Carboxylate Derivatives of Oligopyridines Bearing Bromomethyl Groups

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Abstract: The synthesis of various oligopyridines possessing a carboxylate and at least one bromoethyl group is reported. The bipyridine and terpyridine cores were constructed in good yields via a Stille cross-coupling, starting from bromopicolines and ethyl bromopicolinate. The bromomethyl function was obtained by free radical bromination using NBS in benzene or bromine in benzene/water biphasic mixture. The building of two model podands by nucleophilic displacement of benzylic bromine by an amine or by a phenol group is described.

Key words: Stille reaction, bipyridines, terpyridines, carboxylate, halogenation

In the last two decades, significant efforts have been made in the development of efficient luminescent lanthanide complexes with the aim of labeling biomolecules for time-resolved fluoroimmunoassay.[1] Many strategies were developed to design lanthanide systems that combine high stability in coordinating solvent and high long life-time luminescence properties.[2] Indeed, the organic system must associate strong coordination functions suitable for Ln^{3+} such as carboxylates, and chromophores whose function is to sensitize the metal emission through an energy transfer process. For the chromophoric part, most of the criteria can be filled by bipyridine or terpyridine subunits, which possess appropriate excited states, high absorption and coordination ability. Many lanthanide receptors incorporating these heterocycles have shown very efficient absorption – ligand to metal energy transfer – metal centered emission process (A-ET-E).[3–5] To obtain water stable lanthanide complexes, standard oligopyridines must be associated with ionizable groups. One solution was brought by Ziessel and co-workers with the building of a bipyridine bearing a carboxylate group on the *ortho* position from one nitrogen,[6] forming a tridentate ligand N,N,COO^-. The association of three of these tridentate ligands create an ideal nonadentate cavity for lanthanide (III) ions,[7] leading to highly stable and fluorescent Eu(III) and Tb(III) complexes.

We simultaneously developed another synthetic way to obtain bipyridine carboxylate structures. In our case, the final structure associates a bromomethyl group to the oligopyridine carboxylate, and thus can be directly attached to a molecular platform, to create podands.

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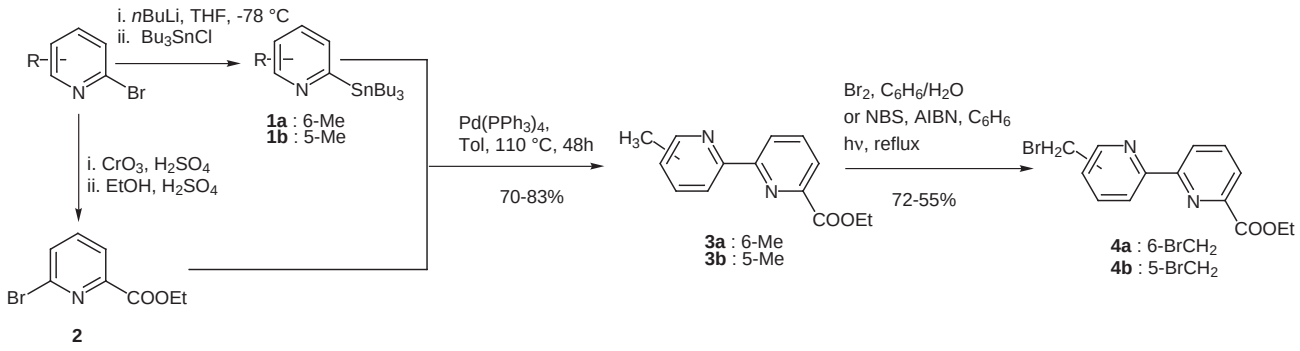
For these reasons, we have used a multicombination synthesis based on Stille coupling of various functional pyridine moieties, in order to obtain polytopic oligopyridines bearing an ester group. We opted for this function which offers two possibilities: 1) to be the precursor of carboxylate to form tritopic N,N,COO^- ligands when in α position to the pyridine nitrogen, and 2) to be a grafting function for a spacer group that could be linked to a biomolecule. For this purpose, an ester function on *para* position from one pyridine nitrogen, of a dibromomethylbipyridine or terpyridine could lead to interesting macrocycles.[8]

Our synthetic strategy was based on the use of Pd(0) cross-coupling of various pyridines building blocks. This methodology, based on Stille method,[9] was inspired from previous works on the synthesis of 5,5′-bis-functionalized-2,2′:6′,2″-terpyridines,[10–12] pyridine-based oligotridentate ligands[13] and carboxylate derivatives of oligopyridines.[14] We opted for the use of organotin compounds, despite their toxicity and the purification problems induced by the resulting tributyltin halides, because we were confident to build the bipyridine or terpyridine core by following the described methods.[14,15] The coupling of organozinc derivatives, by the Negishi method,[16–18] seems to be a good alternative way for the building of a bipyridine core. But in our case, the described method for oligopyridine[19,20] generated few or none of the desired compounds.

