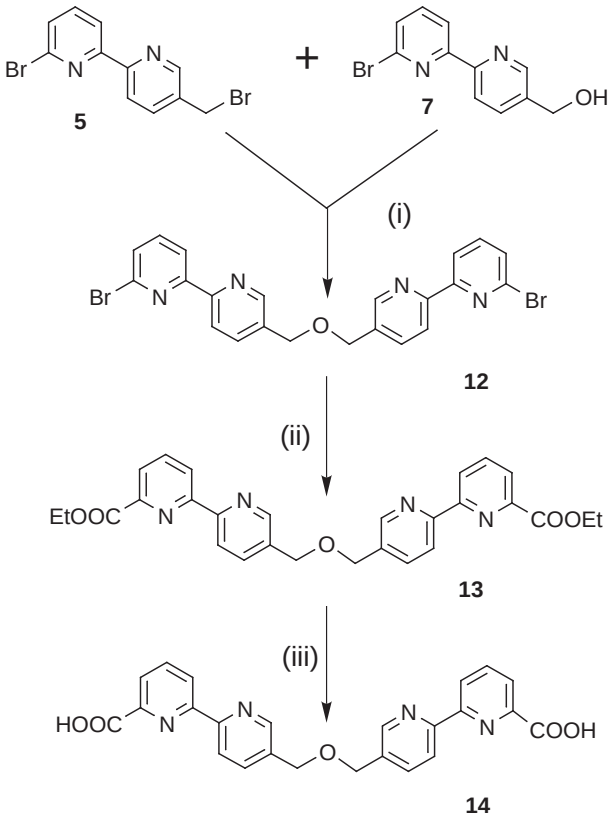
Furthermore, alkylation of the primary amine **8** with 2.2 equivalents of **5** can also be carried out in the presence of a mineral base to reach the tripode ligand **15** in excellent yield. In this case, the carboalkoxylation sequence lead to the tris-tridentate ligand **16**. The ethyl ester **16** was hydrolysed under basic conditions to provide the tris-acid **17** in acceptable yield. Deprotonation of the acid functions of derivatives **14** and **17** provides di- and tri-anionic ligands which are excellent targets for lanthanide complexation (Scheme 4).

In order to induce more flexibility and solubility within the central polyamine frame and also to introduce an additional pendant arm which could ultimately be linked to a protein with an anchoring function, we have protected one nitrogen atom of ethylenediamine with a *p*-nitrobenzyl group[25] affording the product **18** as outlined in Scheme 5. Further alkylation of the remaining three positions with 5′-bromomethyl-6-bromo-2,2′-bipyridine afforded ligand **19** in 74% isolated yield. This compound was allowed to react smoothly with carbon monoxide and ethanol in a carboethoxylation reaction catalyzed by low valent palladium(0). The corresponding triester compound **20** was then saponified under basic conditions to afford the triacid derivative **21** in fair yield.

The synthetic protocol described herein provides an expedient access to a novel family of polydendate bipyridyl



Scheme 2 *Reagents and conditions:* (i) NaOAc, DMF, 120 °C; MeOH, H_2O, NaOH, 100 °C, 89%; (ii) hexamethylenetetramine, CH_2Cl_2, 40 °C; concd HCl, EtOH, 78%; (iii) potassium phthalimidate 1.1 equiv, THF, 70 °C, 16 h, 90%; (iv) $Pd(PPh_3)_2Cl_2$, EtOH, Et_3N, CO (1 atm), 70 °C, 67%; (v) $H_2NNH_2{\cdot}H_2O$, EtOH, 80 °C; HCl 3 M, 70 °C, 65%.



Scheme 3 *Reagents and conditions:* (i) NaH, THF, 80 °C, 84%; (ii) $Pd(PPh_3)_2Cl_2$ (10 mol% per Br atom), EtOH, Et_3N, CO (1 atm), 80 °C, 39%; (iii) MeOH, H_2O, NaOH, 80 °C; dilute HCl, 89%.

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, and also by alcohols. The presence of a bromine atom at the 6 position facilitates a Pd-assisted carboethoxylation reaction leading to esters, which after hydrolysis gave the corresponding carboxylic acids. In addition, we reported an optimized synthesis of 5′-bromomethyl-6-bromo-2,2′-bipyridine, which makes this compound an attractive and more available template for ligand synthesis and represents the most efficient synthesis of these pivotal derivatives to date (three steps with overall yield of 47%). The chosen protocols allow an amalgamation of several distinct functionalities and properties. The basic architecture of the target molecules is the presence of a three anionic N, N, O donor fragment which is an ideal arrangement for the complexation of tricationic lanthanides. Finally, the presence of an additional pendant arm carrying a potential activated function is especially appealing for bioconjugation to proteins and biological material. The utility of the ligands prepared in this study as auxiliaries in the preparation of luminescent lanthanide complexes is under current investigation. From preliminary results obtained in screening experiments with europium cations the bipyridylcarboxylate frameworks seem to promise good luminophoric properties, whereas the prospects seem less favourable concerning some of their thermodynamic stability behavior in aqueous medium.

The 200.1 MHz (^1H) and 50.3 MHz (^{13}C) NMR spectra were recorded at r.t. on a Bruker AC 200 spectrometer, using perdeuterated solvents as internal standard: δ (H) in ppm relative to residual protiated solvent or *t*-BuOH (δ = 1.30) for D_2O solutions; δ (C) in ppm relative to the solvent or to *t*-BuOH (δ = 31.6 and 68.7) for D_2O solutions. For compound **20**, the NMR spectra were recorded before protonation of the compound in order to avoid the broadening of the signals. FT-IR spectra were recorded as KBr pellets on a Nicolet 210 spectrometer. High resolution mass spectral analysis (HRMS) were performed using a Mariner ESI-Tof instrument from Applied Bio-System/Perking Elmer. Melting points were obtained on a Büchi 535 capillary melting point apparatus in open-ended capilliaries and are uncorrected. Chromatographic purification was conducted using 0.063–0.200 mm silica gel or aluminium oxide 90 standardized obtained from Merck. Thin layer chromatography (TLC) were performed on silica or aluminium oxide plates (Merck) coated with fluorescent indicator. All mixtures of solvents are given in v/v ratio.

