Fast, efficient syntheses of linear poly(dipyrromethene)s

Qingqi Chen and David Dolphin

Abstract: The synthesis of three octapyrrolic, **8**–**10**, and four dodecapyrrolic, **15**–**18**, oligomers is reported. They are linear poly(dipyrromethene)s and potential ligands as building blocks for supramolecular architectures through self-assembly. Octapyrrolic oligomers **8**–**10** were prepared in 90–95% yields by condensation of 2 equiv of a tripyrrolic compound **4** with 1 equiv of diformyldipyrrolic compounds **5**–**7**. A similar procedure, involving the condensation of 2 equiv of a pentapyrrolic starting material **13** with 1 equiv of **5**–**7** or **14**, was found to give rise to the corresponding dodecameric systems **15**–**18** in 41–56% yields.

Key words: poly(dipyrromethene), linear polypyrroles, dipyrromethane, dipyrromethene.

Résumé : On rapporte la synthèse de trois oligomères octapyrroliques (**8**–**10**) et de quatre dodécapyrroliques (**15**–**18**). Il s'agit de poly(dipyrrométhènes) linéaires et des ligands potentiels comme blocs pouvant servir à la construction d'architectures supramoléculaires par le biais d'autoassemblages. Les oligomères octapyrroliques **8**–**10** ont été préparés avec des rendements allant de 90 à 95% par le biais de condensations de deux équivalents d'un composé tripyrrolique (**4**) avec un équivalent de composés diformylpyrroliques (**5**–**7**). Une procédure semblable impliquant la condensation de deux équivalents d'un produit de départ pentapyrrolique (**13**) avec un équivalent de composés **5**–**7** ou **14** conduit à la formation des systèmes dodécamères correspondant (**15**–**18**) avec des rendements allant de 41 à 56%.

Mots clés : poly(dipyrrométhène), polypyrroles linéaires, dipyrrométhane, dipyrrométhène.

[Traduit par la Rédaction]

Introduction

Dipyrromethenes (**I**) are yellow colored and fully conjugated flat compounds containing 10-π-electrons and can be precursors of chlorins; expanded, contracted, and isomeric porphyrins (1); bilirubins (2); biliverdin (2); and many other bile pigments (3). They have been extensively used in the synthesis of porphyrins (1) and linear polypyrroles (4). Owing to their stable monoanionic nature, dipyrromethenes have been found to be useful ligands for a variety of metal ions (5). In addition, bile pigments containing dipyrromethene moieties linked by a methylene group such as biladienes-*ac* (**II**) are useful ligands for the formation of well-defined architectures through self-assembly (6). A salient feature of dipyrromethene superstructures is that counterions are not required, since the dipyrromethene unit is a monoanionic ligand and the complex will be neutral when chelated with divalent metal ions. This is in contrast to bipyridine ligands, the standard building blocks for supramolecular assemblies used by Lehn and co-workers (7, 8).

The use of dipyrromethenes as novel ligands to build double helical supramolecules was originally proposed by one of us in 1965 (9), when it was suggested that a 2:2 bis(dipyrromethene) ligand – Co^{II} complex exists in a helical conformation. Since then several crystal structures of 2:2 biladiene-*ac* ligand – M^{II} complexes have been reported where the 2:2 complex existed as a helix (10). Our group re-examined these reactions (6) and explored the use of a 2,2-spacer between dipyrromethene units (such as **III**) and the 3,3′- positions (such as **IV**) and hexapyrins (**V**) (Scheme 1).

Like biladienes-*ac* (**II**), bis(dipyrromethenes) (**III**) and hexapyrrins (**V**) reacted with Zn^{II} to form a double stranded helical complex (5), while the complex of the 3,3′-bidipyrromethene **IV** ($n = 0$) with Zn^{II} showed triangular geometry with the ligand linking the three metal centers in an overlapping progressive fashion. For each ligand one dipyrromethene binding domain lies above the averaged plane of the molecule, while the other dipyrromethene lies below this plane (Scheme 2).

To extend our work, we were interested in linear polydipyrromethenes, which include 2,2′-linked (**A**), 3,3′-linked (**B**), 3,3′- sulfur bridged (**C**), and 2,2- directly linked intermediates (**D**). In this paper we will report on the synthesis and characterization of novel ligands that contain multiple dipyrromethene units.

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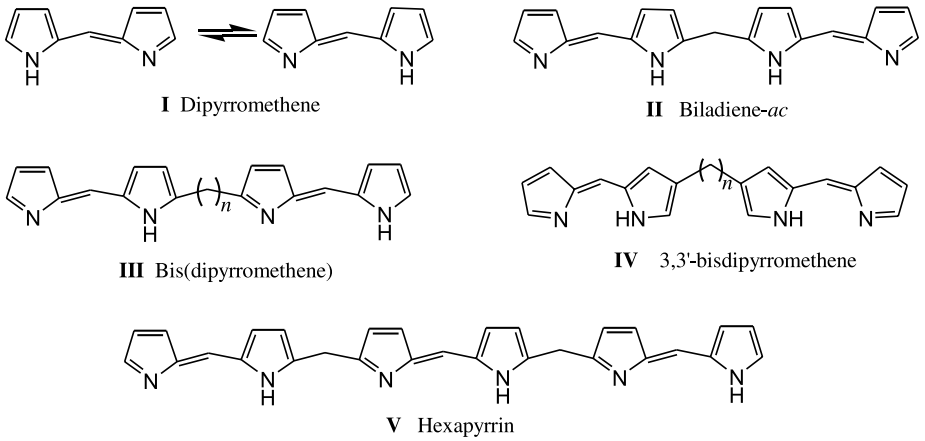
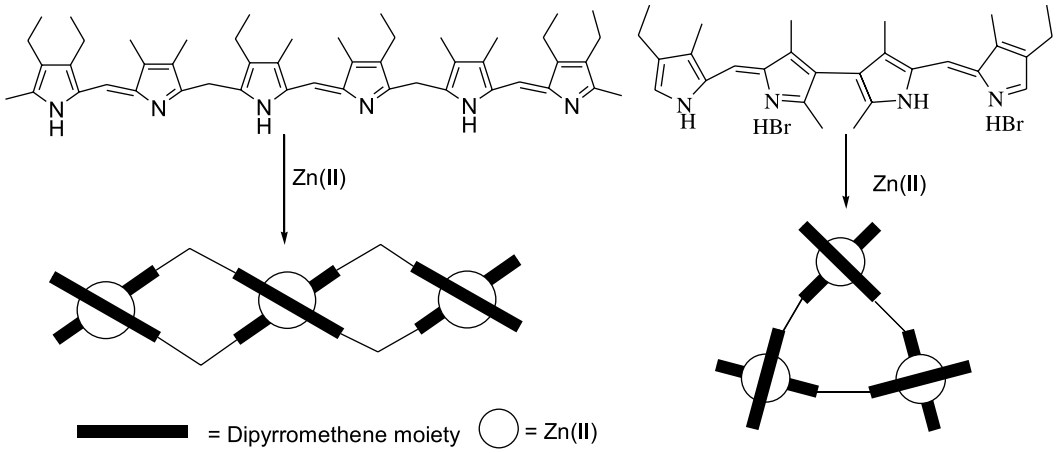
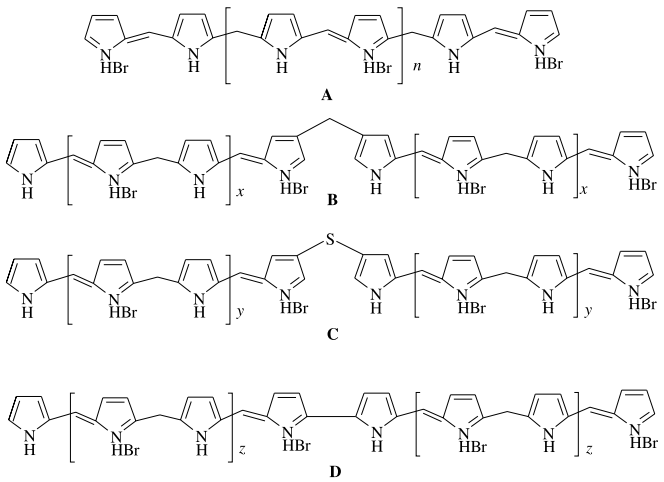
Scheme 1.



