3,4-Dialkoxypyrroles and 2,3,7,8,12,13,17,18-Octaalkoxyporphyrins

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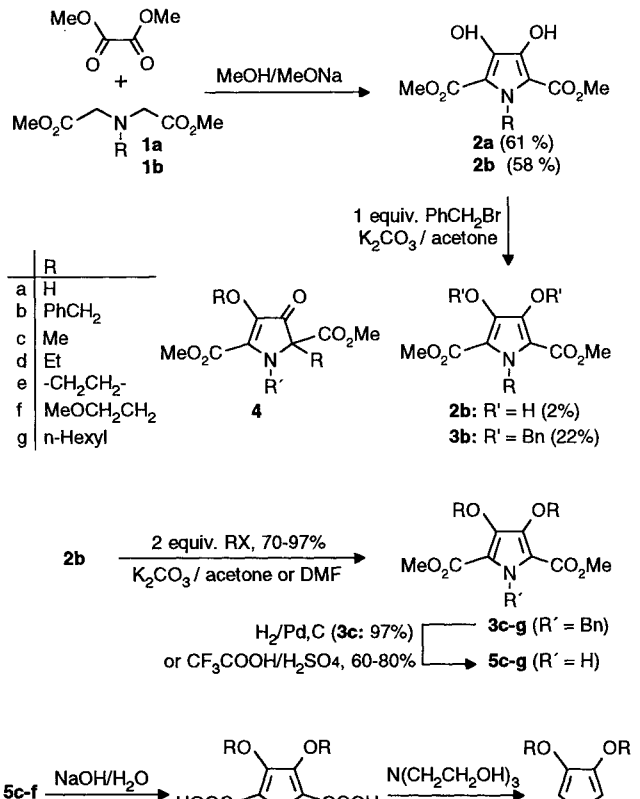
A five-step general synthesis of 3,4-dialkoxypyrroles **7c–f** is described starting with the condensation of dimethyl *N*-benzyliminodiacetate (**1b**) and diethyl oxalate to give dimethyl 1-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate (**2b**), which is bis-*O*-alkylated to the corresponding 3,4-diethers **3c–g**. Pyrrole *N*-benzyl cleavage followed by ester hydrolysis and decarboxylation leads to **7c–f** in 10–50% overall yield. Pyrroles **7c–f** react with formaldehyde or benzaldehydes to give *meso*-H- (**8a–d**) or *meso*-tetraaryloctaalkoxyporphyrins **9a–g** in moderate yields.

Recently, we reported on the synthesis of 3,4-dimethoxypyrrole (**7c**) the first member of the 1,2,5-unsubstituted 3,4-dialkoxypyrroles, and its conversion into octamethoxyporphyrin **8a**.[1] The chemical or electrochemical oxidation of **7c** affords powders or films of poly(dimethoxypyrrole) which show a surprisingly high electrical conductivity.[2,3] In this work we describe a geneneral synthesis of dialkoxypyrroles and their further conversion into a representative series of new octaalkoxyporphyrins **8b–d** with free *meso*-positions and **9a–g** with aromatic substitutents in the *meso*-positions.

In the course of our work, we found that the attempted direct bis-*O*-alkylation of the readily accessible methyl ester of 3,4-dihydroxypyrrole-2,5-dicarboxylic acid (**2a**)[4] is inevitably accompanied or dominated by alkylation at the pyrrole nitrogen. For instance we have found that in the benzylation of **2a** with benzyl bromide/K_2CO_3/acetone, the only detected monobenzylation product was the *N*-benzyl derivative **2b**, along with the tribenzyl compound **3b**. A PM3 calculation of the respective proton affinities[5] at the OH and NH positions, defined as the difference of the enthalpies of formation of **2a** and either its N or mono-O anion, shows indeed that the proton affinity of the NH bond is 20.5 kJ/mol smaller. For an exclusive and high-yield *O*-alkylation procedure, it was therefore necessary to make use of a protective group strategy involving the benzyl protected dihydroxypyrrole **2b** which was prepared in good yield from **1b** and diethyl oxalate. The cleavage of the *N*-benzyl group was expected to occur readily by Pd-catalyzed hydrogenolysis following the alkylation step.

The dianion of **2b** is highly resonance stabilized and of limited reactivity. Furthermore it can be regarded as an ambident enolate of a double β-keto ester for which *C*-alkylation at C-2 giving rise to products of type **4** can be expected. The latter was indeed observed in a series of analogous thiophene compounds.[6] Following the HSAB[7] or allopolarization[8] principle, the rate of alkylation at the "hard" *O*-nucleophile can be enhanced by selection of a dipolar aprotic solvent, a "hard" leaving group and a "soft" cation. Good to excellent yields of alkylated products **3c–g** are consequently obtained with dimethyl and diethyl sulfate in acetone or with the less reactive alkyl mesylates in DMF with K_2CO_3 as a base in all cases. The crude products are always slightly yellow, probably due to small amounts of the *C*-alkylated products **4** which are removed by recrystallization.



