Synthesis of a Series of Mono-*meso*-arylmesoporphyrins III of Biological Interest and Their Biliverdin Derivatives

Fernando Niemevz, Ma. Soledad Vazquez, Graciela Y. Buldain*

Cátedra de Química Orgánica II, Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, (C1113AAD) Ciudad Autónoma de Buenos Aires, Argentina
Fax +54(11)49648250; E-mail: gbuldain@ffyb.uba.ar

Received 22 November 2006; revised 30 April 2007

Abstract: Synthesis of a series of mono-*meso*-arylmesoporphyrins III using a MacDonald-type 2+2 condensation is described. In this method, the substituted 1,9-diformyldipyrromethane is treated with a dipyrromethane-1,9-dicarboxylic acid under acidic conditions. The 5-aryldipyrrolic unit was obtained by condensation of *tert*-butyl, ethyl, or benzyl 4-ethyl-3-methyl-1*H*-pyrrole-2-carboxylate with different aromatic aldehydes in the presence of 4-toluenesulfonic acid. In order to obtain the corresponding mesobiliverdins, chemical oxidation of each mesoporphyrin was carried out. Each *meso*-arylmesoporphyrin rendered two isomeric arylbiliverdins, as the porphyrin *meso*-aryl bridge is not cleaved.

Key words: porphyrin synthesis, mono-*meso*-arylporphyrin, chemical oxidation, biliverdin

Heme oxygenase, the rate-limiting enzyme in the heme degradation pathway, oxidizes heme to biliverdin, carbon monoxide, and free iron[1] (Figure 1). In humans and other mammals, the heme is cleaved exclusively at the α-*meso* position to give biliverdin IXα.

The HO-1-catalyzed oxidation of heme involves sequential α-*meso*-hydroxylation, oxygen-dependent fragmentation of the α-*meso*-hydroxyheme to verdoheme, and oxidative cleavage of verdoheme to biliverdin IXα.[2]

In 1996, Torpey and Ortiz de Montellano[3] attempted the use of α-*meso*-methylmesoheme to block α-*meso*-hydroxylation and thus to inhibit the heme oxygenase reaction. Surprisingly, this compound was itself oxidized to biliverdin IXα, albeit without the formation of carbon monoxide. Equally surprising was the finding that a 15-methyl substituent caused exclusive cleavage at the γ-*meso*-carbon rather than at the normal, unsubstituted α-*meso*-carbon. No carbon monoxide was formed in these reactions, but the fragment cleaved from the porphyrin eluded identification.

Enzymatic oxidation of synthetic 5-phenyl and 15-phenyl-substituted hemes was then assayed.[4] Human heme oxygenase cleaved 5-phenylheme to give biliverdin IXα and oxidized 15-phenylheme at the α-*meso* position to give 10-phenylbiliverdin IXα. The fragment extruded in the oxidation of 5-phenylheme was identified as benzoic acid.[4]

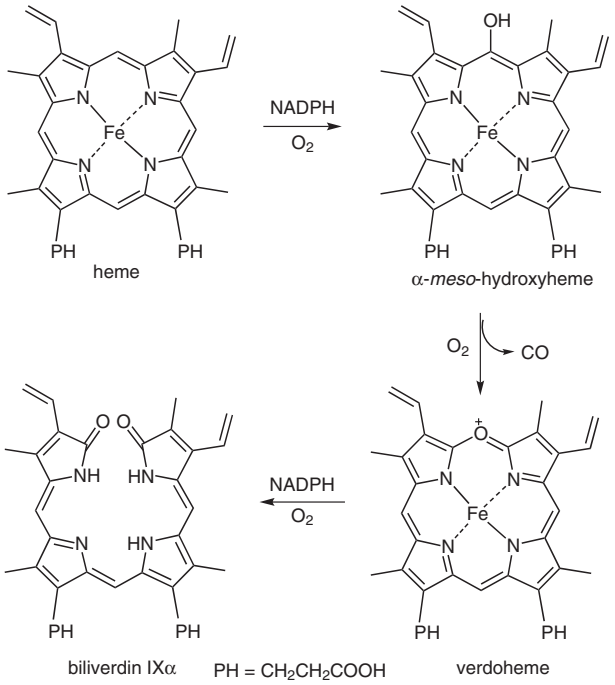


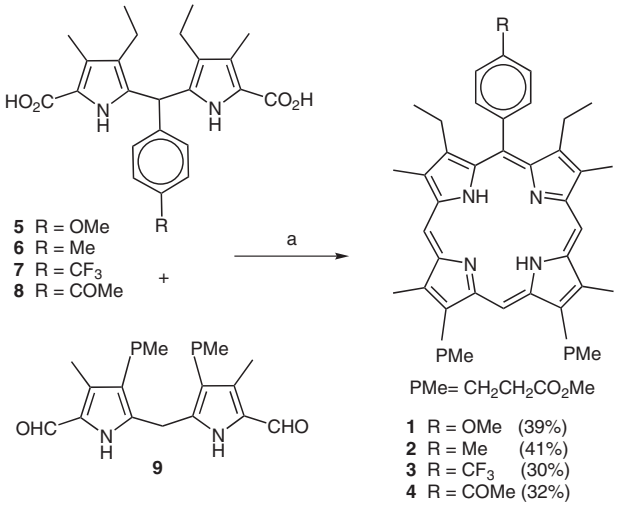
Figure 1 Enzymatic oxidation of iron–protoporphyrin IX to give biliverdin IXα, carbon monoxide, and free iron.

To further characterize the influence of electronic effects of the *meso*-substituted heme group on the regioselectivity of the enzymatic cleavage, we report the synthesis of four other 5-*meso*-arylmesoporphyrins bearing electron-withdrawing or -donating substituents on the aryl moiety. We also describe the chemical oxidation of the corresponding 5-arylmesoporphyrin–iron complexes, to yield all biliverdin derivatives. These compounds would be useful references to be compared with products of enzymatic oxidation, in the same manner as previously described.[4]

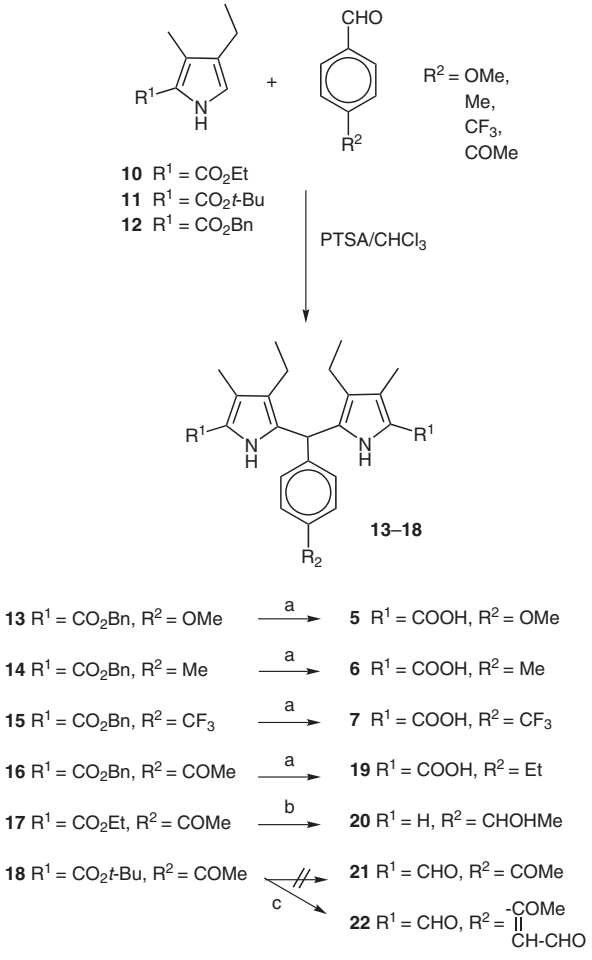
One of the most efficient approaches to obtain a mono-*meso*-substituted porphyrin in a pure form is the use of MacDonald's original method[5] in its simplified form[6–9] consisting of the condensation of a diformyldipyrromethane with a dicarboxydipyrromethane.