6-Bromo-2-acetylpyridine (**1**)[16] and *N*-(*p*-nitrobenzyl)ethylenediamine (**18**) (in its non-protonated form)[25] were prepared according to literature procedures. CH_2Cl_2 (Prolabo) was distilled from CaH_2. THF (Riedel-de-Haën) was dried over Na/benzophenone prior to distillation. MeCN (Riedel-de-Haën) was filtered over aluminium oxide (Merck, Act III) and distilled over P_2O_5. $Pd(PPh_3)_2Cl_2$ (Aldrich) was recrystallized from hot DMSO. Methacrolein (Fluka, 95%), NH_4OAc (Prolabo 97%), iodine (Prolabo), pyridine (Prolabo, 99.7%), Et_3N (Riedel-de-Haën, >99%), EtOH (Merck, absolute), NBS (Fluka, 97%), azobisisobutyronitrile (Janssen Chimica, 98%), hexamethylenetetramine (Prolabo, 99%), DMF (SDS, 99.8%), formamide (Acros, 99.5%) and 1,4,7-triazacyclononane (Fluka, 97%) were used as purchased.

6-Bromo-5′-methyl-2,2′-bipyridine (2)

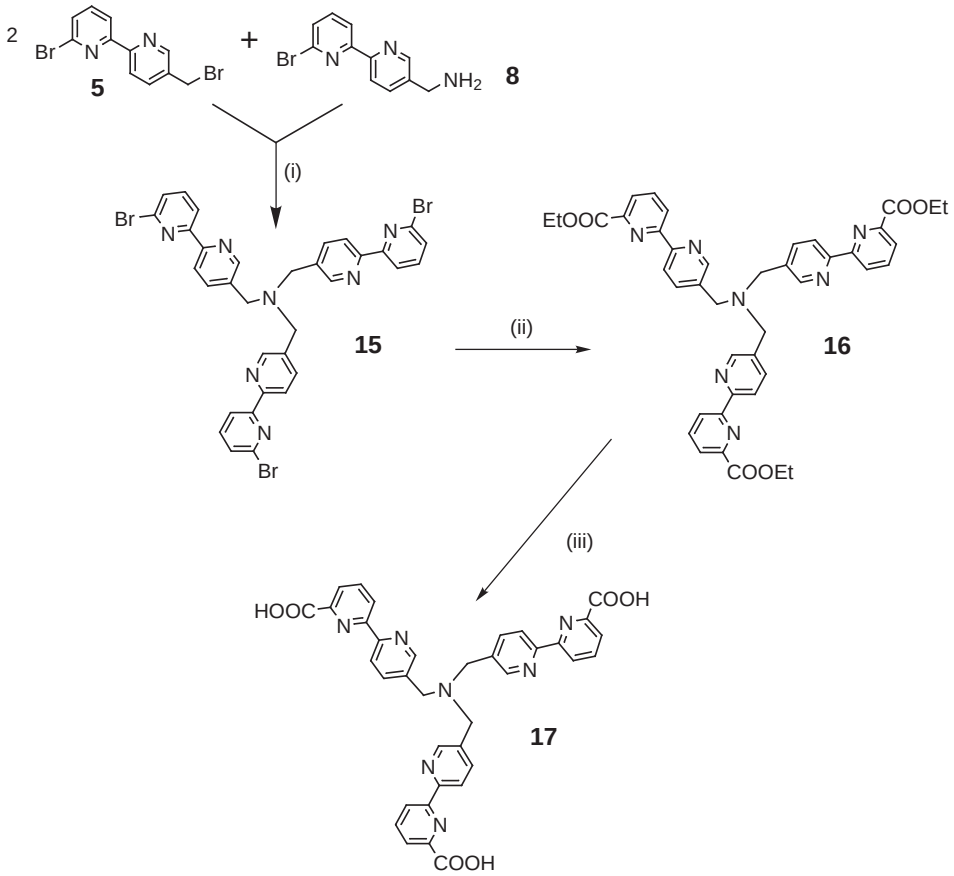
A mixture of **1** (5.0 g, 25 mmol) and I_2 (6.3 g, 25 mmol) was refluxed for 1 h in pyridine (30 mL). The solution was cooled to r.t., resulting in the precipitation of the 6-bromo-2-acetylpyridiniumiodide in quantitative yield. The solid was filtered, dispersed in $CHCl_3$ (30 mL), sonicated and filtered. This washing process was repeated and the solid filtered off and dried for 1 h under reduced pressure. The pyridinium salt was dissolved in formamide (60 mL) containing NH_4OAc (28.5 g, 370 mmol) and methacrolein (2.05 mL, 25 mmol). The solution was heated to 90 °C for 2 h. The solution rapidly turned orange and a precipitate appeared. The mixture was cooled to r.t. and washed CH_2Cl_2 (2 × 250 mL). The combined organic layers were washed with H_2O (50 mL), dried ($MgSO_4$) and evaporated to dryness. Purification by flash column chromatography (SiO_2; CH_2Cl_2–hexane, 50:50; R_f 0.52, aluminium oxide; CH_2Cl_2–hexane, 50:50) gave **2** (6.22 g, 68%) as a white solid. All analyses correspond to those described in the literature.[26]

6-Carboethoxy-5′-methyl-2,2′-bipyridine (3)

A solution of **2** (500 mg, 2.0 mmol) and $Pd(PPh_3)_2Cl_2$ (50 mg, 0.07 mmol) in a mixture of EtOH (10 mL) and Et_3N (3 mL) was heated to 80 °C for 18 h under a CO atmosphere. After the solution had cooled to r.t., the solvents were removed under reduced pressure and the resulting solid was purified by column chromatography (SiO_2 previously deactivated with Et_3N; CH_2Cl_2–hexane, 80:20) to give **3**.

Yield: 475 mg (98%); pale yellow solid; mp 59–60 °C.

IR (KBr): 2980 (w), 2925 (w), 1731 (s), 1577 (m), 1557 (m), 1442 (m), 1423 (m), 1249 (m), 1161 (s) cm^{-1}.



Scheme 4 *Reagents and conditions:* (i) MeCN, Na_2CO_3, **5** (2.2 equiv), 80 °C, 86%; (ii) $Pd(PPh_3)_2Cl_2$ (7.0 mol%), EtOH, Et_3N, CO (1 atm), 80 °C, 33%; (iii) MeOH, NaOH, H_2O, 90 °C; dilute HCl, 30%.

^{1}H NMR ($CDCl_3$): δ = 1.38 (t, 3 H, ^3J = 5.0 Hz), 2.29 (s, 3 H), 4.41 (q, 2 H, ^3J = 5.0 Hz) 7.54 (br d, 1 H, ^3J = 8.0 Hz), 7.84 (t, 1 H, ^3J = 8.0 Hz), 8.03 (d, br, 1 H, ^3J = 8.0 Hz), 8.32–8.55 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 14.1, 18.2, 61.6, 121.0, 123.6, 124.4, 133.7, 137.3, 137.5, 147.5, 149.4, 152.5, 156.3, 165.1.

