Simple Methodology for the Synthesis of *meso*-Unsubstituted β-Substituted Alkyl Porphyrins

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Abstract: The MacDonald [2+2]-type condensation of *meso*-free β-alkyldipyrromethane with different *meso*-free-1,9-bis(formyl)dipyrromethanes yields new asymmetric sterically unencumbered porphyrins.

Key words: β-alkylporphyrins, MacDonald condensation, disymmetric β-alkyldipyrromethane, pyrroles

Sterically encumbered porphyrins have been the subject of intensive research.[1] In contrast, much less is known about the chemistry of derivatives of porphine, bearing only a few substituents, in particular in β-pyrrole position.[2] Despite the simple structure, there is a limited accessibility of porphine, if we discount the recent and nice synthesis from β-pyrrole or *meso*-tetra(*tert*-butyl)porphyrin.[3,4] Although, porphine could be a possible starting material for simple *meso*-substituted porphyrins, it still remains the fact that if the β-pyrrole substitution is necessary, a different methodology is required.[5] As part of our ongoing work on reconstituted myoglobins with unencombered metalloporphyrins, we needed to prepare a range of porphyrins with few β-pyrrole substituents. In this paper, we report the synthesis of disymmetric and symmetric porphyrins bearing methyl and ethyl group on the β-pyrrole carbons (Figure 1), utilizing MacDonald dipyrromethane procedure.[6]

In our strategy, 1,9-diformyldipyrromethanes **6c** and **7c**[7] were the key intermediates (Figure 2). We first turned to the new dipyrromethane diester **6a**, which was prepared from condensation of ethyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate with ethyl pyrrole-2-carboxylate in the presence of *p*-toluenesulfonic acid in dichloromethane solution. The mixture was heated under nitrogen at 40 °C for 48 hours giving **6a** in 53% yield. The prerequisite decarboxylation can be achieved easily in one step from the diester precursor. Compound **6a** was refluxed in ethylene glycol containing NaOH for 1.5 hours giving **6b** with 92% yield. The resultant dipyrromethane was formylated with excess $POCl_3$/DMF in dichloromethane, giving the expected compound **6c** with 60% yield.

Compounds **7a–c** have been previously prepared by various methods.[8] The procedure used in our laboratory for **7c** is summarized herein.[9] Compound **7b** was readily formed in 89% yields by treatment of 1,9-bis(ethoxycarbonyl)-3,7-diethyl-2,8-dipyrromethane (**7a**) with sodium hydroxide.[8] Reaction of **7b** with excess $POCl_3$/DMF in dichloromethane produced stable **7c**[7] with 52% yield.

