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# Straightforward Syntheses that Avoid Scrambling of *meso*-Substituted [28]Hexaphyrins

Rémi Plamont,[a] Teodor Silviu Balaban,[a] and Gabriel Canard*[b]

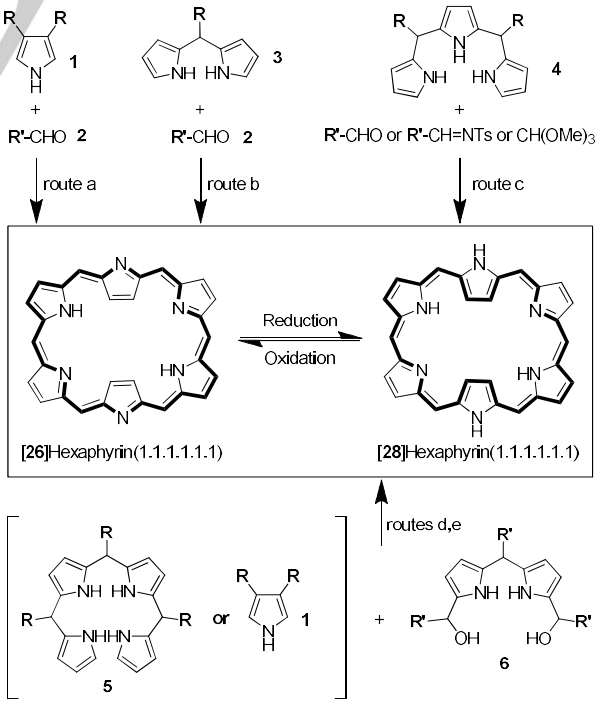
Dedication ((optional))

**Abstract:** A two-step synthesis of *meso*-substituted [28]hexaphyrins using an aqueous medium was developed, optimized and was shown to avoid the scrambling process despite the use of high concentration of acid. The efficiency of this procedure relies on the nature of the starting material and it can be extended to the straightforward preparation of unprecedented $AB_2C_2D$-[28]hexaphyrins bearing up to four different kinds of *meso* appended aryl groups.

## Introduction

Expanded porphyrins and their core-modified analogues have been the subject of a growing interest because of their versatile chemical, optical, electrochemical properties as well as their unique coordination chemistry.[1] Among the numerous described expanded porphyrinoids structures, hexaphyrin(1.1.1.1.1.1) derivatives (Scheme 1) that can be viewed as the first expanded porphyrin homologues (alternating pyrrolic units and bridging carbon atoms) were the subject of a particularly intense research activity because of their fascinating physico-chemical properties. For example, their cavities are suitable for the concomitant coordination of two identical or different metallic centers.[2] Moreover, if most of the [26]hexaphyrins are planar macrocycles exhibiting Hückel aromaticity,[1g, 3] their reduced forms namely [28]hexaphyrins (Scheme 1) and their metal complexes may have twisted Möbius structures in solution.[1g, 4] Consequently, the oxidation form of hexaphyrins has a crucial impact on their light-absorption and emission properties.[5]

The main synthetic procedures giving access to *meso*-substituted hexaphyrins are summarized on Scheme 1. The first stable derivative bearing six *meso* pentafluorophenyl groups was prepared through a simple and straightforward synthesis starting from commercially available pyrrole **1** (**R** = H) and pentafluorobenzaldehyde (route a).[6] This strategy can be used to introduce various kind of *meso* substituents together with various *β* groups when these are born by the starting pyrrolic unit **1** (**R** ≠ H).[7] Nevertheless, this one-pot procedure produces a complex mixture of expanded porphyrins which are difficult to separate and purify. This problem can be overcome through ring size selective syntheses of hexaphyrins using oligopyrranes. For example, the acidic condensation of *meso*-substituted dipyrromethanes **3** with aldehydes **2** can produce, after oxidation $A_3B_3$-hexaphyrin derivatives bearing up to two different kinds of *meso* groups (route b).[8] The first example of a *meso*-substituted hexaphyrin bearing six phenyl groups was prepared starting from the condensation of a tripyrrane **4** with benzaldehyde in acidic media (Scheme 1, route c).[9] This approach was later used to synthesize from simple to very sophisticated hexaphyrin derivatives such as $A_2B_4$ type compounds bearing an internal strap or dyes incorporating Bodipy units.[3a, 10] Less symmetric compounds were prepared using the acidic condensation of tetrapyrranes **5** with dipyrromethane dicarbinols **6** (route d). This elegant strategy, that could allow an access to derivatives bearing up to six different *meso* groups, was used to prepare unsymmetrical compounds bearing a *meso* free position or hexaphyrin dimers.[11] Reactive compounds **6** were also condensend with *β*-substituted pyrrolic units **1** to prepare partially *β*-substituted hexaphyrins (route e).[12]




**Scheme 1.** Synthetic preparations of *meso*-substituted hexaphyrins.

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The use of cyclic or linear oligopyrranes suffers often from a major drawback called “scrambling”. These compounds are usually condensed or prepared using an acidic medium which can also causes their acidolysis into fragments that then recombine into other different oligopyrranes.[13] This scrambling process was for example put into evidence during the condensation of a tripyrrane **4** with an aldehyde or an *N*-sulfonyl aldimine that leads to the formation of unexpected *N*-fused pentaphyrins, heptaphyrins or octaphyrins.[8c, 10f] If the acidolysis of oligopyrranes can be avoided by sterically hindered or strongly electron-withdrawing *meso* aryl substituents,[14] a spectacular breakthrough, reported by Koszarna and Gryko in 2006, showed that it can also be suppressed when the solvent is an alcohol-water mixture despite the use of very high concentrations of aqueous HCl.[15] This efficient preparation of *trans* $A_2B$ corroles was later extended to the synthesis of porphyrins bearing up to three different kinds of *meso* substituents.[16] We report herein how this strategy can be extended to the straightforward preparation of simple to complex *meso*-substituted [28]hexaphyrins bearing up to four different kinds of *meso* groups.