MS (FAB$^+$): *m*/*z* = 243.2 ([M + H]$^+$, 100%).

Anal. Cald for $C_{14}H_{14}N_2O_2$ (242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.31; H, 5.66; N, 11.31.

5′-Methyl-2,2′-bipyridine-6-carboxylic Acid (4)

A solution of **3** (400 mg, 1.65 mmol) in EtOH (3 mL), concd HCl (2 mL) and H_2O (7 mL) was heated to 100 °C for 12 h. The solvents were removed under reduced pressure and the solid residue recrystallised from MeOH–THF in the freezer. The crystals were filtered off and dried under vacuum to give **4**.

Yield: 316 mg (89%); pale pink solid; mp 250–251 °C.

IR (KBr): 1744 (s), 1551 (m), 1465 (m), 1345 (s), 1259 (m) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.65 (s, 3 H), 8.16–8.30 (m, 2 H), 8.49 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 8.56–8.77 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 18.9, 125.4, 126.8, 128.9, 141.4, 142.2, 143.2, 145.8, 147.8, 149.0, 149.7, 167.8.

MS (ESI-ToF): *m*/*z* = 215.1 ([M + H]$^+$, 100%), 237.1 ([M + Na]$^+$, 85%).

6-Bromo-5′-bromomethyl-2,2′-bipyridine (5)

A solution of **2** (2.0 g, 8.0 mmol), NBS (1.79 g, 10.0 mmol) and AIBN (66 mg, 0.4 mmol) in CCl_4 (120 mL) was refluxed for 40 min with irradiation with a conventional desk lamp. The solution was filtered hot over a thin layer of aluminium oxide, evaporated to dryness and **5** was isolated by column chromatography (SiO_2; CH_2Cl_2–hexane, 50:50 to 100:0; R_f 0.38, SiO_2, CH_2Cl_2).

Yield: 1.80 g (69%); mp 166–167 °C.

IR (KBr): 1542 (s), 1431 (s), 1391 (m), 1156 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.53 (s, 2 H), 7.50 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 7.67 (t, 1 H, ^3J = 8.0 Hz), 7.85 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 2.5 Hz), 8.37 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.0 Hz), 8.40 (d, 1 H, ^3J = 8.5 Hz), 8.67 (d, 1 H, ^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.

MS (ESI-ToF): *m*/*z* = 326.9 ([M + H]$^+$, 30%), 328.9 ([M + H]$^+$, 83%), 330.9 ([M + H]$^+$, 24%), 348.9 ([M + Na]$^+$, 45%), 350.9 ([M + Na]$^+$, 83%), 352.9 ([M + Na]$^+$, 32%).

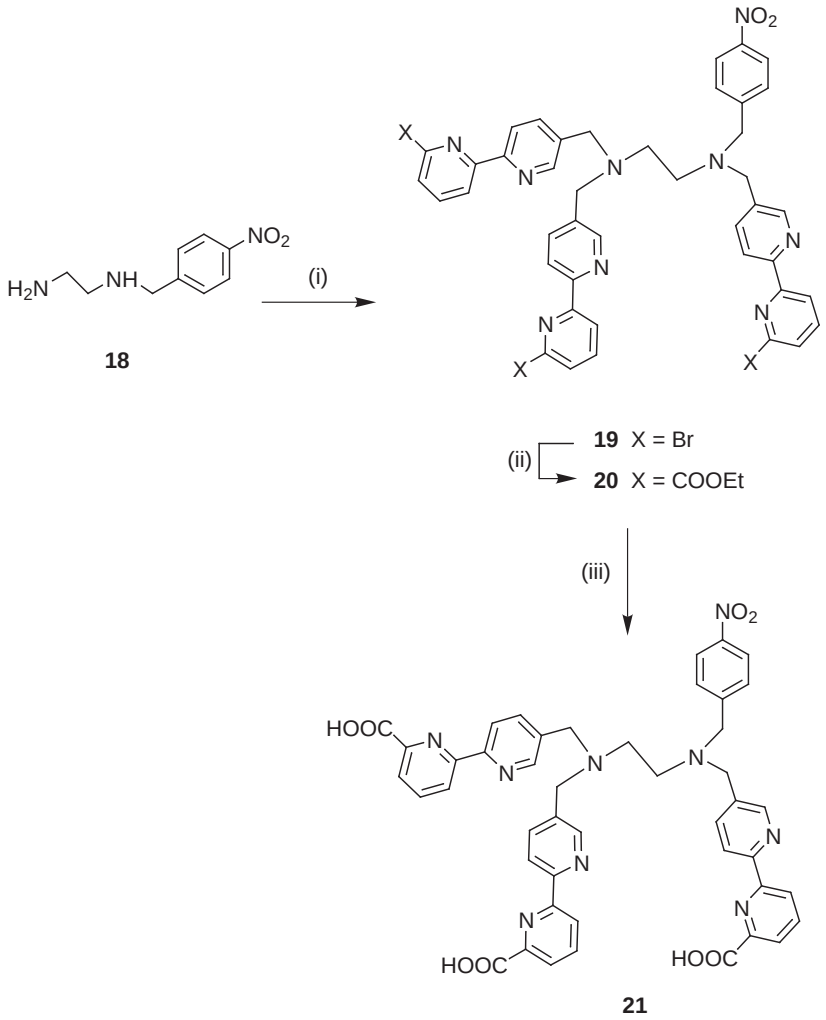
Anal. Calcd for $C_{11}H_8Br_2N_2$ (328.01): C, 40.28; H, 2.46; N, 8.54. Found: C, 39.91; H, 2.14; N, 8.22.

6-Bromo-5′-dibromomethyl-2,2′-bipyridine (6)

Compound **6** was obtained in 28% yield as a by-product of the radical bromination of **2** (R_f 0.57, SiO_2, CH_2Cl_2); mp 106–107 °C.

IR (KBr): 3013 (w), 2923 (w), 1581 (m), 1546 (s), 1387 (s), 763 (s), 642 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ = 6.71 (s, 1 H), 7.52 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 7.69 (t, 1 H, ^3J = 8.0 Hz), 8.08 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 3.0 Hz), 8.39 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 8.46 (d, 1 H, ^3J = 8.0 Hz), 8.76 (br s, 1 H).



Scheme 5 *Reagents and conditions:* (i) MeCN, Na_2CO_3, **5** (3.3 equiv), 80 °C, 74%; (ii) $Pd(PPh_3)_2Cl_2$ (5 mol% per Br atom), EtOH, Et_3N, CO (1 atm), 80 °C, 36%; (iii) MeOH, H_2O, NaOH, 80 °C; dilute HCl, 80%.