The starting buildings blocks were obtained using literature procedure. The stannylated compounds were made by lithiation of 2-bromo-6-methyl-pyridine (**1a**)[21] or 2-bromo-5-methylpyridine (**1b**),[22] and the organolithium compound thus obtained reacted with tributyltin chloride[13] to generate the organotin derivatives in good yields (96 and 82%, respectively) (Scheme 1, Table). The pyridine ester building block **2** was obtained by oxidation of 2-bromo-6-methylpyridine (**1a**) with chromium trioxide in concentrated sulfuric acid, and the corresponding carboxylic acid was further esterified with ethanol under acid-catalyzed conditions.[23] The trifunctional pyridine **5** was obtained in two steps from the commercial citrazinic acid, which was first reacted with $POBr_3$ at 180 °C in a sealed tube[24], and the 2,6-dibromopyridine-4-carboxylic acid thus obtained was esterified in ethanol under acid-catalyzed conditions.[14]

The coupling of pyridine blocks **1** and **2** with $Pd(PPh_3)_4$ as catalyst, in refluxing degassed toluene during two days, generated the methyl-2,2′-bipyridine-6′-esters **3** in fair yields (Scheme 1). To produce the useful corresponding



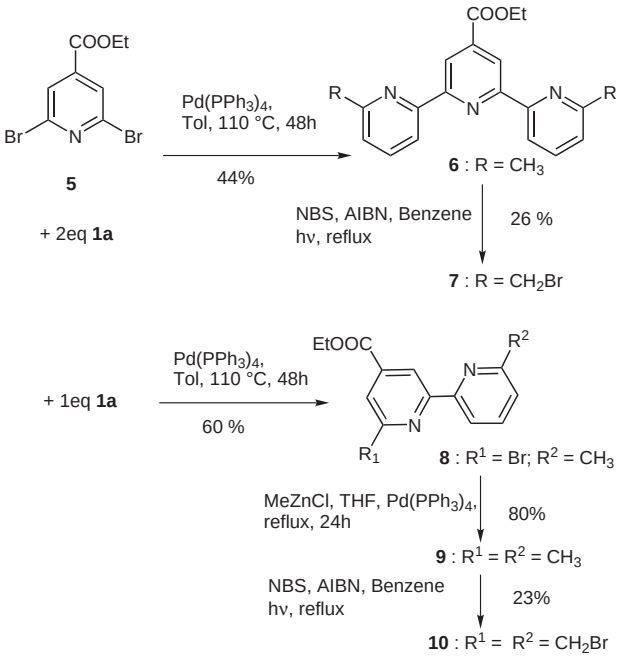
Scheme 1

bromomethyl bipyridine derivatives, we opted for a free-radical bromination of the benzylic methyl groups. The high yielding method developed by Fraser et al.[18] to obtain benzylic bromides on bipyridine could not be used due to the presence of the ester function, incompatible with the generation of a methyl anion. In order to improve the free radical method, which is not very high yielding and selective in its classical conditions (NBS, CCl_4), we were inspired by the studies of Vögtle et al. on the solvent effect of the selectivity of the reaction.[25,26] We developed a short study on picoline model compounds in order to find the best couple of solvent/bromine donors which could raise the yield of the synthesis and the ratio of bromomethyl/dibromomethyl derivatives.[27] The most appropriate solvent for these pyridine based compounds appeared to be benzene. Concerning the bromine donor, we had relatively good results with the classical NBS (with AIBN as initiator) in refluxing benzene and under irradiation with a 150 W halogen lamp, during 3 hours. The yields of the brominated products **3a** and **3b** were 55 and 56%, respectively. A better result was obtained by using a biphasic refluxing mixture of benzene and water, under irradiation, and with Br_2 as bromine donor. This new method is really convenient due to its rapidity (15–30 min), its selectivity, and the high yield (72%), but could only be performed with bipyridines bearing a benzylic methyl on the *meta* position from the pyridine nitrogen.

The oligopyridines designed for the construction of macrocycles were obtained by coupling of the dibromopyridine **5** using the standard Pd(0) catalytic conditions (Scheme 2, Table) with two equivalents of organotin compounds **1a** for the construction of the terpyridine **6** in 55% yield and one equivalent of **1a** to obtain ethyl 6-bromo-6′-methyl-2,2′-bipyridine-4-carboxylate (**8**) in 60% yield. The bipyridine **8** was converted in 80% yield to ethyl 6,6′-dimethyl-2,2′-bipyridine-4-carboxylate (**9**) by a Negishi type coupling using methylzinc chloride,[19] generated in situ from methyllithium and zinc chloride, and $Pd(PPh_3)_4$ as catalyst in refluxing THF. The two dimethyl compounds **6** and **9** were brominated by free radical procedure using NBS in refluxing benzene under irradiation to give the two dibromomethyl derivatives **7** and **10** in 26 and 23% yields, respectively. Our three step synthesis for **10** seems more convenient than the synthesis described,[28] starting from 6,6′-dimethylbipyridine.

In order to validate our concept for the construction of nonadentate podands, we choose two model molecular platforms having three nucleophilic functions, where three tridentate N,N,COO^- arms could be grafted. These two structures can be derivatized to be linked to a biomolecule, if the preliminary results on the fluorescent properties of their Eu(III) or Tb(III) complexes are encouraging.

The first model is a cyclic polyamine, a mono-functionalized cyclen **11**.[29] The three secondary amine groups were alkylated with 3 equivalents of **4b** using Hünig's base in DMF at room temperature to give **12a** in fair yield (51%) involving a convenient purification step (Scheme 3, Table). The use of alkali cation bases such as K_2CO_3 leads to purification problems, probaly due to alkali metal complexation.