Scheme 1

While the Pd-catalyzed hydrogenolytic cleavage of **3c** gave the *N*-deprotected ester **5c** in high yield, this method was not reliably working for **3d–g**, presumably due to very sensitive catalyst deactivation by trace impurities, possibly **4**. Some samples of commercially available Pd/C powders were unsatisfactory even with **3c**. Fortunately, the benzylic protective group could be maintained thoughout, since the deprotection is also achieved with acceptable yields by solvolysis in CF_3CO_2H/H_2SO_4 in the presence of anisole which effectively traps the benzyl cation.[9] The tribenzyl derivative **3b** is not useful for further conversion because *all*, and predominantly the *O*-benzyl groups, are cleaved.

The alkaline hydrolyses of the deprotected esters **5c–g** have to be performed in water or water/methanol mixtures (> 5:1 v/v); in solutions with higher alcohol content hydrolysis definitely does not occur. We ascribe this to the higher basicity of OH^- ions in alcohols which by

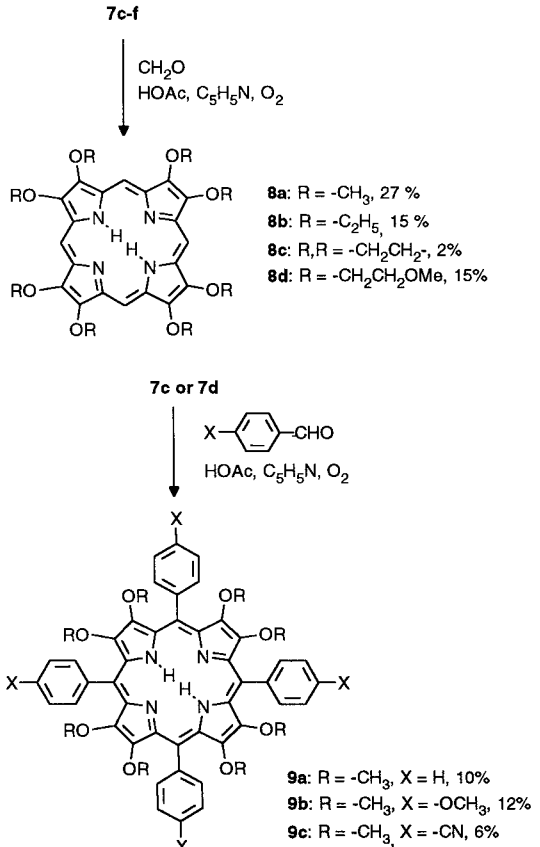
NH-deprotonation leads to a less reactive conjugated anion. From **5g** which is insoluble in water, the pure diacid **6g** could not yet be isolated. Most of the diacids **6c–f** are quite soluble in water and, for optimized yields, have to be isolated by continuous extraction with diethyl ether. The decarboxylation of **6c–f** in boiling ethanolamine is straightforward and affords the dialkoxypyrroles **7c–f** which are readily purified to colorless crystals by sublimation. The dialkoxypyrroles are sensitive to oxygen and need to be stored under argon at low temperature. Compound **7c** is the most sensitive and blackens after some weeks even under these conditions.

The synthesis of D_{4h} symmetric porphyrins from pyrroles and aldehydes with catalysis by Brönsted or Lewis acids in the presence of oxidizing agents is in principle the most simple one,[10,11] provided 2,5-unsubstituted pyrroles are available, as is the case here. However, the pronounced sensitivity of the dialkoxypyrroles poses problems due to the competition of oxidative polypyrrole formation. Note that the electrochemical oxidation potential of **7c** is about 300 mV lower than that of pyrrole itself.[2]

We have examined four literature procedures which give comparatively high yields in the synthesis of octaethylporphyrin (OEP) from 3,4-diethylpyrrole and formaldehyde. Cheng and LeGoff[12] have prepared OEP in 65% yield in ethanol solution with HBr as the catalyst and air as the oxidant. With **7c** as a substrate, however, a mass of black material was formed and the presence of only minute amounts of porphyrin **8a** was detected by UV/VIS spectroscopy. The recently reported procedure of Sessler[13] (benzene, TosOH, air) designed for larger quantities of OEP gave only 6%, and the frequently used method of Lindsay[14] ($CH_2Cl_2/BF_3 \cdot EtO$, then DDQ) afforded 12% yield of **8a**. By far the best results with the dialkoxypyrroles **7c–f** were obtained following a protocol of Treibs and Häberle[15] (HOAc/pyridine, air) which after optimization produced **8a** in 27% yield. By this method, all porphyrins **8a–d** and **9a–g** have been prepared in moderate yields. In most cases, a fraction of the porphyrin crystallizes directly from the reaction mixture. For the extremely sensitive ethylenedioxypyrrole **7e**, the procedure had to be modified and the corresponding porphyrin **8c** was obtained in 2% when the reaction was conducted at $-20\,^{\circ}C$.

