ORGANIC LETTERS

2006
Vol. 8, No. 6
1169−1172

Synthesis of Pyrrolidine-Fused [34]- and [36]Octaphyrins via 1,3-Dipolar Cycloaddition

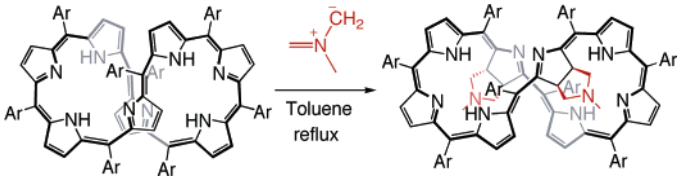
Hiroshi Hata, Yiho Kamimura, Hiroshi Shinokubo,* and Atsuhiro Osuka*

Department of Chemistry, Graduate School of Science, Kyoto University and PRESTO & CREST, Japan Science and Technology Agency (JST), Kyoto 606-8502, Japan

osuka@kuchem.kyoto-u.ac.jp; hshino@kuchem.kyoto-u.ac.jp

Received January 10, 2006

ABSTRACT



The utility of expanded porphyrins as a dipolarophile in cycloaddition reactions has been investigated. The 1,3-dipolar cycloaddition of *meso*-octakis(pentafluorophenyl)[36]octaphyrin(1.1.1.1.1.1.1.1) with an azomethine ylide provides mono- and bis-pyrrolidine-fused octaphyrins regio- and stereoselectively. Treatment of the cycloadduct with MnO_2 afforded [34]octaphyrin quantitatively.

Recently, the reactivity of *meso*-tetraarylporphyrins in concerted cycloaddition reactions has been investigated extensively for the development of new methods of modification of porphyrins.[1−3] For instance, treatment of *meso*-tetraarylporphyrins with an azomethine ylide furnishes pyrrolidine-fused chlorins and isobacteriochlorins in good yields via a 1,3-dipolar cycloaddition. On the other hand, the use of expanded porphyrins in cycloadditions has remained almost unexplored.[4]

Expanded porphyrins, which are porphyrin analogues with more than five pyrrolic subunits, have attracted increasing attention because of their unique properties, such as their interesting structural features, multiple redox behavior, and unique metal-coordination capability.[5] A series of *meso*-aryl-substituted expanded porphyrins can be synthesized in moderate yields from condensation of pyrrole and pentafluorobenzaldehyde.[6] We have also reported an improved synthesis of *meso*-aryl-expanded porphyrins from dipyrromethane or tripyrromethane as starting substrates (Scheme 1).[7] Then, we undertook an investigation on the reactivity of [36]octaphyrin, which can be synthesized in a reasonably good yield, in cycloaddition reactions.[8] [36]Octaphyrin takes a characteristic conformation of a figure-eight structure in the solid state, which could exhibit intriguing features regarding stereo- and regioselectivity of cycloaddition. Here, we wish to report that *meso*-octakis(pentafluorophenyl)[36]-octaphyrin(1.1.1.1.1.1.1.1) (**1**) serves as a dipolarophile in

(1) For an excellent review, see: Cavaleiro, J. A. S.; Neves M. G. P. M. S.; Tomé, A. C. *Arkivoc* **2003**, *xiv*, 107.

(2) For Diels−Alder reactions, see: (a) Tomé, A. C.; Lacerda, P. S. S.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *Chem. Commun.* **1997**, 1199. (b) Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2000**, *41*, 3065.

(3) 1,3-Dipolar addition: (a) Silva, A. M. G.; Tomé, A. C.; Neves, P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Org. Chem.* **2005**, *70*, 2306. (b) Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *Chem. Commun.* **1999**, 1767. (c) Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Perrone, D.; Dondoni, A. *Tetrahedron Lett.* **2002**, *43*, 603. (d) Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *Synlett* **2002**, 1155. (e) Flemming, J.; Dolphin, D. *Tetrahedron Lett.* **2002**, *43*, 7281.

(4) Hata, H.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2397.

(5) (a) Jasat, A.; Dolphin, D. *Chem. Rev.* **1997**, *97*, 2267. (b) Lash, T. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1763. (c) Furuta, H.; Maeda, H.; Osuka, A. *Chem. Commum.* **2002**, 1795. (d) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134. (e) Chandrashekar T. K.; Venkatraman, S. *Acc. Chem. Res.* **2003**, *36*, 676.