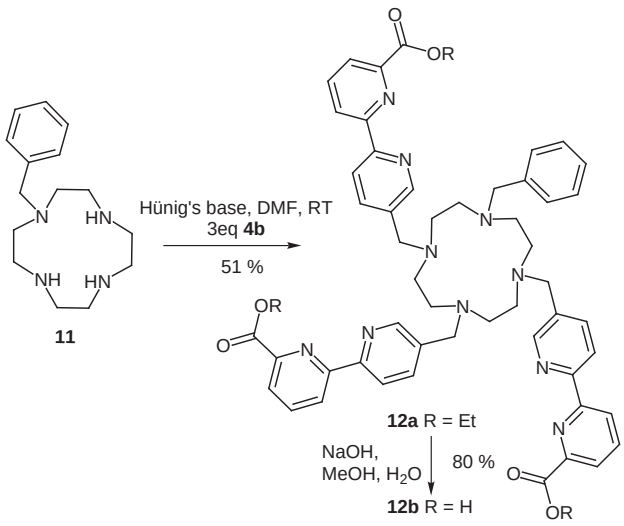


Scheme 2

Table Selected Spectroscopic Data for Precursors and Polypyridine Ligands

Product	Yield (%)	MS *m/z*	IR (cm^{-1})[a] $\nu_{C=O}$	UV/Vis[b] λ (nm) [ε ($M^{-1}cm^{-1}$)] ($\pi\rightarrow\pi^*$, py)	^{1}H NMR[c] BpyCH_2X	^{13}C NMR[c] C=O	BpyCH_2X
3a	70	243[d]	1742	287 (15200)	2.61	165.4	24.7
3b	83	243[d]	1738	286 (17700)	2.39	165.2	18.3
4a	55	321/323[d]	1713	287 (13100)	4.62	165.3	34.1
4b	72	321/323[e]	1738	290 (21000)	4.53	165.3	36.3
6	56	334[e]	1717	285 (18900)	2.67	165.7	24.6
7	28	490/492/494[e]	1727	288 (18200)	4.52	165.6	34.1
8	60	321/323[e]	1724	293 (9700)	2.65	164.0	24.6
9	80	257[e]	1724	294 (10900)	2.58/2.63	165.6	24.6
10	23	413/415/417[e]	1725	290 (11400)	4.66/4.67	165.0	33.5/33.9
12a	51	983[e]	1738	286 (50400)	3.42/3.45	165.4	57.1/57.4
14a	51	847[e]	1737	288 (42800)	5.09	165.3	67.6

[a] KBr pellets.
[b] Measured in CH_2Cl_2 for **7**, in MeOH for the rest.
[c] Recorded in $CDCl_3$.
[d] ES^+: $[M + H]^+$.
[e] FAB^+, *m*NBA: $[M + H]^+$.



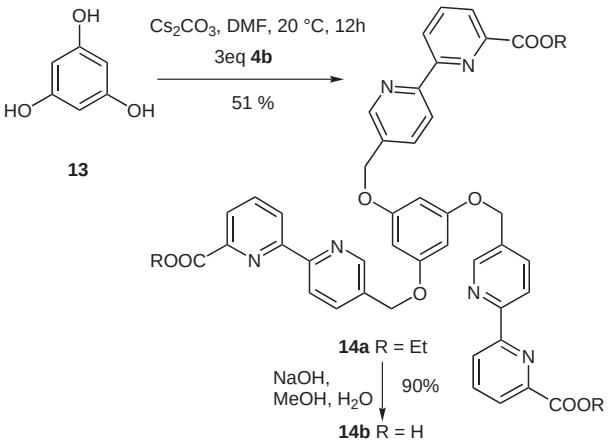
Scheme 3

As a second model, we chose a triphenol, the phloroglucinol, which possess a rich chemistry and can be easily derivatized.[30] In order to have a complete trialkylation, we had to use cesium carbonate in DMF with 3 equivalents of **4b** (Scheme 4). Under this condition, the reaction is complete in overnight at room temperature, with a yield of 51%. These two triesters **12a** and **14a** can be easily saponified in the corresponding triacids **12b** an **14b** following the described method.[7] Lanthanides salts complexation studies of these triacids are under progress.

The synthetic protocol described here provide access to various symmetrical or unsymmetrical oligopyridines bearing different chemical functions. We were able to obtain via Stille cross-coupling two bipyridines bearing a carboxylate, known to be an adapted chromophore for lanthanide complexation. Moreover, the association of a bromomethyl function on these molecules allows their fixation on various molecular platform. The bipyridine and the terpyridine derivatives bearing two bromomethyl functions could be of great interest in the construction of macrocyclic structures.

Reactions were carried out in THF dried over sodium and benzophenone, MeCN was dried over P_2O_5 and distilled before use. Column chromatography was carried out on silica gel (Merck, 60–200 μm, porosity 60Å) and on alumina (Macherey-Nagel, activity IV, 50–200 μm). Melting points were determined on a Electrothermal IA9200 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200 or AC250 spectrometers; chemicals shifts are given in ppm according to the solvent peak. IR spectra were recorded on a Perkin Elmer FT-IR 1725X spectrometer. UV spectra were recorded on a Hewlet Packard 8453 UV/Vis spectrometer at 23 °C. Fast Atom Bombardment (FAB) and Electrospray (ES) mass spectra were obtained on a Nermag R10-10H spectrometer and a Perkin Elmer SCIEX API 100 spectrometer, respectively.

