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Synthesis of 5,10,15,20-Tetrakis(4-*tert*-butyl-2,6-dicarboxyphenyl)porphyrin: A Versatile Bis-Faced Porphyrin Synthon for D_4-Symmetric Chiral Porphyrins

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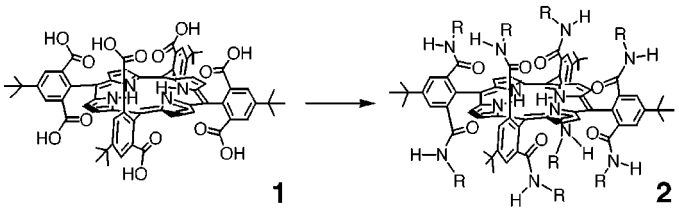
ABSTRACT



A versatile bis-faced porphyrin synthon, 5,10,15,20-tetrakis(4-*tert*-butyl-2,6-dicarboxyphenyl)porphyrin, was synthesized. The eight carboxyl groups were readily converted into various amide groups, and condensation with chiral amines led to various D_4-symmetric chiral porphyrins with rigid structures.

To synthesize porphyrins bearing a molecular recognition site, porphyrin synthons that have functional groups at the *o*-positions of the *meso*-phenyl groups are usually employed, since the chemically modified functional groups can be located near the central metal to enhance selectivity in the porphyrin-catalyzed reactions. Among available synthons, tetrakis(*o*-monosubstituted phenyl)porphyrins[1] such as 5,10,15,20-tetrakis(*o*-aminophenyl)porphyrin have the disadvantage that it is difficult to isolate one atropisomer. Tetrakis(*o*-disubstituted phenyl)porphyrin synthons have several advantages: (1) as many as eight positions of *meso*-phenyl groups can be used to form a molecular recognition site; (2) separation of atropisomers is not required; and (3) both sides of the porphyrin plane can be modified. However, existing tetrakis(*o*-disubstituted phenyl)porphyrin synthons have serious limitations. For example, 5,10,15,20-tetrakis-(2,6-dihydroxyphenyl)porphyrin[2] is widely used as a tetrakis-(*o*-disubstituted phenyl)porphyrin synthon, but the flexible ether linkage should be covalently bound with the neighboring ether functional group to form a bridged structure in order to shape the rigid cavity above the porphyrin ring.[3] As a result, porphyrin synthesis requires multiple reaction steps and is of limited practical use. The same problem arises with *o*-(bromomethyl)-substituted tetraphenylporphyrin.[4] Another synthon, 5,10,15,20-tetrakis(4-*tert*-butyl-2,6-diaminophenyl)-porphyrin,[5] is difficult to synthesize[6] and air-sensitive. In

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(1) (a) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427. (b) Leondiadis, L.; Momenteau, M. *J. Org. Chem.* **1989**, *54*, 6135.

(2) (a) Collman, J. P.; Lee, V. J., Zhang, X. *Inorg. Synth.* **1997**, *31*, 117. (b) Tsuchida, E.; Komatsu, T.; Hasegawa, E.; Nishide, H. *J. Chem. Soc., Dalton Trans.* **1990**, 2713.

(3) (a) Naruta, Y.; Ishihara, N.; Tani, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 158. (b) Gross, Z.; Ini, S. *Org. Lett.* **1999**, *1*, 2077.

(4) Jux, N. *Org. Lett.* **2000**, *2*, 2129.

(5) Rose, E.; Kossanyi, A.; Quelquejeu, M.; Soleilhavoup, M.; Duwavran, F.; Bernard, N.; Lecas, A. *J. Am. Chem. Soc.* **1996**, *118*, 1567.

(6) Condensation of 2,6-dinitrobenzaldehyde and pyrrole afforded a poorer yield than expected, and reduction of nitro groups proved difficult by the reported method.[5]