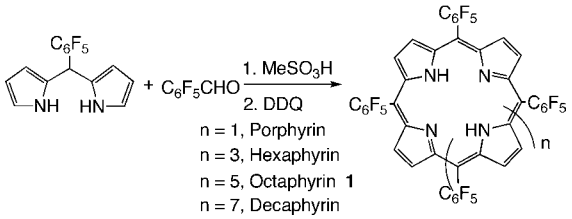
(6) Shin, J.-Y.; Furuta, H.; Yoza, K.; Igarashi, S.; Osuka, A. *J. Am. Chem Soc.* **2001**, *123*, 7190.

(7) Taniguchi, R.; Shimizu, S.; Suzuki, M.; Shin, J.-Y.; Furuta, H.; Osuka, A.; *Tetrahedron Lett.* **2003**, *44*, 2505.

(8) The compounds appearing in this letter are named partly based on the nomenclature defined by Frank and Nonn. Franck, B.; Nonn, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1795.

10.1021/ol060067c CCC: $33.50
Published on Web 02/22/2006

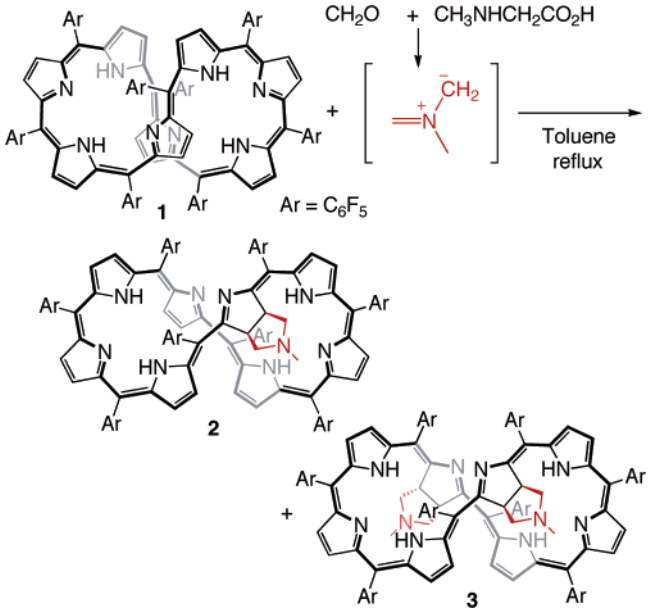
Scheme 1. Synthesis of Expanded Porphyrins



the thermal 1,3-dipolar addition reaction[9] with an azomethine ylide to construct modified octaphyrins, mono- and bis-pyrrolidine-fused adducts, in a highly regio- and stereoselective manner.[10]

For the preparative method of azomethine ylide, we employed the decarbonylative condensation of aldehydes with amino acids.[11] A toluene (2 mL) solution of **1** (0.02 mmol), *N*-methylglycine (0.02 mmol), and paraformaldehyde (0.15 mmol) was heated at reflux for 2 h under nitrogen atmosphere. After evaporation of the solvent, purification by column chromatography with CH_2Cl_2/hexane (1/5) as an eluent yielded monopyrrolidine-fused adduct **2**[12] (3%) and bis-pyrrolidine-fused adduct **3**[13] (7%) along with recovered starting [36]octaphyrin (30%) and reduced **1** ([38]octaphyrin,[14] 26%) (Scheme 2). High-resolution electrospray-ionization time-of-flight (HR-ESI-TOF) mass spectra of **2** and **3**

Scheme 2. 1,3-Dipolar Cycloaddition of Octaphyrin **1**



displayed their parent ion peaks at m/z = 2006.1761 (calcd for $C_{91}H_{28}F_{40}N_9$ = 2006.1823 [$(M + H)^+$]) and 2063.2309 (calcd for $C_{94}H_{35}F_{40}N_{10}$ = 2063.2402 [$(M + H)^+$]), respectively, indicating addition of one and two azomethine ylide units to **1**. Judging from the yields of **2** and **3**, the second addition of azomethine ylide to **2** proceeds faster than the first addition to **1**. In sharp contrast, [38]octaphyrin, which can be obtained by the reduction of [36]octaphyrin with $NaBH_4$, was totally unreactive toward the azomethine ylide under the same conditions, and only decomposition of the starting material was observed. The use of an increased amount of reagents (4.0 equiv of *N*-methylglycine and 10 equiv of paraformaldehyde) improved the yield of **3** to 34% without the formation of monoadduct **2**. However, none of the tri- and tetra-addition products could be detected, although bis-adduct **3** still has pyrrolic C_β−C_β double bonds.