N,*N*-Diisopropylethylamine (Avocado), NBS (Lancaster), AIBN (Janssen), Br_2 (Aldrich), MeLi (1 M in THF–cumene 10:90) (Ald-



Scheme 4

rich) were used as received. Cs_2CO_3 (Aldrich), $ZnCl_2$ (Aldrich) were flame dried under vacuum prior to use. 1,3,5-Trihydroxybenzene (**13**) (Avocado) was refluxed in toluene using a Dean–Stark apparatus before use. Tetrakistriphenylphosphinepalladium,[31] 2-tributylstannyl-6-methylpyridine (**1a**),[13] 2-tributylstannyl-5-methylpyridine (**1b**), ethyl 2,6-dibromo-4-pyridinecarboxylate[24] (**5**) and 1-benzyl-1,4,7,10-tetraazacyclododecane (**11**)[29] were prepared according to literature procedures. Petroleum ether used refers to the fraction with bp 45–60 °C.

Stille Cross-Coupling Reactions;[14] General Procedure

A mixture of ethyl bromopyridinecarboxylate **2** or **5** (1 equiv), methyltributylstannylpyridine **1** (1.2 or 2.2 equiv) and $Pd(PPh_3)_4$ (0.05 or 0.1 equiv) in degassed toluene (100 mL) was refluxed under N_2 for 2 d. The resulting solution was filtered over Celite and evaporated under reduced pressure. Conc. HCl (100 mL) was added and the solution was washed with CH_2Cl_2 (3 × 50 mL). The aqueous phase was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed to afford the desired product (Table).

Ethyl 6′-Methyl-6-(2,2′-bipyridine)carboxylate (3a)

From **1a** (4 g, 10.4 mmol), **2** (2 g, 8.7 mmol), and $Pd(PPh_3)_4$ (0.5 g, 0.44 mmol) in toluene (100 mL). Column chromatography (silica gel, eluent: CH_2Cl_2–MeOH with a gradient of MeOH 0–1%) yielded 1.46 g (70%) of white crystals; mp 68–69 °C; R_f 0.15 (silica gel, CH_2Cl_2–MeOH, 99:1).

IR (KBr): 1742 (s, C=O), 1580 (m), 1568 cm^{-1} (m).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 (t, 3 H, ^3J = 7.3 Hz, OCH_2CH_3), 2.61 (s, 3 H, CH_3), 4.48 (q, 2 H, ^3J = 7.3 Hz, OCH_2CH_3), 7.17 (d, 1 H, ^3J = 7.6 Hz), 7.70 (t, 1 H, ^3J = 7.8 Hz), 7.91 (t, 1 H, ^3J = 7.8 Hz), 8.10 (dd, 1 H, ^3J = 7.6, ^4J = 1.0 Hz), 8.34 (d, 1 H, ^3J = 7.6 Hz), 8.61 (d, 1 H, ^3J = 7.9 Hz).

$^{13}C\{^1H\}$ JMOD NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 24.7 (CH_3), 61.9 (CH_2O), 118.7 (CH), 123.8 (CH), 124.2 (CH), 124.8 (CH), 137.2 (CH), 137.8 (CH), 147.8 (Cq), 154.6 (Cq), 156.7 (Cq), 157.9 (Cq), 165.4 (C=O).

MS (ES^+, MeCN): *m*/*z* (%) = 243 (100, $[M + H^+]$), 265 (65, $[M + Na^+]$).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 243 (10250), 287 nm (15200).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.42; H, 5.75; N, 11.58.

Ethyl 5′-Methyl-6-(2,2′-bipyridine)carboxylate (3b)

From **1b** (4 g, 10.4 mmol), **2** (2 g, 8.7 mmol), and $Pd(PPh_3)_4$ (0.5 g, 0.44 mmol) in toluene (100 mL). Column chromatography (silica gel, eluent: CH_2Cl_2–MeOH with a gradient of MeOH 0–1%) gave 1.74 g (83%) of white crystals; mp 84–85 °C; R_f 0.15 (silica gel, CH_2Cl_2–MeOH, 99:1).

IR (KBr): 1738 (s, C=O), 1588 (m), 1556 cm^{-1} (m).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.46 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 2.39 (s, 3 H, CH_3), 4.49 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 7.64 (ddd, 1 H, ^3J = 8.1, ^4J = 2.1, ^5J = 0.7 Hz), 7.92 (t, 1 H, ^3J = 7.8 Hz), 8.09 (dd, 1 H, ^3J = 7.7 Hz ^4J = 1.2 Hz), 8.46 (m, 2 H), 8.56 (dd, 1 H, ^3J = 7.9, ^4J = 1.2 Hz).

