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SYNTHESIS OF BICYCLO[2.2.2]OCTADIENE-FUSED SAPPHYRINS AND THEIR THERMAL CONVERSION

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Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

Abstract – A series of sapphyrins fused with bicyclo[2.2.2]octadiene were successfully synthesized *via* [3+1+1] porphyrinoid synthesis. The retro Diels–Alder thermal conversion afforded the corresponding di-, tri-, tetra-, and pentabenzosapphyrins.

Sapphyrin, [22]pentaphyrin(1.1.1.1.0), is one of the first ring-expanded porphyrins, which contains one direct pyrrole-pyrrole bond in pentapyrrolic macrocycle,[1] and has attracted much interest due to their large cavities, optical and electronic properties, and basicity. Protonated sapphyrins have been investigated as an anion receptor.[2,3] The interaction of water-soluble sapphyrins with nucleic acids have been studied.[4] Sapphyrins are usually synthesized *via* various synthetic routes such as classical [3+2] MacDonald-type,[1] [4+1],[5,6] [3+1+1],[7] [1+1+1+1+1] Rothemund-type,[8] and [2+1+1+1] Lindsey-type[9] condensations. In 2004, Lash reported synthesis of π-extended sapphyrins fused with acenaphthylene and phenanthrene, which exhibited red-shifted Soret bands compared to those of β-alkylsapphyrins.[10] Structural modification such as ring-annelation is effective to induce the red-shift of the absorptions. Recently, we have reported synthesis of benzosapphyrin **1**, dibenzosapphyrin **2**, and trithiapentabenzosapphyrin **3** *via* acid-catalyzed [3+2] condensation and thermal-convertible precursor method (Figure 1).[11,12] Herein, we report synthesis of a series of bicyclo[2.2.2]octadiene (BCOD)-fused sapphyrins **4**–**8** *via* [3+1+1] synthesis, which afforded desired sapphyrins in short-step route compared to [3+2] synthesis, and thermal conversion to give the corresponding benzosapphyrins.