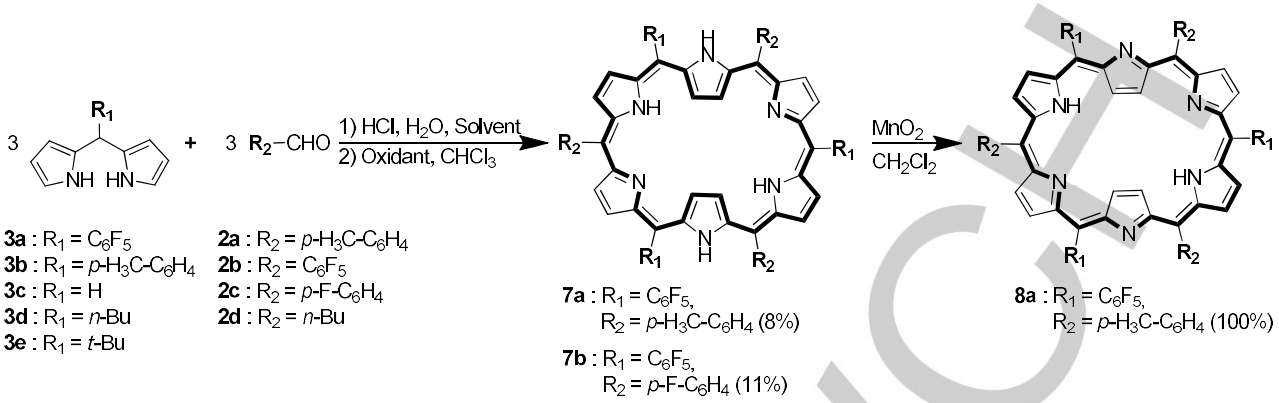
## Results and Discussion

The optimized preparation of a *trans*-$A_2B_2$ porphyrin starting from dipyrromethane **3** (DPM) and an aldehyde **2** in an aqueous medium were chosen as the starting point to develop a new synthetic access to *meso*-substituted expanded porphyrin derivatives (Scheme 2). Equal amounts of DPM and aldehyde were dissolved in 4 mM concentrations in an ethanol/water mixture in a 4 to 1 ratio in the presence of an HCl concentration of 38 mM. The porphyrinogen is then oxidized by *p*-chloranil during one hour in boiling chloroform. Within these conditions and using DPM **3a,** aldehyde **2a** and 2 equivalents of *p*-chloranil (Table 1, entry 1), no expanded porphyrin was observed in the final mixture. The concentration of the starting materials was then raised to 100 mM because this value was optimal to produce $A_4B_4$-octaphyrins starting from DPM (Table 1, entry 2).[8e] The chromatographic purification of the oxidized reaction mixture revealed that only one supplementary colored compound was eluted after the *trans* $A_2B_2$ porphyrin. A combination of $^1$H NMR, UV-vis spectroscopy and mass spectrometry analyses proved that this compound was the [28]hexaphyrin **7a** (Scheme 2) and not the expected $A_4B_4$-octaphyrin. This result was quite surprising since previous syntheses of [26]hexaphyrins starting from DPM **3a** and aldehydes were requiring *ortho* substituted benzaldehyde derivatives.[8b] Moreover, despite the strong acidic conditions, no scrambling occurred as demonstrated by the single isotopic cluster in the corresponding HRMS spectrum (see the Supporting Information). Consequently, we chose to improve the first isolated synthetic yield (2%) of **7a** by varying the different reactions parameters such as the concentration of the reactants or the time of the acidic condensation (Table 1).

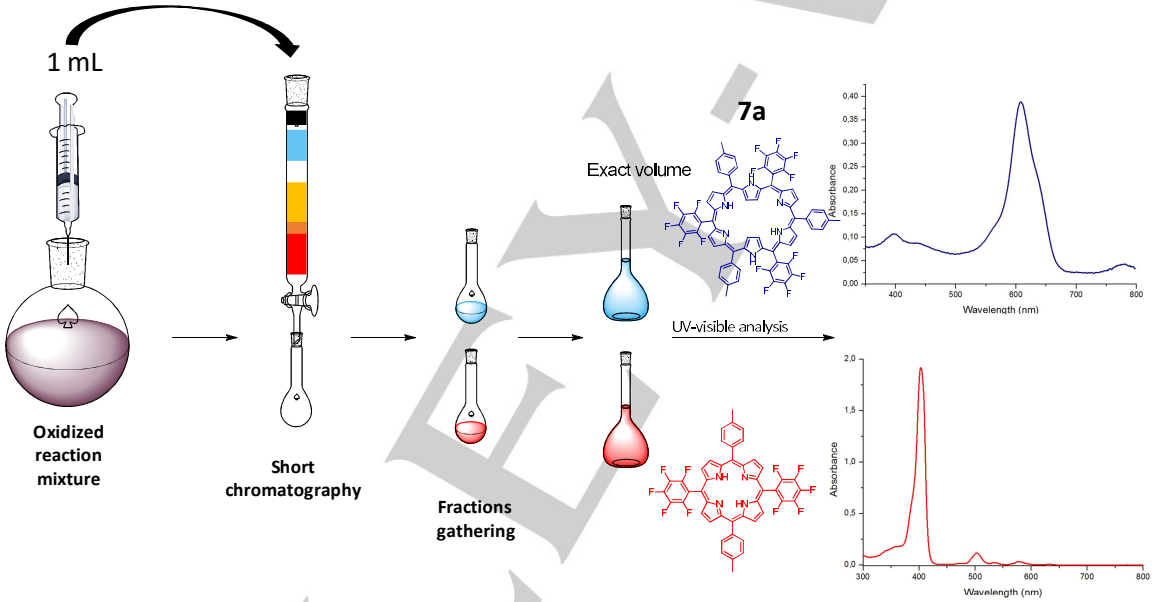
The first short sample of **7a** was used to record its UV-Visible spectrum and to measure the molar absorptivity at the Soret-like band maximum ($\lambda_{max}$= 610 nm). For each subsequent experiment, the solvent volume was kept constant (25 mL) during the acidic condensation and the oxidation steps. On the contrary, variations were applied to the concentrations of the reactants, the nature of the organic solvent, the amount and the nature of the oxidant. After the oxidation step, multiple colored species are present in the reaction mixture and can be detected by TLC or UV-Visible spectroscopy. Consequently, an aliquot of 1 mL was collected from this mixture and was passed over a short chromatography on silica gel and using dichloromethane as solvent (See scheme 3). The first red fractions containing the *trans*-$A_2B_2$ porphyrin and traces of *p*-chloranil were removed before the elution of **7a** (Scheme 3) All the following blue fractions containing **7a** were gathered in a volumetric flask completed with dichloromethane. The UV-Visible spectrum of the resulting solution was then recorded and used to attribute the corresponding UV-yield value. Considering the different prior steps (extraction, washing, purification etc.), a probable overestimation of the UV-yields cannot be excluded and can be partly responsible of the discrepancies between the values of the UV and isolated yields. Since these uncertainties cannot be the principal source of the trends affecting the UV-yields values, we kept this short and quick procedure to optimize the synthetic preparation of **7a**.