$^{13}C\{^1H\}$ JMOD NMR (50 MHz, $CDCl_3$): δ = 14.2 (CH_3), 18.3 (CH_3), 61.7 (CH_2O), 121.0 (CH), 123.7 (CH), 124.5 (CH), 133.8 (Cq), 137.4 (CH), 137.6 (CH), 147.6 (Cq), 149.5 (CH), 152.6 (Cq), 156.4 (Cq), 165.2 (C=O).

MS (ES^+, MeCN): *m*/*z* (%) = 243 (100, $[M + H^+]$), 265 (88, $[M + Na^+]$).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 248 (13200), 286 nm (17700).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.24; H, 5.69; N, 11.41.

Ethyl 6,6″-Dimethyl-4′-(2,2′:6′,2″-terpyridine)carboxylate (6)

From **5** (2 g, 6.4 mmol), **1a** (5.4 g, 14 mmol), and $Pd(PPh_3)_4$ (0.74 g, 0.64 mmol) in toluene (150 mL). Column chromatography (alumina activity IV, eluent: petroleum ether–CH_2Cl_2, 1:1) yielded 1.17 g (55%) of a white solid; mp 134–135 °C; R_f 0.1 (silica gel, CH_2Cl_2).

IR (KBr): 1717 (s, C=O), 1560 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.47 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 2.67 (s, 6 H, CH_3), 4.50 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 7.21 (d, 2 H, ^3J = 7.6 Hz), 7.75 (t, 2 H, ^3J = 7.7 Hz), 8.40 (d, 2 H, ^3J = 7.8 Hz), 8.97 (s, 2 H).

$^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$) : δ = 14.4 (CH_3), 24.6 (CH_3), 61.7 (CH_2O), 116.3 (CH), 120.1 (CH), 123.6 (CH), 137.0 (CH), 139.7 (Cq), 154.9 (Cq), 156.8 (Cq), 158.1 (Cq), 165.7 (C=O).

MS (FAB^+, *m*NBA): *m*/*z* (%) = 334 (100, $[M + H^+]$).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 285 (18900), 322 nm (9450).

Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.86; H, 5.65; N, 12.39.

Ethyl 6-Bromo-6′-methyl-4-(2,2′-bipyridine)carboxylate (8)

From **5** (1 g, 3.1 mmol), **1a** (1.3 g, 3.3 mmol), and $Pd(PPh_3)_4$ (0.18 g, 0.17 mmol) in toluene (50 mL). Column chromatography (silica gel, eluent: CH_2Cl_2–petroleum ether 5:5→7:3) afforded 0.610 g (61%) of a white powder; mp 115–116 °C; R_f 0.4 (silica gel, CH_2Cl_2).

IR (KBr): 1724 (s, C=O), 1581 (m), 1544 cm^{-1} (s).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.45 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 2.65 (s, 3 H, CH_3), 4.46 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 7.22 (d, 1 H, ^3J = 7.7 Hz), 7.71 (t, 1 H, ^3J = 7.8 Hz), 8.01 (d, 1 H, ^4J = 1.1 Hz), 8.20 (d, 1 H, ^3J = 7.9 Hz), 8.91 (d, 1 H, ^4J = 1.1 Hz).

$^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$): δ = 14.3 (CH_3), 24.6 (CH_3), 62.2 (CH_2O), 118.6 (CH), 119.3 (CH), 124.3 (CH), 127.1 (CH), 137.2 (CH), 141.0 (Cq), 142.9 (Cq), 153.1 (Cq), 158.3 (Cq), 158.6 (Cq), 164.0 (C=O).

MS (FAB^+, *m*NBA): *m*/*z* (%) = 321/323 (100/95, $[M + H^+]$).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 241 (11750), 287 (9650), 293 (9700), 312 nm (11100).

Anal. Calcd for $C_{14}H_{13}BrN_2O_2$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.51; H, 4.00; N, 8.56.

Ethyl 6,6′-Dimethyl-4-(2,2′-bipyridine)carboxylate (9)

$ZnCl_2$ (0.76 g, 5.6 mmol) in THF (10 mL) was cooled at 0 °C. MeLi (1 M in THF/cumene, 10:90, 2.8 mL, 2.8 mmol) was added, the solution was allowed to warm to r.t. and was stirred for 2 h. Compound **8** (0.61 g, 1.9 mmol) and $Pd(PPh_3)_4$ (0.1 g, 0.09 mmol) were added and the solution was refluxed for 2 d. The mixture was poured onto an aqueous solution (40 mL) of EDTA (5 g), neutralized with K_2CO_3, extracted with CH_2Cl_2 (3 × 20 mL) and dried ($MgSO_4$). Column chromatography (silica gel, eluent: CH_2Cl_2–MeOH with a gradient of MeOH 0–2%) afforded 0.39 g (80%) of a white powder; mp 73–74 °C; R_f 0.1 (silica gel, CH_2Cl_2–MeOH, 99:1).

IR (KBr): 1724 (s, C=O), 1585 (m), 1571 cm^{-1} (m).

^1H NMR (250MHz, $CDCl_3$): δ = 1.37 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 2.58 (s, 3 H, CH_3), 2.63 (s, 3 H, CH_3), 4.38 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 7.09 (d, 1 H, ^3J = 7.7 Hz), 7.58–7.64 (m, 2 H), 8.14 (d, 1 H, ^3J = 7.7 Hz), 8.67 (s, 1 H).