Accordingly, synthesis of 5-arylporphyrins **1**–**4** were achieved via condensation of the 1,9-dicarboxydipyrromethanes **5**–**8** with the known diformyldipyrromethane **9**[10] (Scheme 1).

SYNTHESIS 2008, No. 6, pp 0875–0882
Advanced online publication: 28.02.2008
DOI: 10.1055/s-2008-1032203; Art ID: M07106SS



Scheme 1 Synthesis of 5-arylmesoporphyrins III. *Reagents and conditions*: (a) (1) PTSA, CH_2Cl_2, MeOH, (2) $Zn(OAc)_2$, MeOH, (3) 5% H_2SO_4–MeOH.



Scheme 2 Synthesis of dipyrromethanes. *Reagents and conditions*: (a) H_2, Pd/C (3.45 bar), 3 h; (b) ethyleneglycol, NaOH; (c) (1) TFA, (2) $HC(OMe)_3$.

A very convenient method to synthesize the substrate dipyrromethanes **13**–**16** was the treatment of benzyl 4-ethyl-3-methyl-1*H*-pyrrole-2-carboxylate (**12**)[11] with the corresponding aromatic aldehydes [4-methoxybenzaldehyde, 4-acetylbenzaldehyde, 4-methylbenzaldehyde, 4-(trifluoromethyl)benzaldehyde] in the presence of 4-toluenesulfonic acid. Hydrogenolysis of benzyl ester groups in compounds **13**, **14**, and **15** afforded the corresponding dicarboxydipyrromethanes **5**, **6**, and **7** (Scheme 2).

Unfortunately, in the hydrogenolysis reaction of compound **16** (3.45 bar H_2, 3 h), cleavage of benzyl groups was accompanied by reduction of acetyl group to give the ethyl derivative **19**. Other attempts to protect the acetyl group by treatment with ethylene glycol and 4-toluenesulfonic acid,[12] in the presence of Montmorillonite clay[13] failed to afford the desired ketal.

We then synthesized the dipyrromethane 1,9-diethyl ester **17**, which was able to afford the desired 1,9-unsubstituted dipyrromethane by saponification with sodium hydroxide and ethyleneglycol followed by in situ decarboxylation of the resulting 1,9-dicarboxylic acid. Unluckily, in these conditions the acetyl group was converted into a 1-hydroxyethyl group to give compound **20**, a reaction that has been previously reported for benzophenone and other ketones[14] (Scheme 2).

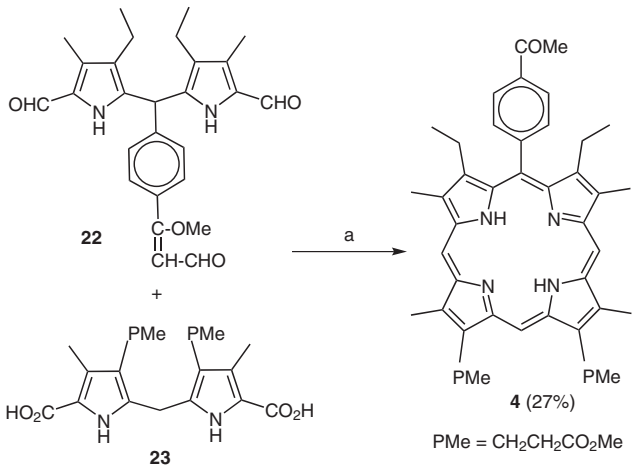
An alternative approach via *tert*-butyl pyrrole **11**, consisting of the treatment of the corresponding dipyrromethane **18** with trifluoroacetic acid, followed with trimethyl orthoformate to obtain directly the diformyldipyrromethane **21** was unsuccessful, because the acetyl group was reactive in these conditions and the β-formyl enol ether **22** was obtained (Scheme 2). Similar results were reported for the reaction of 20-ketosteroids with ortho esters.[15] However, synthesis of 5-(4-acetylphenyl)mesoporphyrin III (**4**) was achieved, though with a lower yield (27%) than the other analogues, by condensation of the diformyldipyrromethane **22** with the dicarboxylic acid **23**[16] (Scheme 3). The β-formyl enol ether group reverted to the desired acetyl derivative under the acidic conditions of the MacDonald's reaction. However, porphyrin **4** was finally obtained with higher yields (32%) through condensation of dipyrromethane **8** with **9**, the former obtained via selective hydrogenolysis of benzyl esters of compound **16**, controlling the reaction conditions to prevent the acetyl group from being reduced (Scheme 1).

All mesoporphyrins III dimethyl esters were converted into the corresponding iron complexes[17] and coupled oxidation (O_2 and ascorbic acid) was carried out, a reaction that afforded all biliverdin derivatives resulted from cleavage of all *meso* bridges. In the case of iron(III)–mesoporphyrin III dimethyl ester (a compound that we here synthesized by means of a procedure similar to the one previously reported),[18] three biliverdins were obtained (**24**α, **24**β, and **24**γ), it is important to observe that β or δ cleavage rendered the same biliverdin isomer (Scheme 4). Their unequivocal assignment was made on the basis of chemical shifts of each of the three methine bridges, and a detailed analysis of the *exo* or *endo* β-substituents, in the same manner as we previously analyzed protobiliverdins IX.[19] It is known that biliverdin β-substituents located at 2 or 8 positions (*exo*) show a lower chemical shift than that of *endo* β-substituents.[20] In this case, the two *exo*-methyl groups of mesobiliverdin **24**β show

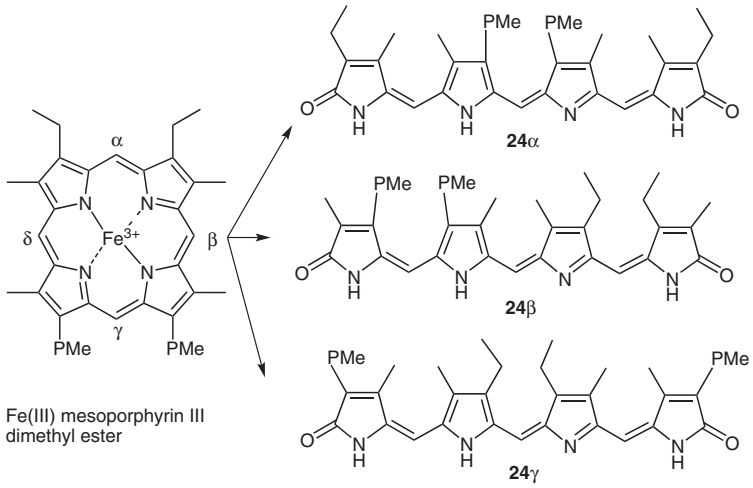
chemical shifts of δ = 1.81 and 1.84 (*endo* methyl groups at δ = 2.17 and 2.19), while in biliverdins **24**α and **24**γ there were no *exo*-methyl groups and the *endo* ones were observed at δ = 2.07, 2.09; and 2.03, 2.11, respectively. To differentiate between biliverdins **24**α and **24**γ, the *exo*- or *endo*-methylenes of the ethyl groups gave us the same information as that mentioned for methyl groups.

