Preparation of Bis-Pocket Porphyrins with Carboxylic Acid Synthons

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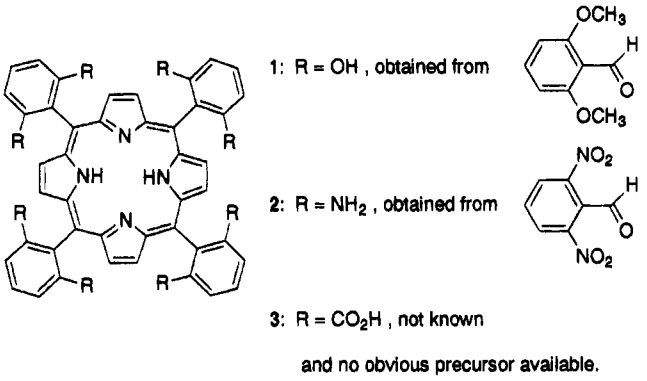
Synthetic metalloporphyrins have been extensively studied as models for heme-dependent enzymes and other biological processes in which porphyrin derivatives are involved.[1] Numerous porphyrins were prepared with the aim of controlling variables such as identity of the metal, its oxidation state, its coordination number, the identity of the ligands and more.[2] These approaches resulted in a wide variety of architecturally different model porphyrins, such as Collman's picket-fence porphyrin for mimicking myoglobin,[3] iron(III) and manganese(III) porphyrins for cytochrome P-450 like oxygenation catalysis[4] and many chiral porphyrins for catalytic asymmetric induction.[5] In these perspectives, tetraphenylporphyrins in which all the *ortho*-phenyl positions are substituted (bis-pocket porphyrins) used to be quite rare,[2,6] not least because the direct porphyrin synthesis from pyrrole and aromatic aldehydes was highly inefficient for bis-*ortho*-substituted benzaldehydes.[7] A major breakthrough was introduced by Lindsey et al., who showed that the relatively high yield cyclocondensation of pyrrole with a large variety of substituted benzaldehydes by $BF_3{\cdot}OEt_2$ catalysis can also be applied for *ortho*-disubstituted aldehydes.[8]

However, the preparation of bis-pocket porphyrins in which the *ortho*-substituents are suitable for further chemical manipulations (Chart 1) still remains a serious challenge. The only one of this subgroup which is quite easily prepared (from commercially available 2,6-dimethoxybenzaldehyde) is the octahydroxyporphyrin **1**, which is recently utilized by several research groups.[9] The octaaminoporphyrin **2** was prepared from 2,6-dinitrobenzaldehyde and subsequent reduction of the nitro groups in low yield (yields of 0%,[8] 0.75%,[10a] and 2–10%[10b]) and only rarely used.[10] Finally, the octacarboxyporphyrin **3** has never been prepared. Moreover, even benzaldehydes which are properly substituted so as to serve as precursors for the synthesis of **3** are unknown. In this study we report the preparation of the smallest hydrolytic

Chart 1



precursor, 2,6-dicyanobenzaldehyde (**4**), attempts to prepare porphyrin **3** by cyclocondensation of **4** with pyrrole, and the isolation of four new porphyrins by a mixed-aldehyde synthetic approach.

Results and Discussion

The starting material for the synthesis of **4**, which is described in Scheme 1, was 1,3-dicyanobenzene (**5**). Krizan and Martin have shown that its 2-hydrogen can be selectively functionalized by LDA to form the corresponding organolithium complex, which is converted to 2,6-dicyanotoluene (**6**) in high yield (90% in our hands) by treatment with CH_3I.[11,12] Compound **6** was converted to **4** by the Kröhnke method,[13] which included the benzylic bromination of **6** to α-bromo-2,6-dicyanotoluene (**7**), the substitution of the bromine in **7** by pyridine to form 2,6-dicyanobenzyl pyridinium bromide (**8**) and treatment of **8** with 4-nitroso-N,N-dimethylaniline and base, followed by acid hydrolysis. One necessary modification in the Kröhnke method was the change of the solvent from EtOH to THF in the last steps of the synthesis (iii–v in Scheme 1), because otherwise the hydrolysis resistant acetal of **4** was obtained. The aldehyde **4** could not be purified by column chromatography because it was not stable toward silica, alumina or Florisil. Instead, sublimation (0.15 mm Hg, 120 °C) was used for analytical purification, while for synthetic purposes, **4** was crystallized by adding hexane to its CH_2Cl_2 solution.[14]