The X-ray structural analyses of mono- and bis-adducts unambiguously elucidate their octaphyrin frameworks as nearly C_2-symmetric figure eight structures (Figure 1).[15] The 1,3-dipolar addition reaction occurred at the carbon−carbon double bonds in pyrroles C and G, which are the double bonds that are not participating in the 36π conjugate circuit. The introduced pyrrolidine rings direct to the outside of the octaphyrin framework. The frameworks of mono-adduct **2** and bis-adducts **3** are quite similar to each other. In both structures, the methine bridge between pyrroles B and C and that between F and G were flipped in comparison with **1**. This structural change makes adducts **2** and **3** more stretched compared to the original octaphyrin **1**. The increased vacant space after the first addition can explain the reason the second addition proceeds more easily than the initial addition.

Octaphyrin is a flexible molecule and probably adopts several different conformations in solution (Figure 2). It

(9) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.

(10) We have also attempted several cycloadditions such as the Diels−Alder reaction with *o*-xylylene with no success.

(11) (a) Nyerges, M.; Balázs, L.; Kádas, I.; Bitter, I.; Kövesdi, I.; Tõke, L. *Tetrahedron* **1995**, *51*, 6783. (b) Nyerges, M.; Tõke, L. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. S., Ed.; Oxford University PressNew York, 2002; p 209.

(12) Spectroscopic data for **2**: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 12.41 (s, 1H, NH), 12.17 (s, 1H, NH), 12.06 (s, 1H, NH), 11.27 (s, 1H, NH), 8.38 (d, J = 5.0 Hz, 1H, β-H), 8.35 (d, J = 5.0 Hz, 1H, β-H), 7.74 (s, 1H, β-H), 7.32 (s, 1H, β-H), 7.05 (s, 2H, β-H), 6.65 (d, J = 4.6 Hz, 1H, β-H), 6.62 (d, J = 4.6 Hz, 1H, β-H), 6.50 (d, J = 5.0 Hz, 1H, β-H), 6.48 (d, J = 5.0 Hz, 1H, β-H), 6.31 (d, J = 5.0 Hz, 1H, β-H), 6.30 (d, J = 5.0 Hz, 1H, β-H), 6.08 (d, J = 4.6 Hz, 1H, β-H), 6.05 (d, J = 4.6 Hz, 1H, β-H), 5.72 (dd, J = 7.3, 7.3 Hz, 1H, pyrrolidine β-H), 4.99 (dd, J = 7.3, 7.3 Hz, 1H, pyrrolidine β-H), 3.41 (d, J = 9.0 Hz, 1H, pyrrolidine α-H), 3.39 (d, J = 9.0 Hz, 1H, pyrrolidine α-H), 3.28 (dd, J = 7.3, 9.0 Hz, 1H, pyrrolidine α-H), 3.10 (dd, J = 7.3, 9.0 Hz, 1H, pyrrolidine α-H), 2.42 (s, 3H, CH_3); λ_{max} (CH_2Cl_2) (ϵ [M^{-1} cm^{-1}]) = 663 (3.6 × 10^4), 611 (5.5 × 10^4), 581 (6.0 × 10^4), 545 (5.2 × 10^4), 420 (2.9 × 10^4), 364 nm (3.0 × 10^4); HR-ESI-MS m/z = 2006.1761, calcd for $C_{91}H_{28}F_{40}N_9$ 2006.1823 [$(M + H)^+$]. Crystal data for **2**: $C_{107}H_{47}N_9F_{40}Cl_4O$, M_W = 2376.36, triclinic, space group P-1 (No. 2), a = 15.037(9) Å, b = 18.91(1) Å, c = 19.84(1) Å, α = 81.38(6)°, β = 87.14(6)°, γ = 66.80(5)°, V = 5127(6) Å^3, T = 123 K, ρ_{calcd} = 1.539 g cm^{-3}, Z = 2. For 76930 reflections measured, R = 0.098, R_w = 0.139 for 7782 reflections with [$I > 3\sigma(I)$], GOF = 1.272.