Coupled oxidation of each of the four iron(III)–5-arylmesoporphyrin III dimethyl esters afforded two biliverdin isomers, by cleavage at each of the three unsubstituted *meso* bridges (Scheme 5).

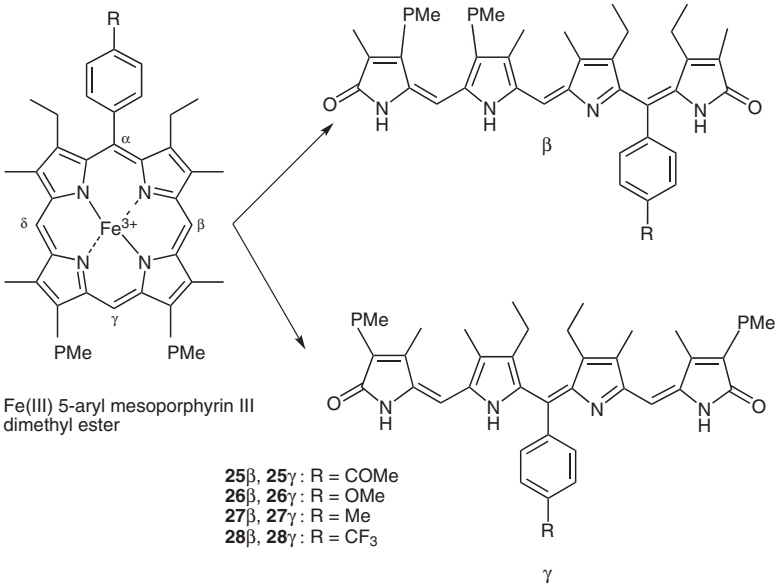
By comparison of chemical shifts observed in mesobiliverdins **24**β and **24**γ with those of arylbiliverdins **25**–**28**β and **25**–**28**γ (Tables 1 and 2), as expected, a diamagnetic shift of the ethyl groups could be observed.



Scheme 3 Synthesis of 5-(4-acetylphenyl)mesoporphyrin III. *Reagents and conditions*: (a) (1) PTSA, CH_2Cl_2, MeOH, (2) $Zn(OAc)_2$, MeOH, (3) 5% H_2SO_4–MeOH.



Scheme 4 Chemical oxidation of iron(III)–mesoporphyrin III dimethyl ester. Note that β or δ cleavage gives the same biliverdin isomer.



Scheme 5 Chemical oxidation of each of the four iron(III)–5-arylmesoporphyrin III dimethyl esters.

Table 1 ^{1}H NMR Data of Mesobiliverdin IIIγ Dimethyl Esters **24**–**28**

	24γ	**25**γ	**26**γ	**27**γ	**28**γ
CH_2CH_3	1.14	0.83	0.68	0.72	0.70
CH_2CH_3	2.50–2.56	2.01–2.20	2.06–2.21	2.07–2.20	2.06–2.20
CH_3 *endo*	2.03 2.11	2.01–2.20	2.06–2.21	2.07–2.20	2.06–2.20
CH 5 and 15	5.85	6.14	6.14	6.14	6.14
CH 10	6.56	–	–	–	–
$CH_2CH_2CO_2Me$	2.50–2.56		2.61–2.65	2.61–2.63	
		2.55–2.70			2.51–2.63
$CH_2CH_2CO_2Me$	2.50–2.56		2.49–2.53	2.51–2.53	
$CH_2CH_2CO_2CH_3$	3.66	3.66	3.66	3.66	3.66
CH (10^2)	–	7.59	7.63	7.37	7.34
CH (10^3)	–	8.08	7.72	6.96	7.23
aryl CH_3	–	2.55–2.70	–	3.90	2.47

Table 2 ^{1}H NMR Data of Mesobiliverdin IIIβ Dimethyl Esters **24**–**28**

	24β	**25**β	**26**β	**27**β	**28**β
CH_3 *exo*	1.81 1.84	1.94–2.00	1.89–2.16	1.88–2.02 2.17–2.30	1.86–2.00
CH_2CH_3	1.12 1.21	0.81 0.92	0.75 0.97	0.75 0.94	0.75 0.94
CH_2CH_3	2.48–2.53	1.94–2.00 2.25–2.37	1.89–2.16 2.28	1.88–2.02 2.17–2.30	1.86–2.00 2.10–2.35
CH_3 *endo*	2.17 2.19	2.25–2.37	1.89–2.16 2.22	2.17–2.30	2.10–2.35
CH 10	6.68	7.09	6.75	6.77	6.76
$CH_2CH_2CO_2Me$	2.79 2.84	2.85 2.90	2.77 2.84	2.75–2.86	2.78 2.85
$CH_2CH_2CO_2Me$	2.48–2.53 2.65	2.50–2.57	2.46 2.58	2.46 2.60	2.46 2.60
CH 5	5.92/ 6.01	6.03	5.93	5.93	5.92
$CH_2CH_2CO_2CH_3$	3.67 3.71	3.65 3.67	3.64 3.69	3.65 3.69	3.64 3.69
CH (15^2)	–	7.64	7.50	7.31	7.30
CH (15^3)	–	8.03	7.55	6.78	7.05
aryl CH_3	–	2.64	–	3.78	2.10–2.35

UV and vis spectra were recorded on Jasco 7850 and Jasco V-570 spectrophotometers. ^{1}H NMR spectra were determined in $CDCl_3$ and recorded using a Bruker MSL-300 spectrometer. MS-EI were obtained with a Shimadzu QP 5000-GC 17 and MS-ES-IT (positive ion mode) in a Finnigan LCQ DUO. HRMS (EI): VG AutoSpec (Micromass Inst.). Melting points were measured on an Electrothermal 9100 and a Ionomex, and are uncorrected. Elemental analysis were determined in a Carlo Erba EA 1108 analyzer.

Dibenzyl 3,7-Diethyl-2,8-dimethyl-5-(4-methoxyphenyl)dipyrromethane-1,9-dicarboxylate (13); Typical Procedure

Pyrrole **12**[11] (290 mg, 1.20 mmol) was refluxed for 2 h with 4-methoxybenzaldehyde (0.15 mL, 167 mg, 1.20 mmol) and PTSA (114 mg, 0.60 mmol) in $CHCl_3$ (35 mL). The mixture was diluted with CH_2Cl_2 (50 mL), washed with 5% $NaHCO_3$ (30 mL), and then with H_2O (30 mL). The soln was dried (anhyd Na_2SO_4), filtered, and the solvent was evaporated at reduced pressure (40 °C). The product

was purified by column chromatography (silica gel, 14 × 2.5 cm, CH_2Cl_2–hexane, 2:1) to give **13** (290 mg, 80%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 [t, *J* = 7.6 Hz, 6 H, CH_3 (3^2, 7^2)], 2.27 [m, 10 H, CH_2 (3^1, 7^1) CH_3 (2^1, 8^1)], 3.79 [s, 3 H, CH_3 (5^6)], 5.26 [s, 4 H, CH_2 (1^3, 9^3)], 5.48 [s, 1 H, CH (5)], 6.84 [d, *J* = 8.6 Hz, 2 H, CH (5^3)], 6.99 [d, *J* = 8.6 Hz, 2 H, CH (5^2)], 7.29–7.38 [m, 10 H, CH (1^5, 1^6, 1^7, 9^5, 9^6, 9^7)], 8.24 [br, 2 H, NH].