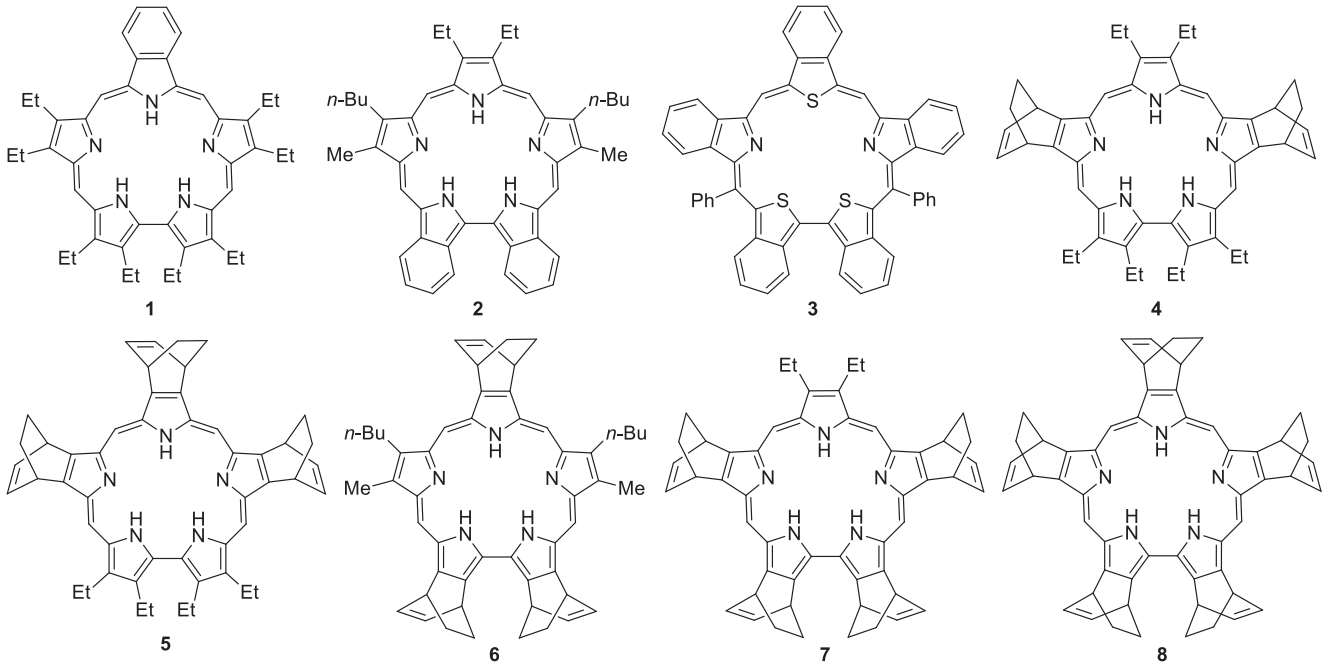
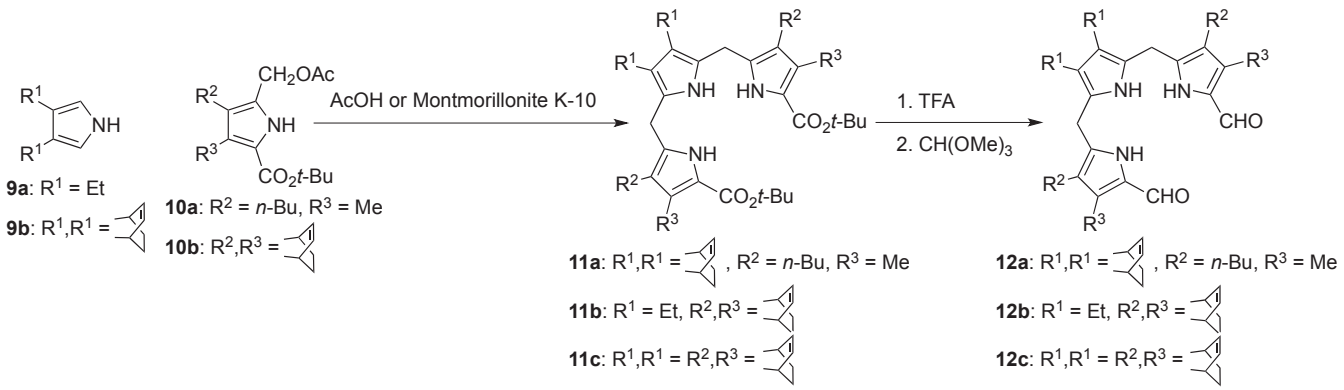


Figure 1. Structures of benzosapphyrin **1**, dibenzosapphyrin **2**, trithiapentabenzosapphyrin **3** and BCOD-fused sapphyrins **4**–**8**

Tripyrranes **11** were prepared by condensation of **9** with **10** in the presence of AcOH or Montmorillonite K-10 according to literature procedure.[13,14] Tripyrranes **11** were treated with TFA to remove *t*-butoxycarbonyl groups, and then with $CH(OMe)_3$ to give diformyltripyrranes **12**.[15] Tripyrranes **12** were used in the sapphyrin synthesis without further purification after filtration of reaction mixture and NMR measurement. Condensation of **12a** with 2 molar amounts of **9b** in the presence of $BF_3 \cdot OEt_2$, followed by oxidation with DDQ afforded triBCODsapphyrin **6** in 9% yield. Di-, tri-, tetra-, and pentaBCODsapphyrins **4**, **5**, **7**, and **8** were also obtained *via* similar reaction of **12** and **9**. On the other hand, [3+2] condensation method of **9b** and **12c** resulted in the formation of a trace amount of **8**. The sapphyrins **4**–**8** are characterized by MS and NMR.



Scheme 1. Synthesis of BCOD-fused tripyrranes

Thermogravimetric analysis (TGA) of **4**–**8** was carried out to estimate the temperature of the retro Diels–Alder reactions (Figure 2). The TGA curves of **4**–**6** showed the continuous weight loss. Weight loss corresponding to the removal of two or three ethylenes is observed at around 180 °C (for **4**) and 200 °C (for **5** and **6**). In contrast, the weight loss of **7** and **8** start at around 160 °C and is completed at 200 °C.