Attempted condensation of **4** with pyrrole by the Adler method,[15a] its modification,[13b] and by the Lindsey method,[8] did not yield any amount of the expected tetrakis-(2,6-dicyanophenyl)porphyrin **9** (R = CN in the structure of

(1) Mansuy, D. *Coord. Chem. Rev.* **1993**, *125*, 129.
(2) Morgan, B.; Dolphin, D. *Structure Bonding* **1987**, *64*, 115.
(3) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *96*, 1427.
(4) (a) McMurry, T. J.; Groves, J. T. In *Cytochrome P-450: Structure, Mechanism and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum Press: NY, 1986; pp 1–28. (b) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
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(6) Suslick, K. S.; Fox, M. M. *J. Am. Chem. Soc.* **1983**, *105*, 3507.
(7) Kim, J. B.; Adler, A. D.; Longo, F. R. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 1, pp 85–100.
(8) (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969. (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearny, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827. (c) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828.
(9) (a) Naruta, Y.; Tani, F.; Ishihara, N.; Maruyama, K. *J. Am. Chem. Soc.* **1991**, *113*, 6865. (b) Tsuchida, E.; HaseGawa, E.; Komatsu, T.; Nakata, T.; Nakao, K.; Nishide, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 888. (c) Wagner, R. W.; Ruffing, J.; Breakwell, B. V.; Lindsey, J. S. *Tetrahedron Lett.* **1991**, *32*, 1703.
(10) (a) Drain, C. M.; Corden, B. B. *Inorg. Chem.* **1991**, *28*, 4374. (b) Quintana, C. A.; Assink, R. A.; Shelnutt, J. A. *Inorg. Chem.* **1991**, *28*, 3421.
(11) Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681.
(12) We attempted direct hydroformylation of the 2-Li complex of **5** by DMF and with Gold's reagent (*Aldrichimica Acta* **1986**, *19*, 43). With DMF as reagent, the first formed $ArCH(NMe_2)O^-$ intermediate reacted internally with one of the *ortho*-cyano groups and even when this reaction was avoided (Gold's reagent) no aldehyde was formed. In the direct oxidation of **6** with $CrO_3/Ac_2O/H_2SO_4$ the expected α,α-diacetoxy-2,6-dicyanotoluene was formed, but its attempted hydrolysis was unsuccessful as it decomposed to unidentified products under quite mild conditions (1–2 N HCl, reflux).
(13) Kröhnke, F. *Chem. Ber.* **1938**, *71*, 2583.
(14) The mother liquor contained varying amounts of 3-cyanophtalimide, identified by MS, ^1H and ^{13}C NMR, as well as by its IR and m.p. which were identical to the values reported in: Wenkert, E.; Lin, L. H.; Johnston, D. B. R. *J. Org. Chem.* **1965**, *30*, 722.
(15) (a) Adler, A. D.; Longo, F. R.; Shergalis, W. *J. Am. Chem. Soc.* **1964**, *86*, 3145. (b) d'A. Rocha Gonsalves, A. M.; Varejano J. M. T. B.; Pereira, M. M. *J. Heterocyclic Chem.* **1991**, *28*, 635.

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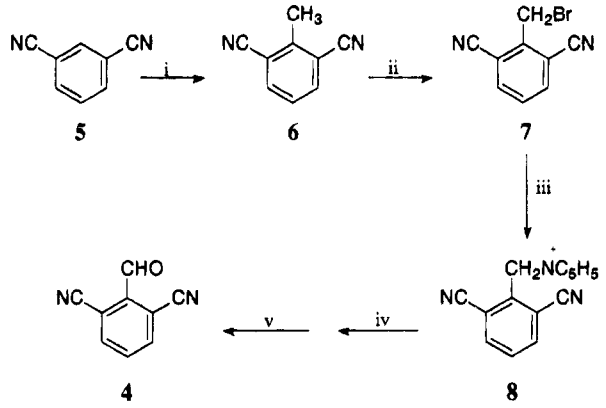
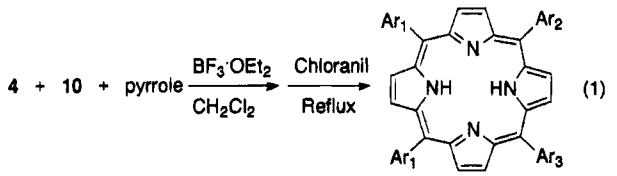
Scheme 1