MS (EI, 20 eV): *m*/*z* (%) = 604 (5) $[M]^+$, 91 (100).

Dibenzyl 3,7-Diethyl-2,8-dimethyl-5-(4-methylphenyl)dipyrromethane-1,9-dicarboxylate (14)

Following the typical procedure for **13** using **12**[11] (240 mg, 0.99 mmol), 4-methylbenzaldehyde (0.12 mL, 119 mg, 0.99 mmol), and PTSA (95 mg, 0.50 mmol) in $CHCl_3$ (30 mL) at reflux for 1 h. Column chromatography (silica gel, 14 × 2.5 cm, CH_2Cl_2–hexane, 3:1) gave **14** (256 mg, 88%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 [t, *J* = 7.6 Hz, 6 H, CH_3 (3^2, 7^2)], 2.23–2.32 [br, 13 H, CH_2 (3^1, 7^1), CH_3 (2^1, 8^1), CH_3 (5^5)], 5.25 [s, 4 H, CH_2 (1^3, 9^3)], 5.49 [s, 1 H, CH (5)], 6.95 [d, *J* = 7.9 Hz, 2 H, CH (5^3)], 7.10 [d, *J* = 7.9 Hz, 2 H, CH (5^2)], 7.26–7.39 [m, 10 H, CH (1^5, 1^6, 1^7, 9^5, 9^6, 9^7)], 8.26 [br, 2 H, NH].

MS (EI, 20 eV): *m*/*z* (%) = 588 (2) $[M]^+$, 318 (5), 91 (100).

Dibenzyl 3,7-Diethyl-2,8-dimethyl-5-[4-(trifluoromethyl)phenyl]dipyrromethane-1,9-dicarboxylate (15)

Following the typical procedure for **13** using **12**[11] (250 mg, 1.03 mmol), 4-(trifluoromethyl)benzaldehyde (185 mg, 1.04 mmol), and PTSA (100 mg, 0.53 mmol) in $CHCl_3$ (30 mL) at reflux for 30 min. Column chromatography (silica gel, 12 × 2 cm, CH_2Cl_2–hexane, 3:1) gave **15** (284 mg, 85%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 [t, *J* = 7.5 Hz, 6 H, CH_3 (3^2, 7^2)], 2.28 [br, 10 H, CH_2 (3^1, 7^1), CH_3 (2^1, 8^1)], 5.26 [s, 4 H, CH_2 (1^3, 9^3)], 5.60 [s, 1 H, CH (5)], 7.17–7.25 [m, 2 H, CH (5^2)], 7.27–7.55 [m, 10 H, CH (1^5, 1^6, 1^7, 9^5, 9^6, 9^7)], 7.56–7.60 [d, *J* = 8.2 Hz, 2 H, CH (5^3)], 8.27 [br, 2 H, NH].

MS (EI, 20 eV): *m*/*z* (%) = 642 (3) $[M]^+$, 91 (100).

Dibenzyl 5-(4-Acetylphenyl)-3,7-diethyl-2,8-dimethyldipyrromethane-1,9-dicarboxylate (16)

Following the typical procedure for **13** using **12**[11] (250 mg, 1.03 mmol), *p*-acetylbenzaldehyde (157 mg, 1.03 mmol), and PTSA (98 mg, 0.52 mmol) in $CHCl_3$ (30 mL) at reflux for 30 min. Column chromatography (silica gel, 8 × 2 cm) eluting first with CH_2Cl_2 gave the excess aldehyde and then with CH_2Cl_2–MeOH (99:1) gave **16** (260 mg, 82%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 [t, *J* = 7.4 Hz, 6 H, CH_3 (3^2, 7^2)], 2.27–2.31 [m, 10 H, CH_2 (3^1, 7^1) CH_3 (2^1, 8^1)], 2.56 [s, 3 H, CH_3 (5^6)], 5.23 [s, 4 H, CH_2 (1^3, 9^3)], 5.60 [s, 1 H, CH (5)], 7.17 [d, *J* = 8.4 Hz, 2 H, CH (5^2)], 7.31–7.36 [m, 10 H, CH (1^5, 1^6, 1^7, 9^5, 9^6, 9^7)], 7.88 [d, *J* = 8.4 Hz, 2 H, CH (5^3)], 8.46 [br, 2 H, NH].

MS (EI, 20 eV): *m*/*z* (%) = 616 (5) $[M]^+$, 91 (100).

Di-*tert*-butyl 5-(4-Acetylphenyl)-3,7-diethyl-2,8-dimethyldipyrromethane-1,9-dicarboxylate (18)

Pyrrole **11**[11] (280 mg, 1.34 mmol), 4-acetylbenzaldehyde (198 mg, 1.34 mmol), and PTSA (127 mg, 0.67 mmol) in $CHCl_3$ (35 mL) were stirred at r.t. for 3 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with 5% $NaHCO_3$ (30 mL) and H_2O (30 mL). The soln was dried (anhyd Na_2SO_4), filtered, and the solvent evaporated at reduced pressure (40 °C). The crude product was subjected to column chromatography (silica gel, 4 × 4 cm) eluting first with CH_2Cl_2 gave the excess aldehyde and then with CH_2Cl_2–MeOH (99:1) gave **18** as a clear oil, which was crystallized (CH_2Cl_2–hexane) to give a white powder; yield: 275 mg (76%); mp 132–133 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 [t, *J* = 7.5 Hz, 6 H, CH_3 (3^2, 7^2)], 1.52 [s, 18 H, $C[CH_3]_3$], 2.23 [s, 6 H, CH_3 (2^1, 8^1)], 2.28 [q, *J* = 7.5 Hz, 4 H, CH_2 (3^1, 7^1)], 2.58 [s, 3 H, CH_3 (5^6)], 5.58 [s, 1 H, CH (5)], 7.18 [d, *J* = 8.4 Hz, 2 H, CH (5^2)], 7.88 [d, *J* = 8.4 Hz, 2 H, CH (5^3)], 8.28 [br, 2 H, NH].

MS (EI, 20 eV): *m*/*z* (%) = 548 (7) $[M]^+$.

Anal. Calcd for $C_{33}H_{44}N_2O_5$: C, 72.23; H, 8.08; N, 5.11. Found: C, 72.25; H, 8.09; N, 5.08.

3,7-Diethyl-5-[4-(2-formyl-1-methoxyvinyl)phenyl]-2,8-dimethyldipyrromethane-1,9-dicarbaldehyde (22)

Finely, ground dipyrromethane **18** (100 mg, 0.18 mmol) was added to a flask containing TFA (1 mL) at 20 °C, and after 15 min of stirring $HC(OMe)_3$ (0.5 mL) was added. After a further period of 10 min, the mixture was poured into a cold mixture of H_2O–NH_3 (4:1, 25 mL). The resulting mixture was extracted with CH_2Cl_2 (30 mL), the organic phase was washed with H_2O (20 mL), dried (anhyd Na_2SO_4), filtered, and evaporated to dryness at reduced pressure (40 °C). The oil thus obtained was purified by column chromatography (silica gel, 14 × 2.5 cm, CH_2Cl_2–MeOH, 97:3). The product was crystallized (CH_2Cl_2–hexane) to yield **22** (29.5 mg, 37%) as a cream-colored solid; mp 205–206 °C (dec).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 [t, *J* = 7.5 Hz, 6 H, CH_3 (3^2, 7^2)], 2.30 [s, 6 H, CH_3 (2^1, 8^1)], 2.40 [q, *J* = 7.5 Hz, 4 H, CH_2 (3^1, 7^1)], 3.87 [s, 3 H, OCH_3], 5.65 [d, *J* = 7.7 Hz, 1 H, =CHCHO], 5.69 [s, 1 H, CH (5)], 7.14 [d, *J* = 8.3 Hz, 2 H, CH (5^2)], 7.43 [d, *J* = 8.3 Hz, 2 H, CH (5^3)], 9.42 [d, *J* = 7.7 Hz, 1 H, =CHCHO], 9.47 [s, 2 H, CHO (1^1, 9^1)], 9.70 [br, 2 H, NH].