Scheme 2.





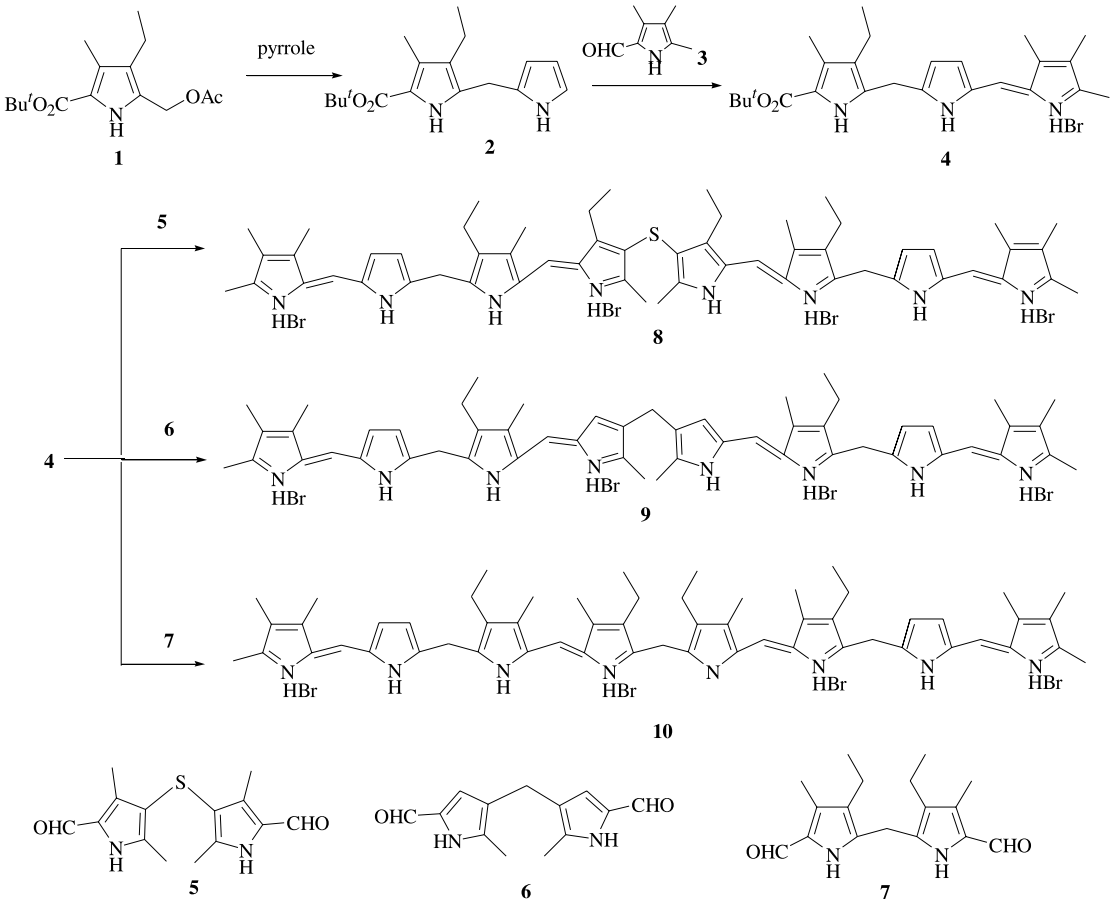
Linear polypyrroles such as hexanornonapyrrin (11*a*), decahydrohexapyrrin (11*b*–11*d*), and pentapyrrole (11*e*) have been recently reported and characterized. However, synthetic methods for linear oligopyrroles containing more than three dipyrromethene units are not currently available.

The key precursor required for the synthesis of **8**–**9** was tripyrrole **4**. It was synthesized from the known 5-acetoxymethylpyrrole (**1**) via two steps, as shown in Scheme 3. Briefly, the procedure involved first treatment of **1** with pyrrole at reflux in a mixture of *p*-toluenesulfonic acid and dichloromethane or at 40°C in acetic acid, followed by purification of the reaction mixture by direct crystallization from dichloromethane–hexane. The asymmetric dipyrromethane **2** was obtained in 66% yield. Acid-catalyzed coupling of this intermediate with 3,4,5-trimethyl-5-formylpyrrole (**3**) then afforded the requisite hydrobromide salt of tripyrrole **4** in an 86% yield after crystallization.