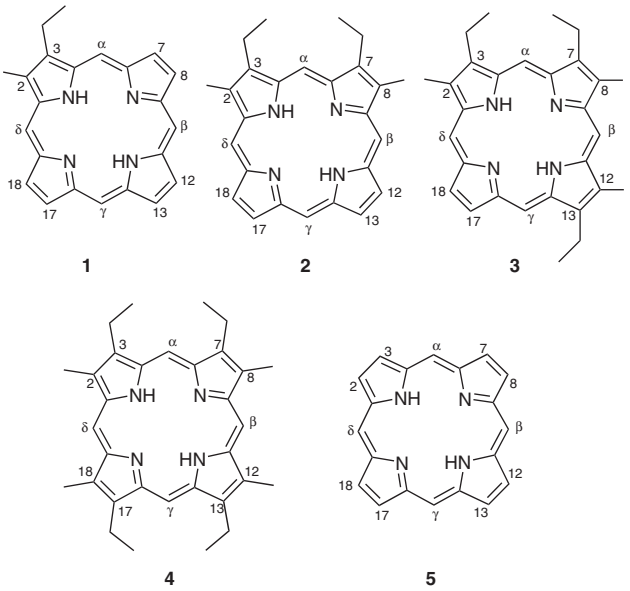

Figure 1

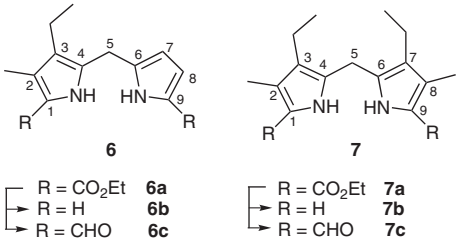

Figure 2

To prepare the two porphyrins **1** and **2**, we followed MacDonald's [2+2] pathway. 1,9-Bis(formyl)dipyrromethane **6c** (or **7c**) was condensed with dipyrromethane, a dipyrromethane without any substituent, in CH_2Cl_2 in the presence of trifluoroacetic acid. This afforded, after oxidation with *p*-chloranyl and chromatographic purification, monopyrrole-substituted porphyrin **1** (yield: 8%) and dipyrrole-substituted porphyrin **2** (yield: 22%). In a typical experimental procedure for **1**, dipyrromethane (3

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mmol) and 1,9-diformyldipyrromethane **6c** (3 mmol) dissolved in 1 L of distilled CH_2Cl_2 under argon were stirred in the presence of 670 μL (9.2 mmol) of trifluoroacetic acid for 14 hours at room temperature. After addition of *p*-chloranyl (0.512 mmol) and 1 hour more stirring, 6.7 mL of Et_3N were added and then the solvent was removed. The residue was purified by two subsequent column chromatographies on silica gel using dichloromethane as eluant to give **1**. Traces of porphine **5** were detected in the mass spectra of **1**. Using a similar procedure, the expected porphine was not obtained from condensation of dipyrromethane with 1,9-diformyldipyrromethane.

Dipyrromethane **6b** was similarly condensed with diformyldipyrromethane **7c** to give the asymmetric porphyrin **3** in 26% yield. It should be noted that the reverse reaction, i.e. the condensation of **6c** with **7b**, gave a lower yield of porphyrin **3** (13%). To complete the series of these alkyl porphyrins, **4** was classically prepared by condensing **7c** with 7**b** to give the previously obtained etioporphyrin II in 40% yield. The following remarks derive from these results:

– The porphyrin yield increases as substitution on β-pyrrole increases, the best yield being obtained for the preparation of etioporphyrin **4**,
– as the number of β-substitution in a dipyrromethane increases, dipyrromethanes may become more resistant toward scrambling, as expected for this MacDonald condensation,
– the yield is higher when MacDonald condensation results from a substituted diformyldipyrromethane to dipyrromethane rather than the reverse situation.

The electronic spectra of porphyrins **1** and **2** exhibited a strong Soret band near 400 nm and a phyllo-type Q band region, as expected when four or more peripheral β-pyrrole positions are unsubstituted.[10] In contrast, the etio-type spectrum is found both in porphyrins **3** and **4** in which, respectively, six and eight peripheral positions carry side-chains such as methyl and ethyl groups. All the UV/vis data are summarized in Table 1.

In the NMR spectra of **1**–**4**, the regiochemical arrangement and substitution pattern was easily obtained from 2D spectra, such as COSY, HMQC and HMBC. Thus, if we consider the ^{1}H NMR spectrum of **1**, the magnetic anisotropy of the porphyrin ring due to the two different alkyl groups on a pyrrole ring, although very weak, is enough to see the four different *meso*-protons at 500 MHz (δ = 10.24, 10.25, 10.33 and 10.34 ppm). Many ^{1}H NMR studies have investigated the effects of substituents on the porphyrin-ring-current effect.[2] A general conclusion from previous studies is that substitution at the *meso*-position appears to decrease the ring current more than substitution at the pyrrole ring. Thus it is quite surprising that methyl vs. ethyl substitution affects sufficiently the whole current flow to detect the four different *meso*-H in **1**. If we consider porphyrins **1** and **2**, the changes in symmetry are clearly reflected in the ^{1}H NMR spectra. For example, the porphyrin **2** shows characteristic splitting of the *meso*-protons along the C_2 axis. The pattern of **2** is characterized by three singlets for the *meso*-protons at 10.11 (α-H_{meso}), 10.19 (β and δ-H_{meso}) and 10.27 ppm (γ-H_{meso}). Such weak structural perturbations may be useful to study the structure of some myoglobins reconstituted with unnatural hemes.