MS (ES): *m*/*z* (%) = 447 (10) $[M + H]^+$, 469 (100) $[M + Na]^+$.

Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.58; H, 6.79; N, 6.25.

Mesoporphyrin III Dimethyl Esters; General Procedure

The corresponding dipyrromethane dibenzyl ester (0.56 mmol) was dissolved in EtOH (50 mL), 10% Pd/C (300 mg) was added and the mixture was hydrogenolyzed for 3 h at 3.45 bar. The mixture was filtered through Celite (which was previously washed with EtOH). The filtrate was evaporated to dryness (40 °C) and the dipyrromethane-1,9-dicarboxylic acid (0.50 mmol, 90%) (as a pale pink oil) was used without further purification. This compound was then dissolved in a mixture of anhyd CH_2Cl_2 (200 mL) and MeOH (30 mL), and the corresponding dipyrromethane-1,9-dicarbaldehyde (0.50 mmol) was added followed by PTSA (380 mg, 2 mmol). The mixture was kept at r.t. for 24 h protected from light and sat. $Zn(OAc)_2 \cdot 2H_2O$ in anhyd MeOH (40 mL) was added. After a period of 72 h under the same conditions, the mixture was concentrated at reduced pressure (40 °C), and a soln of 5% H_2SO_4 in MeOH (100 mL) was then added. After a period of 16 h, the mixture was diluted with CH_2Cl_2 (150 mL) and the organic phase was washed with H_2O (50 mL), 5% $NaHCO_3$ (50 mL), and H_2O (50 mL). The resulting soln was dried (anhyd Na_2SO_4), filtered, and evaporated to dryness at reduce pressure (40 °C). The dark residue was purified by column chromatography (silica gel, 12 × 2 cm, CH_2Cl_2–MeOH, 98:2), eluting the red band. The resulting compound was crystallized (CH_2Cl_2–hexane) to give a purple powder.

Mesoporphyrin III Dimethyl Ester

This porphyrin was synthesized in 1965 by Sklyar, Yu. E. et al.[18] by treatment of dipyrrolic units in AcOH–HCl, followed by oxidation with chloranil. In our case, following the general procedure using 3,7-diethyl-2,8-dimethyldipyrromethane-1,9-dicarboxylic acid[21] (230 mg, 0.72 mmol) and **9**[10] (311 mg, 0.77 mmol), with column chromatography (silica gel, 8 × 2 cm, CH_2Cl_2–MeOH, 98:2) followed by crystallization (CH_2Cl_2–hexane) yielded the porphyrin (67 mg, 16%); mp 289–290 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 [t, *J* = 7.63 Hz, 6 H, CH_3 (3^2, 7^2)], 3.30 [t, *J* = 7.6 Hz, 4 H, CH_2 (13^2, 17^2)], 4.09 [q, *J* = 7.63 Hz, 4 H, CH_2 (3^1, 7^1)], 3.66 [br, 12 H, CH_3 (2^1, 8^1, 12^1, 18^1)], 3.63 [s, 6 H, OCH_3 (13^5, 17^5)], 4.43 [t, *J* = 7.6 Hz, 4 H, CH_2 (13^1, 17^1)], 10.09 and 10.08 [s, s, 1 H, 1 H, CH (5, 15)], 10.10 [s, 2 H, CH (10, 20)].

MS (ES): *m*/*z* (%) = 595 (100) $[M + H]^+$.

MS/MS: *m*/*z* (%) = 521 (27) [595 – $CH_2CO_2CH_3$], 506 (51) [595 – $CH_2CH_2CO_2CH_3$], 420 (36) [595 – 2 $CH_2CO_2CH_3$].

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 398 (5.24), 498 (4.26), 531 (4.13), 567 (4.00), 620 nm (3.89).

Anal. Calcd for $C_{36}H_{42}N_4O_4$: C, 72.70; H, 7.12; N, 9.42. Found: C, 72.51; H, 7.15; N, 9.39.

5-(4-Methoxyphenyl)mesoporphyrin III Dimethyl Ester (1)

Following the general procedure using **5** (194 mg, 0.46 mmol) and **9**[10] (196 mg, 0.49 mmol). Column chromatography (silica gel, 8 × 2 cm, CH_2Cl_2–MeOH, 98:2) followed by crystallization (CH_2Cl_2–hexane) yielded the porphyrin (123 mg, 39%); mp 269–270 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 [t, *J* = 7.4 Hz, 6 H, CH_3 (3^2, 7^2)], 2.80 [q, *J* = 7.4 Hz, 4 H, CH_2 (3^1, 7^1)], 3.29 [t, *J* = 7.8 Hz, 4 H, CH_2 (13^2, 17^2)], 3.55 [s, 6 H, OCH_3 (13^5, 17^5)], 3.66 [br, 12 H, CH_3 (2^1, 8^1, 12^1, 18^1)], 4.12 [s, 3 H, OCH_3 (5^6)], 4.39 [t, *J* = 7.8 Hz, 4 H, CH_2 (13^1, 17^1)], 7.21 [d, *J* = 7.9 Hz, 2 H, CH (5^3)], 8.07 [d, *J* = 7.9 Hz, 2 H, CH (5^2)], 9.91 [s, 1 H, CH (15)], 10.18 [s, 2 H, CH (10, 20)].

MS (ES): *m*/*z* (%) = 701 (100) $[M + H]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 405 (5.37), 504 (4.28), 537 (3.90), 572 (3.90), 625 nm (3.43).

Anal. Calcd for $C_{43}H_{48}N_4O_5$: C, 73.69; H, 6.90; N, 7.99. Found: C, 73.61; H, 7.01; N, 7.93.

5-(4-Methylphenyl)mesoporphyrin III Dimethyl Ester (2)

Following the general procedure using **6** (174 mg, 0.43 mmol) and **9**[10] (184 mg, 0.46 mmol). Column chromatography (silica gel, 8 × 2 cm, CH_2Cl_2–MeOH, 98:2) followed by crystallization (CH_2Cl_2–hexane) gave **2** (119 mg, 41%); mp 264–265 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –3.2 and –3.1 [br s, br s, 1 H, 1 H, NH], 1.13 [t, *J* = 7.4 Hz, 6 H, CH_3 (3^2, 7^2)], 2.73 [s, 3 H, CH_3 (5^5)], 2.76 [q, *J* = 7.4 Hz, 4 H, CH_2 (3^1, 7^1)], 3.29 [t, *J* = 7.8 Hz, 4 H, CH_2 (13^2, 17^2)], 3.55 [s, 6 H, OCH_3 (13^5, 17^5)], 3.66 [br, 12 H, CH_3 (2^1, 8^1, 12^1, 18^1)], 4.39 [t, *J* = 7.8 Hz, 4 H, CH_2 (13^1, 17^1)], 7.46 [d, *J* = 7.9 Hz, 2 H, CH (5^3)], 8.04 [d, *J* = 7.9 Hz, 2 H, CH (5^2)], 9.91 [s, 1 H, CH (15)], 10.18 [s, 2 H, CH (10, 20)].