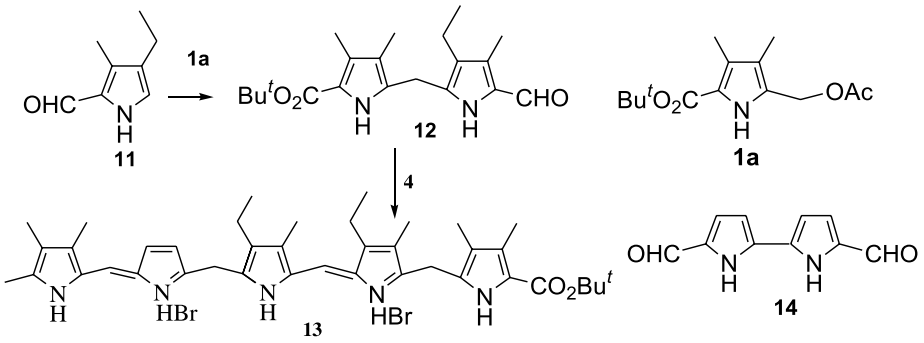
Once **4** was in hand, the synthesis of the target compounds **8**–**10** proved straightforward. After simple precipitating using anhydrous ether, the acid-catalyzed condensation of 2 equiv of **4** and 1 equiv of **5**–**7** in methanol–dichloromethane was found to give the desired linear octapyrrins **8**–**10** as their corresponding tetrahydrobromide salts, in excellent yields. (detailed in Scheme 3).

Our synthetic procedure for dodecapyrrins **15**–**18** is outlined in Schemes 4 and 5. For this purpose, the key precursor **13** was required; this was prepared from 5-acetoxymethylpyrrole **1a** via two steps. The procedure involved first treating **1** with the 5-unsubstituted 2-formylpyrrole (**11**) at 50°C in acetic acid or at room temperature in a mixture of dichloromethane and *p*-toluenesulfonic acid. Crystallization from dichloromethane–hexane gave the asymmetric dipyrro-

Scheme 3.



Scheme 4.



methane **12** in 72% yield. Condensation of **12** with tripyrrole acid, generated in situ by treating **4** with trifluoroacetic acid at room temperature for 20 min, afforded the desired intermediate as the dihydrobromide salt **13** in 93% yield after precipitating with anhydrous ether. Acid-catalyzed condensation between **14** and 2 equiv of **13** with 1 equiv of **5**–**7** gave, in good yields, the desired dodecapyrrins **15**–**18** as their corresponding hexahydrobromide salts.

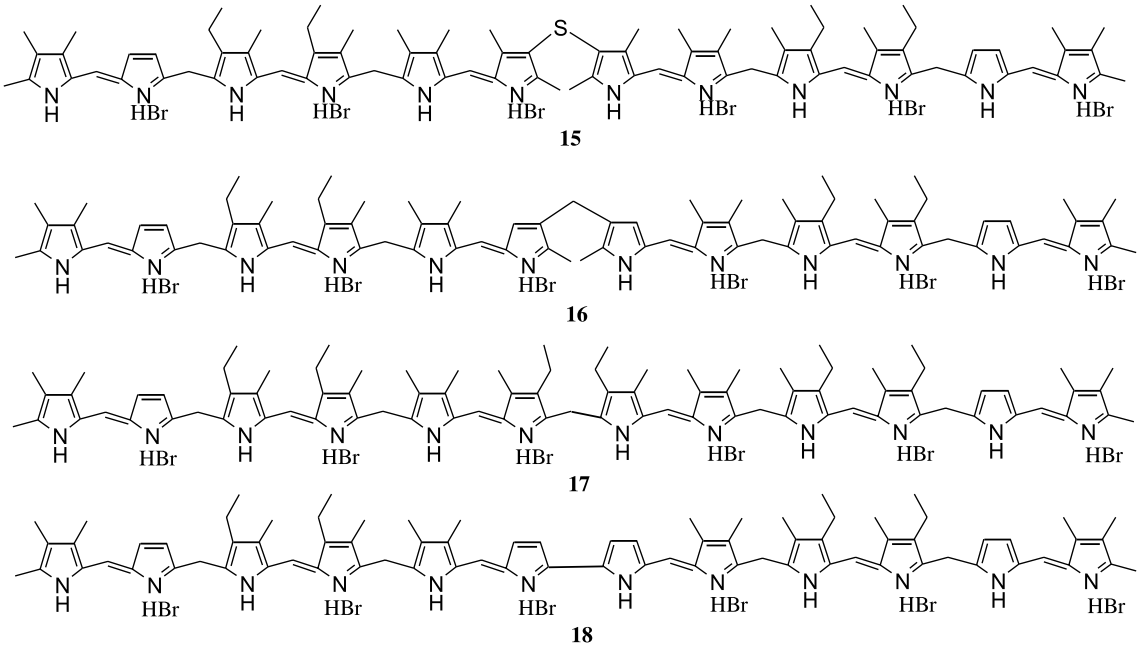
Experimental section

5-Acetoxymethyl-4-ethyl-3-methyl-2-*tert*-butoxycarbonylpyrrole (**1**) (12), 5-acetoxymethyl-3,4-dimethyl-2-*tert*-butoxycarbonylpyrrole (**1a**) (12), 3,4,5-trimethyl-2-formyl-pyrrole (**3**) (13), bis(2,4-dimethyl-5-formyl-pyrrole-3-yl) sulfide (**5**) (14), 5-methyl-2-benzoxycarbonylpyrrole (15), 5,5′-diformyl-4,4′-dimethyl-3,3′-diethyl-dipyrromethane **7** (14), 3-methyl-4-ethyl-2-formylpyrrole (**11**) (16), and 5,5′-diformylbipyrrole (**14**) (15) were synthesized according to the previously reported procedures.

5,5′-Bisethoxycarbony-2,2′-dimethyl-3,3′-dipyrromethane

Paraformaldehyde (1.40 g, 47 mmol, 2.0 mol equiv) was suspended in ethanol (300 mL) containing hydrochloric acid (33%, 5 mL). The mixture was stirred with heating until all

Scheme 5.



the solid dissolved. After cooling to room temperature, 2-benzoxycarbonyl-5-methylpyrrole (20 g, 46.8 mmol) was added. The mixture was allowed to stir at 40°C for 3 h. After removal of solvent, the residue was crystallized from methanol. The product was obtained as white crystals (11.32 g, 55%); mp 222–224°C. ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) δ: 2.20 (s, 6H, 2 CH_3), 3.20 (s, 2H, CH_2), 5.20 (s, 4H, 2OCH_2), 6.60 (s, 2H, 2 pyrrolyl-H), 7.40 (m, 10H, 2 phenyl), 9.20 (s, 2H, 2NH). ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) δ: 11.57 (CH_3), 19.51 (s, CH_2), 65.55 (OCH_2), 113.13, 116.74, 119.38, 121.71, 128.12, 128.53, 130.76, 136.43, 162.55 (COO). LSIMS *m/e*: 443 ([M^+ + 1]). Anal. calcd. for $C_{27}H_{26}N_2O_4$: C 73.29, H 5.92, N 6.33; found: C 73.02, H 5.90, N 5.98.

