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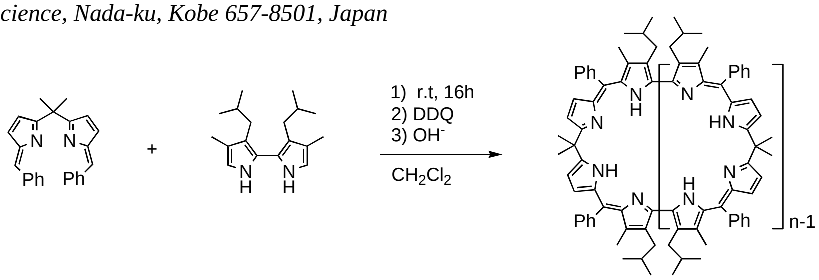

4n

(n = 1 - 11)

Pergamon

TETRAHEDRON
LETTERS

Synthesis of isocorrole and the higher homologues

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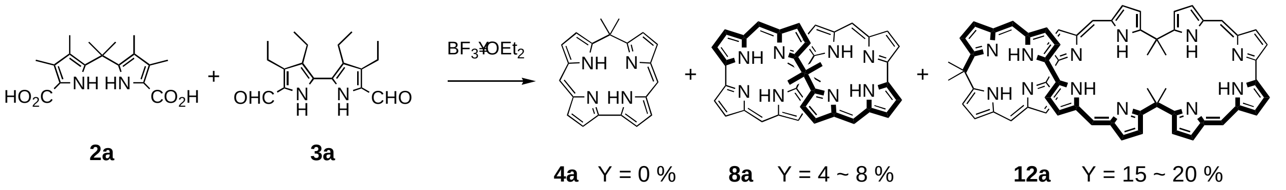
Abstract— Bis(azafulvene) derivative of *gem*-dimethyldipyrrylmethane reacted with 2,2'-bipyrrole under neutral conditions without catalyst to give a mixture of expanded isocorroles in ca. 50% total yields. GPC separation gave eleven porphyrinoids containing 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 units of pyrrole. © 2007 Elsevier Science. All rights reserved.

Isocorrole is a tautomeric form of corrole where one of three *meso*-carbons of the (1.1.1.0)-type tetrapyrrolic macrocycle is sp^3-hybridized and two NH protons are inside the cavity,[1,2] although a (2.0.1.0)-type structural isomer is also called the same name.[3] The isocorrole nucleus has only recently been synthesized by the condensation of two parts of 3,4-diethyl-2-formylpyrrole **1** with *gem*-dimethyl-3,3',4,4'-tetramethyldipyrrylmethane-5,5'-dicarboxylic acid **2a** followed by the oxidative coupling of the resulting *a,c*-biladiene in the presence of $Ni(OAc)_2•4H_2O$.[2] On the other hand, the [2+2]-type condensation of the diacid **2a** and 5,5'-diformyl-3,3',4,4'-tetraethyl-2,2'-bipyrrole **3a** did not give isocorrole **4a** at all, but afforded cyclooctapyrrole **8a** and cyclododecapyrrole **12a** (see Scheme 1).[1] These expanded isocorroles are closely related to the calixphyrins where both sp^2- and sp^3-hybridized bridging carbons are present in the porphyrin framework.[4] Thus, more flexible ring structure is expected for the expanded isocorroles in comparison with the expanded porphyrins with complete cycloconjugation. In view of the fact that there has been very little work on the isocorrole derivatives in spite of their importance as a member of porphyrinoids, we have applied our original synthetic method using bis(azafulvene) to the preparation of *gem*-dimethylisocorrole and the higher homologues.[5]



Scheme 1: Synthesis of cyclooctapyrrole **8a** and cyclododecapyrrole **12a** by Vogel and co-workers (ref. 1).