^{13}C NMR ($CDCl_3$): δ = 36.9, 120.0, 120.2, 121.5, 128.3, 128.6, 136.0, 138.3, 139.4, 146.4, 149.5.

MS (ESI-ToF): *m*/*z* = 406.8 ([M + H]$^+$, 100%), 428.8 ([M + H]$^+$, 62%).

Anal. Calcd for $C_{11}H_7Br_3N_2$ (406.90): C, 32.47; H, 1.73; N, 6.88. Found: C, 32.15; H, 1.41; N, 6.63.

6-Bromo-5′-hydroxymethyl-2,2′-bipyridine (7)

A mixture of **5** (866 mg, 2.64 mmol) and NaOAc (5.0 g, 61 mmol) was dissolved in DMF (20 mL) and heated to 120 °C for 3 h. The DMF was distilled under reduced pressure and the solid residue was dissolved in a mixture of MeOH (20 mL) and H_2O (20 mL) containing NaOH (1.5 g, 0.57 mol) and refluxed for 2 h. The pH of the cooled solution was brought to 7 by careful addition of 10% aq HCl. The MeOH was evaporated under reduced pressure resulting in the precipitation of a white solid. The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL) and the combined organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. Purification by column chromatography (aluminium oxide; CH_2Cl_2–MeOH, 100:0 to 95:5) gave **7**.

Yield: 622 mg (89%); white solid; mp 112–113 °C.

IR (KBr): 3293 (br s), 2923 (w), 2855 (w), 1595 (m), 1567 (m), 1543 (s), 1432 (s), 1391 (m), 1125 (m), 1051(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.80 (s, 2 H), 7.49 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 7.67 (t, 1 H, ^3J = 8.0 Hz), 7.84 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 8.37 (dd, 1 H, ^3J = 7.0 Hz, ^4J = 1.0 Hz), 8.41 (d, 1 H, ^3J = 8.5 Hz), 8.65 (d, 1 H, ^4J = 1.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 62.6, 119.8, 121.4, 128.1, 135.9, 137.0, 139.4, 141.7, 148.0, 153.9, 157.1.

MS (ESI-ToF): *m*/*z* = 264.9 ([M + H]$^+$, 35%), 266.9 ([M + H]$^+$, 38%), 286.9 ([M + Na]$^+$, 98%), 288.9 ([M + Na]$^+$, 100%).

Anal. Calcd for $C_{11}H_9BrN_2O$ (265.11): C, 49.84; H, 3.42; N, 10.57. Found: C, 49.65; H, 3.11, N, 10.36.

6-Bromo-5′-aminomethyl-2,2′-bipyridine (8)

A mixture of **5** (400 mg, 1.22 mmol) and hexamethylenetetramine (206 mg, 1.47 mmol) in CH_2Cl_2 (200 mL) was refluxed for 5 h. Upon cooling the solution to –30 °C, a white precipitate formed, which was filtered off and dried under vacuum. The solid was dissolved in concd HCl (2.8 mL) and EtOH (20 mL) and refluxed for 1 d. Sat aq NaOH (2 mL) was added and the solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness to give **8**.

Yield: 250 mg (78%); white solid; mp >160 °C (decomp).

IR (KBr): 3437 (br s), 2922 (w), 2852 (w), 1619 (m), 1583 (br s), 1546 (m), 1430 (m), 1384 (m), 1124 (m), 1074 (br m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.97 (s, 2 H), 7.48 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.5 Hz), 7.66 (t, 1 H, ^3J = 8.0 Hz), 7.80 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 2.0 Hz), 8.36 (d, 1 H, ^3J = 7.5 Hz), 8.38 (d, 1 H, ^3J = 8.5 Hz), 8.65 (d, 1 H, ^4J = 1.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 43.5, 119.3, 120.9, 127.5, 135.5, 138.8, 139.0, 141.3, 148.1, 152.9, 157.0.

MS (ESI-ToF): *m*/*z* = 263.9 ([M + H]$^+$, 97%), 265.9 ([M + H]$^+$, 100%), 285.9 ([M + Na]$^+$, 29%), 287.9 ([M + Na]$^+$, 29%).

Anal. Calcd for $C_{11}H_{10}BrN_3$ (264.13): C, 50.02; H, 3.82; N, 15.91. Found: C, 49.58; H, 3.63; N, 15.73.

_N_-[(6′-Bromo-2,2′-bipyridine-5-yl)methyl]phthalimide (9)

A mixture of potassium phthalimidate (620 mg, 3.35 mmol) and **5** (1.0 g, 3.05 mmol) was heated at 70 °C in a Schlenk tube under an argon atmosphere for 16 h. The resulting suspension was dissolved with MeOH (20 mL) and evaporated to dryness. The resulting solid was purified by column chromatography (SiO_2; CH_2Cl_2–MeOH, 100:0 to 99:1; R_f 0.16, SiO_2, CH_2Cl_2) to give **9**.

Yield: 1.08 g (90%); white solid; mp 218–220 °C.

IR (KBr): 1710 (s), 1430 (w), 1389 (m), 1135 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.91 (s, 2 H), 7.46 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.5 Hz), 7.64 (t, 1 H, ^3J = 8.0 Hz), 7.71–7.91 (m, 5 H), 8.34 (m, 2 H), 8.74 (d, 1 H, ^4J = 2.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 38.9, 119.8, 121.3, 123.5, 128.0, 131.9, 132.6, 134.2, 137.4, 139.2, 141.6, 149.5, 154.1, 156.9, 167.8.

MS (FAB$^+$): *m*/*z* = 394.2, 396.2 ([M + H]$^+$, 100%).

Anal. Calcd for $C_{19}H_{12}BrN_3O_2$ (394.23): C, 57.89; H, 3.07; N, 10.66. Found: C, 57.56; H, 2.70; N, 10.44.

_N_-[(6′-Carboethoxy-2,2′-bipyridine-5-yl)methyl]phthalimide (10)

Compound **10** was obtained according to the methodology used for **3**, starting from **9** (840 mg, 2.1 mmol) and $Pd(PPh_3)_2Cl_2$ (90 mg, 0.13 mmol) in EtOH–Et_3N (1:1, 70 mL) at 70 °C for 16 h. The resulting solution was evaporated to dryness, dissolved in CH_2Cl_2 (10 mL), filtered and recrystallised by addition of hexane to give **10**.

Yield: 544 mg (67%); white solid; mp 198–200 °C.