1,2-Bis(5-carboxy-2,4-dimethyl-pyrrole-3-yl)methane

1,2-Bis(5-benzoxycarbonyl-2-methylpyrrole-3-yl)methane (20 g, 63 mmol) was dissolved in tetrahydrofuran (400 mL). Palladium on carbon (10%, 1.0 g) and triethylamine (1 mL) were added to this solution. The mixture was stirred for 20 h under hydrogen at atmospheric pressure and room temperature. The catalyst was removed by filtration. After removal of solvent, the residue was dried under vacuum. The product was obtained as a white powder (16 g, 98%), which was used directly for the next step without further purification. An analytical sample was purified by twice repeating the following procedure: the crude product (100 mg) was dissolved in aqueous saturated sodium bicarbonate (5 mL); the mixture was then filtrated to remove any insoluble materials and carefully adjusted to pH 4 with glacial acetic acid. The white precipitate was collected by suction filtration; mp 220°C (decomposition temperature (dec.)). ^{1}H NMR (200 MHz, DMSO-d_6) (ppm) δ: 2.10 (s, 6H, 3 CH_3), 3.30 (s, 2H, CH_2), 6.40 (s, 2H, 2 pyrr-H), 11.02 (s, 2H, 2 COOH), 11.85 (s, 2H, 2 NH). ^{13}C NMR (50 MHz, DMSO-d_6) (ppm) δ: 9.30 (CH_3), 19.20 (CH_2), 119.90, 127.55, 131.44, 137.55, 161.33 (COO). Anal. calcd. for $C_{13}H_{14}N_2O_4$: C 59.54, H 5.38, N 10.68; found: C 59.33, H 5.28, N 10.39.

5-*tert*-Butoxycarbonyl-4-methyl-3-methoxycarbonylmethyl-2,2′-dipyrromethane (2)

Method A

A 500 mL three-necked, round-bottomed flask equipped with magnetic stirrer bar and a nitrogen inlet was charged with 5-acetoxymethyl-4-ethyl-3-methyl-2-*tert*-butoxycarbonylpyrrole (**1**, 10.0 g, 35.5 mmol) and acetic acid (250 mL). After 20 min of stirring under nitrogen, pyrrole (2.86 g, 42.7 mmol, 1.2 mol equiv) and *p*-toluenesulfonic acid monohydrate (330 mg) were added. The reaction mixture was stirred at 40°C overnight. The solvent was removed under vacuum. The residue was taken into dichloromethane (500 mL) and washed successively by water (2 × 100 mL), aqueous saturated sodium bicarbonate (2 × 100 mL), and saturated brine (100 ml). After drying over anhydrous sodium sulfate and removing solvent under vacuum, the residue was crystallized from dichloromethane–hexane to give the product (3.33 g, 32%).

Method B

A 500 mL three-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, and reflux condenser was charged with 5-acetoxymethyl-4-ethyl-3-methyl-2-*tert*-butoxycarbonylpyrrole (**1**, 18.6 g, 66 mmol), pyrrole (4.6 mL, 66 mmol, 1.0 mol equiv), and dichloromethane (200 mL). The mixture was stirred at room temperature for 30 min while nitrogen was bubbled through the solution. *p*-Toluenesulfonic acid monohydrate (250 mg) was then added in one portion. The solution immediately turned yellow-red. The mixture was stirred under reflux for 30 min. TLC then showed the reaction was complete (CH_2Cl_2, 5-acetoxymethylpyrrole R_f = 0.4, product R_f = 0.5, and pyrrole R_f = 0.9). The product dipyrromethane turned yellow-red, pyrrole

turned to brown-black, and the starting 5-acetoxymethyl-pyrrole remained unchanged upon contacting the TLC plate over bromine vapor. After cooling to room temperature, triethylamine (1 mL) in methanol (5 mL) was added to neutralize the acid. Solvent was completely removed under vacuum (first rotovapor, then high vacuum). The yellow semi-solid was mixed with aqueous methanol (90%, 30 mL) and ultrasonicated to aid solidification. The crude material was immediately collected by suction filtration to yield the expected product (11.6 g, 61%), which was pure enough for subsequent use, as judged by ^{1}H NMR. Note that this compound is not very stable and should be stored in the dark and at low temperature. mp 120–122°C. ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) δ: 1.05 (t, J = 7.32 Hz, 3H, CH_3), 1.50 (s, 9H, 3 CH_3), 2.20 (s, 3H, CH_3), 2.30 (q, J = 7.32 Hz, 2H, CH_2), 3.80 (s, 2H, CH_2), 5.80 (s, 1H, pyrrole-H), 6.05 (s, 1H, pyrrole-H), 6.60 (s, 1H, pyrrole-H), 7.60 (s, 1H, NH), 8.60 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) δ: 10.23 (CH_3), 14.55 (CH_3), 24.44 (CH_2), 28.33 (CH_2), 29.35 (CH_3), 86.88 ($OCMe_3$), 113.44, 114.55, 116.77, 123.55, 124.56, 125.44, 127.44, 128.33, 161.20 (COO). EI-MS (150 °C) *m*/*z* (%): 288 ([M^+], 52), 232 (40), 165 (100), 147 (25). Anal. calcd. for $C_{17}H_{24}N_2O_2$: C 70.80, H 8.39, N 9.71; found: C 70.60, H 8.61, N 8.53.