Table 1 UV/vis Data for the Porphyrins **1**–**5** in Dichloromethane Solution

	λ, nm (ε $mM^{-1}cm^{-1}$)				
Porphyrin	Soret band	IV	III	II	I
1	394 (158.9)	490 (8.1)	526 (2.8)	560 (3.7)	615 (0.5)
2	393 (216.9)	491 (19.1)	523 (7.4)	560 (7.8)	613 (2.7)
3	395 (180.7)	496 (10.5)	532 (6.7)	563 (5.5)	617 (1.9)
4	396 (162.9)	497 (12.3)	530 (8.9)	565 (6.0)	619 (4.3)
5[a]	394 (272)	489 (16.4)	519 (3.2)	560 (5.4)	613 (1.1)

[a] Taken from ref. 3.

In summary, we have developed a simple procedure for the preparation of a series of simple β-alkyl porphyrins with different symmetries using a MacDonald-type condensation. It may be comparable to a different and nice route using tripyrrane as an intermediate and recently reported by Taniguchi et al.[11] The herein method is particularly attractive owing its simplicity although the yield is quite weak for the simplest porphyrin **1**.[12]

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(12) **Selected Data**

Compound **1**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = –3.94 (br s, 2 H, NH), 1.93 (t, 3 H, CH_2CH_3), 3.71 (s, 3 H, CH_3), 4.18 (q, 2 H, CH_2CH_3), 9.46 (m, 4 H, 7,8,17,18-$H_{pyrrolic}$), 9.54 (s, 2 H, 12,13-$H_{pyrrolic}$), 10.24 (s, 1 H, α- or δ-H_{meso}), 10.25 (s, 1 H, α- or δ-H_{meso}), 10.33 (s, 1 H, β- or γ-H_{meso}), 10.34 (s, 1 H, β- or γ-H_{meso}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.45 (CH_3), 17.53 (CH_2CH_3), 19.78 (CH_2CH_3), 99.89 (Cα,δ), 104.37 (Cβ,γ), 129.00 (C12,13), 132.96 (C7,8,17,18), 142.07 (C3), 153,03 (C2) ppm. UV/vis (CH_2Cl_2): λ_{max} (ε $mM^{-1}cm^{-1}$): 394 (158.9), 490 (8.1), 526 (2.8), 560 (3.7), 615 (0.5) nm. HRMS: *m/z* calcd for $C_{23}H_{21}N_4$ $[M + H]^+$: 353.1766; found: 353.1766.

Compound **2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = –3.81 (br s, 2 H, NH), 1.92 (t, 6 H, CH_2CH_3), 3.65 (s, 6 H, CH_3), 4.12 (q, 4 H, CH_2CH_3), 9.45 (dd, 4 H, $H_{pyrrolic}$), 10.11 (s, 1 H, α-H_{meso}), 10.19 (s, 2 H, β,δ-H_{meso}), 10.27 (s, 1 H, γ-H_{meso}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.52 (CH_3), 17.71 (CH_2CH_3), 19.90 (CH_2CH_3), 95.57 (Cα), 100.19 (Cβ,δ), 104.71 (Cγ), 130.21 (C11,19), 130.50 (C12,13,17,18), 136.15 (C2,8), 142.74 (C3,7) ppm. UV/vis (CH_2Cl_2): λ_{max} (ε $mM^{-1}cm^{-1}$): 393 (216.9), 491 (19.1), 523 (7.4), 560 (7.8), 613 (2.7) nm. HRMS: *m/z* calcd for $C_{26}H_{27}N_4$ $[M + H]^+$: 395.2236; found: 395.2243.