A CH_2Cl_2 solution (40 ml) of *gem*-dimethyl-2,2'-bis(6-phenylazafulvenyl)methane **2**[6] (0.48 mmol) and 3,3'-di-*iso*-butyl-4,4'-dimethyl-2,2'-bipyrrole **3**[7] (0.48 mmol) was stirred at room temperature for 16 h under argon. After oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (abbreviated hereafter as DDQ) (1.44 mmol), the reaction mixture was purified by column chromatography to give isocorrole **4** in 27.8% yield. The higher homologues **8**, **12**, **16**, **20**, and **24** containing 8, 12, 16, 20, and 24 pyrrole units were separated by gel permeation chromatography (GPC) in 9.5%, 5.8%, 3.2%, 2.5%, and 1.5% yield, respectively, as shown in Table 1. When the reactant concentration was increased from 0.012 to 0.027 mol/L, the yield of higher homologues increased in sacrifice of the yield of **4** and the total yield of the macrocycles decreased from 50.5% to 44.2% (Table 1, entry 2). Addition of 2 molar equivalents

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Keywords: porphyrinoids, calixphyrin, macrocycle, porphyrins, expanded porphyrins, corrole

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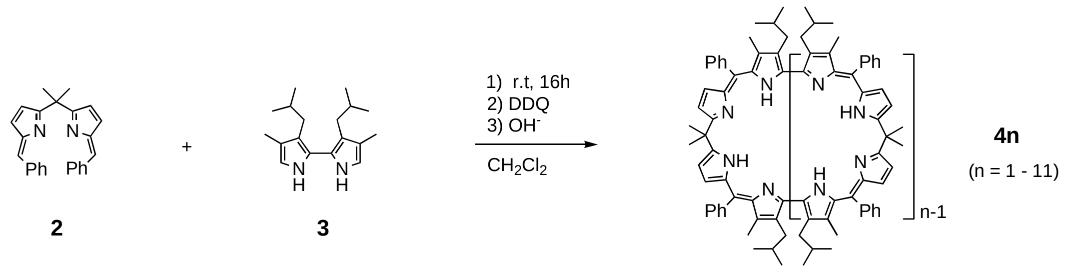
of zinc(II) *p*-*t*-butylbenzoate further changed the products distribution in favor of the higher homologues without affecting the total yield (Table 1, entry 3). Thus, expanded isocorroles **28** and **32** with 28 and 32 pyrrole units were isolated in 1.6% and 0.7% yield, respectively. The first fraction in the GPC was further separated by using polystyrene-polydivinylbenzene gel with a larger pore size to result in the isolation of giant homologues **36**, **40** and **44** with 36, 40, and 44 pyrrole units in the yield of 0.5% ~ 0.1%.[8] However, the total yield decreased to only 15% at the reactant concentration of 0.080 mol/L.

Table 1. Synthesis of cyclopolypyrroles **4n**.



entry	Additive[a)]	conc.[b)]	yield (%) of **4n** (n = 1 – 8)								
			4	**8**	**12**	**16**	**20**	**24**	**28**	**32**	total
1	none	0.012	27.8	9.5	5.8	3.2	2.5	1.5	tr	-	50.5
2	none	0.027	10.3	10.4	9.4	6.8	3.8	2.3	1.2	tr	44.2
3	$Zn(p\text{-}t\text{-}BuC_6H_4CO_2)_2$	0.027	4.5	12.8	9.6	7.6	4.6	2.7	1.6	0.7	44.1

a) Zinc *p*-*t*-butylbenzoate (2 molar equiv) was added. b) concentration of **2** and **3** (mol/L).

These expanded isocorroles were identified by ESIMS. The largest homologue, cyclotetratetracontapyrrole **44**, (MW = 6807.1) showed seven signals corresponding to the di-protonated species at 3405.6 mass (3404.6 calcd. for $C_{473}H_{506}N_{44} + 2H^+$) through the octa-protonated species at 852.0 mass (851.9 calcd. for $C_{473}H_{506}N_{44} + 8H^+$) as depicted in Figure 1.