1-*tert*-Butoxycarbonyl-2-methyl-3-ethyl-12,13,14-trimethyl-4,5-dihydro-tripyrrin hydrogen bromide salt (4)

A 250 mL round-bottomed flask equipped with magnetic stirrer bar was charged with 2-*tert*-butoxycarbonyl-3-methyl-4-methoxycarbonylmethyl-dipyrromethane (**2**) (1.0 g, 3.47 mmol), 3,4,5-trimethyl-2-formyl-pyrrole (**3**) (0.48 g, 3.47 mmol, 1.0 mol equiv), dichloromethane (50 mL), and methanol (20 mL). Hydrogen bromide (48% in glacial acetic acid, 3 mL) was added with stirring. The red mixture was allowed to stir for 2 h at room temperature. Anhydrous ether (50 mL) was added and the suspension was allowed to stir for another 30 min. The red solid was collected by suction filtration and washed with anhydrous ether. The crude product was suspended in methanol (50 mL) containing 5 drops of hydrogen bromide (45% in glacial acid) and stirred for 30 min. The solid was collected by filtration (1.46 g, 86%). An analytical sample was obtained as follows: crude product was dissolved in a minimum amount of dichloromethane, and methanol (~1 mL) containing a drop of hydrogen bromide (45% in glacial acid) was added, followed by anhydrous ether to precipitate the product. The red solid was collected by suction filtration; mp 220 (dec.). UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 483 (80 400). ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) δ: 1.05 (t, J = 7.35 Hz, 3H, CH_3), 1.55 (s, 9H, $3CH_3$), 2.00 (s, 3H, CH_3), 2.20 (s, 6H, 2 CH_3), 2.40 (q, J = 7.35 Hz, 2H, CH_2), 2.60 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 6.30 (s, 1H, pyrrole-H), 7.00 (s, 1H, -CH=), 7.05 (s, 1H, pyrrole-H), 10.05 (s, 1H, NH), 13.10 (s, 1H, NH), 13.20 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) δ: 8.89 (CH_3), 10.29 (CH_3), 13.55 (CH_3), 15.55 (CH_3), 17.28 (CH_3), 24.77 (CH_2), 28.71 (CH_3), 30.05 (CH2), 80.20 ($OCMe_3$), 114.93, 119.57, 123.57, 124.13, 125.83, 126.11, 126.39, 127.33, 128.28, 133.13, 144.65, 152.49, 159.68 (C=N), 160.91 (COO). FAB-MS *m*/*e*: 408 ([M^+ + 1]), 334. Anal. calcd. for $C_{25}H_{33}N_3O_2$·HBr: C 61.47, H 7.02, N 8.60, Br 16.31; found: C 61.58, H 7.10, N 8.32, Br 16.25.

5,5′-Diformyl-2,2′-dimethyl-3,3′-dipyrromethane (6)

5,5′-Dicarboxy-2,2′-dimethyl-3,3′-dipyrromethane (3.0 g, 11 mmol) was suspended in trifluoroacetic acid (15 mL). The mixture was stirred at 40°C until all the solid had dissolved. The mixture was then cooled to –5°C using an ice–salt bath. Trimethyl orthoformate (4.5 mL) was added dropwise over 5 min and the mixture was allowed to stir another 10 min before being poured into a solution of 10% ammonia (100 mL), which was pre-cooled to 0°C. The yellow-brown precipitated was collected by filtration and washed with water. After drying under vacuum and crystallizing from dichloromethane–hexane, the title compound was obtained (2.1 g, 80%); mp 210–212°C. ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) δ: 1.90 (s, 6H, 2 CH_3), 3.30 (s, 2H, CH_2), 6.35 (s, 2H, 2 pyrr-H), 9.40 (s, 2H, 2 CHO), 10.50 (s, 2H, 2NH). ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) δ: 9.50 (CH_3), 19.50 (CH_3), 121.44, 126.78, 130.45, 136.55, 177.55 (CHO). LSIMS *m*/*e*: 231 ([M^+ + 1]). Anal. calcd. for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; found: C 67.51, H 5.90, N 11.89.

General procedure for 8–10

Tripyrrole (**4**, 100 mg, 0.20 mmol) was suspended in trifluoroacetic acid (5 mL), and stirred at room temperature until all solid had dissolved. To this brown-red mixture **5**, **6**, or **7** (0.10 mmol, 0.5 mol equiv) was added under continuous stirring. After 10 min, a mixture of dichloromethane (20 mL), methanol (20 mL), and hydrogen bromide (48% in acetic acid) was added. The red mixture was stirred at room temperature and anhydrous ether (100 mL) was added. The suspension was then allowed to stir for another 30 min. The red solid was collected by suction filtration and washed with anhydrous ether. The crude product was suspended in methanol (50 mL) containing 5 drops of hydrogen bromide (45% in glacial acid) and stirred at room temperature for 30 min. The solid was collected by filtration to afford the expected product. An analytic sample was obtained by repeating the following procedure three times: The crude product (~20 mg) was dissolved in a minimum amount of trifluoroacetic acid. To this red mixture, dichloromethane (1 mL) and methanol (1 mL) containing a drop of HBr (48% in acetic acid) were added, followed by anhydrous ether to precipitate the product. The red solid was collected by suction filtration.

Octapyrrin tetrahydrobromide salt (8)

Yield 95%, mp 300°C (dec.). UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 544 (110 600), 505 (97 700), 444 (81 000). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 200 MHz) (ppm) δ: 1.05 (t, J = 7.35 Hz, 6H, $2CH_3$), 2.00 (s, 6H, $2CH_3$), 2.15 (s, 6H, $2CH_3$), 2.20 (s, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$), 2.50 (q, J = 7.35 Hz, 4H, CH_2), 2.60 (s, 6H, $2CH_3$), 2.70 (s, 6H, $2CH_3$), 4.50 (s, 4H, $2CH_2$), 6.40 (s, 2H, 2CH), 7.20 (s, 2H, 2CH), 7.26 (m, 4H, 4 pyrrole-H), 11.80–12.05 (m, 8H, 8NH). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 400 MHz) (ppm) δ: 1.05 (t, J = 7.6 Hz, 6H, 2 CH_3), 2.05 (s, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 2.29 (s, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 2.53 (q, J = 7.6 Hz, 4H, $2CH_2$), 2.64 (s, 6H, $2CH_3$), 2.66 (s, 6H, $2CH_3$), 4.52 (s, 4H, 2 CH_2), 6.42 (s, 2H, 2 -CH=), 7.24 (m, 4H, 4 pyrrolyl-H), 12.10–12.40 (m, 8H, 8 NH). ^{13}C NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 100 MHz) (ppm) δ: 8.78 (CH_3),

10.14 (CH_3), 10.27 (CH_3), 11.25 (CH_3), 13.33 (CH_3), 13.49 (CH_3), 14.15 (CH_3), 17.11 (CH_2), 25.42 (CH_2), 115.48, 119.22, 121.55, 124.14, 126.36, 126.51, 127.67, 127.84, 128.17, 129.74, 132.12, 145.06, 145.94, 147.44, 148.08, 151.48, 156.69 (C=N), 162.46 (C=N). FAB-MS *m/z*: 1017 ([M^+ + 1 + 2HBr]), 937 ([M^+ + 2 + HBr]), 855 ([M^+ + 1]). HR-MS (LSIMS, matrix: thioglycerol) for $C_{54}H_{63}N_8S$ calcd.: 855.48964; found: 855.48906. Anal. calcd. for $C_{54}H_{62}N_8S{\cdot}4HBr$: C 55.02, H 5.64, N 9.51; found: C 55.33, H 5.86, N 9.38.