$^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$): δ = 14.2 (CH_3), 24.6 (CH_3), 61.6 (CH_2), 117.5 (CH), 118.3 (CH), 122.1 (CH), 123.4 (CH), 134.0 (CH), 138.9 (Cq), 155.0 (Cq), 157.0 (Cq), 158.0 (Cq), 158.8 (Cq), 165.6 (C=O).

MS (FAB^+, *m*NBA): *m*/*z* (%) = 257 (100, $[M + H^+]$), 279 (39, $[M + Na^+]$).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 237 (11700), 294 nm (10900).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.75; H, 6.19; N, 10.35.

Radical Bromination Reactions; General Procedure

Method A: A mixture of methyl-oligopyridine (1 equiv), NBS (1.1 equiv) and a catalytic amount of AIBN in benzene or benzene–H_2O (1:1) was irradiated and refluxed using a halogen lamp (150 W) for 3 h. The hot mixture was filtered and evaporated under reduced pressure. Purification by column chromatography afforded the desired compound.

Method B: Methyl-oligopyridine (1 equiv) in a mixture benzene–H_2O (1:1) was irradiated and refluxed using a halogen lamp (150 W). Br_2 (1 equiv) was added and the refluxing was continued for 30 min. The solution was concentrated under reduced pressure and neutralized with an aq solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated in vacuo. The crude residue was chromatographed to give the product.

Ethyl 6′-Bromomethyl-6-(2,2′-bipyridine)carboxylate (4a)

Method A: From **3a** (0.68 g, 2.8 mmol), and NBS (0.55 g, 3 mmol) in benzene (50 mL). Purification by column chromatography (silica gel, eluent: CH_2Cl_2–petroleum ether–MeOH, 80:20:0→99:00:1) afforded 0.49 g (55%) of a white solid; mp 90–91 °C; R_f 0.2 (silica gel, CH_2Cl_2).

IR (KBr): 1713 (s, C=O), 1580 cm^{-1} (m).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.47 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.49 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.62 (s, 2 H, CH_2Br), 7.48 (dd, 1 H, ^3J = 7.7, ^4J = 1.0 Hz), 7.85 (t, 1 H, ^3J = 7.8 Hz), 7.96 (t, 1 H, ^3J = 7.8 Hz), 8.13 (dd, 1 H, ^3J = 7.7, ^4J = 1.2 Hz), 8.48 (dd, 1 H, ^3J = 7.9, ^4J = 1.0 Hz), 8.66 (dd, 1 H, ^3J = 7.9, ^4J = 1.2 Hz).

$^{13}C\{^1H\}$ JMOD NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 34.1 (CH_2Br), 61.9 (CH_2O), 120.9 (CH), 123.9 (CH), 124.4 (CH), 125.1 (CH), 137.9 (CH), 138.1 (CH), 147.8 (Cq), 155.0 (Cq), 155.9 (Cq), 156.3 (Cq), 165.3 (C=O).

MS (ES^+, MeCN): *m*/*z* (%) = 321/323 (65/67, $[M + H^+]$), 343/345 (98/100, $[M + Na^+]$).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 245 (10600), 287 nm (13100).

Anal. Calcd for $C_{14}H_{13}BrN_2O_2$: C, 52.36; H, 4.08; N, 8.72. Found. C, 52.21; H, 4.03; N, 8.61.

Ethyl 5′-Bromomethyl-6-(2,2′-bipyridine)carboxylate (4b)

Method B: From **3b** (1.56 g, 6.4 mmol), and Br_2 (0.33 mL, 6.4 mmol) in benzene–H_2O (1:1, 200 mL). The crude solid was purified by column chromatography (silica gel, eluent: CH_2Cl_2–petroleum ether–MeOH, 80:200→99:0:1) to give 1.48 g (72%) of a white compound; mp 106–107 °C; R_f 0.2 (silica gel, CH_2Cl_2).

IR (KBr): 1738 (s, C=O), 1589 (m), 1557 cm^{-1} (m).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.46 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.48 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.53 (s, 2 H, CH_2Br), 7.86 (dd, 1 H, ^3J = 8.2, ^4J = 2.3 Hz), 7.94 (t, 1 H, ^3J = 7.8 Hz), 8.12 (dd, 1 H, ^3J = 7.7, ^4J = 1.2 Hz), 8.56 (m, 2 H), 8.66 (d, 1 H, ^4J = 2.3 Hz).

$^{13}C\{^1H\}$ JMOD NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 29.6 (CH_2Br), 61.9 (CH_2O), 121.7 (CH), 124.3 (CH), 125.2 (CH), 134.2 (Cq), 137.7 (CH), 137.9 (CH), 147.9 (Cq), 149.3 (CH), 155.2 (Cq), 155.8 (Cq), 165.3 (C=O).

MS (FAB^+, *m*NBA): *m*/*z* (%) = 321/323 (100/95, $[M + H^+]$), 343/345 (23/21, $[M + Na^+]$).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 251 (14300), 290 nm (21000).

Anal. Calcd for $C_{14}H_{13}BrN_2O_2$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.18; H, 4.03; N, 8.62.