[a] Reagents and Conditions: (i) ref 11; (ii) NBS, CCl_4, $h\nu$, reflux, 12 h, 90%; (iii) pyridine, Δ, 12 h, 91%; (iv) 4-$(CH_3)_2NC_6H_4NO$, KOH, THF, 20 min; (v) 10% HCl, 40%.

Chart 1). Since the Lindsey method was originally optimized for a different porphyrin, we varied the amount of the BF_3·OEt_2 catalyst, the concentration of **4**, temperature, reaction times and checked also $CHCl_3$ (containing 0.75% EtOH) as solvent,[8] but without positive results. However, applying the Lindsey method for the condensation of pyrrole with mixtures of **4** and pentafluorobenzaldehyde (**10**) was successful and three porphyrins were isolated (equation 1). The aldehyde **10** was chosen



11: $Ar_1 = Ar_2 = Ar_3 = C_6F_5$

12a: $Ar_1 = Ar_2 = C_6F_5$, $Ar_3 = C_6H_3(CN)_2$

13a: $Ar_1 = C_6F_5$, $Ar_2 = Ar_3 = C_6H_3(CN)_2$

because of three reasons; a) it condenses very well with pyrrole.[7,8] b) the iron(III) complex of the corresponding porphyrin (tetrakis-(pentafluorophenyl)porphyrin, **11**) is a very efficient oxidation catalyst.[16] c) the identification of the possible porphyrinic products was expected to be easier due to the non interference of the pentafluorophenyl ring in the ^1H NMR and the possibility of utilizing ^{19}F NMR. The last factor is the most important one, since six different porphyrins with very similar spectroscopic features are expected in a mixed-aldehyde synthesis.[17]

Besides porphyrin **11**, two new porphyrins were isolated from the reaction mixture; 5-(2,6-dicyanophenyl)-10,15,20-tris(pentafluorophenyl)porphyrin (**12a**) and 5,-10-bis(2,6-dicyanophenyl)-15,20-bis(pentafluorophenyl)porphyrin (**13a**), each of them in about two percent yield. The reaction conditions were varied in terms of the amount of the BF_3·OEt_2 catalyst, solvent (CH_2Cl_2 vs $CHCl_3$), temperature, reaction times and the relative ratio of **4** and **10**, but under all conditions we were unable to isolate any additional porphyrins. Most surprisingly, even the isomer of **13a**, 5,15-bis(2,6-dicyanophenyl)-10,20-bis(pentafluorophenyl)porphyrin (**14a**, Figure 1), was not obtained.

The identification of **12a** and **13a** was based on their NMR spectra, shown in Figure 1. In the ^1H NMR spectrum of **12a** (Figure 1a) the ratio between the porphyrin's skeleton *pyrrole*-hydrogens (8.9–8.6 ppm, typical chemical shifts and typical J values of 5 Hz) and the aromatic *meta*-hydrogens (8.36 ppm, typical aromatic J value of 8 Hz) was 8:2. This ratio suggests that only one dicyanophenyl group (and three "^1H NMR silent" pentafluorophenyl groups) is present in this porphyrin. In its ^{19}F NMR spectrum (Figure 1b) two types of pentafluorophenyl rings in the ratio of 2:1 were evident, most clearly seen for the *ortho*-F peaks, centered around −137.5 ppm. This leaves the suggested structure for **12a** as the only possible choice for this set of spectra. Similarly, the ^1H NMR spectrum shown in Figure 1c clearly indicates the presence of two 2,6-dicyanophenyl rings and two pentafluorophenyl rings in that porphyrin, as the relative ratio between the *pyrrole*-hydrogens (8.9–8.6 ppm) and the aromatic *meta*-hydrogens (8.35 ppm) was 8:4, while only one type of pentafluorophenyl rings was observed in its ^{19}F NMR spectrum (Figure 1d). The two possible isomers, **13a** and **14a**, can not be distinguished by the ^{19}F NMR pattern, since in both compounds the two pentafluorophenyl rings must be identical. Differentiation between **13a** and **14a** was based on the ^1H NMR (Figure 1c), where two singlets and two doublets were observed for the *pyrrole*-hydrogens. This is exactly the expected pattern for **13a** (C_{2v}), whereas the more symmetrical **14a** (D_{2h}) should have no singlets, but only two doublets.