Octapyrrin tetrahydrobromide salt (9)

Yield 93%; mp 320°C (dec.). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 200 MHz) (ppm) δ: 1.05 (t, *J* = 7.35 Hz, 6H, $2CH_3$), 2.00 (s, 6H, $2CH_3$), 2.18 (s, 6H, $2CH_3$), 2.20 (s, 6H, $2CH_3$), 2.45 (q, *J* = 7.35 Hz, 4H, CH_2), 2.55 (s, 6H, $2CH_3$), 2.60 (s, 6H, $2CH_3$), 3.70 (s, 4H, $2CH_2$), 4.00 (s, 4H, $2CH_2$), 6.45 (s, 2H, 2CH), 7.05 (s, 2H, 2CH), 7.10–7.20 (m, 4H, 4 pyrrole-H), 7.80 (s, 2H, 2 pyrrole-H), 11.80–12.05 (m, 8H, 8NH). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 300 MHz) (ppm) δ: 1.10 (t, *J* = 7.5 Hz, 6H, $2CH_3CH_2$), 2.00 (s, 6H, 2 CH_3), 2.25 (s, 6H, 2 CH_3), 2.28 (s, 6H, 2 CH_3), 2.50 (q, *J* = 7.5 Hz, 4H, $2CH_3CH_2$), 2.60 (s, 6H, 2 CH_3), 2.70 (s, 6H, 2 CH_3), 3.60 (s, 2 H, -CH_2-Bridge-), 4.40 (s, 4H, 2 CH_2 -Bridge-), 6.50 (s, 2H, 2 pyrrolyl-H), 7.00–7.30 (m, 8H, 4 -CH=, 4 pyrrolyl-H), 11.80–12.30 (m, 8H, 8 NH). ^{13}C NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 75 MHz) (ppm) δ: 8.60 (CH_3), 9.86 (CH_3), 10.14 (CH_3), 12.83 (CH_3), 13.37 (CH_3), 14.10 (CH_3), 17.08 (CH_2), 21.75 (CH_2), 25.18(CH_2), 115.48, 124.12, 124.86, 126.60, 127.63, 127.85, 128.01, 129.73, 131.77, 132.49, 134.90, 144.69, 145.71, 147.68, 149.36, 150.01, 154.90 (C=N), 162.98 (C=N). FAB-MS *m/z*: 809 ([M^+ + 1]). HR-MS (LSIMS: matrix: thioglycerol) for $C_{53}H_{61}N_8$ calcd.: 809.50192, found: 809.50203. UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 538 (111 400), 504 (81 800), 444 (108 400). Anal. calcd. for $C_{53}H_{60}N_8{\cdot}4HBr{\cdot}0.5H_2O$: C 54.97, H 5.62, N 9.68; found: C 55.16, H 5.83, N 9.36.

Octapyrrin tetrahydrobromide salts (10)

Yield 91%; mp 310°C (dec.). UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 555 (71 200), 499 (107 900), 445 (88 300), 380 (27 300). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 200 MHz) (ppm) δ: 1.05 (t, *J* = 7.35 Hz, 6H, $2CH_3$), 2.05 (s, 6H, $2CH_3$), 2.20 (s, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$), 2.35 (s, 6H, $2CH_3$), 2.45 (q, *J* = 7.35 Hz, 4H, CH_2), 3.60 (s, 6H, $2CH_3$), 4.50 (s, 4H, $2CH_2$), 4.80 (s, 2H, CH_2), 7.20 (m, 8H, 4 pyrrole-H, 4 -CH=), 11.80–12.00 (m, 8H, 8 NH). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 300 MHz) (ppm) δ: 0.95 (m, 12H, 4 CH_3CH_2), 2.05 (s, 6H, 2 CH_3), 2.25 (s, 6H, 2 CH_3), 2.33 (s, 6H, 2 CH_3), 2.40 (s, 6H, 2 CH_3), 2.45 (m, 8 H, 4 CH_3CH_2), 4.50 (s, 4H, 2 -CH_2-bridge), 4.70 (s, 2H, -CH_2-bridge), 7.22 (s, 2H, 2 pyrrolyl-H), 7.35 (s, 2H, 2 pyrrolyl-H), 7.45 (s, 4H, 4 –CH=), 11.80–12.00 (m, 8H, 8 NH). ^{13}C NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 75 MHz) (ppm) δ: 8.60 (CH_3), 9.97 (CH_3), 9.99 (CH_3), 10.13 (CH_3), 13.44 (CH_3), 13.83 (CH_3), 13.97 (CH_3), 17.07 (CH_2), 17.33 (CH_2), 24.88 (-CH_2-bridge), 25.78 (CH_2-bridge), 119.96, 121.99, 124.45, 124.92, 127.74, 127.80, 128.05, 128.24, 129.87, 131.31, 144.78, 145.20, 145.33, 147.45, 148.46, 148. 88, 150.84 (C=N), 162.36 (C=N). FAB-MS *m/z*: 865 ([M^+ + 1]), 665, 439. HR-MS (LSIMS, matrix: thioglycerol) for $C_{57}H_{69}N_8$ calcd.: 865.56452; found: 865.56457. Anal. calcd. for $C_{57}H_{68}N_8{\cdot}4HBr$: C 57.59, H 6.10, N 9.43; found: C 57.43, H 6.31, N 9.21.