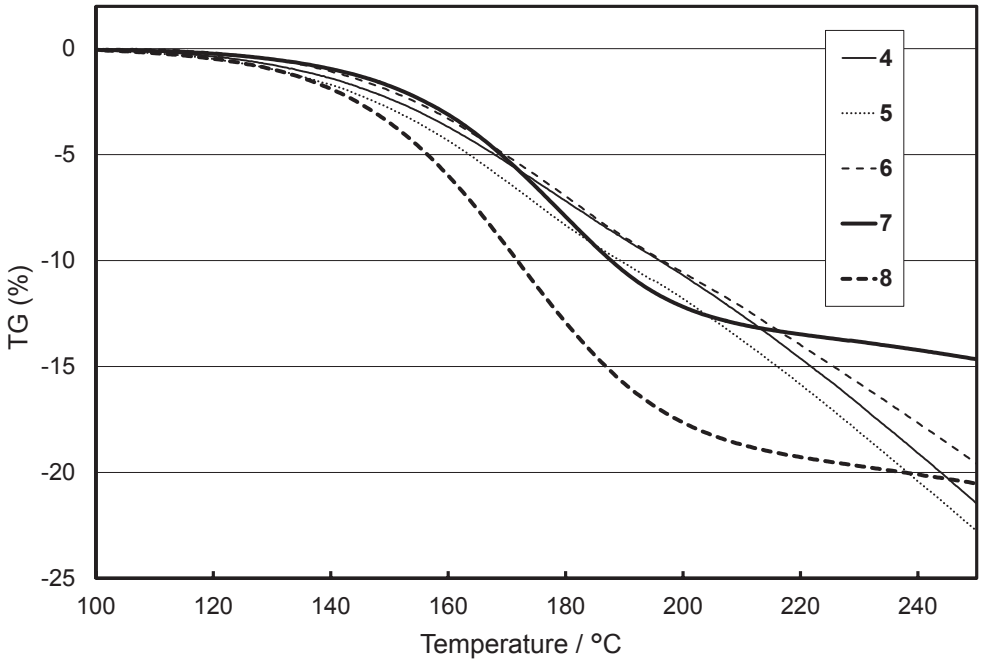


Figure 2. TGA of BCOD-fused sapphyrins **4**–**8**

When **4**–**8** were heated as solids at 200 °C for 1 h in glass tubes under reduced pressure, the corresponding benzosapphyrins **13**–**17** were obtained in nearly quantitative yields (Figure 3). The absorption and mass spectra of the products indicated formation of benzosapphyrins **13**–**17** although the NMR spectra could not be measured due to their solubility and yielded amounts. The absorption spectra of BCODsapphyrins **4**–**8** and benzosapphyrins **13**–**17** are shown in Figures 4 and 5. The Soret and Q bands of **4**–**8** are observed at ca. 450 nm and 610–710 nm. The number and position of BCOD rings did not affect their absorption spectra. On the other hand, the Soret bands of benzosapphyrins showed a gradual bathochromic shift as the number of fused benzene rings (475 nm for **13**, 479 nm for **14**, 487 nm for **15**, 498 nm for **16**, and 509 nm for **17**). The Q bands are observed at 630–730 nm. The longest absorption maxima of dibenzosapphyrin **13** and pentabenzosapphyrin **17** are 731 and 752 nm, respectively, while those of tribenzosapphyins **14** and **15** are about the same for tetrabenzosapphyrin **16** (743 nm for **14**, 739 nm for **15**, 741 nm for **16**). The similar result was observed for mono-, di-, and tribenzoporphyrins.[16] The HOMO–LUMO energy gaps of **13**–**17** would depend on not only the number of fused-benzenes but also the position of them. However, the contribution of NH tautomers resulted in the small difference of the longest absorption maxima.[17]