Finally, the validity of the nitrile groups as synthons for carboxylic acids was demonstrated. The acid catalyzed hydrolysis of all the cyano groups in the porphyrins **12a** and **13a** afforded the corresponding acids **12b** and **13b**. Both the ^1H and ^{19}F NMR patterns (not shown) were identical to their precursors. In accord with their structures, the tetracarboxylic acid **13b** was much more soluble in basic water than the dicarboxylic acid **12b**, while the opposite behavior was noticed for organic solvents. In summary, the preparation of 2,6-dicyanobenzaldehyde and its condensation with pyrrole in the presence of **10** resulted in the isolation of two new porphyrins, which after hydrolysis afforded two bis-pocket porphyrins with carboxylic acids, the first report of this kind of compounds.

Experimental Section

General. All chemicals were analytical grade Aldrich products and were used as received unless stated otherwise. CH_2Cl_2 for the synthesis of porphyrins was dried by distillation over CaH_2. NBS was recrystallized from 10 times its weight of water and air dried. 4-nitroso-N,N-dimethylaniline was recrystallized from hexane.

2,6-Dicyanobenzaldehyde (4). 2,6-Dicyanotoluene (**6**) was prepared by the procedure of Krizan and Martin in 90% yield.[11] A solution of **6** (5 g, 35.2 mmol) in CCl_4 (500 mL) was reacted with NBS (12.5 g, 70.4 mmol) under irradiation with a 250 watt sunlamp for 12 h. The cold reaction mixture was filtered to remove precipitated succinimide, which was washed by additional CCl_4 and the solvent was evaporated to dryness. This yielded 8 g of yellowish solid, which contained 90% α-bromo-2,6-dicyanotoluene (**7**) contaminated by 10% α,α-dibromo-2,6-dicyanotoluene (NMR, ^1H NMR ($CDCl_3$) of **7**: δ 7.90 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 7.8 Hz, 1H), 4.77 (s, 2H)). The solid was

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(17) For a recent review on this subject, see: Lindsey, J. S. In *Metalloporphyrin Catalyzed Oxidations*; Montanari, F.; Casella, L., Eds.; Kluwer Academic Press: The Netherlands 1994; pp 49–86.