5-*tert*-Butoxycarbonyl-3,4-dimethyl-5′-formyl-4′-ethyl-3′-methyl-2,2′-dipyrromethane (12)

Method A

A 250 mL three-necked, round-bottomed flask equipped with a magnetic stirrer bar and a nitrogen inlet was charged with 5-acetoxymethyl-3,4-dimethyl-2-*tert*-butoxycarbonylpyrrole (3.44 g, 12.5 mmol) and acetic acid (100 mL). Nitrogen was bubbled through the solution with stirring, and after 20 min 2-formyl-3-ethyl-4-methylpyrrole (1.71 g, 12.5 mmol, 1.0 mol equiv) was added. The reaction mixture was stirred at 50°C overnight. The solvent was removed under vacuum (rotovapor). The residue was taken up in dichloromethane (200 mL) and washed successively with water (2 × 100 mL), aqueous saturated sodium bicarbonate (2 × 100 mL), and saturated brine (100 ml). After drying over anhydrous sodium sulfate and removing solvent (rotovapor), the solid was crystallized from dichloromethane–hexane, yielding 0.85 g (20%).

Method B

A 250 mL three-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, and a reflux condenser was charged with 5-acetoxymethyl-3,4-dimethyl-2-*tert*-butoxycarbonylpyrrole (1.94 g, 7.30 mmol), 4-methyl-3-ethyl-2-formylpyrrole (1.0 g, 7.30 mmol, 1.0 mol equiv), and dichloromethane (150 mL). The mixture was stirred at room temperature for 30 min while nitrogen was bubbled through the solution. *p*-Toluenesulfonic acid monohydrate (150 mg) was then added in one portion. The solution turned yellow-red immediately. The mixture was stirred under reflux for 30 min. TLC showed the reaction was complete (CH_2Cl_2, 5-acetoxymethylpyrrole R_f = 0.4, product R_f = 0.5, and pyrrole R_f = 0.9). The product dipyrromethane turned red, the pyrrole turned brown-black, and the starting 5-actoxymethylpyrrole remained unchanged upon contacting the TLC plate over bromine vapor. After cooling to room temperature, triethylamine (1 mL) in methanol (5 mL) was added to neutralize the acid. Solvent was completely removed under vacuum (first rotovapor, then high vacuum). The yellow semi-solid was mixed with aqueous methanol (90%, 30 mL) and ultrasonicated to aid solidification. The suspension was kept at 0°C for 4 h. The solid was collected by suction filtration to yield the product (1.80 g, 72%), mp 189–191°C. ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) δ: 1.02 (t, *J* = 7.32 Hz, 3H, CH_3), 1.45 (s, 9H, 3 CH_3), 1.70 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.50 (q, *J* = 7.32 Hz, 2H, CH_2), 3.80 (s, 2H, CH_2), 9.25 (s, 1H, CHO), 9.85 (s, 1H, NH), 10.80 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) δ: 8.85 (CH_3), 9.00 (CH_3), 10.67 (CH_3), 16.49 (CH_3), 17.35 (CH_2), 28.58 ($OC(CH_3)_3$), 80.18($OCMe_3$), 116.88, 117.35, 119.33, 126.22, 127.55, 127.99, 137.40, 140.53, 161.35 (COO), 176.49 (CHO). EI-MS *m/e* (%): 402 (2), 344 ([M]$^+$, 80), 288 (90), 271 (20), 259 (20), 244 (30), 149 (100). Anal calcd. for $C_{20}H_{28}N_2O_3$: C 69.74, H 8.19, N 8.13; found: C 69.26, H 8.27, N 7.94.

Pentapyrrole (13)

Starting tripyrrole (**4**) (300 mg, 0.61 mmol) was suspended in trifluoroacetic acid (10 mL) and stirred at room temperature for 10 min until all the solid had dissolved. A solution of 5-*tert*-butoxycarbonyl-3,4-dimethyl-5′-formyl-4-ethyl-3-methyl-2,2′-dipyrromethane (**12**) (211 mg, 0.61 mmol, 1.0 mol equiv) in dichloromethane (20 mL) was added to the brown-red solution under continuous stirring. After 10 min, a mixture of methanol (20 mL) and hydrogen bromide (2 mL, 48% in acetic acid) was added. The red mixture was allowed to stir for 3 h at room temperature. Anhydrous ether (100 mL) was then added and the suspension was stirred for another 30 min. The red solid was collected by suction filtration and washed with anhydrous ether to afford the product (450 mg, 93%); mp 252°C (dec.). UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 525 (71 800), 447 (62 800). ^{1}H NMR ($CDCl_3$, 200 MHz) (ppm) δ: 0.95 (t, *J* = 7.35 Hz, 3H, CH_3), 1.00 (t, *J* = 7.35 Hz, 3H, CH_3), 1.50 (s, 9H, 3 CH_3), 1.80 (s, 6H, 2 CH_3), 2.20 (m, 9H, 3 CH_3), 2.40 (s, 6H, 2 CH_3), 2.60 (q, *J* = 7.32 Hz, 2H, -CH_2-), 3.40 (q, *J* = 7.32 Hz, 2H, -CH_2-), 4.20 (s, 2H, -CH_2-), 4.80 (s, 2H, -CH_2-), 6.80 (s, 2H, 2 –CH=), 6.90 (s, 2H, 2 pyrrole-H), 7.20 (m, 2H, 2 pyrrole-H), 10.40 (s, 1H, NH), 13.20 (s, 2H, 2 NH), 13.40 (s, 2H, 2 NH). FAB-MS *m*/*z*: 634 ([M^+ + 1]), 425, 199. HR-MS (LSIMS, matrix: thioglycerol) for $C_{40}H_{52}N_5O_2$, calcd.: 634.41210; found: 634.41180. Anal calcd. for $C_{40}H_{51}N_5O_2 \cdot 2HBr \cdot H_2O$: C 59.04, H 6.84, N 8.61, Br 19.64; found: C 58.89, H 6.64, N 8.66, Br 19.30.

General procedure for 15–18

The pentapyrrole (**13**, 100 mg, 0.125 mmol) was suspended in trifluoroacetic acid (5 mL) and stirred at room temperature for 10 min until all the solid had dissolved. To this brown-red solution was added a solution of **5**, **6**, **7**, or **14** (0.0625 mmol, 0.5 mol equiv) in dichloromethane (20 mL) under continuous stirring. After 10 min, a mixture of methanol (20 mL) and hydrogen bromide (2 mL, 48% in acetic acid) was added. The red mixture was stirred for 3 h at room temperature. Anhydrous ether (100 mL) was added and the suspension was allowed to stir for another 30 min. The red solid was collected by suction filtration and washed by anhydrous ether containing a few drops of HBr (48% in acetic acid) to afford the expected product. An analytic sample was obtained by repeating the following procedure three times: the crude product (~20 mg) was dissolved in dichloromethane (1 mL), and methanol (1 mL) containing a few drops of HBr (48% in acetic acid) was added, followed by the addition of anhydrous ether to precipitate the product. The red solid was collected by suction filtration.