The highest UV-yield was reached when a DPM concentration of 33.3 mM was used as observed previously in the synthesis of [26]hexaphyrins (20%, Table 1 entry 4)).[8b] The replacement of ethanol by other organic solvents as well as the modification of the acidic condensation time did not increase the yield of **7a** (Table 1, entries 7-12). Interestingly, no expanded porphyrin was detected when a higher quantity of *p*-chloranil (3 equivalents) was introduced during the oxidation step or when air was the oxidizing agent (Table 1, entries 13-14). Consequently, *meso* substituted [28]hexaphyrins or [26]hexaphyrins are probably unstable within strong oxidative conditions which have to be avoided when considering their interconversion. This transformation was effective when **7a** was dissolved in a suspension of $MnO_2$ in dichloromethane affording quantitatively its oxidized form [26]hexaphyrins **8a** (Scheme 2).

The optimized conditions were used on a preparative scale to produce [28]hexaphyrins **7a** and **7b** with respective yields of 8 and 11%. The nature of the starting compounds is crucial. For example, only 2% of **7a** was formed when DPM **3a** and aldehyde **2a** were replaced by **3b** and **2b** respectively (Scheme 2). Even if the *meso*-pentaflurophenyl group is known to slightly stabilize dipyrromethane **3a** towards acidolysis,[14] no scrambling occurred during the utilization of **3b** as illustrated by the concomitant formation of only the corresponding *trans*-$A_2B_2$ porphyrin. Moreover, a single and pure hexaphyrin (**7a**) was formed as proved by its exact mass spectrum. The difference between the two yields could be due to a different pre-organisation of the intermediate olygopyrranes towards the cylisation. In the same way, we did not succeed to prepare *meso* free or *meso* alkyl derivatives from the condensation of DPMs **3c-e** with aldehyde **2b** or using DPM **3a** with aldehyde **2d** (Scheme 2).




**Scheme 2.** Syntheses of *meso*-substituted [28]Hexaphyrins **7a**, **7b** and [26]Hexaphyrins **8a**.




**Scheme 3.** Schematic presentation of the procedure used to measure the UV yields of **7a**-during the optimization of the synthetic parameters.

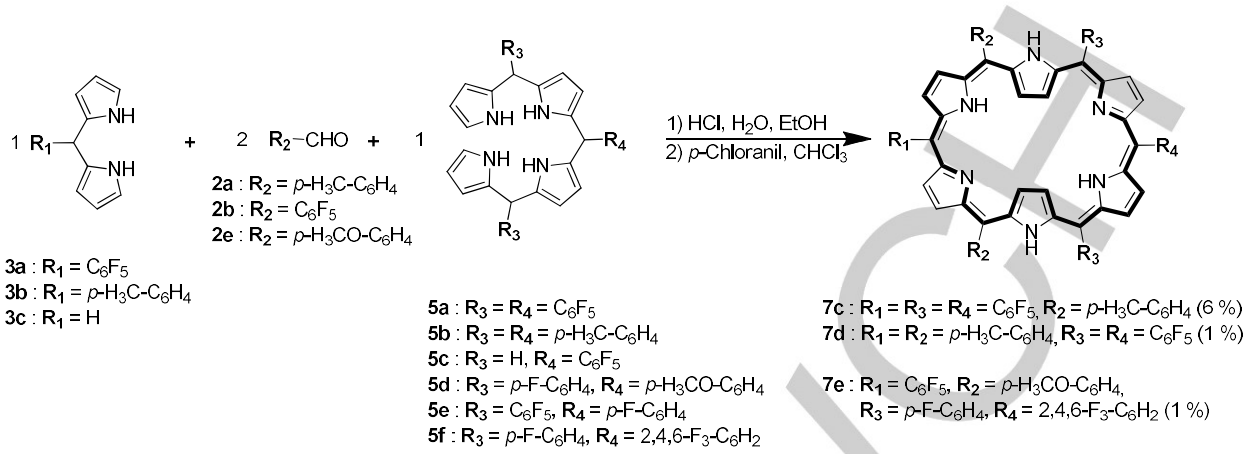
**Table 1.** Optimization of the synthesis of [28]hexaphyrin **7a**.

| Entry | [**3a**] (mmol/L) | Solvent | *t* (h) | Oxidation step[a] | UV yield (%) |
|---|---|---|---|---|---|
| 1 | 4 | EtOH | 16 | a | 0 |
| 2 | 100 | EtOH | 16 | a | 14 (2 %)[b] |
| 3 | 10 | EtOH | 16 | a | 1 |
| **4**[c] | **33.3** | **EtOH** | **16** | **a** | **20 (8 %)**[b] |
| 5 | 50 | EtOH | 16 | a | 17 |
| 6 | 75 | EtOH | 16 | a | 16 |
| 7 | 33 | MeOH | 16 | a | 7 |
| 8 | 33 | iPrOH | 16 | a | 8 |
| 9 | 33 | THF | 16 | a | 0 |
| 10 | 33 | EtOH | 2 | a | 1 |
| 11 | 33 | EtOH | 6 | a | 3 |
| 12 | 33 | EtOH | 48 | a | 12 |
| 13 | 33 | EtOH | 16 | b | 0 |
| 14 | 33 | EtOH | 16 | c | 0 |

[a] Oxidation step: a) *p*-Chloranil (2 equiv.) in $CHCl_3$ at reflux (1 hour). B) *p*-Chloranil (3 equiv.) in $CHCl_3$ at reflux (1 hour). c) Air in $CHCl_3$ at reflux (1 hour). [b] Isolated yield. [c] The optimal conditions of entry 4 highlighted in bold.