MS (ES): *m*/*z* (%) = 685 (100) $[M + H]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 405 (5.37), 503 (4.26), 537 (3.90), 572 (3.90), 625 nm (3.41).

Anal. Calcd for $C_{43}H_{48}N_4O_4$: C, 75.41; H, 7.06; N, 8.18. Found: C, 75.35; H, 7.12; N, 8.13.

5-[4-(Trifluoromethyl)phenyl]mesoporphyrin III Dimethyl Ester (3)

Following the general procedure using **7** (195 mg, 0.42 mmol) and **9**[10] (181 mg, 0.45 mmol). Column chromatography (silica gel, 8 × 2 cm, CH_2Cl_2–MeOH, 99:1) followed by crystallization (CH_2Cl_2–hexane) gave **3** (92 mg, 30%); mp 232–233 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –3.2 and –3.1 [br s, br s, 1 H, 1 H, NH], 1.13 [t, *J* = 7.4 Hz, 6 H, CH_3 (3^2, 7^2)], 2.69 [q, *J* = 7.4 Hz, 4 H, CH_2 (3^1, 7^1)], 3.30 [t, *J* = 7.8 Hz, 4 H, CH_2 (13^2, 17^2)], 3.55 [s, 6 H, OCH_3 (13^5, 17^5)], 3.66 [br, 12 H, CH_3 (2^1, 8^1, 12^1, 18^1)], 4.40 [t, *J* = 7.8 Hz, 4 H, CH_2 (13^1, 17^1)], 7.96 [d, *J* = 7.9 Hz, 2 H, CH (5^2)], 8.35 [d, *J* = 7.9 Hz, 2 H, CH (5^3)], 9.96 [s, 1 H, CH (15)], 10.20 [s, 2 H, CH (10, 20)].

MS (ES): *m*/*z* (%) = 739 (100) $[M + H]^+$, 371 (84) $[M + 2 H]^{2+}$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 404 (5.29), 503 (4.25), 537 (3.96), 572 (3.92), 625 nm (3.61).

Anal. Calcd for $C_{43}H_{45}F_3N_4O_4$: C, 69.90; H, 6.14; N, 7.58. Found: C, 69.93; H, 6.19; N, 7.54.

5-(4-Acetylphenyl)mesoporphyrin III Dimethyl Ester (4)

Method A: Following the general procedure using **23**[16] (116 mg, 0.27 mmol) and **22** (112 mg, 0.25 mmol). Column chromatography (silica gel, 8 × 2 cm, CH_2Cl_2–MeOH, 98:2) followed by crystallization (CH_2Cl_2–hexane) gave **4** (45 mg, 27%); mp 255–256 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –3.2 and –3.1 [br s, br s, 1 H, 1 H, NH], 1.12 [t, *J* = 7.4 Hz, 6 H, CH_3 (3^2, 7^2)], 2.70 [q, *J* = 7.4 Hz, 4 H, CH_2 (3^1, 7^1)], 2.90 [s, 3 H, $COCH_3$ (5^6)], 3.30 [t, *J* = 7.7 Hz, 4 H, CH_2 (13^2, 17^2)], 3.58 [s, 6 H, OCH_3 (13^5, 17^5)], 3.66 [br, 12 H, CH_3 (2^1, 8^1, 12^1, 18^1)], 4.40 [t, *J* = 7.7 Hz, 4 H, CH_2 (13^1, 17^1)], 8.28 [d, *J* = 8.5 Hz, 2 H, CH (5^2)], 8.33 [d, *J* = 8.5 Hz, 2 H, CH (5^3)], 9.95 [s, 1 H, CH (15)], 10.20 [s, 2 H, CH (10, 20)].

MS (ES): *m*/*z* (%) = 713 (100) $[M + H]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 406 (5.23), 503 (4.15), 537 (3.78), 572 (3.77), 625 nm (3.34).

Anal. Calcd for $C_{44}H_{48}N_4O_5$: C, 74.13; H, 6.79; N, 7.86. Found: C, 74.08; H, 6.83; N, 7.82.

Method B. Dipyrromethane dibenzyl ester **16** (200 mg, 0.32 mmol) was dissolved in THF (50 mL) with Et_3N (2 drops), 10% Pd/C (40 mg) was added and the mixture was hydrogenolyzed for 3 h at 2.07 bar. The mixture was adjusted to pH 10 with concd NH_3 to increase dicarboxylic acid solubility and the mixture was filtered through Celite. The filtrate was then acidified with 2 M AcOH to pH 5, and the dipyrromethane-1,9-dicarboxylic acid **8** precipitate was filtered at reduced pressure; yield: 121 mg (85%); mp 147–148 °C (with decarboxylation).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.96 [t, *J* = 7.3 Hz, 6 H, CH_3 (3^2, 7^2)], 2.23 [s, 6 H, CH_3 (2^1, 8^1)], 2.46–2.49 [m, 7 H, CH_2 (3^1, 7^1) $COCH_3$ (5^6)], 5.68 [s, 1 H, CH (5)], 7.10 [d, *J* = 7.9 Hz, 2 H, CH (5^2)], 7.86 [d, *J* = 7.9 Hz, 2 H, CH (5^3)], 11.09 [s, 2 H, COOH (1^3, 9^3)].

Following the general procedure **9**[10] (119 mg, 0.28 mmol) was treated with **8** (121 mg, 0.28 mmol) to give **4** (63 mg, 32%).

Iron(III) Complexes of Mesoporphyrin Dimethyl Esters

These were obtained according to the described procedures;[17] all hemins were purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5) followed by crystallization (CH_2Cl_2–hexane).

Iron(III)–Mesoporphyrin III

Yield: 87%; mp >300 °C.

MS (ES-IT): *m*/*z* (%) = 648 (100) $[M]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 381 (4.90), 539 nm (3.89).

Iron(III)–5-(4-Acetylphenyl)mesoporphyrin III Dimethyl Ester

Yield: 70%; mp >300 °C.

MS (ES-IT): *m*/*z* (%) = 766 (100) $[M]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 390 (4.60), 556 (3.54), 641 nm (2.95).

Iron(III)–5-(4-Methylphenyl)mesoporphyrin III Dimethyl Ester

Yield: 94%; mp >300 °C.

MS (ES-IT): *m*/*z* (%) = 738 (100) $[M]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 385 (4.99), 506 (3.95), 538 (3.87), 633 nm (3.61).

Iron(III)-5-[4-(Trifluoromethyl)phenyl]mesoporphyrin III Dimethyl Ester

Yield: 90%; mp >300 °C.

MS (ES-IT): *m/z* (%) = 792 (100) $[M]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 385 (4.99), 508 (4.02), 539 (3.96), 639 nm (3.70).

Iron(III)-5-(4-Methoxyphenyl)mesoporphyrin III Dimethyl Ester

Yield: 84%; mp >300 °C.

MS (ES-IT): *m/z* (%) = 754 (100) $[M]^+$.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 386 (4.99), 504 (3.93), 540 (3.86), 631 nm (3.59).