Dodecapyrrin hexahydrogen bromide salt (15)

Yield 41%, mp 300°C (dec.). UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 565 (211 100), 543 (209 100), 494 (142 700), 448 (142 700), 376 (47 900). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 200 MHz) (ppm) δ: 0.90 (br s, 6H, 2CH_3), 1.40 (br s, 6H, 2CH_3), 1.80 (s, 12H, 4 CH_3), 2.00 (s, 12H, 4 CH_3), 2.40 (m, 26H, 6 CH_3, 4 CH_2), 2.60 (m, 12H, 4 CH_3), 5.00 (s, 4H, 2 CH_2), 5.10 (s, 4H, 2 CH_2), 7.20 (m, 10H, 4 pyrrole-H, 6 -CH=), 13.20–13.40 (m, 12H, 12 NH). FAB-MS (matrix: 3-NBA) *m*/*z*: 1308 ([M^+ + 2]). HR-MS (LSIMS, thioglycerol) for $C_{84}H_{99}N_{12}S$ calcd.: 1307.78364; found: 1307.78342. Anal calcd. for $C_{84}H_{98}N_{12}S \cdot 6HBr$: C 56.25, H 5.80, N 9.37; found: C 56.87, H 6.07, N 9.00.

Dodecapyrrin hexahydrobromide salt (16)

Yield 45%, mp 280°C (dec.). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 200 MHz) (ppm) δ: 0.95 (t, *J* = 7.6 Hz, 6H, 2CH_3), 1.05 (t, *J* = 7.6 Hz, 6H, 2CH_3), 1.60 (s, 6H, 2 CH_3), 1.90 (s, 6H, 2 CH_3), 2.20 (m, 26H, 6 CH_3, 4 CH_2), 2.60 (m, 18H, 6 CH_3), 3.40 (s, 2H, -CH_2-bridge), 4.9–5.10 (m, 4H, 2 -CH_2-bridge), 7.30 (m, 12H, 6 pyrrole-H, 6 -CH=), 13.20–13.40 (m, 12H, 12 NH). LSIMS (matrix: thioglycerol) *m*/*z*: 1262 ([M^+ + 2]), 1064. HR-MS (LSIMS, thioglycerol) for $C_{83}H_{97}N_{12}$ calcd.: 1261.78809; found: 1261.79638. UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 554 (258 000), 486 (242 000), 442 (173 700), 369 (57 000). Anal. calcd. for $C_{87}H_{106}N_{12} \cdot 6HBr \cdot H_2O$: C 56.46, H 5.90, N 9.52; found: C 56.32, H 6.09, N 9.11.

Dodecapyrrin hexahydrobromide salt (17)

Yield 56%, mp 288°C (dec.). UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 569 (70 800), 539 (72 500), 498 (63 700), 450 (53 800), 377 (32 000). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 200 MHz) (ppm) δ: 0.85 (t, *J* = 7.35 Hz, 6H, 2CH_3), 1.05 (t, *J* = 7.35 Hz, 6H, 2CH_3), 1.20 (t, *J* = 7.35 Hz, 6H, 2CH_3), 2.00 (m, 18H, 6 CH_3), 2.30 (m, 26H, 6 CH_3, 4 CH_2), 2.60 (m, 10H, 2 CH_3, 2 CH_2), 4.50–4.80 (m, 10H, 5 CH_2), 7.30 (m, 10H, 4 pyrrole-H, 6 -CH=), 12.00–12.40 (m, 12H, 12 NH). FAB-MS (matrix: 3-NBA) *m*/*z*: 1558 ([M^+ + 3HBr]), 1399 ([M^+ + HBr]), 1318 ([M^+ + 2]), 1119, 878, 651, 465. HR-MS (LSIMS, thioglycerol) for $C_{87}H_{106}N_{12}$ calcd.: 1318.86634; found: 1318.86809. Anal calcd. for $C_{87}H_{106}N_{12} \cdot 6HBr$: C 57.59, H 6.15, N 9.32, Br 26.60; found: C 57.61, H 6.00, N 9.07, Br 26.30.

Dodecapyrrin hexahydrobromide salt (18)

Yield 47%, mp 320°C (dec.). UV–Vis (CH_2Cl_2) (nm): $\lambda_{max}(\varepsilon)$ = 585 (88 900), 515 (137 000), 475 (113 000), 446 (114 300). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9:1 (v/v), 200 MHz) (ppm) δ: 0.95 (t, *J* = 7.6 Hz, 6H, 2CH_3), 1.20 (t, *J* = 7.6 Hz, 6H, 2 CH_3), 2.00 (s, 6H, 2 CH_3), 2.05 (s, 6H, 2 CH_3), 2.10 (s, 6H, 2 CH_3), 2.20 (s, 6H, 2 CH_3), 2.30 (s, 6H, 2 CH_3), 2.36 (s, 6H, 2 CH_3), 2.40 (q, *J* = 7.6 Hz, 2H, CH_2), 2.50 (s, 6H, 2 CH_3), 2.60 (q, *J* = 7.6 Hz, 2H, CH_2), 4.60 (s, 2H, CH_2), 4.70 (s, 2H, CH_2), 7.20 (m, 14H, 8 pyrrole-H, 6 -CH=), 12.00–12.40 (m, 12H, 12 NH). LSIMS (matrix: thioglycerol) *m*/*z*: 1219 ([M^+ + 1]). HR-MS (LSIMS, thioglycerol) for $C_{80}H_{90}N_{12}$ calcd.: 1218.74114; found: 1218.74182. Anal calcd. for $C_{80}H_{90}N_{12} \cdot 6HBr \cdot 2H_2O$: C 55.17, H 5.75, N 9.65; found: C 55.19, H 5.86, N 9.16.

Conclusion

In summary, we have developed a fast, highly efficient synthetic methodology that appears to be of versatile utility in terms of allowing for the construction of linear polypyrromethenes. The resulting compounds are stable and exist as the corresponding hydrobromide salts. Self-assembly of those novel ligands with transition metal ions is currently being studied.

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