The lack of scrambling observed when the optimized conditions are applied, prompted to introduce bilanes **5** in the reaction mixture (Scheme 4). Triaryl bilanes (**5a-f**) were then prepared using the conditions of Gryko's group and purified on silica (see the experimental section).[15] Assuming that during the first step of the [28]hexaphyrins synthesis, bilanes are formed *in situ* by the condensation of two DPM on an aldehyde, we studied the condensation of bilanes with aldehyde and DPM in a 1/2/1 ratio and using a three times lower DPM concentration of 11.1 mM (Scheme 4). **7c** was then produced with a mixture of different porphyrins and was isolated with an encouraging yield of 6% starting from the condensation of **3a**, **2a** and **5a** (Scheme 3). The yield of this synthesis is again depending on the nature of the starting materials and is decreasing with the electron-withdrawing strength of the substituents. Several combinations were tested (**3a**/**2a**/**5b**; **3a**/**2a**/**5d**; **3c**/**2b**/**5c** and **3b**/**2e**/**5e**) and failed to give any expanded porphyrins. However, when the procedure was applied to the two sets **3b**/**2a**/**5a** and **3a**/**2e**/**5f**, the purification of the final reaction mixture afforded the novel compounds **7d** and **7e** with a yield of 1%. **7d** is the *cis* isomer of **7a** where the identical substituents are born by three successive *meso* carbon atoms. Even if the synthetic yield of **7e** is low (1%), it puts into evidence how this simple procedure can conduct to sophisticated compounds bearing up to four different kinds of *meso* aryl groups. However, we have noticed that [28]hexaphyrins display a moderate stability emphasized by electron-donating substituents. After one year, the solid compounds 7a-e were slowly converted into a mixture of colored compounds containing their [26] isomer, albeit being stored at -20 °C under argon.

The complete $^1$H NMR characterization of [28]hexaphyrins is difficult because of the equilibrium existing between the different interconverting twisted Möbius isomers.[4b] The complexity of this task is here increased by the presence of different tautomeric forms resulting from the substitution. Consequently, the complete assignment of the $^1$H NMR signals of **7a-e** and **8a** is far beyond the scope of the present work which focuses on their synthetic preparation. We chose to report in the experimental part their $^1$H NMR spectra recorded in deuterated tetrahydrofuran because this solvent gave the best resolved spectra at room temperature (see the supporting information). On the other hand, the UV-Visible spectra of [28]hexaphyrin **7a-e** give first insights of the relationship between the nature of the *meso* aryl groups and the physico-chemical properties of these derivatives (see the supporting information). The Soret-like band maxima of **7a-e** are reported in Table 2 and are compared with the one of **7f** bearing six *meso* pentaflurophenyl groups.[6a] Peripheral electron-donating groups produce a red-shift of the absorption maxima. For example, when the three 5,15,25 *meso* groups of **7f** are replaced by *p*-fluorophenyl groups in **7b** and by *p*-tolyl ones in **7a**, the Soret like band is red-shifted by 44 nm and 49 nm respectively. A higher red-shift is observed for **7e** bearing several electron-donating groups. Even if the bulkiness of the *meso*-substituents cannot be excluded from the sources of these shifts, the light absorption properties of [28]hexaphyrin are also controlled by their symmetry as illustrated by the different absorption maxima of the two isomeric compounds **7a** and **7d** (610 and 602 nm respectively).




**3a** : $R_1 = C_6F_5$
**3b** : $R_1 = p\text{-}H_3C\text{-}C_6H_4$
**3c** : $R_1 = H$

**2a** : $R_2 = p\text{-}H_3C\text{-}C_6H_4$
**2b** : $R_2 = C_6F_5$
**2e** : $R_2 = p\text{-}H_3CO\text{-}C_6H_4$

**5a** : $R_3 = R_4 = C_6F_5$
**5b** : $R_3 = R_4 = p\text{-}H_3C\text{-}C_6H_4$
**5c** : $R_3 = H$, $R_4 = C_6F_5$
**5d** : $R_3 = p\text{-}F\text{-}C_6H_4$, $R_4 = p\text{-}H_3CO\text{-}C_6H_4$
**5e** : $R_3 = C_6F_5$, $R_4 = p\text{-}F\text{-}C_6H_4$
**5f** : $R_3 = p\text{-}F\text{-}C_6H_4$, $R_4 = 2,4,6\text{-}F_3\text{-}C_6H_2$

**7c** : $R_1 = R_3 = R_4 = C_6F_5$, $R_2 = p\text{-}H_3C\text{-}C_6H_4$ (6 %)
**7d** : $R_1 = R_2 = p\text{-}H_3C\text{-}C_6H_4$, $R_3 = R_4 = C_6F_5$ (1 %)

**7e** : $R_1 = C_6F_5$, $R_2 = p\text{-}H_3CO\text{-}C_6H_4$, $R_3 = p\text{-}F\text{-}C_6H_4$, $R_4 = 2,4,6\text{-}F_3\text{-}C_6H_2$ (1 %)

**Scheme 4.** Synthesis of *meso*-substituted [28]hexaphyrins starting from tetrapyrranes.

**Table 2.** Selected UV-vis maxima of [28]hexaphyrins in dichloromethane (Numbering scheme of Scheme 3) .

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $\lambda_{max}$ (nm) |
|---|---|---|---|---|---|
| **7a** | $C_6F_5$ | $p$MeC$_6$H$_4$ | $C_6F_5$ | $p$MeC$_6$H$_4$ | 610 |
| **7b** | $C_6F_5$ | $p$FC$_6$H$_4$ | $C_6F_5$ | $p$FC$_6$H$_4$ | 605 |
| **7c** | $C_6F_5$ | $p$-MeC$_6$H$_4$ | $C_6F_5$ | $C_6F_5$ | 605 |
| **7d** | $p$MeC$_6$H$_4$ | $p$MeC$_6$H$_4$ | $C_6F_5$ | $C_6F_5$ | 602 |
| **7e** | $C_6F_5$ | $p$MeOC$_6$H$_4$ | $p$FC$_6$H$_4$ | 2,4,6-F$_3$C$_6$H$_2$ | 615 |
| **7f**[a] | $C_6F_5$ | $C_6F_5$ | $C_6F_5$ | $C_6F_5$ | 561 |

[a] From ref [6].

## Conclusions

We have described herein a new strategy to produce *meso*-substituted [28]hexaphyrin using a mixture of ethanol and water as a solvent and high concentrations of HCl. The yields are modest but these syntheses afford a single expanded porphyrin without any scrambling and which is easily separated from the other porphyrin products. Starting from bilanes, this new procedure can afford unprecedented [28]hexaphyrins bearing up to four different kinds of *meso*-substituents thereby extending the variety of these compounds enabling the study of their physico-chemical properties.