Chemical Oxidation of Iron(III)–Mesoporphyrin Dimethyl Esters

Biliverdins were obtained by coupled oxidation with O_2 and ascorbic acid according to published procedures.[19]

Mesobiliverdin IIIα Dimethyl Ester (24α)

Yield: 7.4%; mp 247–248 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 [t, *J* = 7.5 Hz, 6 H, CH_3 (2^2, 18^2)], 2.09 and 2.07 [s, s, 6 H, 6 H, CH_3 (3^1, 7^1, 13^1, 17^1)], 2.27 [q, *J* = 7.5 Hz, 4 H, CH_2 (2^1, 18^1)], 2.54 [c, *J* = 7.6 Hz, 4 H, CH_2 (8^2, 12^2)], 2.90 [c, *J* = 7.6 Hz, 4 H, CH_2 (8^1, 12^1)], 3.67 [s, 6 H, OCH_3 (8^5, 12^5)], 5.87 [s, 2 H, CH (5, 15)], 6.71 [s, 1 H, CH (10)].

MS (ES): *m/z* (%) = 615 (64) $[M + H]^+$, 637 (19) $[M + Na]^+$.

MS/MS: *m/z* (%) = 313 (100).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{35}H_{42}N_4O_6$: 614.310435; found: 614.309862.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 366 (4.73), 629 nm (4.12).

Mesobiliverdin IIIβ Dimethyl Ester (24β)

Yield: 9.2%; mp 229–230 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 and 1.21 [t, t, *J* = 7.5 Hz, 3 H, 3 H, CH_3 (13^2, 17^2)], 1.81 and 1.84 [s, s, 3 H, 3 H, CH_3 (2^1, 18^1)], 2.17 and 2.19 [s, s, 3 H, 3 H, CH_3 (8^1, 12^1)], 2.48–2.53 [m, 6 H, CH_2 (13^1, 17^1, 3^2 or 7^2)], 2.65 [t, *J* = 7.6, 2 H, CH_2 (3^2 or 7^2)], 2.79–2.84 [m, 4 H, CH_2 (3^1, 7^1)], 3.67 and 3.71 [s, s, 3 H, 3 H, OCH_3 (3^5, 7^5)], 5.92 and 6.01 [s, s, 1 H, 1 H, CH (5, 15)], 6.68 [s, 1 H, CH (10)].

MS (ES): *m/z* (%) = 615 (100) $[M + H]^+$, 637 (90) $[M + Na]^+$.

MS/MS: *m/z* (%) = 371 (25).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{35}H_{42}N_4O_6$: 614.310435; found: 614.310198.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 367 (4.78), 642 nm (4.22).

Mesobiliverdin IIIγ Dimethyl Ester (24γ)

Yield: 9.0%; mp 234–235 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 [t, *J* = 7.5 Hz, 6 H, CH_3 (8^2, 12^2)], 2.03 and 2.11 [s, s, 6 H, 6 H, CH_3 (3^1, 7^1, 13^1, 17^1)], 2.50–2.56 [m, 12 H, CH_2 (8^1, 12^1, 2^1, 2^2, 18^1, 18^2)], 3.66 [s, 6 H, OCH_3 (2^5, 18^5)], 5.85 [s, 2 H, CH (5, 15)], 6.56 [s, 1 H, CH (10)].

MS (ES): *m/z* (%) = 615 (97) $[M + H]^+$, 637 (100) $[M + Na]^+$.

MS/MS: *m/z* (%) = 313 (100).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{35}H_{42}N_4O_6$: 614.310435; found: 614.310006.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 370 (4.92), 636 nm (4.26).

5-(4-Acetylphenyl)mesobiliverdin IIIβ Dimethyl Ester (25β)

Yield: 3.0%; mp 139–140 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 and 0.92 [t, t, 3 H, 3 H, CH_3 (13^2, 17^2)], 1.94–2.00 [m, 8 H, CH_3 (2^1, 18^1), CH_2 (13^1 ó 17^1)], 2.25–2.37 [m, 8 H, CH_3 (8^1, 12^1), CH_2 (13^1 or 17^1)], 2.50–2.57 [m, 4 H, CH_2 (3^2 or 7^2)], 2.64 [s, 3 H, CH_3 (15^6)], 2.85 and 2.90 [t, t, *J* = 7.2 Hz, *J* = 7.0 Hz, 2 H, 2 H, CH_2 (3^1 or 7^1)], 3.65 and 3.67 [s, s, 3 H, 3 H, OCH_3 (3^5, 7^5)], 6.03 [s, 1 H, CH (5)], 7.09 [s, 1 H, CH (10)], 7.64 [d, *J* = 8.0 Hz, 2 H, CH (15^2)], 8.03 [d, *J* = 8.0 Hz, 2 H, CH (15^3)].

MS (ES): *m/z* (%) = 733 (68) $[M + H]^+$, 755 (100) $[M + Na]^+$.

MS/MS: *m/z* (%) = 373 (100), 371 (52).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{43}H_{48}N_4O_7$: 732.352300; found: 732.346852.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 372 (4.30), 319 (4.43), 586 nm (4.15).

10-(4-Acetylphenyl)mesobiliverdin IIIγ Dimethyl Ester (25γ)

Yield: 2.2%; mp 155–156 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 [t, 6 H, CH_3 (8^2, 12^2)], 2.01–2.20 [m, 16 H, CH_2 (8^1, 12^1), CH_3 (3^1, 7^1, 13^1, 17^1)], 2.55–2.70 [m, 11 H, CH_2 (2^1, 2^2, 18^1, 18^2), CH_3 (15^6)], 3.66 [s, 6 H, OCH_3 (2^5, 18^5)], 6.14 [s, 2 H, CH (5, 15)], 7.59 [d, *J* = 7.9 Hz, 2 H, CH (10^2)], 8.08 [d, *J* = 7.9 Hz, 2 H, CH (10^3)].

MS (ES): *m/z* (%) = 733 (14) $[M + H]^+$, 755 (100) $[M + Na]^+$.

MS/MS: *m/z* (%) = 431 (100).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{43}H_{48}N_4O_7$: 732.352300; found: 732.349853.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 383 (4.31), 307 (3.94), 653 nm (3.57).

5-(4-Methoxyphenyl)mesobiliverdin IIIβ Dimethyl Ester (26β)

Yield: 10.8%; mp 184–185 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 and 0.94 [t, t, *J* = 7.4 Hz, *J* = 7.4 Hz, 3 H, 3 H, CH_3 (13^2, 17^2)], 1.88–2.02 [m, 8 H, CH_3 (2^1, 18^1), CH_2 (13^1 or 17^1)], 2.17–2.30 [m, 8 H, CH_3 (8^1, 12^1), CH_2 (13^1 or 17^1)], 2.46 and 2.60 [t, t, *J* = 7.6 Hz, *J* = 7.6 Hz, 2 H, 2 H, CH_2 (3^2, 7^2)], 2.77 and 2.84 [t, t, *J* = 7.6 Hz, *J* = 7.6 Hz, 2 H, 2 H, CH_2 (3^1, 7^1)], 3.65 and 3.69 [s, s, 3 H, 3 H, OCH_3 (3^5, 7^5)], 3.78 [s, 3 H, OCH_3 (15^5)], 5.93 [s, 1 H, CH (5)], 6.77 [s, 1 H, CH (10)], 6.78 [d, *J* = 8.7 Hz, 2 H, CH (15^3)], 7.31 [d, *J* = 8.7 Hz, 2 H, CH (15^2)].