IR (KBr): 2972 (w), 2932 (w), 1735 (m), 1716 (s), 1428 (m), 1395 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ = 1.46 (t, 3 H, ^3J = 7.0 Hz), 4.48 (q, 2 H, ^3J = 7.0 Hz), 4.92 (s, 2 H), 7.70–7.98 (m, 6 H), 8.10 (d, 1 H, ^3J = 6.5 Hz), 8.49–8.58 (m, 2 H), 8.76 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.2, 38.9, 61.6, 121.5, 123.4, 124.1, 124.9, 131.9, 132.4, 134.1, 137.4, 137.8, 147.7, 149.4, 154.8, 155.9, 165.2, 167.7.

MS (FAB$^+$): *m*/*z* = 388.3 ([M + H]$^+$, 100%).

Anal. Calcd for $C_{22}H_{17}N_3O_4$ (387.40): C, 68.21; H, 4.42; N, 10.85. Found: C, 67.92; H, 4.14; N, 10.58.

6-Carboxy-5′-aminomethyl-2,2′-bipyridine Dihydrochloride Salt (11)

Compound **10** (526 mg, 1.36 mmol) and hydrazine hydrate (0.27 mL, 5.4 mmol) were dissolved in EtOH (50 mL). The solution was refluxed for 3 h. The solution was evaporated to dryness and the solid purified by column chromatography (SiO_2; CH_2Cl_2–MeOH–Et_3N, 99:1:0 and 95:3:2) to give 265 mg of a colorless oil (R_f = 0.19; SiO_2 TLC; CH_2Cl_2–MeOH, 95:5) identified as the free amine by its NMR. The oily residue was dissolved in aq HCl (3 M, 10 mL) and heated at 70 °C for 2 h. The solution was cooled to r.t., the insoluble material filtered off on cotton wool and the solution was evaporated to dryness to give **11**.

Yield: 235 mg (65%); white solid; mp >260 °C (decomp).

IR (KBr): 2850 (br s), 1736 (s), 1459 (m), 1345 (s), 1266 (m) cm^{-1}.

^{1}H NMR (D_2O–CD_3OD, 1:1) : δ = 4.53 (s, 2 H); 8.18–8.23 (m, 2 H); 8.38–8.50 (m, 1 H), 8.68–8.80 (m, 2 H); 9.02 (s, 1 H).

^{13}C NMR (D_2O–CD_3OD, 1:1) : δ = 41.8, 127.2, 128.5, 130.2, 135.3, 143.3, 145.4, 148.6, 149.7, 150.1, 150.4, 169.4.

MS (ESI-ToF): *m*/*z* = 230.1 ([M + H]$^+$, 100%).

Anal. Calcd for $C_{12}H_{11}O_2N_3 \cdot 2$ HCl (229.24 + 72.92): C, 47.70; H, 4.34; N, 13.91. Found: C, 47.56; H, 4.10; N, 13.78.

Bis-[(6′-bromo-2,2′-bipyridine-5-yl)methyl] Ether (12)

In a Schlenk tube under argon were added compound **7** (90 mg, 0.34 mmol) and NaH (60% suspension in mineral oil, 19 mg, 0.47 mmol) in freshly distilled THF (15 mL). The mixture was agitated at r.t. for 1 h. Compound **5** (140 mg, 0.43 mmol) was added and the temperature raised to 80 °C overnight. After addition of H_2O (0.5 mL) the solvents were removed under reduced pressure. MeOH (10 mL) was added to the solid and the mixture was refluxed for 1 h. Upon slow cooling to 4 °C, a white precipitate formed which was collected by filtration and dried under vacuum, to give **12**.

Yield: 146 mg (84%); white solid; mp 192–193 °C.

IR (KBr): 2925 (w), 2867 (w), 1620 (w), 1569 (m), 1545 (m), 1429 (s), 1384 (s), 1125 (m), 1062 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.68 (s, 4 H), 7.49 (d, 2 H, ^3J = 8.0 Hz), 7.67 (t, 2 H, ^3J = 7.5 Hz), 7.84 (dd, 2 H, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 8.38 (d, 2 H, ^3J = 7.0 Hz), 8.42 (d, 2 H, ^3J = 8.5 Hz), 8.65 (d, 2 H, ^4J = 2.0 Hz).

^{13}C NMR ($CDCl_3$) : δ = 69.9, 119.8, 121.4, 128.1, 134.0, 136.6, 139.3, 141.7, 148.7, 154.3, 157.2.

MS (ESI-ToF): *m*/*z* = 512.9 ([M + H]$^+$, 53%), 534.9 ([M + Na]$^+$, 100%).

Anal. Calcd for $C_{22}H_{16}Br_2N_4O$ (512.21): C, 51.59; H, 3.15; N, 10.94. Found: C, 51.33; H, 2.85; N, 10.58.

Bis-[(6′-carboethoxy-2,2′-bipyridine-5-yl)methyl] Ether (13)

The same procedure as used for synthesis of **3** was employed, starting from **12** (135 mg, 0.26 mmol), $Pd(PPh_3)_2Cl_2$ (37 mg, 0.053 mmol) in MeOH (20 mL) and Et_3N (20 mL). After column chromatography (SiO_2; CH_2Cl_2–MeOH, 99:1) **13** was isolated.

Yield: 51 mg, (39%); white solid; mp 221–222 °C; R_f 0.36 (SiO_2; CH_2Cl_2 with 3% MeOH).

IR (KBr): 2926 (s), 2855 (s), 1737 (s), 1631 (m), 1590 (m), 1452 (m), 1369 (m), 1279 (s), 1140 (m), 1077 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, 6 H, ^3J = 7.0 Hz), 4.44 (q, 4 H, ^3J = 7.0 Hz), 4.53 (s, 4 H), 7.82 (d, 2 H, ^3J = 8.0 Hz), 7.90 (t, 2 H, ^3J = 8.0 Hz), 8.07 (d, 2 H, ^3J = 7.5 Hz), 8.47–8.58 (m, 4 H), 8.63 (br s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.3, 61.8, 69.8, 121.4, 124.1, 124.9, 133.7, 136.5, 138.0, 147.8, 148.5, 154.9, 156.1, 165.2.

MS (ESI-Tof): *m*/*z* = 521.2 ([M + Na]$^+$, 100%).

Anal. Calcd for $C_{28}H_{26}N_4O_5$ (498.54): C, 67.46; H, 5.26; N, 11.24. Found: C, 67.32; H, 5.17; N, 11.02.

Bis-[(6′-carboxy-2,2′-bipyridine-5-yl)methyl] Ether (14)

A mixture of **13** (41 mg, 82 μmol) in MeOH (10 mL) and NaOH (69 mg, 1.72 mmol) in H_2O (2 mL) was refluxed for 2 h. The pH was brought to 3 with dilute aq HCl resulting in the precipitation of a white solid. The solid was isolated by centrifugation, washed with H_2O (5 mL), centrifuged, the aqueous layer was decanted and the solid dried under vacuum to give **14**.