## Experimental Section

Pure pyrrole was freshly purified by passing over a short chromatography column filled with neutral alumina. All others reagents were purchased from commercial suppliers and were used without further purifications. Column chromatographies were performed on GEDURAN silica gel 40 – 63 µm from VWR. Reactions were controlled by thin layer chromatography (Merck 60 F254). $^1$H-NMR spectra were recorded either at 500 MHz on a BRUKER Avance DPX-500, at 400 MHz on a BRUKER Avance DPX-400, at 300 MHz on a BRUKER Avance DPX-300 instrument and at 200 MHz on a BRUKER Avance DPX-200 instrument. $^1$H NMR Chemical shifts are given in ppm relative to the residual solvent peaks of $CDCl_3$ ($\delta$ = 7.26) or THF-$d_8$ ($\delta$= 1.72 and 3.58 ppm). UV/Vis spectra were measured with a Shimadzu UV-2401 (PC) instrument or with a Varian Cary 1E spectrophotometer. HRMS-ESI mass spectra were recorded on a QStar Elite (Applied Biosystems SCIEX) spectrometer which is equipped with an ion source at atmospheric pressure (API). Dipyrromethanes **3a-f**[17] and bilanes **5a-b**[16, 18] were prepared according to literature procedures.

**General procedure for the investigation of the reaction conditions forming $A_3B_3$-[28]hexaphyrins.** 5-(Pentafluorophenyl)dipyrromethane **3a** (1 equiv.) and *p*-tolualdehyde **2a** (1 equiv.) were dissolved in an organic solvent (20 mL) before an aqueous solution of HCl (37% 0.1 mL) in water (5 mL) was added. The reaction mixture was stirred during a certain time and then extracted with $CHCl_3$ (150 mL). The organic phase was washed three times with water (100 mL), washed once with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried on $MgSO_4$ and filtered before the oxidation step using *p*-chloranil or air. The resulting mixture was heated to reflux during 1 hour and then cooled to room temperature. A 1 mL aliquot of the resulting mixture was then subjected to a very short chromatography on silica gel using a Pasteur pipette and $CH_2Cl_2$ as solvent. The first eluting fractions containing porphyrin derivatives together with un-reacted oxidant were removed. The second eluting blue fraction was entirely collected in a 25 mL volumetric flask which was completed with $CH_2Cl_2$. The UV-visible spectra of these solutions were recorded and used to determine the corresponding amount of [28]hexaphyrin **7a** in the crude mixture.

**5,15,25-Tris(pentafluorophenyl)-10,20,30-tris(4-methylphenyl)hexaphyrin[28] 7a**: A solution of 5-(pentaflurophenyl)dipyrromethane **3a** (0.26 g, 0.83 mmol, 1 equiv.) and *p*-tolualdehyde **2a** (98 µl, 0.83 mmol, 1 equiv.) in ethanol (20 mL) was

stirred before an aqueous solution of HCl (37% 0.1 mL) in water (5 mL) was added. The reaction mixture was stirred for 16 hours and then extracted with $CHCl_3$ (150 mL). The organic phase was washed three times with water (100 mL), one time with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried on $MgSO_4$ and filtered before *p*-chloranil (410 mg, 1.67 mmol, 2 equiv.) was added. The resulting mixture was heated to reflux during 1 hour, cooled to room temperature and concentrated under reduced pressure. The residue was purified by chromatography on silica gel ($CH_2Cl_2$) to afford pure **7a** a dark blue powder (27 mg, 22 µmol, 8%). $^1$H-NMR (400 MHz, THF-$d_8$, 25 °C): $\delta$= 9.22 (brs, $NH_{outer}$), 8.03 (d, $^3J$(H, H)= 7.8 Hz, 2H, Ar-H), 7.92 (m, 6H, $\beta$-$H_{outer}$), 7.68 (d, $^3J$(H, H)= 7.8 Hz, 2H, $\beta$-$H_{outer}$), 7.54 (d, $^3J$(H, H)= 7.8 Hz, 2H, Ar-H), 7.49 (d, $^3J$(H, H)= 7.7 Hz, 4H, Ar-H), 7.26 (d, $^3J$(H, H)= 7.9 Hz, 4H, Ar-H), 4.72 (s, 2H, $NH_{inner}$), 2.38 (brs, 4H, $\beta$-$H_{inner}$), 2.58 (s, 3H, $CH_3$), 2.38 ppm (s, 6H, $CH_3$); UV-VIS ($CH_2Cl_2$): $\lambda_{max}$ (log $\varepsilon_{max}$)= 397 (4.59), 441 (4.47), 610 (5.19), 640 (4.93), 778 (4.16), 869 (3.99), 925 (3.92), 1051 nm (3.83); HRMS-ESI ($[M+H]^+$): 1235.2919; calcd. for $C_{69}H_{38}N_6F_{15}^+$: 1235.2913.

**5,15,25-Tris(pentafluorophenyl)-10,20,30-tris(4-fluorophenyl)hexaphyrin[28] 7b:** A solution of 5-(pentafluorophenyl)dipyrromethane **3a** (0.26 g, 0.83 mmol, 1 equiv.) and of *p*-fluorobenzaldehyde **2c** (89 µl, 0.83 mmol, 1 equiv.) in ethanol (20 mL) was stirred before a solution of HCl (37% 0.1 mL) in water (5 mL) was added. The reaction mixture was stirred for 16 hours and then extracted with $CHCl_3$ (150 mL). The organic phase was washed three times with water (100 mL), one time with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried on $MgSO_4$ and filtered before *p*-chloranil (410 mg, 1.67 mmol, 2 equiv.) was added. The resulting mixture was heated to reflux during 1 hour, cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel ($CH_2Cl_2$) to afford pure **7b** a dark blue powder (38 mg, 30 µmol, 11%). $^1$H-NMR (400 MHz, THF-$d_8$, 25 °C): $\delta$= 8.16 (m, 2H, Ar-H), 7.97 (m, 2H, $\beta$-$H_{outer}$), 7.92 (m, 4H, $\beta$-$H_{outer}$), 7.74 (m, 2H, $\beta$-$H_{outer}$), 7.64 (m, 4H, Ar-H), 7.49 (m, 2H, Ar-H), 7.22 (m, 4H, Ar-H), 4.75 (brs, 1H, $NH_{inner}$), 4.10 (brs, 1H, $NH_{inner}$), 2.18 (s, 2H, $\beta$-$H_{inner}$), 1.93 ppm (s, 2H, $\beta$-$H_{inner}$); UV-VIS ($CH_2Cl_2$), $\lambda_{max}$ (log $\varepsilon_{max}$)= 398 (4.69), 605 (5.17), 776 (4.16), 864 (4.03), 918 (3.97), 1041 nm (3.81); HRMS-ESI ($[M+H]^+$): 1247.2161; calcd. for $C_{66}H_{29}N_6F_{18}^+$: 1247.2161.