We have conducted a number of experiments to explore the further scope of the octaalkoxyporphyrin syntheses. Thus, with benzaldehydes, octaalkoxy *meso*-tetraarylporphyrins **9a–g** are formed in 10–24% yield but no porphyrin was detected with 4-nitrobenzaldehyde and no tetraarylporphyrins could hitherto be obtained from **7c**. Treibs and Häberle were successful with aliphatic aldehydes when pyrrole or 3,4-dialkylpyrroles were employed, but our experiments with **7a** and acetaldehyde, butyraldehyde or trimethylacetaldehyde were absolutely negative. A recent procedure especially recommended for aliphatic aldehydes with catalysis by acid montmorillonite K1[16] failed as well.

Selected analytical and spectroscopic data for the porphyrins are given in Table 1. The *meso*-unsubstituted octaalkoxyporphyrins form dark blue lustrous crystals;



Scheme 2

a crystal structure of **8a** has already been published.[1] The green platelets of tetraarylporphyrins obtained directly from the reaction mixture contain acetic acid as shown by IR and ^1H NMR spectroscopy. The elemental analysis of the green crystals of tetraphenyloctamethoxyporphyrin **9a** is in accordance with an adduct of **9a** with 6 molecules of AcOH. Interestingly, the FAB-MS of this sample shows mass peaks for free **9a** and adducts with one up to four solvent molecules. Lattice clathrates are not unusual for tetraarylporphyrins and several types have recently been structurally characterized.[17] Recrystallization of **9a–g** from toluene affords the solvent-free porphyrins as deep purple microcrystalline powders.

The solubility of most of the porphyrins in Table 1 is similar to analogous alkyl substituted species. Remarkably, the tetrakisethylenedioxyporphyrin **8c** shows an extremely low solubility: at saturation concentration in $CDCl_3$ (99.8% D), the residual CH-peak of the NMR solvent is 4-fold more intense than the porphyrin-CH_2 signal, and a ^{13}C NMR spectrum could not be produced; one may expect that this compound is absolutely planar. Compound **8c** also exhibits with 15.1 ppm the largest chemical shift difference between the NH and *meso*-H. On the other hand, the methoxyethoxy derivative **8d** with the unusually low mp of 143–144 °C is well soluble and can be recrystallized from acetonitrile.

Table 1. Spectroscopic Properties of Porphyrins **8a–d** and **9a–g**

Compound	mp (°C)	^{1}H NMR ($CDCl_3$, 250 MHz; TMS), δ, J (Hz)				UV/VIS λ (nm) (ζ)	FAB[a] *m/z*
		NH	*meso*-H	OR	*meso*-ArX		
8a[b]	307–309	–4.41	10.05	4.79	–	377 (155000), 494 (96900), 530 (12200), 564 (570), 618 (6000)	551
8b	249–250	–4.39	10.08	1.86 (t, J = 7.0 H), 5.05 (q)	–	377 (156000), 498 (11200), 533 (12300), 564 (7000), 618 (6000)	663
8c	> 360	–5.00	10.09	5.06	–	377 (152000), 494 (7600), 529 (6300), 562 (4400), 616 (1300)	–
8d	143–144	–4.40	10.08	3.68 (s, 24 H), 4.15 (m, 16 H), 5.16 (m, 16 H)	–	378 (181800), 498 (11800), 533 (12600), 565 (7000), 618 (5500)	903
9a	302	–3.33	–	3.54	7.63–7.70 (12 H), 8.18–8.22 (8 H)	423 (138000), 526 (7100), 600 (3000), 671 (2500)	855
9b	316–317	–3.18	–	3.52	4.05 (s, 12 H), 7.23 (d, J = 8.4, 8 H), 8.16 (d, 8 H)	435 (132000), 532 (12200), 589 (87), 685 (5200)	975
9c	360	–3.49	–	3.58	7.98 (d, 8 H, J = 8), 8.25 (d, 8 H)	420 (160000), 523 (14600), 596 (7000), 660 (3000)	955
9d	> 360	–3.41	–	3.59	7.81 (d, 8 H, J = 8.4 H), 8.05 (d, 8 H)	424 (116000), 537 (11500), 601 (6600), 671 (4000)	1170
9e	294–295	–3.23	–	0.79 (t, J = 7.0 H), 3.74 (q)	7.62–7.67 (m, 12 H), 8.22–8.26 (m, 8 H)	427 (144000), 532 (13600), 606 (4800), 676 (4800)	967
9f	333–334	–3.11	–	0.83 (t, J = 7.0 H), 3.70 (q)	4.04 (s, 12 H), 7.22 (d, 8 H, J = 8.2 H), 8.18 (d, 8 H)	437 (167000), 536 (6000), 585 (2300), 681 (1500)	1087
9g	> 360	–3.36	–	0.88 (t, J = 7.0 H), 3.80 (q)	7.79 (d, 8 H, J = 8.4), 8.08 (d, 8 H)	425 (145000), 530 (12500), 603 (5700), 678 (6500)	1282

[a] FAB-MS (solvent: CH_2Cl_2, matrix: *p*-nitrobenzaldehyde), (M + 1)-peak matches calculated molecular weight in all cases
[b] ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 63.18 (OMe), 94.28 (*meso*-C), 137 (N-quadrupole broadened, α-C), 143.78 (β-C).