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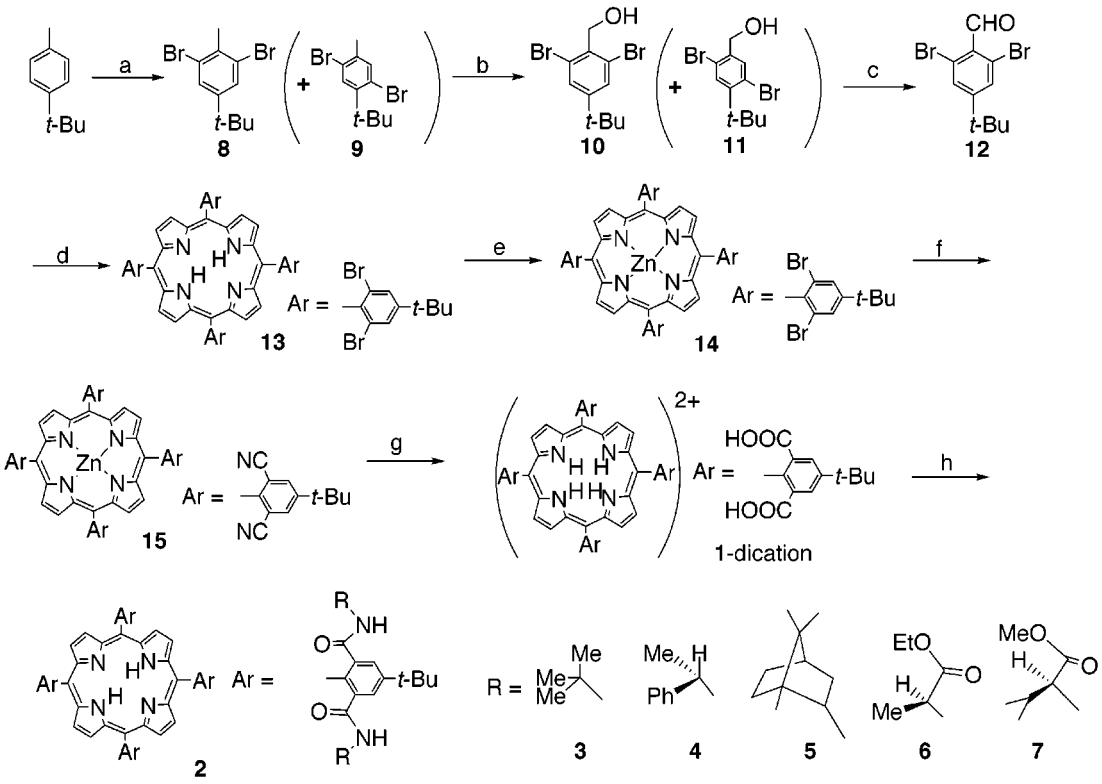
Scheme 1[a]



[a] Reagents and conditions: (a) CCl_4, 40 °C, iron powder, Br_2, 44%; (b) (1) CCl_4, halogen lamp, *N*-bromosuccinimide (2) CH_3CN, reflux, AcOK (3) H_2O, EtOH, reflux, KOH, 85% (based on **8**); (c) CH_2Cl_2, 0 °C, 4-methoxy-2,2,6,6-tetramethylpiperidine *N*-oxyl (4-Me-TEMPO), NaOCl, **10** was recovered in 85% yield (2) CH_3CN, rt, tetra-*n*-propylammonium perruthenate (TPAP), *N*-methyl-morpholine *N*-oxide (NMO), 65%; (d) $CHCl_3$, rt, pyrrole, $BF_3{\cdot}Et_2O$, DDQ, 22%; (e) DMF, reflux $Zn(OAc)_2{\cdot}2H_2O$, 80%; (f) *N*-methylpyrrolidone, reflux, CuCN, 61%; (g) H_2O, reflux, H_2SO_4; (h) (1) CH_2Cl_2, reflux, oxalyl chloride (2) CH_2Cl_2, rt, RNH_2, 40−60% (based on **15**).

addition, *meso*-*o*-acylaminophenyl porphyrins are known to decompose to inactive isoporphyrins in the catalytic oxidation.[7]

Here we report a convenient synthesis of a versatile bis-faced porphyrin synthon, 5,10,15,20-tetrakis(4-*tert*-butyl-2,6-dicarboxyphenyl)porphyrin **1**. From compound **1**, various derivatives of D_4-symmetric chiral porphyrins with a chiral cavity around a catalytic site containing a metal ion can be easily prepared.

Synthesis of benzaldehydes such as 2,6-dicarboxybenzaldehyde is difficult, and in addition the condensation of these benzaldehydes with pyrrole failed to afford the corresponding porphyrins with eight carboxyl groups. On the other hand, 5,10,15,20-tetrakis(2,6-dibromophenyl)porphyrin[8] may be superior as the bromo functional groups can be converted to carboxyl groups via cyano groups. These porphyrins[9] are insoluble in most solvents, and introduction of *tert*-butyl groups is one approach to improve the solubility. We therefore designed compound **1** as a candidate synthon for the synthesis of bis-faced porphyrins (Scheme 1). At the first step to synthesize **8**, 4-*tert*-butyltoluene was brominated, but an equimolar amount of the undesirable product **9** was obtained and could not be separated from **8** by distillation or silica gel column chromatography. Therefore the mixture was directly used in the following reactions. The 4-MeO-TEMPO/NaOCl system could oxidize **11** selectively to the corresponding aldehyde, and **10** was recovered with high purity. The recovered **10** was oxidized to **12** with the TPAP/NMO system. The target porphyrin synthon **1**-dication was obtained from **8** in eight steps. The **1**-dication could be condensed with amines without purification, and its reaction with various amines afforded D_4-symmetric porphyrins (**3**−**7**, yields 40−60%).