Ethyl 6,6′-Dibromomethyl-4′-(2,2′:6′,2″-terpyridine)carboxylate (7)

Method A: From **6** (0.71 g, 2.14 mmol), and NBS (0.83 g, 4.53 mmol) in benzene (100 mL). After purification by column chromatography (silica gel, eluent: CH_2Cl_2–petroleum ether, 3:7→5:5) 0.27 g (26%) of a white solid was obtained; mp 201–203 °C; R_f 0.4 (silica gel, CH_2Cl_2).

IR (KBr): 1727 (s, C=O), 1583 (m), 1566 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.49 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.52 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.68 (s, 4 H, CH_2Br), 7.52 (d, 2 H, ^3J = 7.7 Hz), 7.86 (t, 2 H, ^3J = 7.8 Hz), 8.50 (d, 2 H, ^3J = 7.8 Hz), 8.99 (s, 2 H).

$^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$): δ = 14.4 (CH_3), 34.1 (CH_2Br), 62.0 (CH_2O), 120.5 (CH), 120.7 (CH), 124.0 (CH), 138.0 (CH), 140.1 (Cq), 155.1 (Cq), 156.1 (Cq), 156.6 (Cq), 165.6 (C=O).

MS (FAB^+, *m*NBA): *m*/*z* (%) = 490/492/494 (54/100/51, $[M + H^+]$).

UV/Vis (CH_2Cl_2): λ_{max} (ε, $M^{-1}cm^{-1}$) = 288 (18200), 323 nm (9700).

Anal. Calcd for $C_{20}H_{17}Br_2N_3O_2$: C, 48.91; H, 3.49; N, 8.56. Found: C, 48.78; H, 3.57; N, 8.25.

Ethyl 6,6′-Dibromomethyl-4-(2,2′-bipyridine)carboxylate (10)

Method A: From **9** (0.15 g, 0.58 mmol), and NBS (0.23 g, 1.25 mmol) in benzene–H_2O (1:1, 20 mL). The residue was purified by column chromatography (silica gel, eluent: CH_2Cl_2–petroleum ether, 3:7→5:5), leading to 0.055 g (23%) of the product; mp 137–138 °C; R_f 0.45 (silica gel, CH_2Cl_2).

IR (KBr): 1725 (s, C=O), 1565 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.46 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.48 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.66 (s, 2 H, CH_2Br), 4.67 (s, 2 H, CH_2Br), 7.52 (d, 1 H, ^3J = 7.5 Hz), 7.85 (t, 1

H, ^3J = 7.85 Hz), 8.01 (d, 1 H, ^4J = 1.3 Hz), 8.39 (d, 1 H, ^3J = 7.6 Hz), 8.88 (d, 1 H, ^4J = 1.3 Hz).

$^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$): δ = 14.3 (CH_3), 33.5 (CH_2), 33.9 (CH_2), 62.1 (CH_2), 120.0 (CH), 120.7 (CH), 122.8 (CH), 124.1 (CH), 138.1 (CH), 140.1 (Cq), 154.6 (Cq), 156.6 (Cq), 156.7 (Cq), 157.3 (Cq), 165.0 (C=O).

MS (FAB$^+$, *m*NBA): *m*/*z* (%) = 413/415/417 (58/100/49, [M + H$^+$]).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 241 (12800), 290 nm (11400).

Anal. Calcd for $C_{15}H_{14}Br_2N_2O_2$: C, 43.51; H, 3.41; N, 6.77. Found: C, 43.16; H, 3.28; N, 6.51.

1-Benzyl-4,7,10-tri[(6′-ethoxycarbonyl-2,2′-bipyridine-5-yl)methyl]-1,4,7,10-tetraazacyclododecane (12a)

To a solution of **11** (0.058 g, 0.22 mmol) and **4b** (0.21 g, 0.66 mmol) in anhyd DMF (20 mL), was added *N*,*N*-diisopropylethylamine (0.21 mL, 1.2 mmol) and the resulting mixture was stirred at r.t. for 2 d. The solvent was removed under vacuum, and the residue was chromatographed over alumina (activity IV) with CH_2Cl_2–MeOH (100:0→98:2) as eluent to give 0.11 g (51%) of an yellowish oil; R_f 0.1 (silica gel, CH_2Cl_2–MeOH, 98:2).

IR (KBr): 1738 (s, C=O), 1714 (s), 1585 (m), 1447 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$) : δ = 1.42 (t, 9 H, ^3J = 7.1 Hz, OCH_2CH_3), 2.68–2.70 (m, 16 H), 3.42–3.45 (m, 8 H), 4.45 (q, 6 H, ^3J = 7.1 Hz, OCH_2CH_3), 7.15–7.34 (m, 5 H), 7.77–7.92 (m, 6 H), 8.03–8.07 (m, 3 H), 8.41–8.65 (m, 9 H).

$^{13}C\{^1H\}$ JMOD NMR (62.5MHz, $CDCl_3$): δ = 14.3 (CH_3), 53.1 (CH_2), 57.1 (CH_2), 57.4 (CH_2), 60.5 (CH_2), 61.8 (CH_2), 121.2 (CH), 124.1 (CH), 124.7 (CH), 128.1 (CH), 129.1 (CH), 135.8 (Cq), 135.9 (Cq), 137.6 (CH), 137.7 (CH),147.7 (Cq), 149.8 (CH), 153.9 (Cq), 156.4 (Cq), 156.5 (Cq), 165.4 (C=O).