Octaalkoxyporphyrins represent a new substitution pattern in porphyrin chemistry. A comparison of the structural and spectroscopic properties of **8a** with the isosteric OEP has already been given.[1] Corresponding and more detailed work on the other porphyrins as well as the electrochemistry of the free porphyrins and their metal complexes is in progress.

The following analytical instruments were used: Varian T60 (60 MHz), Bruker AW (80 MHz) or Bruker WM 250 (240 MHz); Beckman Acculab 2 (IR), Hitachi U 2000 (UV/VIS); MAT 112S (EI-MS); MAT 95 (FAB, *m*-nitrobenzyl alcohol/CH_2Cl_2). Mps (uncorrected) were determined with a Büchi 510 apparatus. Elemental analyses were performed in the microanalytical laboratory of the University of Regensburg, satisfactory microanalyses were obtained for all new compounds except porphyrins **8c–d** and **9a–g** for which correct FAB-(M + 1)-peaks were found. Liquid reagents were distilled prior to use and solvents were purified according to recommended procedures.[18] The PM3 calculations were performed on a Silicon Graphics IRIS-Indigo work station with the program MOPAC.[19]

Dimethyl *N*-Benzyliminodiacetate (1b):
In a flask equipped with a reflux condenser and a gas bubbler, a mixture of dimethyl iminodiacetate **(1a)**[20] (130 g, 0.80 mmol, 400 mL), benzyl bromide (138 g, 805 mmol), and $NaHCO_3$ (163 g, 1.94 mol) in dry DMF (400 mL) was stirred at 40 °C until CO_2 formation ceased (12 to 14 h). Water (400 mL) was added and the solution was extracted with toluene (5 × 100 mL). After removal of the solvent with a rotavapor, the yellow oil was vacuum distilled. Yield: 184.2 g (0.73 mol, 91 %); colorless oil, bp 125 °C/0.1 bar.

IR (KBr): ν = 3100, 2980–2860, 1745, 1600 cm^{-1}.

^{1}H NMR (60 MHz; $CDCl_3$): δ = 3.50 (s, 4 H, CH_2), 3.60 (s, 6 H, CO_2CH_3), 3.88 (s, 2 H, $PhCH_2$), 7.25 (s, 5 H, C_6H_5).

Dimethyl 3,4-Dihydroxypyrrole-2,5-dicarboxylate (2a):
1a (92.0 g, 0.57 mol) and dimethyl oxalate (83.4, 0.57 mol) were added to a methanolate solution prepared from Na (28.2 g, 1.26) and MeOH (200 mL) and the mixture was refluxed (5 h). Glacial AcOH was added to adjust the pH to 5 and the mixture was poured into ice water (1 L). The tan solid was isolated by suction filtration, washed with water, dried in air and recrystallized from water. Yield 75 g (0.35 mol, 61 %), yellow powder, mp 217–218 °c (Lit.[4] 213–214).

IR: ν = 3400 (OH), 3310 (NH), 3110, 3010, 2970–2860, 1700 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ = 3.93 (s, 6 H, CO_2CH_3), 6.80 (br s, 2 H, OH), 8.02 (br s, 1 H, NH).

Compound 2b and Dimethyl 1-Benzyl-3,4-dibenzyloxypyrrole-2,5-dicarboxylate (3b):
A mixture of **2a** (0.5 g, 2.32 mmol), benzyl bromide (0.79 g, 4.64 mmol) and K_2CO_3 (1.38 g, 10 mmol) in acetone (40 mL) was stirred at reflux temperature for 3.5 h. The mixture was filtered and the solvent evaporated. From the yellow oil, colorless crystals of **3b** separated, and from the concentrated mother liquor colorless crystals of **2b** (15 mg, 2 %) were obtained.

Compound **3b**:
Yield 250 mg (22 %), mp 87–88 °C (MeOH).
UV (MeCN): λ (ε) = 280 nm (16500).
IR (KBr): ν = 1710, 1605 cm^{-1}.
^{1}H NMR (250 MHz): δ = 3.60 (s, 6 H, CO_2Me), 4.95 (s, 4 H, OCH_2), 5.80 (s, 2 H, NCH_2), 7.00–7.14 (m, 15 H, C_6H_5).