Yield: 32 mg (89%); white solid; mp 217–218 °C.

IR (KBr): 2924 (w), 1620 (br s), 1453 (m), 1384 (m), 1121 (br m), 1082 (br m) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.75 (s, 4 H), 8.02–8.22 (m, 6 H), 8.58 (d, 2 H, ^3J = 8.0 Hz), 8.60 (dd, 2 H, ^3J = 7.0 Hz, ^4J = 2.0 Hz), 8.75 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 69.0, 121.3, 123.8, 125.1, 135.0, 137.9, 139.0, 147.6, 148.0, 152.8, 153.8, 165.8.

MS (ESI-ToF): *m*/*z* = 465.1 ([M + Na]$^+$, 19%), 242.3 ([M + 2 H]$^{2+}$, 100%).

Anal. Calcd for $C_{24}H_{18}N_4O_5 \cdot H_2O$ (442.43 + 18.01): C, 62.61; H, 4.38; N, 12.17. Found: C, 62.48; H, 4.42; N, 11.88.

Tris-[(6′-bromo-2,2′-bipyridine-5-yl)methyl]amine (15)

Compound **8** (100 mg, 0.38 mmol) and **5** (274 mg, 0.83 mmol) were dissolved in freshly distilled MeCN (15 mL) containing Na_2CO_3 (81 mg, 0.764 mmol) under an argon atmosphere. The solution was heated to 80 °C for 2 days. The residual solid was filtered and dissolved in H_2O (30 mL) and the aq layer washed with CH_2Cl_2 (2 × 50 mL). The mother liquor combined to the CH_2Cl_2 extracts was dried (Na_2SO_4), filtered and evaporated to dryness. Purification by column chromatography (SiO_2; CH_2Cl_2–MeOH, 100:0 to 99:1) gave **15**.

Yield: 249 mg (86%); mp 146–147 °C.

IR (KBr): 2921 (w), 1635 (br s), 1567 (m), 1545 (m), 1430 (s), 1384 (m), 1124 (m) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.68 (s, 6 H), 7.46 (d, 3 H, ^3J = 7.5 Hz), 7.65 (t, 3 H, ^3J = 7.5 Hz), 7.81 (dd, 3 H, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 8.33 (d, 3 H, ^3J = 7.0 Hz), 8.37 (d, 3 H, ^3J = 7.5 Hz), 8.65 (d, 3 H, ^4J = 2.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 55.3, 119.6, 121.3, 128.0, 134.6, 137.4, 139.2, 141.6, 149.6, 153.9, 157.0.

MS (ESI-ToF): *m*/*z* = 759.9 ([M + H]$^+$, 6%), 781.9 ([M + Na]$^+$, 22%).

Anal. Calcd for $C_{33}H_{24}N_7Br_3$ (758.32): C, 52.27; H, 3.19; N, 12.93. Found: C, 52.03; H, 3.07; N, 12.74.

Tris-[(6′-carboethoxy-2,2′-bipyridine-5-yl)methyl]amine (16)

This compound was obtained according to the procedure described for **3** starting from **15** (224 mg, 0.29 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.059 mmol) in a mixture of EtOH (30 mL) and Et_3N (30 mL). After column chromatography (SiO_2 previously treated with Et_3N; CH_2Cl_2–MeOH, 100:0 to 99:1) compound **16** was isolated.

Yield: 73 mg (33%); white solid; mp >270 °C (decomp).

IR (KBr): 2964 (m), 2926 (m), 1716 (s), 1588 (m), 1451 (m), 1139 (s) cm^{-1}.

^1H NMR ($CDCl_3$) : δ = 1.47 (t, 9 H, ^3J = 7.0 Hz), 3.69 (s, 6 H), 4.49 (q, 6 H, ^3J = 7.0 Hz), 7.87 (dd, 3 H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 7.94 (t, 3 H, ^3J = 8.0 Hz), 8.11 (d, 3 H, ^3J = 7.5 Hz), 8.54 (d, 3 H, ^3J = 8.0 Hz), 8.56 (d, 3 H, ^3J = 7.5 Hz), 8.67 (br s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 14.3, 55.1, 61.9, 121.6, 124.1, 124.9, 134.6, 137.5, 137.9, 147.8, 149.5, 154.7, 156.1, 165.3.

MS (ESI-ToF): *m*/*z* = 738.3 ([M + H]$^+$, 5%), 760.2 ([M + Na]$^+$, 100%).

Anal. Calcd for $C_{42}H_{39}N_7O_6$ (737.82): C, 68.37; H, 5.33; N, 13.29. Found: C, 68.05; H, 5.13; N, 12.95.

Tris-[(6′-carboxy-2,2′-bipyridine-5-yl)methyl]amine (17)

A mixture of **16** (73 mg, 0.10 mmol) in MeOH (5 mL) and NaOH (280 mg, 7 mmol) in H_2O (5 mL) was refluxed for 2 h. After cooling to r.t., dilute aq HCl was slowly added until pH 4, resulting in the precipitation of a white solid. The residue was isolated by centrifugation, washed with H_2O (5 mL), the aq. layer was decanted and the solid residue dried under vacuum to give **17**.

Yield: 19 mg (30%); white solid; mp >220 °C (decomp).

IR (KBr): 3411 (s), 1729 (br m), 1640 (w), 1619 (s), 1556 (m), 1346 (m) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.79 (m, 6 H), 8.03–8.12 (m, 9 H), 8.45–8.58 (m, 6 H), 8.75 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 54.6, 121.0, 123.8, 125.1, 135.5, 138.9, 140.4, 147.9 (2C), 150.7, 153.9, 165.7.

FAB$^+$/MS: *m*/*z* = 654.2 ([M + H]$^+$, 100%), 608.2 ([M – COOH + H]$^+$, 30%), 577.2 ([M –2 COOH]$^+$, 10%).

Anal. Calcd for $C_{36}H_{27}N_7O_6 \cdot 0.5\ H_2O$ (653.66 + 9.00): C, 65.25; H, 4.26; N, 14.80. Found: C, 65.61; H, 4.38; N, 14.64.

***N*-(*p*-Nitrobenzyl)ethylenediamine (18)**

Compound **18** was obtained in a procedure similar to that described in the literature,[25] by slow addition of *p*-benzylbromide (1.5 g, 6.9 mmol) in CH_2Cl_2 (20 mL) over a cooled (0 °C) solution of ethylenediamine (7 mL, 104 mmol) in CH_2Cl_2 (25 mL). After 3 h at 0 °C and 2 h at r.t., the organic layer was washed with H_2O (2 × 25 mL). The aq layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to give **18**.