**5,10,15-Tris(pentafluorophenyl)tetrapyrrane 5a**: Pentafluorobenzalldehyde (0.62 mL, 5 mmol) and pyrrole (694 µL, 10 mmol) were dissolved in a mixture of MeOH (200 mL) and water (200 mL). Subsequently, HCl (36%, 4.25 mL) was added and the reaction mixture was stirred at room temperature for 3 hours. The resulting precipitate was filtered, washed with a mixture of MeOH/water (1:1, 100 mL) and with water (100 mL). The resulting paste was purified by chromatography on silica gel (*n*-hexane/ethyl acetate/$CH_2Cl_2$, 7:1:2) to yield the pure bilane **5a** as a mixture of stereoisomers (0.46 g, 0.57 mmol, 34%). $^1$H-NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$= 8.10 (s, 2H, NH), 7.99 (s, 2H, NH), 6.73 (m, 2H, H-α), 6.15 (m, 2H, $\beta$-H), 5.99 (m, 2H, H-β), 5.73-7.99 ppm (m, 7H, H-β/ $H_{meso}$); HRMS-ESI ($[M+H]^+$): 803.1285; calcd. for $C_{37}H_{18}F_{15}N_4^+$: 803.1286. These analytical data are in accordance with literature values.[16, 18]

**5,10,15-Tris(*p*-methylphenyl)tetrapyrrane 5b**: *p*-Tolualdehyde (0.59 mL, 5 mmol) and pyrrole (694 µL, 10 mmol) were dissolved in a mixture of MeOH (200 mL) and water (200 mL). Subsequently, HCl (36%, 4.25 mL) was added and the reaction mixture was stirred at room temperature for 3 hours. The resulting precipitate was filtered, washed with a mixture of MeOH/water (1:1, 100 mL) and with water (100 mL). The resulting paste was purified by chromatography on silica gel (*n*-hexane/ethyl acetate/$CH_2Cl_2$, 7:1:2) to yield the pure bilane **5b** as a mixture of stereoisomers (0.55 g, 0.96 mmol, 57%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$= 7.86 (s, 2H, NH), 7.66 (s, 2H, NH), 7.00-7.1 (m, 12H, Ar-H), 6.66 (m, 2H, H-α), 6.12 (m, 2H, $\beta$-H), 5.86 (m, 2H, $\beta$-H), 5.65-5.76 (m, 4H, $\beta$-H), 5.32 (m, 2H, $H_{meso}$), 5.21 (m, 1H, $H_{meso}$), 2.33 ppm (s, 9H, $CH_3$); HRMS-ESI ($[M+H]^+$): 575.3168; calcd. for $C_{40}H_{40}N_4^+$: 575.3169.

**10-(pentafluorophenyl)tetrapyrrane 5c**: Dipyrromethane **3c** (585 mg, 4 mmol) and pentafluorobenzaldehyde **2b** (247 µL, 2 mmol) were dissolved in MeOH (200 mL). Subsequently, a solution of HCl (36%, 10 mL) in water (200 mL) was added, and the reaction was stirred at room temperature for 2 hours. The resulting precipitate was filtered, washed with a mixture of MeOH/water (1:1, 200 mL) and then with water (100 mL). The subsequent chromatography on silica gel (*n*-hexane/ethyl acetate/$CH_2Cl_2$, 7:1:2) afforded the pure bilane **5c** as a mixture of stereoisomers (380 mg, 0,81 mmol, 40%). $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$= 7.80-7.88 (m, 4H, NH), 6.66 (m, 2Hi, H-α), 6.14 (m, 2H, H-β), 5.96 (m, 2H, H-β), 5.91 (m, 2H, H-β), 5.86 (m, 4H, H-β), 5.73 (s, 1H, $H_{meso}$), 3.91 ppm (s, 4H, $H_{meso}$); HRMS-ESI ($[M+H]^+$): 471.1603; calcd. for $C_{25}H_{20}F_5N_4^+$: 471.1603.

**10-(4-Methoxyphenyl)-5,15-bis(4-fluorophenyl)tetrapyrrane 5d**: 5-(4-Fluorophenyl)dipyrromethane **3f** (480 mg, 2 mmol) and 4-methoxybenzaldehyde **2e** (121 µL, 1 mmol) were dissolved in MeOH (100 mL). Subsequently, a solution of HCl (36%, 5 mL) in water (100 mL) was added, and the reaction was stirred at room temperature for 2 hours. The resulting precipitate was filtered, washed with a mixture of MeOH/water (1:1, 100 mL) and then with water (100 mL). The subsequent chromatography on silica gel (*n*-hexane/ethyl acetate/$CH_2Cl_2$, 7:1:2) afforded the pure bilane **5d** as a mixture of stereoisomers (205 mg, 0.34 mmol, 34%). $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$= 7.91 (s, 2H, NH), 7.69 (s, 2H, NH), 7.12-7.05 (m, 6H, Ar-H), 6.97 (m, 4H, Ar-H), 6.82 (d, $^3J$(H,H) = 8.64 Hz, 2H, Ar-H), ), 6.69 (m, 2H, H-α), 6.12 (m 2H, H-β), 5.82 (m, 2H, H-β), 5.69 (m, 4H, H-β), 5.34 (m, 2H, $H_{meso}$), 5.24 (s, 1H, $H_{meso}$), 3.79 ppm (s, 3H, O-$CH_3$); HRMS-ESI ($[M+H]^+$): 599.2618; calcd. for $C_{38}H_{33}N_4OF_2^+$: 599.2617.