For compound **2b**, see below.

Dimethyl 1-Benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate (2b):
Sodium (27.6 g, 1.20 mol) was dissolved in dry MeOH (300 mL) and **1b** (139 g, 0.55 mol) and diethyl oxalate (80.8 g, 0.55 mol) were added. The mixture was heated at reflux for 18 h and worked up as given above for **2a**. The crude product was recrystallized from

acetone. Yield 98.0 g (321 mmol, 58%); colorless crystals, mp 159–161 °C.

IR (KBr): ν = 3380 (OH), 3080–3000, 2950–2870 (CH_{aliph}), 1685 (C=O), 1600 cm^{-1} (C=C).

^1H NMR (60 MHz; $CDCl_3$): δ = 3.92 (s, 6H, CO_2CH_3), 5.80 (s, 2H, $PhCH_2$), 6.85–7.40 (m, 5H, C_6H_5), 7.70 (s, 2H, OH).

Dimethyl 1-Benzyl-3,4-dialkoxypyrrole-2,5-dicarboxylates 3c–g; General Procedure:

Procedure A (for **3c, d**):

In a 1 L three-necked flask equipped with a heavy-duty mechanical stirrer, reflux condenser and nitrogen supply, a mixture of **2b** (50 mmol), dialkyl sulfate (100 mmol) and K_2CO_3 (0.25 mol) was heated under effective stirring in dry acetone (700 mL) at reflux temperature. After completion (see below), the cooled reaction mixture was filtered, the residue was washed with acetone, and the filtrate was concentrated in vacuo. The product was recrystallized from MeOH or vacuum distilled.

Procedure B (for **3e–g**):

In the same way and using the molar proportions as above, the mixture of an alkyl mesylate, K_2CO_3 and **2b** was heated in dry DMF (700 mL) at 130 °C. After completion, the reaction mixture was poured into 1 L of ice water. The product was isolated by suction filtration or by extraction with CH_2Cl_2.

Dimethyl 1-Benzyl-3,4-dimethoxypyrrole-2,5-dicarboxylate (**3c**):

Reaction time 12 h; yield 27.3 g (82 mmol, 82%), colorless crystals, mp 72 °C.

IR (KBr): ν = 3100–3000, 2980–2880, 2830, 1715 (C=O), 1600 cm^{-1}.

^1H NMR (60 MHz; $CDCl_3$): δ = 3.80 (s, 6H, CO_2CH_3), 3.90 (s, 6H, OCH_3), 5.90 (s, 2H, $PhCH_2$), 6.80–7.30 (m, 5H, C_6H_5).

Dimethyl 1-Benzyl-3,4-diethoxypyrrole-2,5-dicarboxylate (**3d**):

Reaction time: 24 h; yield 31.0 g (86 mmol, 86%); slightly yellow oil, bp 80 °C/0.01 Torr.

IR (KBr): ν = 3040–300, 3000–2880, 1715 cm^{-1} (C=O).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.35 (t, 6H, CH_2CH_3, $^3J_{H-H}$ = 7 Hz), 3.80 (s, 6H, CO_2CH_3), 4.11 (q, 4H, CH_2CH_3, $^3J_{H-H}$ = 7 Hz), 5.99 (s, 2H, CH_2Ph), 6.90–7.26 (m, 5H, C_6H_5).

Dimethyl 1-Benzyl-3,4-ethylenedioxypyrrole-2,5-dicarboxylate (**3e**):

Reaction time 8 h. The product was obtained as a solid after addition of water to the reaction mixture. Yield 28.2 g (86 mmol, 86%), colorless crystals, mp 140–141 °C (MeOH).

IR (KBr): ν = 3070–3000, 2980–2880, 1715 cm^{-1} (C=O).

^1H NMR (250 MHz; $CDCl_3$): δ = 3.82 (s, 6H, CO_2CH_3), 4.33 (s, 4H, OCH_2CH_2O), 6.02 (s, 2H, $PhCH_2$), 6.95–7.25 (m, 5H, C_6H_5).

Dimethyl 1-Benzyl-3,4-bis(2-methoxyethoxy)pyrrole-2,5-dicarboxylate (**3f**):

Reaction time 8 h. The crude brownish oil (20.4 g, 97%) solidified on addition of a few drops of hexanes. Two recrystallizations from CH_2Cl_2/hexanes affords the pure product. Yield 16.1 g (77%), colorless crystals, mp 58 °C.

IR (KBr): ν = 3100, 2980, 2820, 1710, 1600.

^1H NMR (250 MHz; $CDCl_3$): δ = 3.40 (s, 6H, CH_2OCH_3), 3.65 (m, 4H, CH_2OCH_3), 3.80 (s, 6H, CO_2CH_3), 4.22 (m, 4H, $PyOCH_2$), 5.90 (s, 2H, $PhCH_2$), 6.91–7.24 (m, 5H, C_6H_5).