(13) Spectroscopic data for **3**: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 11.93 (s, 2H, NH), 11.26 (s, 2H, NH), 7.12 (s, 2H, β-H), 7.05 (s, 2H, β-H), 6.64 (d, J = 4.1 Hz, 2H, β-H), 6.49 (d, J = 5.3 Hz, 2H, β-H), 6.36 (d, J = 5.3 Hz, 2H, β-H), 6.08 (d, J = 4.1 Hz, 2H, β-H), 5.24 (dd, J = 7.0, 7.0 Hz, 2H, pyrrolidine β-H), 4.60 (dd, J = 7.0, 7.0 Hz, 2H, pyrrolidine β-H), 3.29 (d, J = 9.0 Hz, 2H, pyrrolidine α-H), 3.27 (d, J = 9.0 Hz, 2H, pyrrolidine α-H), 3.03 (dd, J = 7.0, 9.0 Hz, 2H, pyrrolidine α-H), 2.90 (dd, J = 7.0, 9.0 Hz, 2H, pyrrolidine α-H), 2.35 (s, 6H, CH_3); λ_{max} (CH_2Cl_2) (ϵ [M^{-1} cm^{-1}]) = 661 (5.5 × 10^4), 564 (1.0 × 10^5), 545 (1.0 × 10^5), 362 nm (4.9 × 10^4); HR-ESI-MS m/z = 2063.2309, calcd for $C_{94}H_{35}F_{40}N_{10}$ 2063.2402 [$(M + H)^+$]. Crystal data for **3**: $C_{102}H_{36}N_{10}F_{40}Cl_2$, M_w = 2232.31, monoclinic, space group $P2_1/n$ (No. 14), a = 15.4671(13) Å, b = 22.6543(18) Å, c = 27.050(2) Å, β = 102.299(2)°, V = 9260.6(13) Å^3, Z = 4, D_{calc} = 1.601 g/cm^3, T = 120 K, 58572 measured reflections, 21720 unique reflections, R = 0.0846 ($I > 2.0\sigma(I)$), R_w = 0.2883 (all data) GOF = 1.068 ($I > 2.0\sigma(I)$).

(14) For [38]octaphyrin, see ref 6.

(15) The X-ray structure of octaphyrin **1** has been reported; see ref 6.

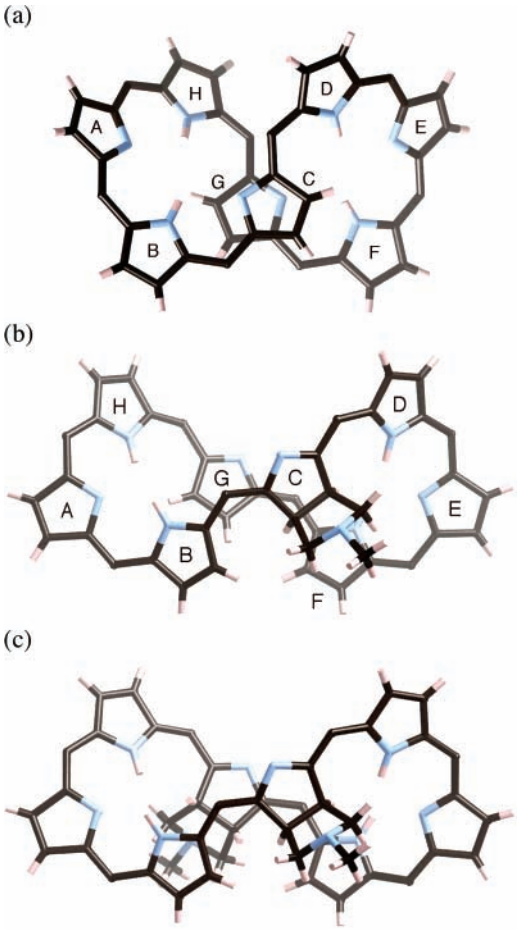


Figure 1. X-ray structures of (a) octaphyrin **1**,[6] (b) pyrrolidine-fused adduct **2**, and (c) bis-pyrrolidine-fused adduct **3**. *meso*-Pentafluorophenyl groups and solvent molecules are omitted for clarity.