**10-(4-Fluorophenyl)-5,15-bis(pentafluorophenyl)tetrapyrrane 5e**: 5-(Pentafluorophenyl)dipyrromethane **3a** (624 mg, 2 mmol) and 4-fluorobenzaldehyde **2c** (107 µL, 1 mmol) were dissolved in MeOH (100 mL). Subsequently, a solution of HCl (36%, 5 mL) in water (100 mL) was added, and the reaction was stirred at room temperature for 2 hours. The resulting precipitate was filtered, washed with a mixture of MeOH/water (1:1, 100 mL) and then with water (100 mL). The subsequent chromatography on silica gel (*n*-hexane/ethyl acetate/$CH_2Cl_2$, 7:1:2) afforded the pure bilane **5e** as a mixture of stereoisomers (400 mg, 0.55 mmol, 55%). $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$= 8.13 (s, 2H, NH), 7.85 (s, 2H NH), 7.10 (m, 2H, Ar-H), 6.98 (m, 2H, Ar-H), 6.72 (m, 2H, H-α), 6.14 (m, 2H, H-β), 5.96 (m, 2H, H-β), 5.88 (m, 2H, H-β), 5.81 (m, 2H, H-β), 5.70 (m, 2H, $H_{meso}$), 5.30 ppm (s, 1H, $H_{meso}$); HRMS-ESI ($[M+H]^+$): 731.1662; calcd. for $C_{37}H_{22}F_{11}N_4^+$: 731.1663.

**10-(2,4,6-Trifluorophenyl)-5,15-bis(4-fluorophenyl)tetrapyrrane 5f**: 5-(4-Fluorophenyl)dipyrromethane **3f** (480 mg, 2 mmol) and 2,4,6-trifluorobenzaldehyde (160 mg, 1 mmol) were dissolved in MeOH (100 mL). Subsequently, a solution of HCl (36%, 5 mL) in water (100 mL) was added, and the reaction was stirred at room temperature for 2 hours. The resulting precipitate was filtered, washed with a mixture of MeOH/water (1:1, 100 mL) and then with water (100 mL). The subsequent chromatography on silica gel (*n*-hexane/ethyl acetate/$CH_2Cl_2$, 7:1:2) afforded the pure bilane **5f** as a mixture of stereoisomers (306 mg, 49%). $^1$H-NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$= 7.88 (s, 2H, NH), 7.69 (s, 2H, NH), 7.12 (m, 4H, Ar-H), 6.97 (m, 4H, Ar-H), 6.70 (m, 2H, H-α), 6.65 (m, 2H, Ar-H), 6.14 (m, 2H, $\beta$-H), 5.80 (m, 4H, $\beta$-H), 5.68 (m, 3H, $\beta$-H + $H_{meso}$), 5.34 ppm (s, 2H, $H_{meso}$); HRMS-ESI ($[M+H]^+$): 623.2231; calcd. for $C_{37}H_{28}F_5N_4O^+$: 623.2229.

**5,10,15,25-Tetrakis(pentafluorophenyl)-20,30-bis(4-methylphenyl)hexaphyrin[28] 7c**: To a solution of 5-(pentafluorophenyl)dipyrromethane **3a** (87 mg, 0.28 mmol, 1 equiv.), bilane **5a** (225 mg, 0.28 mmol, 1 equiv.) and *p*-tolualdehyde **2a** (66 µl, 0.56 mmol, 2 equiv.) in EtOH (20 mL) was added a solution of HCl (36% 0.1 mL) in water (5 mL). This mixture was stirred at room temperature during 16 hours before it was extracted with $CHCl_3$ (150 mL). The organic phase was washed three times with water (100 mL) and one time with a

saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was dried on $MgSO_4$ before *p*-chloranil (410 mg, 1.67 mmol, 2 equiv.) was added. The resulting mixture was heated to reflux during 1 hour, cooled to room temperature and concentrated under reduced pressure. The reaction mixture was purified by chromatography on silica gel ($CH_2Cl_2$) to afford **7c** as a dark blue powder (22 mg, 17 µmol, 6%). $^1$H-NMR (300 MHz, THF-$d_8$, 25 °C): $\delta$= 9.41 (brs, 2H, $NH_{outer}$), 7.82 (d, $^3J$(H,H)= 4.7 Hz, 1H, $\beta$-$H_{outer}$), 7.78 (d, $^3J$(H,H)= 4.7 Hz, 2H, $\beta$-$H_{outer}$), 7.70 (m, 4H, $\beta$-$H_{outer}$), 7.61 (d, $^3J$(H,H)= 4.6 Hz, 2H, $\beta$-$H_{outer}$), 7.43 (d, $^3J$(H,H)= 7.8 Hz, 4H, Ar-H), 7.24 (d, $^3J$(H,H)= 7.8 Hz, 4H, Ar-H), 5.02 (s, 1H, $NH_{inner}$), 4.74 (s, 1H, $NH_{inner}$), 2.37 (s, 4H, $\beta$-$H_{inner}$), 1.28 ppm (s, 6H, $CH_3$); UV-VIS ($CH_2Cl_2$), $\lambda_{max}$ (log $\varepsilon_{max}$)= 398 (4.78), 421 (4.81), 605 (5.01), 776 (4.18), 882 (4.14), 1082 nm (3.60); HRMS-ESI ([M+H]$^+$): 1311.2277; calcd. for $C_{68}H_{31}N_6F_{20}^+$: 1311.2285.

**5,10,15-Tris(pentafluorophenyl)-20,25,30-tris(4-methylphenyl)hexaphyrin[28] 7d**: To a solution of 5-(4-methylphenyl)dipyrromethane **3b** (66 mg, 0.28 mmol, 1 equiv.), bilane **5a** (225 mg, 0.28 mmol, 1 equiv.) and *p*-tolualdehyde **2a** (66 µL, 0.56 mmol, 2 equiv.) in EtOH (20 mL) was added a solution of HCl (36% 0.1 mL) in water (5 mL). This mixture was stirred at room temperature during 16 hours before it was extracted with $CHCl_3$ (150 mL). The organic phase was washed three times with water (100 mL) and one time with a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was dried on $MgSO_4$ before *p*-chloranil (410 mg, 1.67 mmol, 2 equiv.) was added. The resulting mixture was heated to reflux during 1 hour, cooled to room temperature and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel ($CH_2Cl_2$) to afford **7d** as a dark blue powder (3.5 mg, 2.8 µmol, 1%). $^1$H-NMR (500 MHz, THF-$d_8$): $\delta$= 7.76 (d, $^3J$(H, H)= 4.9 Hz, 2H, $\beta$-$H_{outer}$), 7.68 (m, 4H, $\beta$-$H_{outer}$), 7.59 (d, $^3J$(H, H)= 4.2 Hz, 2H, $\beta$-$H_{outer}$), 7.46 (d, $^3J$(H, H)= 7.1 Hz, 2H, Ar-H), 7.43 (d, $^3J$(H ,H)= 7.9 Hz, 4H, Ar-H), 7.32 (d, $^3J$(H, H)= 7.2 Hz, 2H, Ar-H), 7.24 (d, $^3J$(H, H)= 7.1 Hz, 4H, Ar-H), 4.67 (s, 2H, $NH_{inner}$), 4.08 (s, 1H, $NH_{inner}$), 3.10 (s, 2H, $\beta$-$H_{inner}$), 2.90 (s, 2H, $\beta$-$H_{inner}$), 1.28 ppm (s, 9H, $CH_3$); UV-VIS ($CH_2Cl_2$), $\lambda_{max}$ (rel. intensity)= 392 (0.30), 437 (0.26), 602 (1.00), 772 nm (0.12); HRMS-ESI ([M+H]$^+$): 1235.2913; calcd. For $C_{69}H_{38}N_6F_{15}^+$: 1235.2913.