^{13}C NMR (63 MHz): δ = 48.84 ($PhCH_2$), 51.52 (CH_2OCH_3), 58.88 (CO_2CH_3), 71.60 (CH_2OMe), 73.70 ($PyCH_2$), 116.55, 126.86, 128.34, 139.00, 142.35 (C_{arom}).

Dimethyl 1-Benzyl-3,4-dihexyloxypyrrole-2,5-dicarboxylate (**3g**):

Reaction time 36 h; yield 21 g crude dark viscous oil, 16.1 g (34 mmol, 68%), yellow oil, bp 150 °C (Kugelrohr, 0.01 bar).

IR (KBr): ν = 3100–3000, 3000–2860, 1715 (C=O), 1600 cm^{-1} (C=C).

^1H NMR (250 MHz; $CDCl_3$): δ = 0.90 (t, 6H, $C_5H_{11}CH_3$, $^3J_{H-H}$ = 6.50 Hz), 1.26–1.47 [m, 12H, $CH_2(CH_2)_3CH_3$], 1.67–1.78 (m, 4H, $PyOCH_2CH_2C_4H$), 3.79 (s, 6H, CO_2CH_3), 4.03 (t, 4H, $PyOCH_2C_5H_{11}$, $^3J_{H-H}$ = 6.50 Hz), 5.98 (s, 2H, $PhCH_2$), 6.90–7.26 (m, 5H, C_6H_5).

Dimethyl 3,4-Dimethoxypyrrole-2,5-dicarboxylate (5c) by Hydrogenolysis:

To a solution of **3c** (33.3 g, 0.1 mol) in glacial AcOH in a 1 L stirring autoclave was added 10% Pd/C (Merck No. 807104, 8.0 g) and the system was put under a pressure of 20 bar hydrogen. After 24 h, the pressure was released, the contents were filtered first through filter paper then through Celite. Removal of the solvent in vacuo afforded colorless **5c** which was used in the next step without further purification. Yield 23.6 g (97%), colorless crystals, mp 75 °C (EtOH).

IR (KBr): ν = 3280 (NH), 2960, 2840 (OCH_3), 1720 (C=O), 1280 cm^{-1} (C–O).

^1H NMR (60 MHz; $CDCl_3$): δ = 3.91 (s, 6H, CO_2CH_3), 3.96 (s, 6H, $PyOCH_3$), 9.25 (br s, 1H, NH).

Solvolytic Debenzylation of Dimethyl 1-Benzyl-3,4-dialkoxypyrrole-2,5-dicarboxylates 3c–g (→ 5c–g); General Procedure:

A solution of the *N*-benzyl-2,5-bis(methoxycarbonyl)-3,4-dialkoxypyrrole (50 mmol), trifluoroacetic acid (60 mL), methoxybenzene (7 mL, 65 mmol) and 98% H_2SO_4 (1.8 mL) was heated at 90 °C for 30 min. The CF_3CO_2H was distilled off in vacuo into a dry ice-cooled receiver and can be used in further batches. The residue was dissolved in CH_2Cl_2 (150 mL) and with cooling in an ice bath was carefully neutralized with sat. aq $NaHCO_3$ (350 mL). The aqueous organic mixture was extracted with CH_2Cl_2 (4 × 30 mL). The dried CH_2Cl_2 solution (Na_2SO_4) was concentrated in vacuo to give an oil. For **5c–f** the crude products separated as greyish solids on addition of pentane. In the filtrate, a ca. 1:1 mixture of 2- and 4-methoxydibenzyl (74%) was detected by MS and ^1H NMR. The unseparated mixture of **5** and methoxydibenzyls can also be employed directly in the subsequent ester hydrolysis (**5g** could not be isolated in pure form).

Dimethyl 3,4-Dimethoxypyrrole-2,5-dicarboxylate (**5c**):

Yield 8.6 g (71%); analytical data see above.

Dimethyl 3,4-Diethoxypyrrole-2,5-dicarboxylate (**5d**):

Yield 6.6 g (49%), colorless crystals, mp 70–71 °C (MeOH).

IR (KBr): ν = 3300 (NH), 3000–2850, 1710 (C=O), 1600 cm^{-1} (C=C).

^1H NMR (250 MHz; $CDCl_3$): δ = 1.36 (t, 6H, CH_2CH_3, $^3J_{H-H}$ = 7 Hz), 3.89 (s, 6H, CO_2CH_3), 4.17 (q, 4H, CH_2CH_3, $^3J_{H-H}$ = 7 Hz), 8.90 (br s, 1H, NH).

Dimethyl 3,4-Ethylenedioxypyrrole-2,5-dicarboxylate (**5e**):

Yield 9.0 g (73%), colorless crystals, mp 191–192 °C (MeOH).

IR (KBr): ν = 3330 (NH), 3000–2960, 1700 (C=O), 1585 cm^{-1} (C=C).