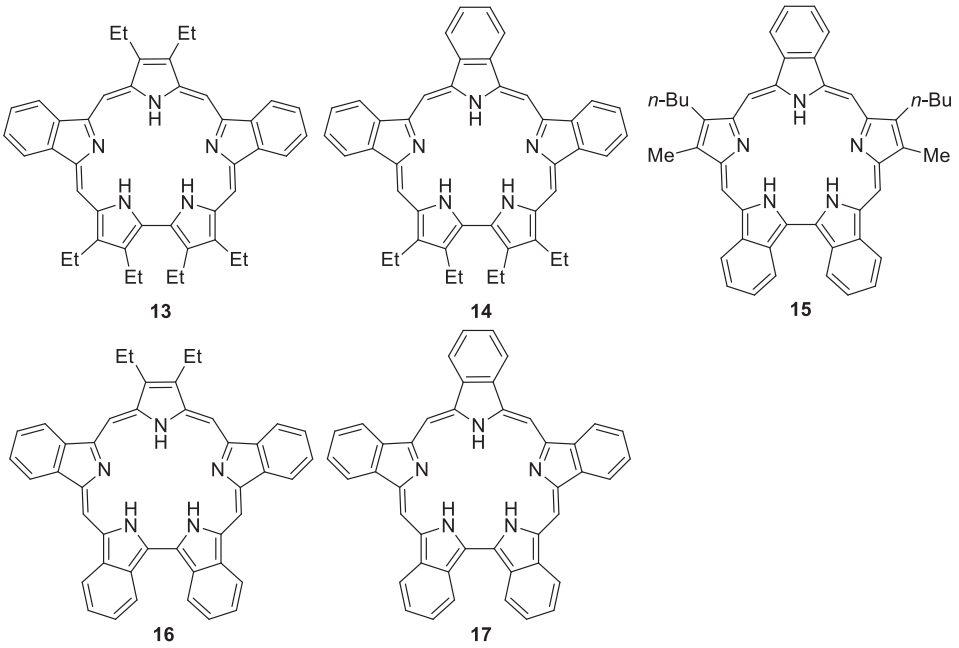


Figure 3. Structures of benzosapphyrins **13**–**17**

In summary, we have successfully synthesized a series of BCOD-fused sapphyrins **4**–**8** *via* acid-catalyzed [3+1+1] condensation of diformyltripyrranes **12** and pyrroles **9**. TGA analysis showed thermal conversion of BCOD moieties to fused benzenes at 160–200 °C. The retro Diels–Alder reactions of **4**–**8** afforded the corresponding benzosapphyrins **13**–**17**, which showed a bathochromic shift in the absorption spectra.