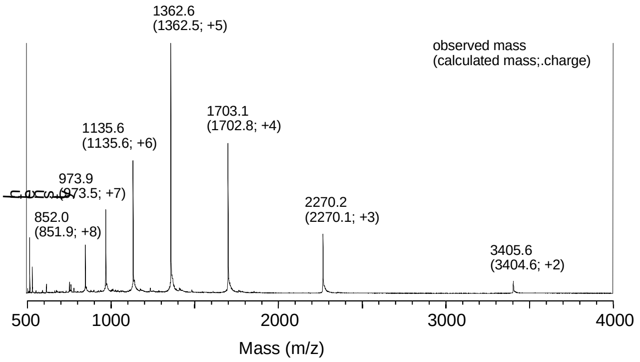


Figure 1. ESIMS spectrum of **44**. The calculated mass and the number of charges are indicated in the parenthesis.

The UV-vis absorption band is red-shifted with increasing the ring size as shown in Figure 2; 420, 541, 538, 557, 574, 582, and 584 nm for **4**, **8**, **12**, **16**, **20**, **24**, and **28**, respectively. The larger homologues **32**, **36**, **40** and **44** showed virtually the same UV-vis feature with an absorption maximum at 586~587 nm. It is noteworthy that the UV-vis feature of **8** (a strong band at 541 nm with shoulders at 459 and 642 nm) is quite different from that of **8a** (a strong band at 435 nm with a weak band at 523 nm), whereas **12** and **12a** show similar UV-vis spectra with a weak band at around 430 nm (433 nm for **12** and 429 nm for **12a**) and a strong band at around 540 nm (538 nm for **12** and 544 nm for **12a**).[1] These UV-vis spectra seem to depend on the conformation of the π-conjugated tetrapyrrolic units and the electronic interaction beyond the bridging sp^3 carbons, that is, homoconjugation or transannular ππ interaction. Thus, the UV-vis spectrum converged to that expected for linear oligomers as the ring size increased.

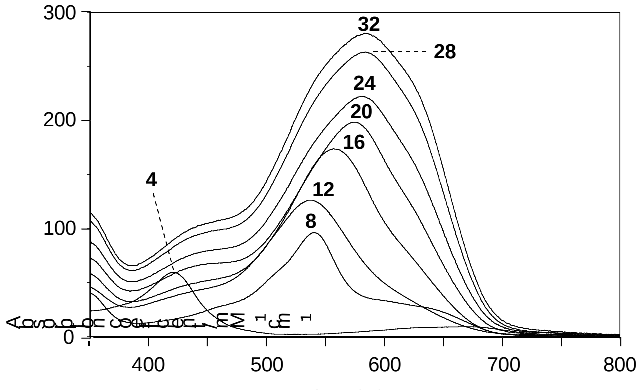
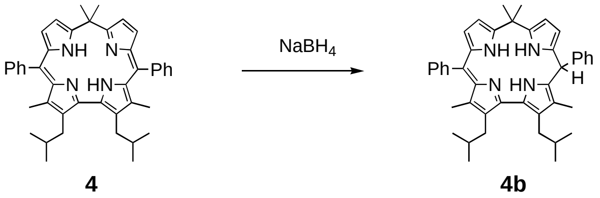


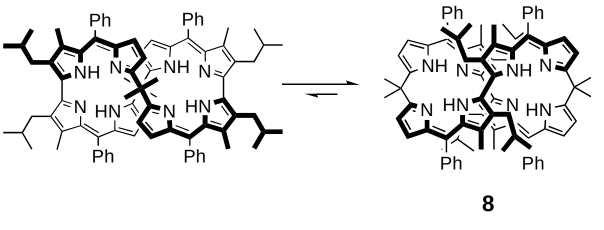
Figure 2. UV-vis spectra of isocorrole **4** and the higher homologues **8**, **12**, **16**, **20**, **24**, **28**, and **32** in CH_2Cl_2.