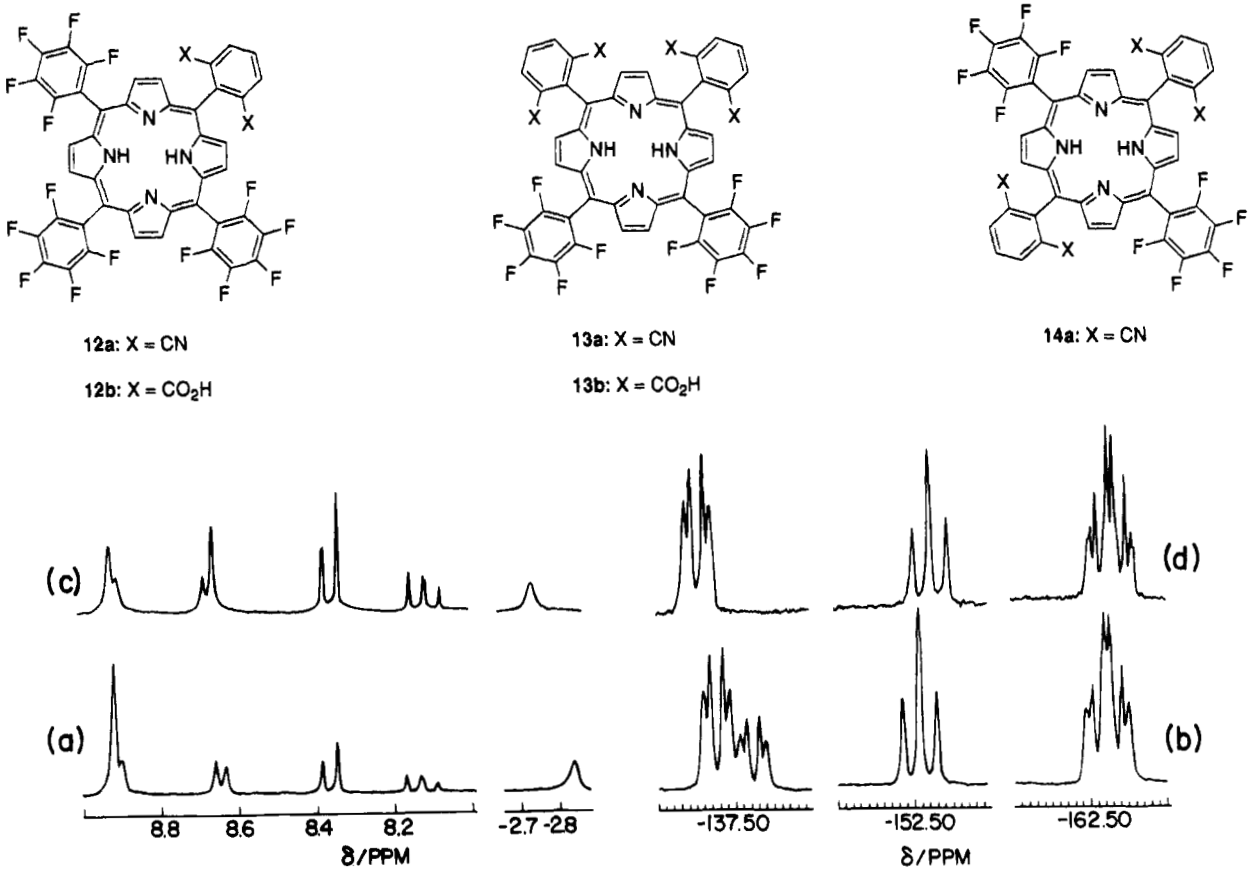

Figure 1. Structures of porphyrins **12a**–**14a** and the ^1H (200 MHz) and ^{19}F NMR (188 MHz) spectra of **12a** (a, b) and **13a** (c, d).

dissolved without purification in hot CCl_4 (500 mL), pyridine (30 mL) was added and the reaction mixture was heated for 12 h. The brownish precipitate was filtered, washed by CCl_4 (α,α-dibromo-2,6-dicyanotoluene remains in the solution) and dried in an oven at 80 °C. Pure 2,6-dicyanobenzyl pyridinium bromide (**8**) was obtained (8.5 g, 28.3 mmol, 81% relative to **6**): ^1H NMR (D_2O) δ 8.74 (d, 2H), 8.44 (t, 1H), 8.01 (d, J = 8 Hz, 2H), 7.92 (t, 2H), 7.66 (t, J = 8 Hz, 1H), 6.32 (s, 2H). The full amount of **8** was added under vigorous stirring to an ice cold solution of 4-nitroso-N,N-dimethylaniline (4.25 g, 28.5 mmol) in 200 mL THF. A solution of KOH (2.24 g, 40 mmol) in 85 mL of H_2O was gradually added to the suspension during 10 min. The mixture became homogeneous and the color changed from green to red. After 20 min, 20 mL of 35% HCl were gradually added, the reaction was allowed to warm up to room temperature, CH_2Cl_2 was added and the organic fraction was separated. After drying over sodium sulfate, the volume was reduced to about 10 mL and hexane was added to precipitate 2,6-dicyanobenzaldehyde (1.8 g, 11.4 mmol, 40% from **8**). For analytical purposes, **4** was further purified by sublimation at 0.15 mmHg and 120 °C: mp 163–4 °C; ^1H NMR ($CDCl_3$) δ 10.50 (s, 1H), 8.08 (d, J = 8 Hz, 2H), 7.88 (t, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 185.4 (CHO), 138.0, 137.7, 134.2, 114.7, 114.6; MS m/z: 156 (M^+, 21), 155 ($M^+ - 1$, 28), 128 (100). Anal. Calcd for $C_9H_4N_2O$: C, 69.23; H, 2.58; N, 17.94. Found: C, 69.00; H, 2.66; N, 17.87.