Yield: 1.3g (96%); light orange oil (which turned brown upon prolonged exposure to air).

IR (KBr): 3054 (w), 2942 (br m), 2850 (br m), 1605 (m), 1521 (s), 1347 (s), 1265 (s), 738 (s) cm^{-1}.

^1H NMR ($CDCl_3$) : δ = 2.69 (m, 2 H), 2.84 (m, 2 H), 3.91 (s, 2 H), 7.51 (d, 2 H, ^3J = 8.0 Hz), 8.17 (d, 2 H, ^3J = 8.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 41.7, 52.0, 53.1, 123.7, 128.7, 148.5, 153.3.

MS (FAB$^+$): *m*/*z* = 196.3 ([M + H]$^+$, 100%).

***N*,*N*,*N*′-Tris[(6-bromo-2,2′-bipyridine-5′-yl)methyl]-*N*′-*p*-nitrobenzylethylenediamine (19)**

Compound **18** (110 mg, 0.56 mmol), **5** (610 mg, 1.86 mmol) and K_2CO_3 (350 mg, 2.5 mmol) were placed in a Schlenk tube under argon containing dry MeCN (20 mL). The temperature was raised to 80 °C for 19 h. The solvent was evaporated to dryness and the residue dissolved with CH_2Cl_2 (30 mL) and H_2O (20 mL). The aq phase was washed with CH_2Cl_2 (20 mL) and the combined organic layers were dried (Na_2SO_4), filtered, evaporated to dryness and purified by column chromatography (SiO_2; CH_2Cl_2–MeOH, 100:0 to 98:2). Compound **19** was finally obtained after recrystalisation with CH_2Cl_2–MeCN.

Yield: 390 mg (74%); white microcrystals;. mp 168–170 °C.

IR (KBr): 2800 (br m), 1567 (m), 1542(s), 1515 (m), 1429 (s), 1343 (m), 1124 (m) cm^{-1}.

^1H NMR ($CDCl_3$) : δ = 2.64 (s, 4 H), 3.56 (s, 2 H), 3.58 (s, 6 H), 7.38 (d, 2 H, ^3J = 8.5 Hz), 7.44 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 7.46 (dd, 2 H, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 7.60–7.69 (m, 6 H), 8.08 (d, 2 H, ^3J = 9.0 Hz), 8.26–8.33 (m, 6 H), 8.51 (br s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 51.8, 52.0, 56.3, 58.3, 119.7, 121.2, 123.7, 128.0, 129.1, 134.9, 135.0, 137.3, 137.4, 139.3, 141.7, 146.9, 147.2, 149.5, 149.6, 153.8, 157.1.

MS (FAB$^+$): *m*/*z* = 936.2 ([M + H]$^+$, 92%), 938.2 ([M + H]$^+$, 100%), 799.3 {[M – $(CH_2C_6H_4NO_2)$]$^+$, 30%}, 801.3 {[M – $(CH_2C_6H_4NO_2)$]$^+$, 30%}.

Anal. Calcd for $C_{42}H_{34}N_9O_2Br_3$ (936.51): C, 53.87; H, 3.66; N, 13.46. Found: C, 53.44; H, 3.39; N, 13.09.

***N,N,N′*-Tris[(6-carboethoxy-2,2′-bipyridine-5′-yl)methyl]-*N′*-*p*-nitrobenzylethylenediamine (20)**

Compound **20** was obtained with a procedure similar to that of **3**, starting from **19** (345 mg, 0.37 mmol) and $Pd(PPh_3)_2Cl_2$ (39 mg, 0.055 mmol) dissolved in a mixture of CH_2Cl_2 (5 mL), EtOH (20 mL) and Et_3N (20 mL). After 4 d, the solution was evaporated to dryness, coevaporated three times with CH_2Cl_2 (20 mL) and purified by column chromatography (SiO_2; CH_2Cl_2–MeOH, 100:0 to 96.5:3.5; R_f 0.15, SiO_2, CH_2Cl_2–MeOH, 98:2). Fractions corresponding to **20** were evaporated to dryness, dissolved in a mixture of CH_2Cl_2 (3 mL) and Et_2O (3 mL) and the solution was saturated with gaseous HCl, resulting in the formation of a white precipitate. The solid was recovered by centrifugation and dried under reduced pressure to give **20**.

Yield: 133 mg (36%); white solid; mp >130 °C (decomp).

IR (KBr): 2985 (w), 1720 (s), 1630 (m), 1585 (w), 1523 (w), 1347 (w), 1306 (w), 1520 (m) cm^{-1}.

^1H NMR ($CDCl_3$, non-protonated form): δ = 1.46 (t, 3 H, ^3J = 7.0 Hz), 1.47 (t, 6 H, ^3J = 7.0 Hz), 2.67 (br s, 4 H), 3.60 (s, 6 H), 3.62 (s, 2 H), 4.48 (q, 2 H, ^3J = 7.0 Hz), 4.49 (q, 4 H, ^3J = 7.0 Hz), 7.40 (d, 2 H, ^3J = 9.0 Hz), 7.70–7.79 (m, 3 H), 7.88–7.98 (m, 3 H), 8.07–8.14 (m, 5 H), 8.46–8.57 (m, 9 H).

^{13}C NMR ($CDCl_3$, non-protonated form): δ = 14.4, 51.7, 51.9, 56.3 (br), 58.2, 61.9, 121.5, 123.7, 124.1, 125.0, 129.1, 134.9, 137.4, 137.5, 137.9, 146.9, 147.3, 147.9, 149.6, 154.7, 156.2, 165.3.

MS (FAB^+): *m*/*z* = 916.5 ($[M + H]^+$, 100%), 779.5 {$[M - (CH_2C_6H_4NO_2)]^+$, 20%}.

Anal. Calcd for $C_{51}H_{49}N_9O_8 \cdot 2\,HCl \cdot H_2O$ (1006.95 + 72.92 + 18.01): C, 60.83; H, 5.31; N, 12.52. Found: C, 60.65; H, 5.18; N, 12.39.

***N,N,N′*-Tris[(6-carboxy-2,2′-bipyridine-5′-yl)methyl]-*N′*-*p*-nitrobenzylethylenediamine (21)**

Compound **20** (118 mg, 0.12 mmol) was dissolved in MeOH (10 mL). NaOH (40 mg, 1 mmol) in H_2O (10 mL) was added resulting in the formation of a white suspension. The solution was heated at 80 °C for 2 h. MeOH was evaporated under reduced pressure, the resulting solution was filtered through cotton wool and acidified to pH 2 with concd aq HCl. The solution was evaporated to dryness, dissolved in MeOH (3 mL) and Et_2O was added until a solid precipitated. The solid was collected by centrifugation and dried under reduced pressure to give **21**.