**5-(Pentafluorophenyl)-10,30-bis(4-methoxyphenyl)-15,25-bis(4-fluorophenyl)-30-(2,4,6-trifluorophenyl)hexaphyrin[28] 7e:** To a solution of 5-(pentafluorophenyl)dipyrromethane **3a** (87 mg, 0.28 mmol, 1 equiv.), bilane **5f** (174 mg, 0.28 mmol, 1 equiv.) and *p*-methoxybenzaldehyde **2e** (68 µL, 0.56 mmol, 2 equiv.) in EtOH (20 mL) was added a solution of HCl (36% 0.1 mL) in water (5 mL). This mixture was stirred at room temperature during 16 hours before it was extracted with $CHCl_3$ (150 mL). The organic phase was washed three times with water (100 mL) and one time with a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was dried on $MgSO_4$ before *p*-chloranil (410 mg, 1.67 mmol, 2 equiv.) was added. The resulting mixture was heated to reflux during 1 hour, cooled to room temperature and concentrated under reduced pressure. The reaction mixture was purified by chromatography on silica gel ($CH_2Cl_2$) to afford **7e** as a dark blue powder (3.2 mg, 2.8 µmol, 1%). $^1$H-NMR (400 MHz, THF-$d_8$): $\delta$= 7.69 (m, 2H, Ar-H), 7.61 (m, 4H, 2H, $\beta$-H, Ar-H), 7.47 (m, 4H, $\beta$-H), 7.36 (d, $^3J$(H, H)= 8.3 Hz, 4H, Ar-H), 7.22 (m, 2H, Ar-H), 7.12 (m, 4H, Ar-H), 6.92 (d, $^3J$(H, H)= 8.4 Hz, 4H, Ar-H), 5.10 (brs, 1H, $NH_{inner}$), 4.80 (brs, 1H, $NH_{inner}$), 3.77 (s, 6 H, $OCH_3$), 2.90 (s, 2H, $\beta$-$H_{inner}$), 2.86 ppm (s, 2H, $\beta$-$H_{inner}$); UV-VIS ($CH_2Cl_2$), $\lambda_{max}$ (rel. intensity)= 402 (0.587), 428 (0.55), 615 (1.00), 778 nm (0.18); HRMS-ESI ([M+H]$^+$): 1163.3123; calcd. for $C_{68}H_{41}N_6F_{10}O_2^+$: 1163.3126.

**5,15,25-Tris(pentafluorophenyl)-10,20,30-tris(4-methylphenyl)hexaphyrin[26] 8a :** $MnO_2$ (1 mg, 12 µmol, 1 equiv.) was added to a solution of hexaphyrin[28] **7a** (15 mg, 12 µmol, 1 equiv.) in $CH_2Cl_2$ (20 mL). The progress of the reaction was monitored using UV-VIS absorption spectroscopy. After 90 minutes, the reaction mixture was purified by chromatography on silica gel ($CH_2Cl_2$) to afford the pure [26]hexaphyrin **8a** (15 mg, 12 µmol, 100%). $^1$H-NMR (400 MHz, THF-$d_8$, 25 °C): $\delta$= 9.43 (d, $^3J$(H, H)= 4.7 Hz, 2H, $\beta$-$H_{outer}$), 9.21 (d, $^3J$(H, H)= 4.8 Hz, 2H, $\beta$-$H_{outer}$), 9.07 (d, $^3J$(H, H)= 4.7 Hz, 2H, $\beta$-$H_{outer}$), 9.05 (d, $^3J$(H, H)= 4.7 Hz, 2H, $\beta$-$H_{outer}$), 8.52 (d, $^3J$(H, H)= 7.6 Hz, 4H, Ar-H), 8.27 (d, $^3J$(H, H)= 7.7 Hz, 2H, Ar-H), 7.73 (d, $^3J$(H, H)= 7.7 Hz, 2H, Ar-H), 7.69 (d, $^3J$(H, H)= 7.7 Hz, 4H, Ar-H), 2.74 (s, 3H, $CH_3$), 2.70 (s, 6H, $CH_3$), -1.53 (s, 2H, β-$H_{inner}$), -1.60 ppm (s, 2H, $\beta$-$H_{inner}$); UV-VIS ($CH_2Cl_2$), $\lambda_{max}$ (log $\varepsilon_{max}$)= 434 (4.47), 577 (4.94), 734 (3.98), 804 (3.95), 912 (3.70), 1049 nm (3.82). HRMS-ESI ([M+H]$^+$): 1233.2764; calcd. For $C_{69}H_{36}N_6F_{15}^+$: 1233.2756.

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**Keywords:** Hexaphyrins • Porphyrinoids • Scrambling

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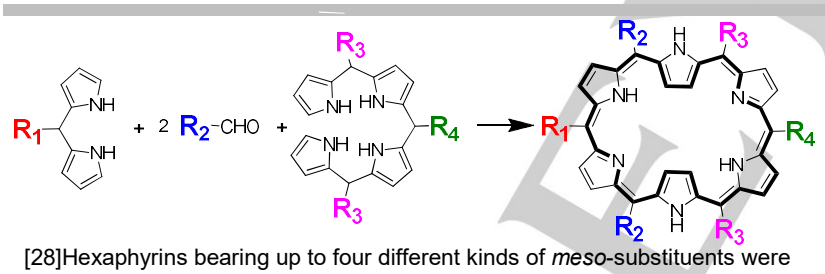


[28]Hexaphyrins bearing up to four different kinds of *meso*-substituents were prepared using a synthesis in a water-ethanol mixture that avoids scrambling.

**Expanded Porphyrinoids**

*Rémi Plamont, Teodor Silviu Balaban, Gabriel Canard**

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**Straightforward Syntheses that Avoid Scrambling of *meso*-Substituted [28]Hexaphyrins**

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