The cyclopolypyrroles larger than cyclododecapyrroles have never been reported in the porphyrinoid chemistry except our previous work on the expanded porphyrins having 16, 20, and 24 pyrrole units.[5] To the best of our knowledge, a free base form of isocorrole has never been reported so far either. The isocorrole **4** shows a B-type band at 420 nm and Q-type bands at 620 and 675 nm in the UV-vis spectrum and signals due to the NH protons at 13.6 ppm and pyrrole β-protons at 6.53 and 6.38 ppm in the ^{1}H NMR. The $NaBH_4$ reduction of **4** in a mixture of CH_2Cl_2 and ethanol quantitatively gave the dihydrocorrole **4b**[9] (see Scheme 2), which showed three ^{1}H NMR signals due to the NH protons at 12.6, 8.56, and 8.23 ppm and a singlet due to the *meso*-proton at 5.49 ppm. Therefore, reduction occurred at one *meso*-carbon and one pyrrole nitrogen but not at two *meso*-carbons. Although condensation of **2a** and **3a** in the presence of a large excess amount of $BF_3 \bullet Et_2O$ failed to give isocorrole,[1] it has recently been reported that the acid-catalyzed condensation of dipyrrylmethane 5,5'-dicarbinol with 2,2'-bipyrrole gave *meso*-triarylcorroles in ca. 10% yield after DDQ oxidation.[10] The latter reaction is closely related to the present reaction, because **2** is a dehydrated form of the dipyrrylmethane 5,5'-dicarbinol.[6] Therefore, preparation of **4** in 27.8% yield is remarkable.



Scheme 2: Reduction of isocorrole **4** to dihydrocorrole **4b**.

It has been reported that the *gem*-dimethyldipyrrylmethane units are at the crossing point of the figure 8 loop of **8a** on the basis of the X-ray crystallographic analysis and the NOE NMR experiment in solution.[1] A remarkable difference in the UV-vis feature between **8a** and **8** noted above suggests that the loop conformation of **8** is not similar to the figure 8 conformation of **8a**. The 2D ROESY NMR spectrum of **8** showed a cross peak between doublets (6.33, 6.18 ppm) due to the β-pyrrole protons and doublets (0.48, 0.47 ppm) due to the methyl protons of the *iso*-butyl group. Therefore, the conformation of **8** is close to the figure 8 loop where the bipyrrole units are at the crossing point as shown in Scheme 3. The conformation of the macrocycle is dependent on the substitution pattern in the macrocycle periphery, especially on the steric bulk of the *meso*-phenyl groups in this case.



Scheme 3: The figure 8 loop conformation of cyclooctapyrrole **8**.

The formation of macrocycles using bis(azafulvene) derivative of *gem*-dimethyldipyrrylmethane and 2,2'-bipyrrole proceeded under neutral conditions to give *gem*-dimethylisocorrole as the smallest member through cyclotetratetracontapyrrole as the largest member. The yield and products distribution were dependent on the reaction conditions and the substitution pattern of the macrocycle periphery as compared with the result of Vogel and coworkers.[1] Availability of these nano-scale cyclooligomers of different ring sizes with the intervals of 4 pyrrole units is of significance in view of their combinatorial application. Further studies aiming at more selective formation of the giant porphyrinoids as well as their use in the supramolecular chemistry are based on this work.