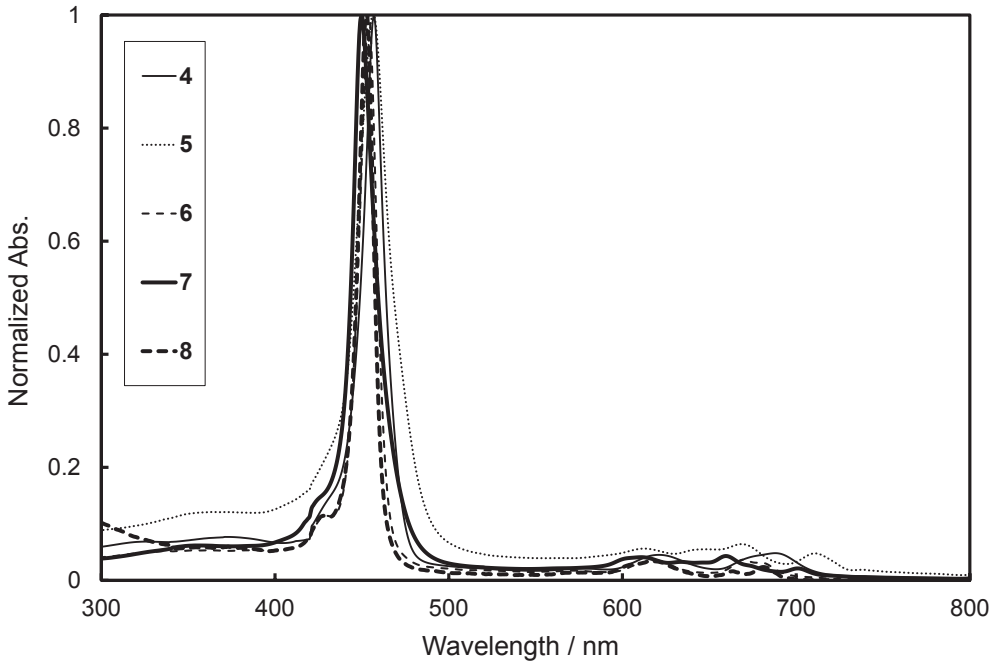


Figure 4. Absorption spectra of BCOD-fused sapphyrins **4**–**8** in $CHCl_3$

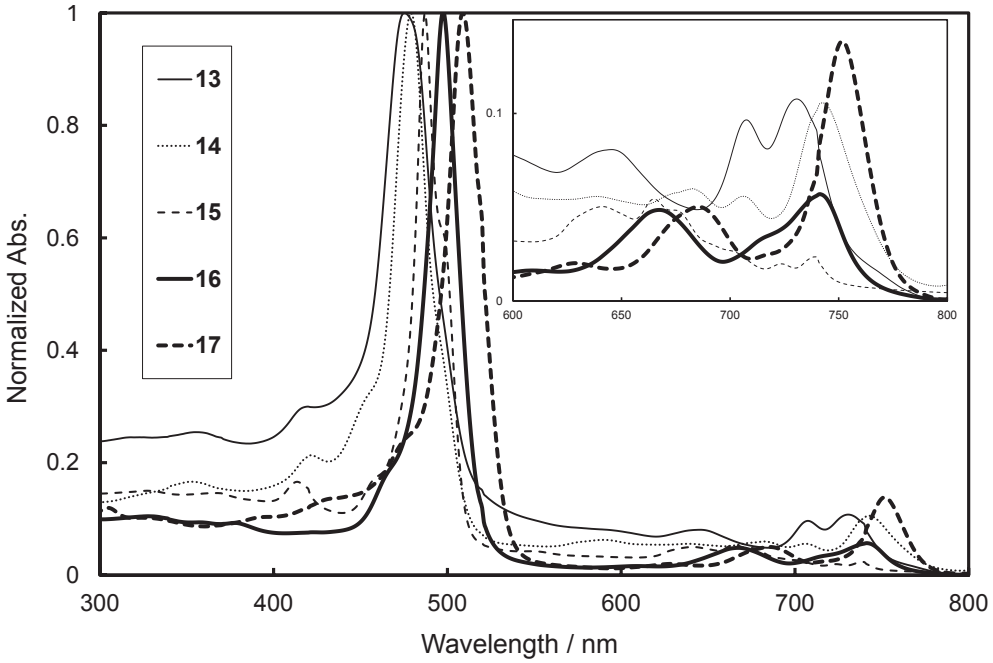


Figure 5. Absorption spectra of benzosapphyrins **13**–**17** in $CHCl_3$

EXPERIMENTAL

General. FAB mass spectra were measured on a JEOL JMS-700. MALDI–TOF mass spectra were measured on an Applied Biosystems Voyager-DE Pro. UV–vis absorption spectra were measured on a JASCO V-570 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL AL-400 at 400 MHz.

Tripyrrane 12a

A solution of **9b** (75 mg, 0.51 mmol) and **10a** (312 mg, 1.01 mmol) in AcOH/*i*-PrOH (10 mL/10 mL) was refluxed for 16 h in the dark. After addition of water (10 mL), the reaction mixture was neutralized with sat. aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give crude **11a**, which was confirmed by NMR. A solution of crude **11a** in TFA (3.6 mL) was stirred at rt for 15 min under N_2 atmosphere and then cooled in ice-salt bath. Trimethyl orthoformate (0.95 mL) was added dropwise to the mixture, which was stirred for 5 min in ice-salt bath. The reaction mixture was poured into water (30 mL) and then stirred for 1 h. The precipitate was collected by filtration and washed with water to give **12a**.

11a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 3H), 6.42 (m, 2H), 3.71–3.84 (m, 6H), 2.34 (t, 4H, J = 7.6 Hz), 2.24 (s, 6H), 1.51 (s, 18H) 1.26–1.46 (m, 12H), 0.89 (t, 6H, J = 7.1 Hz).

12a: Black powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 9.28 (s, 2H), 9.19 (s, 2H), 6.44 (m, 2H), 3.58–3.86 (m, 6H), 2.29–2.42 (m, 4H), 2.20 (s, 6H), 1.51 (s, 18H) 1.23–1.56 (m, 12H), 0.90 (m, 6H).