5-(2,6-Dicyanophenyl)-10,15,20-tris(pentafluorophenyl)-porphyrin (12a) and 5,10-Bis(2,6-dicyanophenyl)-15,20-bis-(pentafluorophenyl)porphyrin (13a). The procedure of Lindsey and Wagner was applied.[8] A solution of **4** (1 g, 7.5 mM), **10** (0.264 mL, 2.5 mM) and pyrrole (0.593 mL, 10 mM) in CH_2Cl_2 (855 mL) was purged with Ar for 10 min, $BF_3{\cdot}OEt_2$ (0.35 mL, 3.3 mM) was added at once and the reaction mixture was left for 1 h at room temperature, while the color changed from yellow to deep red during the first five minutes. The Ar flow was stopped, *p*-chloranil (1.58 g, 7.5 mM) was added and the solution was boiled for one hour. After addition of triethylamine (0.4 mL, 3.3 mM) the solution was evaporated to dryness and the residue purified by a first column of basic Alumina with CH_2Cl_2 eluent, followed by separation of the porphyrinic material on preparative TLC silica plates. Three porphyrins were isolated, **11**, **12a** and **13a** (in that order of elution), each of them in about 2% yield (average of many syntheses). The porphyrins from several runs were combined and recrystallized from CH_2Cl_2–hexanes. Porphyrin **12a**: R_f 0.75 (30% *n*-hexane/CH_2Cl_2); UV–vis (CH_2Cl_2), λ_{max}/nm (rel ε) 414 (100), 508 (7.4), 584 (2.6), 634 (0.6); FAB$^+$ MS 934.7 (MH^+, 100); FAB$^-$ MS 934.0 (M^-, 100); ^1H NMR ($CDCl_3$) δ 8.92 (s, 4H), 8.91 (d, 2H),[18] 8.64 (d, J = 5 Hz, 2H), 8.36 (d, J = 8 Hz, 2H), 8.13 (t, J = 8 Hz, 1H), −2.84 (s, 2H); ^{19}F NMR ($CDCl_3$) δ −137.4 (dd, J_1 = 23 Hz, J_2 = 8 Hz, 4F), −137.6 (dd, J_1 = 23 Hz, J_2 = 8 Hz, 2F), −152.54 (t, J = 21 Hz, 3F), −162.6 (m, 6F). Porphyrin **13a**: R_f 0.3 (30% *n*-hexane/CH_2Cl_2); UV–vis (CH_2Cl_2) λ_{max}/nm (rel ε) 416 (100), 510 (8.4), 584 (3.4), 638 (1.6); FAB$^+$ MS 894.9 (MH^+, 100); FAB$^-$ MS 894.1 (M^-, 100); ^1H NMR ($CDCl_3$) δ 8.92 (s, 2H), 8.91 (d, 2H),[18] 8.67 (d, J = 5 Hz, 2H),[18] 8.65 (s, 2H), 8.35 (d, J = 8 Hz, 4H), 8.10 (t, J = 8 Hz, 2H), −2.75 (s, 2H); ^{19}F NMR ($CDCl_3$) δ −137.3 (dd, J_1 = 22 Hz, J_2 = 7 Hz, 4F), −152.62 (t, J = 21 Hz, 2F), −162.7 (m, 4F).