seems that the solid-state conformation **I** is not a favorable one for the cycloaddition because all pyrrolic $C_\beta-C_\beta$ double bonds are shielded by the pentafluorophenyl groups. In contrast, the plausible conformation **II** has two easily accessible 1,3-dipolar double bonds at pyrroles C and G, since the methine bridges are now flipped to the opposite side of the pyrrolic double bonds. Meanwhile, the addition to the other C−C double bonds is still hampered by the pentafluorophenyl groups. This situation reasonably explains the lack of higher addition products. The observed stereoselectivity can be also account for the access of 1,3-dipolar bonds from the less hindered face of the pyrrole units in the stretched conformer **II**.

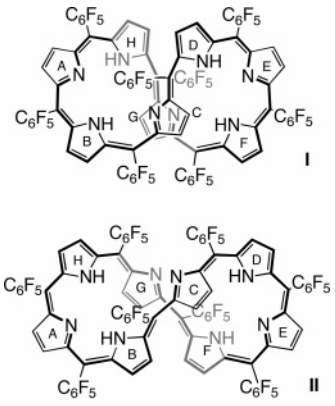


Figure 2. Possible conformations of octaphyrin. Solid-state conformer **I** and plausible conformation with two methine inversions **II**. The conjugate circuit is drawn with bold lines.

The absorption spectra of **2** and **3** in dichloromethane are shown along with that of original octaphyrin **1** in Figure 3.

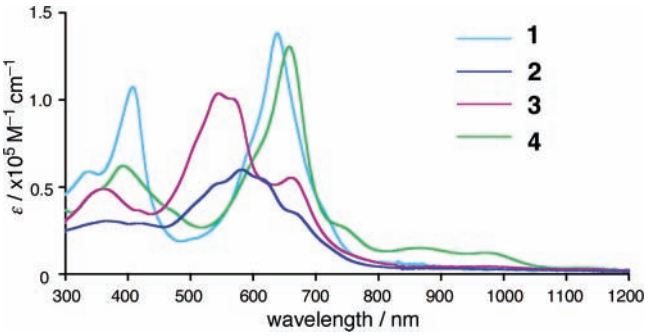


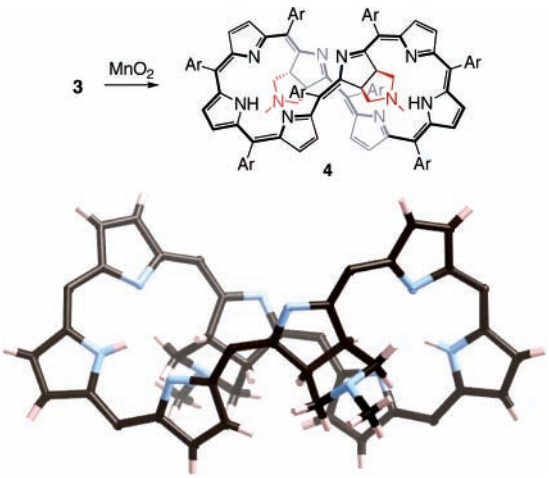
Figure 3. UV−vis absorption spectra of **1**−**4** in dichloromethane.

The Soret-like absorption bands of these compounds are blue-shifted gradually, probably due to the decrease of π-conjugation by the addition reactions to carbon−carbon double bonds.

We then attempted oxidation of **3** to remove four bridgehead protons attached to sp^3 carbons of **3**, expecting the reaction to provide the original [36]octaphyrin skeleton. Unfortunately, the use of DDQ as an oxidant afforded unidentified unstable products. In contrast, **3** can be cleanly oxidized with MnO_2 in dichloromethane with a color change from purple to blue (Scheme 3). After filtration of black powder through a pad of alumina, compound **4**[16] was isolated in quantitative yield. The HR-ESI-TOF mass spectrum of the oxidized product **4** exhibited its parent ion peaks at *m*/*z* = 2061.2192 ($C_{94}H_{33}F_{40}N_{10}$ = 2061.2245 [$(M + H)^+$]), revealing a loss of two hydrogen atoms during oxidation. Contrary to our expectations, the ^{1}H NMR and H−H COSY analyses of **4** indicated that bridgehead protons are still intact.