^1H NMR (60 MHz; $CDCl_3$): δ = 3.90 (s, 6H, CO_2CH_3), 4.35 (s, 4H, OCH_2CH_2O), 9.10 (br s, 1H, NH).

3,4-Dimethoxypyrrole-2,5-dicarboxylic Acid (6c):

5c (24.3 g, 0.1 mol) in 2 N aq NaOH (500 mL) was heated at 65 °C for 4 h. The mixture was cooled in an ice bath and acidified to pH = 2–3 with conc. HCl. Part of the diacid (12–14 g) crystallizes. Another crop is obtained by overnight continuous extraction with Et_2O, total yield: 18.2 g (85%), colorless crystals, mp 180 °C (decomp.) (MeCN).

IR (KBr): ν = 3460 (NH), 3400–2200 (CO_2H), 1680 cm^{-1} (C=O).

^1H NMR (80 MHz; D_2O): δ = 3.96 (s, 6H, OCH_3).

3,4-Ethylenedioxypyrrole-2,5-dicarboxylic Acid (6e):

5e (6.20 g, 155 mmol) was heated at 65 °C (2.5 h) in 2 N aq NaOH (200 mL). Acidification as above yields the monohydrate of **6e** (5.70 g, 87%), mp 185° (decomp.) (CH_3CN).

IR (KBr): ν = 3520 (NH), 3400–2200 (CO_2H), 1680 cm^{-1} (C=O).

^1H NMR (250 MHz; DMSO-d_6): δ = 4.20 (s, 4H, OCH_2CH_2O), 10.78 (s, 1H, NH), 12.54 (br s, 2H, CO_2H).

3,4-Dialkoxypyrrole-2,5-dicarboxylic acids 6d and 6f:
The crude products from the solvolytic debenzylations of **3d** or **3f** containing **5d** or **5f** and methoxydibenzyls (0.05 mol) were stirred in 2 N aq NaOH (250 mL) for 14 h at r.t. The alkaline aqueous solution was extracted with Et_2O (3 × 50 mL) and the extract was discarded. The aqueous phase was adjusted to pH = 2 with conc. HCl and continuously extracted overnight with Et_2O to afford the dicarboxylic acids (from **5g** only a partially hydrolyzed ester was obtained even after prolonged heating of the reaction mixture).

3,4-Diethoxypyrrole-2,5-dicarboxylic Acid **(6d)**:

Yield 9.14 g, tetrahydrate (29.0 mmol, 57%), colorless powder, mp 170°C (decomp.).

IR (KBr): ν = 3400 (NH), 3300–2200 (OH), 1670 cm^{-1} (C=O).

^1H NMR (250 MHz, DMSO-d_6): δ = 1.23 (t, 6H, CH_2CH_3, $^3J_{H,H}$ = 7 Hz), 3.35 (br s, 8H, H_2O), 4.02 (q, 4H, CH_2CH_3, $^3J_{H,H}$ = 7 Hz), 10.94 (s, 1H, NH), 12.68 (br s, 2H, CO_2H).

3,4-Bis(2-methoxyethoxy)pyrrole-2,5-dicarboxylic Acid **(6f)**:

Yield 9.0 g (56%), monohydrate, colorless powder, mp 96–98°C.

IR (KBr): ν = 3400 (NH), 3300–2200 (OH), 1675 cm^{-1} (C=O).

^1H NMR (250 MHz; DMSO-d_6): δ = 3.28 (s, 6H, OCH_3), 3.34 (br s, 2H, H_2O), 3.57 (m, 4H, CH_2OCH_3), 4.12 (m, 4H, $PyOCH_2$), 11.01 (s, 1H, NH), 12.69 (br s, 2H, CO_2H).

Decarboxylation of the Diacids to 3,4-Dialkoxypyrroles (6c–f → 7c–f):
In a two-necked flask fitted with a reflux condenser with a gas bubbler on top, ethanolamine (250 mL) was heated to reflux temperature (180°C). The pure or hydrated diacid **6** (0.1 mol) was added in one portion under stirring, and heating was maintained until CO_2 evolution ceases (5–15 min). The mixture was poured into ice-water (300 mL) and the aqueous solution was extracted with CH_2Cl_2 (7 × 80 mL). The dried organic phase ($MgSO_4$) was concentrated to give a tan solid or oil, which was purified by sublimation or vacuum distillation. The dialkoxypyrroles should be stored under Ar in the dark in a deep-freezer.

3,4-Dimethoxypyrrole **(7c)**:

Yield 10.7 g (84%), colorless crystals, mp 93–94°C (subl. 80°C, 0.01 bar).

IR (KBr): ν = 3390 (NH), 3010 (sp^2-CH), 3000–2900 (sp^3-CH), 2840 (OCH_3), 1585 cm^{-1} (C=C).