Compound **3** was prepared to examine the orientation of the amide groups by ^{1}H NMR spectral analysis (Table 1). The peak due to *tert*-butyl groups bonded to nitrogens showed an upfield shift (0.05 ppm) due to the ring current effect of the porphyrin ring. On the other hand, the shift of the amide protons (5.15 ppm) was not large. This indicates that the *tert*-butyl groups are positioned directly over the porphyrin and inside the shielding cone of the porphyrin and

(7) El-Kasmi, A.; Lexa, D.; Maillard, P.; Momenteau, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1991**, *113*, 1586.

(8) Ostovic, D.; Bruice, T. C. *J. Am. Chem. Soc.* **1988**, *110*, 6906.

(9) 5,10,15,20-Tetrakis(2,6-dicyanophenyl)porphyrin was synthesized by the same method as **14** to **15** but could not be purified sufficiently because of low solubility. FAB mass measurement of the reaction mixture shows $[M - H]^+$ by FAB MS.

Table 1. ^{1}H NMR Shifts (in ppm from TMS) of 5,10,15,20-Tetrakis(*o*-mono- or bis(*N*-*tert*-butylcarbamoyl)phenyl)porphyrin and N-*tert*-Butylcarbamoylbenzene

	NHCO	*N*-*tert*-butyl
octa-substituted **3**	5.15	0.05
tetra-substituted (α,α,α,α)[1b]	5.38	0.10
N-*tert*-butylcarbamoylbenzene	5.94	1.47

the amide protons are directed outside, as shown in Figure 1. Therefore, this porphyrin has a rigid structure.

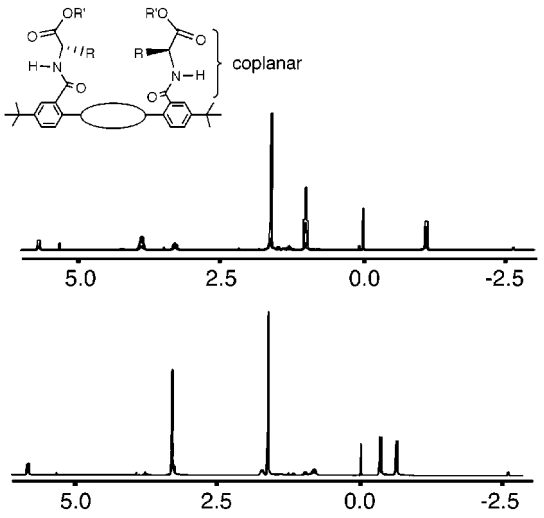


Figure 1.

Figure 1 shows the ^{1}H NMR spectra of **6** and **7**. These porphyrins were designed to form rigid chiral cavities by utilizing coplanarity of amide groups and ester groups attributable to dipole repulsion of the carbonyl groups.[10] The signals of the methyl protons were shifted upfield by the ring current effect (−1.09 ppm for **6**, −0.62 and −0.32 ppm for **7**). This shows the amino acid residues to be positioned inside the shielding cone of the porphyrin, which should form a rigid chiral cavity above the reactive site of the metalloporphyrin.

In conclusion, a versatile new bis-faced porphyrin synthon, 5,10,15,20-tetrakis(4-*tert*-butyl-2,6-dicarboxy-phenyl)porphyrin **1**, was synthesized. This porphyrin should allow the construction of molecular recognition sites over both sides of the porphyrin ring, since it is easy to condense amines to its eight carboxyl groups and these amide groups have a consistent orientation to form a recognition site directed inside the porphyrin ring. Moreover, condensation with amino esters affords rigid chiral cavities. Such compounds could be effective asymmetric epoxidation catalysts[11] since the *meso*-carbons would be more electron-deficient than in the porphyrins derived from previously known bis-faced porphyrin synthons, and higher turnover numbers can be expected. We are currently attempting to prepare such asymmetric catalysts.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015780A

(10) Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853.
(11) For recent review, see: Rose, E.; Quelquejeu, M.; Pandian, R. P.; Lecas-Nawrocka, A.; Vilar, A.; Ricart, G.; Collman, J. P.; Wang, Z.; Straumanis, A. *Polyhedron* **2000**, *19*, 581.