MS (FAB$^+$, *m*NBA): *m*/*z* (%) = 983 (100, [M + H$^+$]).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 246 (38500), 286 nm (50400).

Anal. Calcd for $C_{57}H_{62}N_{10}O_6.H_2O$: C, 68.38; H, 6.44; N, 13.99. Found: C, 68.14; H, 6.22; N, 13.56.

1,3,5-Tri[(6′-ethoxycarbonyl-2,2′-bipyridine-5-yl)methyloxy]benzene (14a)

A mixture of 1,3,5-trihydroxybenzene (**13**; 0.024 g, 0.19 mmol) and Cs_2CO_3 (0.31 g, 0.95 mmol) in anhyd DMF (20 mL) was stirred at r.t. for 30 min. Ethyl 5′-bromomethyl-6-(2,2′-bipyridine)carboxylate (**4b**; 0.2 g, 0.62 mmol) was added and the solution was stirred overnight. The solvent was removed under vacuum, the residue was diluted with CH_2Cl_2 and the CH_2Cl_2 phase was washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under vacuum. Chromatographic separation (silica gel, eluent: CH_2Cl_2–EtOAc, 1:0→0:1) gave 0.08 g (50%) of a white solid; mp 170–172 °C; R_f 0.1 (silica gel, EtOAc).

IR (KBr): 1737 (s, C=O), 1717 (m), 1602 (m), 1156 cm^{-1} (s).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.45 (t, 9 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.47 (q, 6 H, ^3J = 7.1 Hz, OCH_2CH_3), 5.09 (s, 6 H, OCH_2), 6.28 (s, 3 H_{arom}), 7.90 (m, 6 H), 8.10 (dd, 3 H, ^3J = 7.7, ^4J = 0.9 Hz), 8.58 (dd, 6 H, ^3J = 7.8 Hz, ^4J = 0.8 Hz), 8.70 (d, 3 H, ^4J = 2.0 Hz).

$^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$): δ = 14.3 (CH_3), 61.9 (CH_2), 67.6 (CH_2), 95.3 (CH), 121.5 (CH), 124.2 (CH), 125.0 (CH), 132.8 (Cq), 136.3 (CH), 137.9 (CH), 147.8 (Cq), 148.3 (CH), 155.1 (Cq), 156.0 (Cq), 160.3 (Cq), 165.3 (C = O).

MS (FAB$^+$, *m*NBA): *m*/*z* (%) = 847 (100, [M + H$^+$]), 869 (49, [M + Na$^+$]).

UV/Vis (MeOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 245 (34500), 288 nm (42800).

Anal. Calcd for $C_{48}H_{42}N_6O_9$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.68; H, 4.65; N, 9.66.

Saponification of the Triesters 12a and 14a; General Procedure

A mixture of the triester (0.1 mmol) in MeOH (10 mL) and a solution of NaOH (200 mg, 5 mmol) in H_2O (2 mL) was refluxed for 2 h.[7] After cooling, dil. HCl was added slowly until pH 4, the resulting precipitate was collected by centrifugation, washed with H_2O and dried under vacuum to afford the corresponding triacid as a white powder.

1-Benzyl-4,7,10-tri[(6′-carboxy-2,2′-bipyridine-5-yl)methyl]-1,4,7,10-tetraazacyclododecane (12b)

From **12a** (0.08 g, 0.08 mmol) and NaOH (0.16 g, 4 mmol); yield: 0.057 mg (80%).

IR (KBr): 3435 (br),1632 cm^{-1} (m).

^1H NMR (250 MHz, MeOD/NaOD/D_2O): δ = 2.65–2.80 (m, 16 H), 3.40 (br s, 2 H), 3.47 (br s, 6 H), 7.19–7.34 (br m, 6 H), 7.56–7.62 (br m, 2 H), 7.75–8.25 (br m, 12 H), 8.48 (br s, 1 H), 8.54 (br s, 2 H).

MS (FAB$^+$, *m*NBA): *m*/*z* (%) = 899 (67, [M + H$^+$]), 921 (100, [M + Na$^+$]), 943 (58, [M – H$^+$ + 2Na$^+$], 965 (25, [M – 2H$^+$ + 3Na$^+$].

1,3,5-Tri[(6′-carboxy-2,2′-bipyridine-5-yl)methyloxy]benzene (14b)

From **14a** (0.03 g, 0.037 mmol) and NaOH (0.06 g, 1.5 mmol); yield: 0.027 g (90%).

IR (KBr): 3430 (br), 1613 cm^{-1} (m).

^1H NMR (250 MHz, DMSO-d_6): δ = 5.24 (s, 6 H, OCH_2), 6.44 (s, 3 H_{arom}), 8.09 (m, 9 H), 8.56 (d, 6 H, ^3J = 7.4 Hz), 8.7 (s, 3 H).

MS (FAB$^+$, *m*NBA): *m*/*z* (%) = 763 (55, [M + H$^+$]), 785 (91, [M + Na$^+$]), 807 (100, [M – H$^+$ + 2Na$^+$]), 829 (56, [M – 2H$^+$ + 3Na$^+$]).

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