Tripyrrane 12b

Montmorillonite K-10 clay (4.44 g) was added to a degassed solution of **9a** (607 mg, 4.93 mmol) and **10b**

(2.79 g, 8.78 mmol) in $CHCl_3$ (165 mL) under N_2 atmosphere in the dark. The resulting mixture was stirred at rt for 6 h. After filtration, the filtrate was washed with sat. aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give crude **11b**, which was confirmed by NMR. A solution of **11b** in TFA (29 mL) was stirred at rt for 15 min under N_2 atmosphere and then cooled in ice-salt bath. Trimethyl orthoformate (8 mL) was added dropwise to the mixture, which was stirred for 5 min in ice-salt bath. The reaction mixture was poured into water (150 mL) and then stirred for 1 h. The precipitate was collected by filtration and washed with water to give **12b**.

11b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16–9.51 (m, 3H), 6.30–6.85 (m, 4H), 3.24–3.99 (m, 12H), 2.37 (m, 4H), 1.28–1.60 (m, 8H), 1.25 (s, 18H), 0.91 (m, 6H).

12b: Black powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 2H), 9.25 (s, 3H), 6.44 (m, 4H), 3.61–3.84 (m, 12H), 2.37 (m, 4H), 1.28–1.62 (m, 8H), 0.91 (m, 6H).

DiBCODsapphyrin 4

To a mixture of **12b** (100 mg, 0.203 mmol) and **9a** (52 mg, 0.43 mmol) in CH_2Cl_2 (100 mL) were added EtOH (1 mL) and $BF_3{\cdot}OEt_2$ (0.4 mL) under N_2 atmosphere in the dark. The resulting mixture was stirred at rt for 20 h. The reaction mixture was treated with DDQ (60 mg, 0.27 mmol). After stirring for 1 h, the mixture was washed with sat. aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on alumina with $CHCl_3$ and EtOAc to give **4** (3 mg, 2%).

Black powder; MS (FAB) *m/z* 700 [M^++H], 644 [M^++H−$2C_2H_4$]; HRMS calcd for $C_{48}H_{54}N_5$ 700.4374 [M^++H], found 700.4361; UV–vis ($CHCl_3$) λ_{max} 457, 621, 688 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.71 (s, 4H), 7.56–8.71 (m, 4H), 6.08–6.79 (m, 4H), 3.23–4.76 (m, 12H), 1.83–2.67 (m, 26H).

TriBCODsapphyrin 5

To a mixture of **12c** (102 mg, 0.198 mmol) and **9a** (47 mg, 0.38 mmol) in CH_2Cl_2 (100 mL) were added EtOH (1 mL) and $BF_3{\cdot}OEt_2$ (0.4 mL) under N_2 atmosphere in the dark. The resulting mixture was stirred at rt for 20 h. The reaction mixture was treated with DDQ (60 mg, 0.27 mmol). After stirring for 1 h, the mixture was washed with sat. aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on alumina with $CHCl_3$ and EtOAc to give **5** (4 mg, 3%).

Black powder; MS (FAB) *m/z* 722 [M^++H], 666 [M^++H−$2C_2H_4$], 638 [M^++H−$3C_2H_4$]; HRMS calcd for $C_{50}H_{51}N_5$ 722.4217 [M^++H], found 722.4236; UV–vis ($CHCl_3$) λ_{max} 457, 613, 669, 711 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.92 (s, 2H), 11.86 (s, 2H), 7.38–7.50 (m, 6H), 6.63–6.26 (m, 6H), 3.70 (m, 8H),

2.67–1.97 (m, 24H), 11.71 (s, 4H), 7.56–8.71 (m, 4H), 6.08–6.79 (m, 4H), 3.23–4.76 (m, 12H), 1.83–2.67 (m, 26H).

TriBCODsapphyrin 6

To a mixture of **12a** (101 mg, 0.202 mmol) and **9b** (59 mg, 0.41 mmol) in CH_2Cl_2 (100 mL) were added EtOH (1 mL) and $BF_3{\cdot}OEt_2$ (0.4 mL) under N_2 atmosphere in the dark. The resulting mixture was stirred at rt for 20 h. The reaction mixture was treated with DDQ (49 mg, 0.21 mmol). After stirring for 1 h, the mixture was washed with sat. aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on alumina with $CHCl_3$ and EtOAc to give **6** (13 mg, 9%).