Yield: 78 mg (80%); white solid; mp > 160 °C (decomp).

IR (KBr): 2925 (w), 2853 (w), 1720 (br s), 1617 (s), 1588 (s), 1346 (m), 1143 (s) cm^{-1}.

^1H NMR (CD_3OD–$CDCl_3$, 1:1): δ = 2.63 (br s, 4 H), 3.56 (br s, 6 H), 3.63 (br s, 2 H), 7.15–7.23 (br d, 2 H), 7.60–7.90 (br m, 11 H), 7.95–8.20 (br m, 6 H), 8.31 (br s, 3 H).

MS (FAB^+): *m*/*z* = 832.3 ($[M + H]^+$, 100%), 695.5 {$[M - (CH_2C_6H_4NO_2)]^+$, 30%}.

Anal. Calcd for $C_{45}H_{37}N_9O_8$ (831.85): C, 64.98; H, 4.48; N, 15.15. Found: C, 64.61; H, 4.20; N, 14.76.

References

(1) Ziessel, R. In *Photosensitization and Photocatalysis Using Inorganic and Organometallic Compounds*; Kalyanasundaram, K.; Grätzel, M., Eds.; Kluver: Dordrecht, **1993**, 217–240.

(2) Deronzier, A.; Moutet, J.-C. *Coord. Chem. Rev.* **1996**, *147*, 339.

(3) Montalti, M.; Prodi, L.; Zaccheroni, N.; Charbonnière, L. J.; Douce, L.; Ziessel, R. *J. Am. Chem. Soc.* **2001**, *123*, 12694.

(4) Gao, F. G.; Bard, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 7426.

(5) Wang, J.; Wang, R.; Yang, J.; Zheng, Z.; Carducci, M. D.; Cayou, T.; Peyghambarian, N.; Jabbour, G. E. *J. Am. Chem. Soc.* **2001**, *123*, 6179.

(6) (a) Blackburn, G. F.; Shah, H. P.; Kenten, J. H.; Leland, J.; Kamin, R. A.; Link, J. *Clin. Chem.* **1991**, *37*, 1534. (b) Ege, D.; Becker, W. G.; Bard, A. J. *Anal. Chem.* **1984**, *56*, 2413.

(7) (a) Evangelista, R. A.; Pollak, A.; Allore, B.; Templeton, E. F.; Morton, R. C.; Diamandis, E. P. *Clin. Biochem.* **1988**, *21*, 173. (b) Saha, A. K.; Kross, K.; Kloszewski, E. D.; Upson, D. A.; Toner, J. L.; Snow, R. A.; Black, C. D. V.; Desai, V. C. *J. Am. Chem. Soc.* **1993**, *115*, 11032. (c) Hemmilä, I.; Harju, R. In *Biological Applications of Labelling Technologie*; Emmilä, I.; Stahlberg, T.; Mottram, P., Eds.; Wallac Oy and EG&G: Cie, **1995**. (d) Vereb, G.; Jares-Erijman, E.; Selvin, P. R.; Jovin, T. M. *Biophys. J.* **1998**, *74*, 2210. (e) Bornhop, D. J.; Hubbard, D. S.; Houlne, M. P.; Adair, C.; Kiefer, G. E.; Pence, B. C.; Morgan, D. L. *Anal. Chem.* **1999**, *71*, 2607. (f) Griffin, J. M. M.; Skwierawska, A. M.; Manning, H. C.; Marx, J. N.; Bornhop, D. J. *Tetrahedron Lett.* **2001**, *42*, 3823.

(8) Wieder, I. In *Immunofluorescence and Related Staining Techniques. Proceedings of the VIth International Conference on Immunofluorescence and Related Staining Techniques*; Knapp, W.; Holubar, K.; Wick, G., Eds.; Elsevier, North-Holland Biomedical Press: Amsterdam, **1978**, 67.

(9) Soini, E.; Kojola, H. *Clin. Chem.* **1983**, *29*, 65.

(10) Charbonnière, L. J.; Guardigli, M.; Cesario, M.; Roda, A.; Sabbatini, N.; Ziessel, R. *J. Am. Chem. Soc.* **2001**, *123*, 2436.

(11) Charbonnière, L. J.; Weibel, N.; Ziessel, R. F. *Tetrahedron Lett.* **2001**, *42*, 659.

(12) Ulrich, G.; Bedel, S.; Picard, C.; Tisnès, P. *Tetrahedron Lett.* **2001**, *42*, 6113.

(13) (a) Mukkala, V.-M.; Kwiatkowski, M.; Kankare, J.; Takalo, H. *Helv. Chim. Acta* **1993**, *76*, 893. (b) Takalo, H.; Hemmilä, I.; Sutela, T.; Latva, M. *Helv. Chim. Acta* **1996**, *79*, 789.

(14) Piguet, C.; Bünzli, J.-C. G. *Chem. Soc. Rev.* **1999**, *28*, 347.

(15) Charbonnière, L. J.; Weibel, N.; Ziessel, R. F.; *J. Org. Chem*., **2001**, in press.

(16) Parks, J. E.; Wagner, B. E.; Holm, R. H. *J. Organometal. Chem.* **1973**, *56*, 53.

(17) King, L. C. *J. Am. Chem. Soc.* **1944**, *66*, 894.

(18) Kröhnke, F. *Synthesis* **1976**, 1.

(19) El Ghayoury, A.; Ziessel, R. *J. Org. Chem.* **2000**, *65*, 7757.

(20) (a) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048. (b) Fraser, C. L.; Anastasi, N. R.; Lamba, J. J. S. *J. Org. Chem.* **1997**, *62*, 9314. (c) Lamba, J. J. S.; Fraser, C. L. *J. Am. Chem. Soc.* **1997**, *119*, 1801.

(21) Ziessel, R.; Hissler, M.; Ulrich, G. *Synthesis* **1998**, 1339.

(22) Weibel, N.; Charbonnière, L. J.; Ziessel, R.F., unpublished results.

(23) El-ghayoury, A.; Ziessel, R. *Tetrahedron Lett.* **1998**, *39*, 4473, and references cited therein..

(24) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(25) De Almeida, M. V.; Cesar, E. T.; Felicio, E. D. C. A.; Fontes, A. P. S.; Robert-Gero, M. *J. Braz. Chem. Soc.* **2000**, *11*, 154.

(26) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Rivière, E.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *Can. J. Chem.* **1997**, *75*, 169.