^1H NMR (60 MHz; $CDCl_3$): δ = 3.80 (s, 6H, OCH_3), 6.26 (d, 2H, H-2, $^3J_{CH-NH}$ = 3 Hz), 6.26 (br s, 1H, NH).

^{13}C NMR (62.89 MHz): δ = 58.4 (OCH_3), 99.6 (138.1 (C-3).

3,4-Diethoxypyrrole **(7d)**:

Yield 9.8 g (63%), colorless crystals, mp 35–36°C after Kugelrohr distillation (75°C/0.01 bar).

IR (KBr): ν = 3400 (NH), 3110 (CH_{arom}), 3000–2860 (CH_{aliph}), 1575 cm^{-1} (C=C).

^1H NMR (250 MHz; $CDCl_3$): δ = 1.38 (t, 6H, CH_2CH_3, $^3J_{H-H}$ = 7 Hz), 3.93 (q, 4H, CH_2CH_3, $^3J_{H-H}$ = 7 Hz), 6.21 (d, 2H, H-2, $^3J_{CH-NH}$ = 3 Hz), 7.01 (br s, 1H, NH).

^{13}C NMR (62.89 MHz): δ = 15.0 (CH_2CH_3), 66.9 (OCH_2), 100.8 (C-2), 137.2 (C-3).

3,4-Ethylenedioxypyrrole **(7e)**:

Yield 7.4 g (59%), colorless crystals, mp 106–107 (subl. 80°C/0.01 bar).

IR (KBr): ν = 3400 (NH), 3100 (sp^2-CH), 2920, 2860 (sp^3-CH), 1590 cm^{-1} (C=C).

^1H NMR (250 MHz; $CDCl_3$): δ = 4.19 (s, 4H, OCH_2CH_2), 6.19 (d, 2H, H-2, $^3J_{CH-NH}$ = 3 Hz), 7.05 (br s, 1H, NH).

3,4-Bis(2-methoxyethoxy)pyrrole **(7f)**:

Yield 10.0 g (93%, from 50 mmol), colorless crystals, mp 64–65°C after Kugelrohr distillation (120°C/0.01 bar), or sublimation at 145°C/0.01 bar.

IR (KBr): ν = 3390 (NH), 3130 (sp^3-CH), 2960, 2920, 2890, 2860, 2820 (sp^3-C), 1575 cm^{-1} (C=C).

^1H NMR (250 MHz; $CDCl_3$): δ = 3.42 (s, 6H, OCH_3), 3.70, 4.04 (AA'BB'-spectrum, 8H, $PyOCH_2CH_2OCH_3$), 6.25 (d, 2H, H-2, $^3J_{HH-NH}$ = 3 Hz), 7.10 (br s, 1H, NH).

Preparation of Octaalkoxyporphyrins 8a–d with Free *meso*-Positions:
For analytical and spectroscopic data see Table 1.

2,3,7,8,12,13,17,18-Octamethoxyporphyrin **(8a)**; *Typical Procedure:*
To a mixture of glacial AcOH (90 mL) and pyridine (28 mL) was added 35% aq formaldehyde (1.3 mL, 15 mmol) and dimethoxypyrrole **7c** (1.63 g, 12.8 mmol). A gentle stream of air was passed through the solution for 2 h and the mixture, which changes color from yellow through red to a deep-greenish black during this time, was stored uncovered for several days. A crop of ca. 50 mg **8a** was collected by suction filtration. The solution was concentrated under reduced pressure and silica gel was added to obtain a granular solid which was extracted with toluene by continuous hot vapor extraction. The solution is concentrated until crystallization begins and put in a refrigerator overnight. Compound **8a** (ca. 270 mg) was isolated by suction filtration. Another 30 mg could be obtained by column chromatography of the mother liquor (SiO_2/Et_2O, first purple fraction). Total yield: 350 mg (0.63 mmol, 27%), dark-purple needles with bluish lustre, mp 307–309°C (toluene).

For **8c** the reaction mixture was stirred at −20°C and air was admitted without being bubbled through.

Preparation of Octaalkoxyporphyrins 9a–d with Arylated *meso*-Positions:
For analytical and spectroscopic data see Table 1.

2,3,7,8,12,13,17,18-Octamethoxy-5,10,15,20-tetraphenylporphyrin **(9a)**; *Typical Procedure:*
To a mixture of glacial AcOH (30 mL) and pyridine (15 mL) was added benzaldehyde (0.48 g, 0.433 mL, 4.5 mmol) and 3,4-dimethoxypyrrole **(7c)** (0.51 g, 4.0 mmol). Air was bubbled through the yellow solution for 2 h during which time the mixture becomes dark-green. After standing uncovered for 3–4 d, the porphyrin separates as an AcOH adduct, as platelets with a greenish lustre. Recrystallization from toluene yields 85 mg pure porphyrin (0.10 mmol, 10%), mp 302°C. Some more porphyrin can be isolated by chromatography as given for **8a**.

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