Acknowledgements

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References

1. Wytko, J. A.; Michels, M.; Zander, L.; Lex, J.; Schmickler, H.; Vogel, E. *J. Org. Chem.* **2000**, *65*, 8709-8714.
2. Hohlneicher, G.; Bremm, D.; Wytko, J.; Bley-escrich, J.; Gisselbrecht, J.-p.; Gross, M.; Michels, M.; Lex, J.; Vogel, E. *Chem. Eur. J.* **2003**, *9*, 5636-5642.
3. (a) Will, S.; Rahbar, A.; Schmickler, H.; Lex, J.; Vogel, E. *Angew. Chem. Int. Ed.* **1990**, *29*, 1390-1393; (b) Vogel, E.; Binsack, B.; Hellwig, Y.; Erben, C.; Heger, A.; Lex, J.; Wu, Y.-D. *Angew. Chem. Int. Ed.* **1997**, *36*, 2612-2615.
4. (a) Král, V.; Sessler, J. L.; Zimmerman, R. S.; Seidel, D.; Lynch, V.; Andrioletti, B. *Angew. Chem. Int. Ed.* **2000**, *39*, 1055-1058; (b) Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 2278-2281; (c) Bucher, C.; Zimmerman, R. S.; Lynch, V.; Král, V.; Sessler, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2099-2100; (d) Bernatkova, M.; Andrioletti, B.; Král, V.; Rose, E.; Vaissermann, J. *J. Org. Chem.* **2004**, *69*, 8140-8143; (e) Bucher, C.; Seidel, D.; Lynch, V.; Král, V.; Sessler, J. L. *Org. Lett.* **2000**, *2*, 3103-3106; (f) Dolensky, B.; Kroulik, J.; Král, V.; Sessler, J. L.; Dvorakova, H.; Bour, P.; Bernatkova, M.; Bucher, C.; Lynch, V. *J. Am. Chem. Soc.* **2004**, *126*, 13714-13722.
5. Setsune, J.; Maeda, S. *J. Am. Chem. Soc.* **2000**, *122*, 12405-12406.
6. Bis(azafulvenyl)methane **2** was obtained from *gem*-dimethyldipyrrylmethane dicarbinol in more than 90% yield (Setsune, J.; Tanabe, A.; Watanabe, J.; Maeda, S. *to be submitted.*): To a mixture of the dicarbinol (0.53 mmol) and 4-dimethylaminopyridine (0.028 mmol) was added a dry ether solution (8 ml) of di-*t*-butyl dicarbonate (1.57 mmol) under argon. After stirring for 3 h at room temperature, the color of the solution turned bright yellow. Aqueous K_2CO_3 solution (8 mL, 0.02 mol/L) was added to the reaction mixture and it was extracted with diethyl ether. After drying over anhydrous K_2CO_3, hexane (5 ml) was added to the ether solution and condensed under reduced pressure. A small

amount of precipitates formed at first was removed by filtration and the filtrate was evaporated to give **2**. UV-vis (λ_{max} nm (logε) in CH_2Cl_2) 350 (4.61). ^{1}H NMR (δ-value in $CDCl_3$) 8.33 (d, 4H, J=8.3 Hz, *o*-Ph-H); 7.43 (t, 4H, J=7.3 Hz, *m*-Ph-H); 7.38 (t, 2H, J=7.2 Hz, *p*-Ph-H); 6.89 (s, 2H, -CH=); 7.06, 6.62 (d×2, 2H×2, J=4.5 Hz, *β*-pyrrole-H); 1.82 (s, 6H, -CH_3). MS (EI) (found/calcd for $C_{25}H_{22}N_2$) 350/350 (M^+). Analysis calcd (%) for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.48; H, 6.39; N, 8.17.

7. 2,2'-Bipyrrole **3** was prepared in a similar manner to 3,3'-dimethyl-4,4'-diethyl-2,2'-bipyrrole[11]: ^{1}H NMR (δ-value in $CDCl_3$) 7.73 (br, 2H, NH); 6.54 (d, 2H, J=2.5 Hz, α-py-H); 2.34 (d, 4H, C*H*$_2$CHMe); 2.06 (s, 6H, β-py-CH_3); 1.72 (m, 2H, -CH_2C*H*Me_2); 0.82 (d, 12H, -CH_2CH*Me*$_2$). MS (EI) (found/calcd for $C_{18}H_{28}N_2$) 272/272 (M^+). Analysis calcd (%) for $C_{18}H_{28}N_2$: C, 78.96; H, 10.41; N, 10.19. Found: C, 79.36; H, 10.36; N, 10.28.