Compound **3**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = –3.50 (br s, 2 H, NH), 1.91 (m, 9 H, CH_2CH_3), 3.64 (s, 3 H, 8-CH_3), 3.69 (s, 6 H, 2,12-CH_3), 4.10 (q, 2 H, 7-CH_2CH_3), 4.16 (m, 4 H, 3,13-CH_2CH_3), 9.43 (s, 2 H, $H_{pyrrolic}$), 10.14 (s, 1 H, α- or β-H_{meso}), 10.15 (s, 1 H, α- or β-H_{meso}), 10.20 (s, 1 H, δ- or γ-H_{meso}), 10.21 (s, 1 H, δ- or γ-H_{meso}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.51 (CH_3), 17.65 (CH_2CH_3), 19.85 (CH_2CH_3), 96.02 (Cα,β), 100.64 (Cδ,γ), 131.73 (C17,18), 133.86 (C12), 134.69 (C2), 136.73 (C8), 141.00 (C3), 141.70 (C13), 143.81 (C7) ppm. UV/vis (CH_2Cl_2): λ_{max} (ε $mM^{-1}cm^{-1}$): 395 (180.7), 496 (10.5), 532 (6.7), 563 (5.5), 617 (1.9) nm. HRMS: *m/z* calcd for $C_{29}H_{33}N_4$ $[M + H]^+$: 437.2705; found: 437.2694.

Compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = –3.72 (br s, 2 H, NH), 1.91 (t, 12 H, CH_2CH_3), 3.67 (s, 12 H, CH_3), 4.13 (q, 8 H, CH_2CH_3), 10.12 (s, 2 H, H_{meso}), 10.13 (s, 2 H, H_{meso}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.59 (CH_3), 17.75 (CH_2CH_3), 19.92 (CH_2CH_3), 96.29 (C_{meso}), 135.03 (C2), 142.12 (C3) ppm. UV/vis (CH_2Cl_2): λ_{max} (ε $mM^{-1}cm^{-1}$): 396 (162.9), 497 (12.3), 530 (8.9), 565 (6.0), 619 (4.3) nm. HRMS: *m/z* calcd for $C_{39}H_{39}N_4$ $[M + H]^+$: 479.3175; found: 479.3174.

Compound **6a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 and 1.33 (all t, 9 H, 3 CH_2CH_3), 2.32 (s, 3 H, CH_3), 2.45 and 4.29 (two q, 6 H, 3 CH_2CH_3), 3.98 (s, 2 H, CH_2), 6.04 and 7.29 (two s, 2 H, 2 $H_{pyrrolic}$), 9.60 and 10.00 (two br s, 2 H, 2 NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.55, 14.42, 15.53, 17.22, 24.67, 59.86, 60.53, 108.87, 116.26, 117.28, 122.01, 124.20, 127.02, 129.62, 134.87, 161.65, 162.50 ppm. HRMS: *m/z* calcd for $C_{18}H_{24}N_2O_4$ $[M^{+\cdot}]$: 332.1736; found: 332.1704.

Compound **6b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13 (t, 3 H, CH_2CH_3), 2.08 (s, 3 H, CH_3), 2.48 (q, 2 H, CH_2CH_3), 3.94 (s, 2 H, 5-CH_2), 6.04, 6.17, 6.41, 6.68 (all m, 4 H, 4 $H_{pyrrolic}$), 7.49, 7.87 (two br s, 2 H, 2 NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.31, 16.00, 17.40, 24.51, 106.26, 108.50, 113.90, 116.99, 117.90, 121.22, 124.32, 129.21. HRMS: *m/z* calcd for $C_{12}H_{16}N_2$ $[M^{+\cdot}]$: 188.1313; found: 188.1313.

Compound **6c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, CH_2CH_3), 2.32 (s, 3 H, CH_3), 2.50 (q, 2 H, CH_2CH_3), 4.06 (s, 2 H, 5-CH_2), 6.19, 6.91, 9.42, 9.55 (all m, 4 H, 4 $H_{pyrrolic}$), 10.99, 11.36 (two br s, 2 H, 2 NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.86, 15.32, 16.98, 24.79, 110.37, 122.83, 125.31, 128.74, 133.23, 135.51, 138.18, 177.04, 179.04. HRMS: *m/z* calcd for $C_{14}H_{16}N_2O_2$ $[M^{+\cdot}]$: 244.1212; found: 244.1198.