Black powder; MS (MALDI–TOF) *m/z* 722 [M^++H], 666 [M^++H−$2C_2H_4$], 638 [M^++H−$3C_2H_4$]; UV–vis ($CHCl_3$) λ_{max} 454, 619, 670 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (m, 2H), 11.94 (m, 2H), 7.64–7.32 (m, 6H), 6.68–6.32 (m, 6H), 4.91 (m, 4H), 4.36 (s, 6H), 2.79–2.03 (m, 12H), 1.64–1.45 (m, 8H), 1.38 (t, 6H, J = 7.6 Hz).

TetraBCODsapphyrin 7

To a mixture of **12b** (45 mg, 0.092 mmol) and **9b** (27 mg, 0.19 mmol) in CH_2Cl_2 (100 mL) were added EtOH (1 mL) and $BF_3{\cdot}OEt_2$ (0.4 mL) under N_2 atmosphere in the dark. The resulting mixture was stirred at rt for 20 h. The reaction mixture was treated with DDQ (32 mg, 0.14 mmol). After stirring for 1 h, the mixture was washed with sat. aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on alumina with CH_2Cl_2/MeOH (95/5) and GPC with $CHCl_3$ to give **7** (6 mg, 9%).

Black powder; MS (FAB) *m/z* 744 [M^++H], 632 [M^++H−$4C_2H_4$]; HRMS calcd for $C_{52}H_{50}N_5$ 744.4061 [M^++H], found 744.4077; UV–vis ($CHCl_3$) λ_{max} 450, 611, 660, 701 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (m, 2H), 12.02 (m, 2H), 7.79–7.37 (m, 8H), 6.74–6.27 (m, 8H), 4.98–4.81 (m, 4H), 2.61 (m, 6H), 2.46–1.31 (m, 16H).

PentaBCODsapphyrin 8

To a mixture of **12c** (100 mg, 0.194 mmol) and **9b** (64 mg, 0.44 mmol) in CH_2Cl_2 (100 mL) were added EtOH (1 mL) and $BF_3{\cdot}OEt_2$ (0.4 mL) under N_2 atmosphere in the dark. The resulting mixture was stirred at rt for 20 h. The reaction mixture was treated with DDQ (51 mg, 0.22 mmol). After stirring for 1 h, the mixture was washed with sat. aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on alumina with CH_2Cl_2/MeOH (95/5) and GPC with $CHCl_3$ to give **8** (12 mg, 8%).

Black powder; MS (FAB) *m/z* 766 [M^++H], 654 [M^++H−4C_2H_4], 626 [M^++H−5C_2H_4]; HRMS calcd for $C_{54}H_{48}N_5$ 766.3904 [M^++H], found 766.3905; UV–vis ($CHCl_3$) λ_{max} 453, 617, 663, 681 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (m, 2H), 12.02 (m, 2H), 7.74–7.28 (m, 10H), 6.68–6.15 (m, 10H), 2.62–1.31 (m, 20H).

Retro Diels–Alder reaction of BCODsapphyrins

Sapphyrins **4**–**8** (ca. 2 mg each) were heated at 200 °C under reduced pressure for 1 h in a glass tube to give **13**–**17** in quantitative yields.

13: MS (MALDI–TOF) *m/z* 645 [M^++2H]; UV–vis ($CHCl_3$) λ_{max} 475, 646, 708, 731 nm; **14**: MS (MALDI–TOF) *m/z* 638 [M^++H]; UV–vis ($CHCl_3$) λ_{max} 479, 683, 706, 743 nm; **15**: MS (MALDI–TOF) *m/z* 666 [M^++H]; UV–vis ($CHCl_3$) λ_{max} 487, 641, 665, 739 nm; **16**: MS (MALDI–TOF) *m/z* 632 [M^++H]; UV–vis ($CHCl_3$) λ_{max} 498, 667, 741 nm; **17**: MS (MALDI–TOF) *m/z* 626 [M^++H]; UV–vis ($CHCl_3$) λ_{max} 509, 685, 752 nm.

ACKNOWLEDGEMENTS

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