MS (ES): *m/z* (%) = 721 (94) $[M + H]^+$, 743 (100) $[M + Na]^+$.

MS/MS: *m/z* (%) = 371 (43), 361 (55).

HRMS (ES): *m/z* $[M + H^+]$ calcd for $C_{42}H_{48}N_4O_7$: 720.352300; found: 720.358775.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 377 (4.37), 322 (4.43), 596 nm (4.23).

10-(4-Methoxyphenyl)mesobiliverdin IIIγ Dimethyl Ester (26γ)

Yield: 10.8%; mp 208–209 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 [t, 6 H, CH_3 (8^2, 12^2)], 2.07–2.20 [m, 16 H, CH_2 (8^1, 12^1), CH_3 (3^1, 7^1, 13^1, 17^1)], 2.51–2.53 [m, 4 H, CH_2 (12^2, 18^2)], 2.61–2.63 [m, 4 H, CH_2 (2^1, 18^1)], 3.66 [s, 6 H, OCH_3 (2^5, 18^5)], 3.90 [s, 3 H, OCH_3 (10^5)], 6.14 [s, 2 H, CH (5, 15)], 6.96 [d, *J* = 8.7 Hz, 2 H, CH (10^3)], 7.37 [d, *J* = 8.7 Hz, 2 H, CH (10^2)].

MS (ES): *m/z* (%) = 721 (78) $[M + H]^+$, 743 (100) $[M + Na]^+$.

MS/MS: *m/z* (%) = 419 (100).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{42}H_{48}N_4O_7$: 720.352300; found: 720.357951.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 388 (4.63), 310 (4.30), 651 nm (3.90).

5-(4-Methylphenyl)mesobiliverdin IIIβ Dimethyl Ester (27β)
Yield: 13.1%; mp 215–216 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 and 0.94 [t, t, *J* = 7.4 Hz, *J* = 7.4 Hz, 3 H, 3 H, CH_3 (13^2, 17^2)], 1.86–2.00 [m, 8 H, CH_3 (2^1, 18^1), CH_2 (13^1 or 17^1)], 2.10–2.35 [m, 11 H, CH_3 (8^1, 12^1, 15^4), CH_2 (13^1 or 17^1)], 2.46 and 2.60 [t, t, *J* = 7.6 Hz, *J* = 7.6 Hz, 2 H, 2 H, CH_2 (3^2, 7^2)], 2.78 and 2.85 [t, t, *J* = 7.6 Hz, *J* = 7.6 Hz, 2 H, 2 H, CH_2 (3^1, 7^1)], 3.64 and 3.69 [s, s, 3 H, 3 H, OCH_3 (3^5, 7^5)], 5.92 [s, 1 H, CH (5)], 6.76 [s, 1 H, CH (10)], 7.05 [d, *J* = 7.6, 2 H, CH (15^3)], 7.30 [d, *J* = 7.6 Hz, 2 H, CH (15^2)].

MS (ES): *m/z* (%) = 705 (100) $[M + H]^+$, 727 (56) $[M + Na]^+$.

MS/MS: *m/z* (%) = 371 (6).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{42}H_{48}N_4O_6$: 704.357385; found: 704.356624.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 375 (4.23), 320 (4.44), 611 nm (4.23).

10-(4-Methylphenyl)mesobiliverdin IIIγ Dimethyl Ester (27γ)
Yield: 9.3%; mp 193–194 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 [t, 6 H, CH_3 (8^2, 12^2)], 2.06–2.20 [m, 16 H, CH_2 (8^1, 12^1), CH_3 (3^1, 7^1, 13^1, 17^1)], 2.47 [s, 3 H, CH_3 (10^4)], 2.51–2.63 [m, 8 H, CH_2 (2^1, 18^1, 12^2, 18^2)], 3.66 [s, 6 H, OCH_3 (2^5, 18^5)], 6.14 [s, 2 H, CH (5, 15)], 7.34 [d, *J* = 7.6 Hz, 2 H, CH (10^2)], 7.23 [d, *J* = 7.6 Hz, 2 H, CH (10^3)].

MS (ES): *m/z* (%) = 705 (100) $[M + H]^+$, 727 (96) $[M + Na]^+$.

MS/MS: *m/z* (%) = 403 (87).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{42}H_{48}N_4O_6$: 704.357385; found: 704.352486.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 385 (4.79), 308 (4.41), 655 nm (4.10).

5-[4-(Trifluoromethyl)phenyl]mesobiliverdin IIIβ Dimethyl Ester (28β)
Yield: 14.3%; mp 125–126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 and 0.97 [t, t, *J* = 7.4 Hz, *J* = 7.4 Hz, 3 H, 3 H, CH_3 (13^2, 17^2)], 1.89–2.16 [m, 11 H, CH_3 (2^1, 18^1, 8^1 or 12^1), CH_2 (13^1 or 17^1)], 2.22 [s, 3 H, CH_3 (8^1 or 12^1)], 2.28 [c, *J* = 7.4 Hz, 2 H, CH_2 (13^1 or 17^1)], 2.46 and 2.58 [t, t, *J* = 7.6 Hz, *J* = 7.6 Hz, 2 H, 2 H, CH_2 (3^2, 7^2)], 2.77 and 2.84 [t, t, *J* = 7.6 Hz, *J* = 7.6 Hz, 2 H, 2 H, CH_2 (3^1, 7^1)], 3.64 and 3.69 [s, s, 3 H, 3 H, OCH_3 (3^5, 7^5)], 5.93 [s, 1 H, CH (5)], 6.75 [s, 1 H, CH (10)], 7.50 [d, *J* = 8.5 Hz, 2 H, CH (15^2)], 7.55 [d, *J* = 8.5 Hz, 2 H, CH (15^3)].

MS (ES): *m/z* (%) = 759 (89) $[M + H]^+$, 781 (100) $[M + Na]^+$.

MS/MS: *m/z* (%) = 373 (100).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{42}H_{45}F_3N_4O_6$: 758.329120; found: 758.335458.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 373 (4.28), 320 (4.35), 583 nm (4.13).

10-[4-(Trifluoromethyl)phenyl]mesobiliverdin IIIγ Dimethyl Ester (28γ)
Yield: 8.9%; mp 191–192 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 [t, 6 H, CH_3 (8^2, 12^2)], 2.06–2.21 [m, 16 H, CH_2 (8^1, 12^1), CH_3 (3^1, 7^1, 13^1, 17^1)], 2.49–2.53 [m, 4 H, CH_2 (12^2, 18^2)], 2.61–2.65 [m, 4 H, CH_2 (2^1, 18^1)], 3.66 [s, 6 H, OCH_3 (2^5, 18^5)], 6.14 [s, 2 H, CH (5, 15)], 7.63 [d, *J* = 8.2 Hz, 2 H, CH (10^2)], 7.72 [d, *J* = 8.2 Hz, 2 H, CH (10^3)].

MS (ES): *m/z* (%) = 759 (56) $[M + H]^+$, 781 (100) $[M + Na]^+$.

MS/MS: *m/z* (%) = 457 (100).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{42}H_{45}F_3N_4O_6$: 758.329120; found: 758.328547.

UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 380 (4.64), 304 (4.28), 655 nm (3.91).

Acknowledgment

This work was supported by a grant from Universidad de Buenos Aires, UBACyT B005. We thank Dr. Fernando Lafont Déniz (Universidad de Córdoba, Spain) for performing mass spectra.

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