8. *Typical procedure*: A mixture of *gem*-dimethyl-2,2'-bis(6-phenylazafulvenyl)-methane **2** (0.50 mmol), 3,3'-di-*iso*-butyl-4,4'-dimethyl-2,2'-bipyrrole **3** (0.50 mmol), and Zn(II) *p-t*-butylbenzoate (1.0 mmol) in dry CH_2Cl_2 (18 ml) was stirred for 16 h at room temperature under argon. DDQ (1.60 mmol) was then added to the reaction mixture and stirring was continued for additional 2 h at room temperature. The resulting blue-green solution was passed through Celite that was washed with CH_2Cl_2 and then with acetone. The acetone washings were evaporated and the residue was dissolved in a mixture of CH_2Cl_2 and methanol (20/1). The combined organic solution was shaken with 2% aqueous $HClO_4$ solution, water, and 0.5% aqueous NaOH solution, sequentially. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on Al_2O_3 (activity II-III) with toluene to give a mixture of expanded isocorroles. A $CHCl_3$ solution of these expanded isocorroles was injected to HPLC with a combination of GPC columns of JAIGEL-3H (20 ×600 mm, exclusion limit MW 70000 polystyrene) and JAIGEL-2H (20 ×600 mm, exclusion limit MW 5000 polystyrene) and the separation was performed by using a recycle loop. **4**, **8**, **12**, **16**, **20**, **24**, **28**, and **32** were separated at the retention time of 190 (at the 3rd cycle), 188 (at the 3rd cycle), 344 (at the 6th cycle), 499 (at the 9th cycle), 486 (at the 9th cycle), 475 (at the 9th cycle), 466 (at the 9th cycle), and 254 (at the 5th cycle) min, respectively, with a $CHCl_3$ flow rate of 3.8 mL/min. The fraction running faster than **32** was further separated by the combination of GPC columns of JAIGEL-3H and JAIGEL-2.5H (20 ×600 mm, exclusion limit MW 20000 polystyrene). **36**, **40**, and **44** were separated at the retention time of 859, 852, and 844 min at the 16th cycle, respectively, with a $CHCl_3$ flow rate of 3.8 mL/min. The separated fractions corresponding to **4** through **32** were evaporated. Reprecipitation by slowly evaporating the CH_2Cl_2-methanol solution and filtration afforded pure materials of **4** through **32**. The yields of **36**, **40**, and **44** were roughly estimated on the basis of their UV-vis absorbances at 500 nm relative to that of **32** during the GPC separation. Isocorrole **4**: UV-vis (λ_{max} nm (logε) in CH_2Cl_2) 420 (4.77), 620 (3.88), 675 (3.96). ^{1}H-NMR (δ-value in $CDCl_3$) 13.6 (br, 2H, NH); 7.44~7.48 (m,10H, *meso*-Ph-H); 6.53, 6.38 (d×2, 2H×2, J=4.3 Hz, β-py-H); 2.51 (d, 4H, J=7.5 Hz, -C*H*$_2$CHMe); 1.79 (s, 6H, β-py-CH_3); 1.43 (s, 6H, *gem*-CH_3); 1.72~1.77 (m, 2H, -CH_2C*H*Me); 0.87 (d, 12H, J=6.8 Hz, -CH_2CH*Me*$_2$). ESI-MS (found/calcd for $C_{43}H_{46}N_4$ + H^+) 619.39/619.38. Analysis calcd (%) for $C_{43}H_{46}N_4$: C, 83.45; H, 7.49; N, 9.05. Found: C, 83.60; H, 7.48; N, 9.17. Cyclooctapyrrole **8**: UV-vis (λ_{max} nm (logε) in CH_2Cl_2) 459 (sh, 4.44), 541 (4.98), 642 (sh, 4.40). ^{1}H-NMR (δ-value in $CDCl_3$) 12.4 (br, 4H, NH); 7.28~7.46 (m,20H, *meso*-Ph-H); 6.33, 6.18 (d×2, 4H×2, J=4.2 Hz, β-py-H); 2.73, 1.72 (dd×2, 4H×2, J=7.3, 14.6 Hz, -C*H*$_2$CHMe$_2$); 1.69 (s, 12H, β-py-CH_3); 1.23 (s, 12H, *gem*-CH_3); 1.18~1.25 (m, 4H, -CH_2C*H*Me$_2$); 0.48, 0.47 (d×2, 12H×2, J=6.3 Hz, -CH_2CH*Me*$_2$). ESI-MS (found/calcd for $C_{86}H_{92}N_8$ + nH^+) 1238.75/1238.76 (n=1); 619.89/619.88 (n=2). Analysis calcd (%) for $C_{86}H_{92}N_8$: C, 83.45; H, 7.49; N, 9.05. Found: C, 83.29; H, 7.36; N, 9.33. Cyclododecapyrrole **12**: UV-vis (λ_{max} nm (logε) in CH_2Cl_2) 433 (sh, 4.61), 538 (5.10). ^{1}H-NMR (δ-value in $CDCl_3$) 12.9 (br, 6H, NH); 7.37 (br,30H, *meso*-Ph-H); 6.08, 6.02 (br×2, 6H×2, β-py-H); 2.98, 1.98 (br×2, 6H×2, -C*H*$_2$CHMe$_2$); 1.65 (s, 18H, β-py-CH_3); 1.25 (s, 18H, *gem*-CH_3); 1.36 (m, 6H, -CH_2C*H*Me$_2$); 0.63 (br, 36H, -CH_2CH*Me*$_2$). ESI-MS (found/calcd for $C_{129}H_{138}N_{12}$ + nH^+) 1857.16/1857.13 (n=1); 928.98/929.07 (n=2); 619.84/619.71 (n=3). Analysis calcd (%) for $C_{129}H_{138}N_{12}$: C, 83.45; H, 7.49; N, 9.05. Found: C, 83.34; H, 7.62; N, 8.81. Cyclohexadecapyrrole **16**: UV-vis (λ_{max} nm (logε) in CH_2Cl_2) 433 (sh, 4.68), 557 (5.24). ^{1}H-NMR (δ-value in $CDCl_3$) 12.9 (br, 8H, NH); 7.22~7.30 (m,40H, *meso*-Ph-H); 6.03 (d, 8H, J=3.7 Hz, β-py-H); 6.10 (br, 8H, β-py-H); 2.17~2.63 (br, 16H, -C*H*$_2$CHMe$_2$); 1.73 (s, 24H, β-py-CH_3); 1.18 (s, 24H, *gem*-CH_3); 1.47~1.53 (m, 8H, -CH_2C*H*Me$_2$); 0.68 (d, 48H, J=6.3 Hz, -CH_2CH*Me*$_2$). ESI-MS (found/calcd for $C_{172}H_{184}N_{16}$ + nH^+) 2475.00/2475.50 (n=1); 1238.43/1238.76 (n=2); 826.18/826.17 (n=3); 620.03/619.88 (n=4). Analysis calcd (%) for $C_{172}H_{184}N_{16}$: C, 83.45; H, 7.49; N, 9.05. Found: C, 83.63; H, 7.69; N, 9.03.