(16) Spectroscopic data for **4**: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 11.72 (s, 2H, NH), 6.58 (d, J = 4.9 Hz, 2H, β-H), 6.54 (d, J = 4.8 Hz, 2H, β-H), 6.52 (d, J = 4.7 Hz, 2H, β-H), 6.46 (d, J = 4.9 Hz, 2H, β-H), 6.14 (d, J = 4.6 Hz, 2H, β-H), 5.97 (d, J = 4.7 Hz, 2H, β-H), 3.31 (d, J = 9.7 Hz, 2H, pyrrolidine α-H), 2.90 (d, J = 8.9 Hz, 2H, pyrrolidine α-H), 2.80 (t, J = 7.1 Hz, 2H, pyrrolidine β-H), 2.03 (s, 6H, CH_3), 1.52 (t, J = 8.8 Hz, 2H, pyrrolidine β-H), 1.34 (d, J = 10.6 Hz, 2H, pyrrolidine α-H), 1.32 (d, J = 8.2 Hz, 2H, pyrrolidine α-H); λ_{max} (CH_2Cl_2) (ϵ [M^{-1} cm^{-1}]) = 658 (1.3×10^5), 393 nm (6.0×10^4); HR-ESI-MS *m*/*z* = 2061.2192, calcd for $C_{94}H_{33}F_{40}N_{10}$ 2061.2245 [$(M+H)^+$]. Crystal data for **4**: $C_{96}H_{32}N_{10}F_{40}Cl_4$, M_w = 2227.12, monoclinic, space group $P2_1/n$ (No. 14), a = 15.209(3) Å, b = 22.606(4) Å, c = 27.009(5) Å, β = 101.382(3)°, V = 9103(3) Å^3, Z = 4, D_{calc} = 1.625 g/cm^3, T = 90 K, 86713 measured reflections, 16011 unique reflections, R = 0.0828 ($I > 2.0\sigma(I)$), R_w = 0.2549 (all data) GOF = 1.065 ($I > 2.0\sigma(I)$).

Scheme 3. Oxidation of Pyrrolidine Adduct **3** with MnO_2 to [34]Octaphyrin and X-ray Structure of **4**



Furthermore, only two NH protons were detected, whereas [36]octaphyrin should have four NH protons. From these observations, we concluded that the compound **4** is bis-pyrrolidine fused [34]octaphyrin, which was stable in the solid state but was slowly reduced to **3** in a few days in solution. The structure of **4** in the solid state was elucidated by X-ray crystallography. The structure of **4** appears quite similar to **3**, but clearly differs in the bond length alternation (Supporting Information). Interestingly, six protons on the fused pyrrolidine units (four α- and two β-protons) appear in the significantly high-field region (δ = 1.52, 1.34, and 1.32) in the ^{1}H NMR spectrum of **4**. The observed high-field shift can be ascribed to the close placement of these protons to the pyrrole ring in the other side. As shown in Figure 3, the absorption spectrum of **4** exhibited a significantly red-shifted Soret-like band compared to cycloadducts **2** and **3**, and the lower energy absorption of **4** reaches nearly to 1100 nm, probably reflecting the change of conjugation to 34π electronic system upon oxidation. In contrast, treatment of **3** with $NaBH_4$ provided none of reduced products.

In summary, we have found that the reaction of *meso*-octakis(pentafluorophenyl)[36]octaphyrin with azomethine ylide provided cycloadducts regio- and stereoselectively via a 1,3-dipolar addition. The structures of mono- and bis-adducts have been clearly elucidated. The present results demonstrate that modification through regioselective cycloaddition is quite effective not only for porphyrins but also for expanded porphyrins. Further research on cycloaddition of expanded porphyrins and exploration of coordination properties of pyrrolidine-modified octaphyrin is currently underway in our laboratory.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental procedures, compound data, and X-ray crystallographic data for **2**−**4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL060067C