5-(2,6-Dicarboxyphenyl)-10,15,20-tris(pentafluorophenyl)-porphyrin (12b) and 5,10-bis(2,6-dicarboxyphenyl)-15,20-Bis(pentafluorophenyl)porphyrin (13b). The porphyrins **12b** and **13b** were obtained by hydrolysis of **12a** and **13a**, respectively. The precursors (10 mg) were dissolved in 50% H_2SO_4 (10 mL) and boiled overnight. The products were extracted into CH_2Cl_2 (large excess, especially for **13b**) without basification and isolated in quantitative yields by evaporation of the solvent. Porphyrin **12b**: UV–vis (CH_2Cl_2) λ_{max}/nm (rel ε) 416 (100), 510 (9.3), 542 (2.4), 586 (3.8), 644 (1.5); FAB$^+$ MS 973.5 (MH^+, 100); ^1H NMR ($CDCl_3$) δ 8.75 (m, 4H), 8.37 (d, J = 5 Hz, 2H), 8.13 (d, J = 5 Hz, 2H), 7.63 (d, J = 7.8 Hz, 2H), 7.20 (t, J = 7.8 Hz, 1H), −3.10 (s, 2H); ^{19}F NMR ($CDCl_3$) δ −137.3 (m, 6F), −152.3 (t, J = 22.9 Hz, 1F), −152.4 (t, J = 21.6 Hz, 2F), −162.4 (m, 6F). Porphyrin **13b**: UV–vis (CH_2Cl_2) λ_{max}/nm (rel ε) 422 (100), 516 (8.9), 548 (5.7), 588 (5.1); FAB$^+$ MS 971.6 (MH^+, 100); ^1H NMR (DMSO-d_6) δ 9.16 (s, 2H), 8.95 (d, J = 5 Hz, 2H), 8.67 (d, J = 5

(18) Part of the doublet is overlapping with the singlet next to it. The assignment is based on decoupling experiments.

Hz, 2H), 8.56 (s, 2H), 8.30 (d, J = 8 Hz, 4H), 7.99 (t, J = 8 Hz, 2H), −2.76 (s, 2H); ^{19}F NMR (DMSO-d_6) −138.9 (dd, J_1 = 25 Hz, J_2 = 5 Hz, 4F), −153.89 (t, J = 22 Hz, 2F), −162.5 (m, 4F).

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Supplementary Material Available: Copies of various FAB MS and ^{1}H, ^{19}F, and ^{13}C NMR spectra (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Additions and Corrections

Vol. 59, 1994

Michinori Takeshita, Shoko Nishio, and Seiji Shinkai*. A New Basket Molecule Designed from Calix[6]arene by C_3-Symmetrical Capping. Preorganization of Calix[6]arenes for Inclusion of Trimethylammonium Ions.

Pages 4032 and 4034. In the caption of Figure 1, the characters inside the parentheses are written by Delta symbol font, so (E), (C), (H), and (G) should be changed to (○), (△), (▲), and (□). In the caption of Figure 3, (E) and (G) should be changed to (○) and (□).

Michael T. Blanda* and Karl E. Griswold. Synthesis of a Symmetric Octathio Bis(calix[4]arene) Cage Molecule.

Page 4313. Data reported in the Experimental Section indicated that the signal of *m/e* 1796 was the base peak and the signal for the parent ion at *m/e* 1842 (the cage molecule) was 35% intensity. However, upon review of the entire mass range from 200 to 2400 amu, it is clear that this is not the case. There are much more intense signals at smaller masses (>650). More importantly, there is a signal with *m/e* of 921 with 60% intensity. Subsequent single-crystal X-ray analysis of the compound which was reported as the bis calixarene cage molecule proved our structural assignment to be incorrect. The major component of the reaction mixture which was isolated, characterized, and studied was determined to be in fact the "basket handle" calixarene monomer. The cage molecule was present in the reaction mixture in small amounts, but as yet has not been fully characterized.

Scott E. Denmark* and Shinzo Hosoi. Stereochemical Studies on the Addition of Allylstannanes to Aldehydes. The S_E' Component.

Page 5133. Structure **iii** in Scheme 2 was originally depicted as an antiperiplanar transition structure leading to the trans cyclization product. In a related transformation the authors have suggested a synclinal transition structure as shown to explain the production of this diastereomer. We thank Professor Y. Yamamoto for this clarification. The corrected scheme is shown below.

Scheme 2