9. Spectroscopic data of **4b**: UV-Vis (λ_{max} nm (logε) in CH_2Cl_2) 374 (3.93), 425 (3.59), 508 (4.26), 541 (sh, 413). ^{1}H-NMR (δ-value in $CDCl_3$) 12.6, 8.56, 8.23 (s×3, 1H×3, NH); 7.22~7.45 (m, 10H, *meso*-Ph-H); 6.05, 5.91 (d×2, 1H×2, J=4.0 Hz, β-py-H); 5.97, 5.73 (t×2, 1H×2, J=3.0 Hz, β-py-H); 5.49 (s, 1H, *meso*- H); 2.32, 2.45, 2.49, 2.56 (dd×4, 1H×4, J=14.2, 7.5 Hz, -C*H*$_2$CHMe$_2$); 1.70, 1.66 (s×2, 3H×2, β-py-CH_3); 1.78, 1.33 (s×2, 3H×2, *gem*-CH_3); 1.80~1.85 (m, 2H, -CH_2C*H*Me$_2$); 0.91, 0.90, 0.87, 0.78(d×4, 3H×4, J=6.5 Hz, -CH_2CH*Me*$_2$). ESI-MS (found/calcd for $C_{43}H_{48}N_4$ + H^+) 621.58/621.40.

10. (a) Geier III, G. R.; Grindrod, S. C. *J. Org. Chem.* **2004**, *69*, 6404-6412. b) Decréau, R. A.; Collman, J. P. *Tetrahedron Lett.* **2003**, *44*, 3323-3327.

11. Guilard, R.; Aukauloo, M. A.; Tardieux, C.; Vogel, E. *Synthesis* **1995**, 1480-1482.