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Synthesis of benzoporphyrins functionalized with octaester groups

Satoshi Ito,[a] Hidemitsu Uno,[b] Takashi Murashima[a] and Noboru Ono[a,*]

[a]*Department of Chemistry, Faculty of Science, Ehime University, Bunkyo-cho 2-5, Matsuyama 790-8577, Japan*
[b]*Advanced Instrumentation Center for Chemical Analysis, Ehime University, Bunkyo-cho 2-5, Matsuyama 790-8577, Japan*

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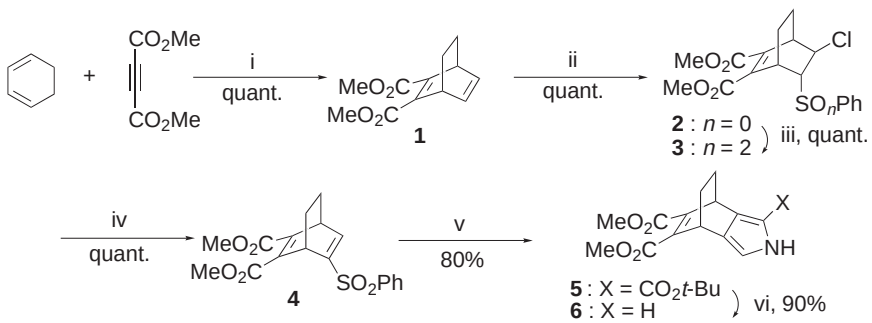
Abstract—Benzoporphyrins with octamethoxycarbonyl groups **8a**,**b** are obtained in near 100% yields by heating the corresponding tetra(bicyclo)porphyrins **7a**,**b** at 200°C without affecting the ester moiety.

Linearly π-extended systems such as benzoporphyrins and phthalocyanines have attracted much attention as conducting and opt-electronic materials or photosensitizers for PDT of cancer tissues in in vivo studies, because they have very strong absorption in the near IR region.[1] However, applications of linearly π-extended porphyrins to these fields are very rare compared to those of phthalocyanines. The reasons are as follows: (1) preparation and functionalization of the starting isoindole derivatives are very difficult owing to their instability,[2] (2) π-extended porphyrins are so insoluble in most solvents that preparation, purification and modification of such porphyrins are very difficult, and (3) established synthetic methods of linearly π-extended porphyrins (benzoporphyrins or [2,3]naphthoporphyrins) require severe reaction conditions such as heating at ca. 350–400°C.[3] Therefore, synthesis of linearly π-extended porphyrins with thermally unstable groups such as sugar, ester and acetal groups has been rarely reported.[4] Recently, we have reported an efficient synthesis of various benzoporphyrins[5] and [2,3]naphthoporphyrins[6] using pyrroles fused with bicyclo[2.2.2]-octadiene (BCOD) rings as synthons of isoindoles. Here we report a synthesis of tetrabenzoporphyrins with octaester groups **7** and **8**, which is based on a retro Diels–Alder strategy using pyrroles fused with BCOD units.

The synthesis of 4,7-dihydro-5,6-dimethoxycarbonyl-4,7-ethano-2*H*-isoindole **6** is summarized in Scheme 1. Dimethyl bicyclo[2.2.2]octadiene-1,2-carboxylate **1** was prepared by the Diels–Alder reaction of 1,3-cyclohexadiene with dimethyl acetylenedicarboxylate,[7] and **1** was converted into sulfide **2** by reaction with PhSCl.[8] Oxidation of **2** with *m*-CPBA (2 equiv.) followed by treatment with DBU gave α,β-unsaturated sulfone **4**. The pyrrole **5** was prepared in good yield by treatment of **4** with *t*-butyl isocyanoacetate in the presence of 1.1 equivalents of *t*-BuOK.[9] The use of a large excess of



Scheme 1. *Reagents and conditions*: (i) $CHCl_3$, 60°C, 16 h; (ii) PhSCl, $CHCl_3$, −78°C, 1 h; (iii) *m*-CPBA, $CHCl_3$, rt, 18 h; (iv) DBU, pyridine, 0°C, 1.5 h; (v) $CNCH_2CO_2t$-Bu, *t*-BuOK, THF, 0°C, 1.5 h; (vi) TFA, rt, 2 h, 90%.

Keywords: retro Diels–Alder reaction; isoindoles; benzoporphyrins.
* Corresponding author. E-mail: ononbr@dpc.ehime-u.ac.jp

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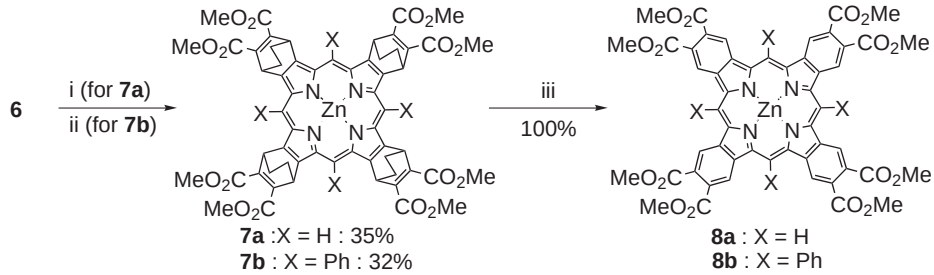

Scheme 2. *Reagents and conditions*: (i) $(HCHO)_n$, $(AcO)_2Zn$, TFA, MeOH/$CHCl_3$, rt, 6.5 h, then DDQ, rt, 17 h; (ii) PhCHO, $BF_3{\cdot}OEt_2$, $(AcO)_2Zn$, $CHCl_3$, rt, 12 h, then *p*-chloranil, rt, 10 h (X = Ph); (iii) 200°C, 10 min.

t-BuOK induces a partial exchange of the methyl ester. Treatment of **5** with trifluoroacetic acid (TFA) at room temperature gave crude 4,7-dihydro-5,6-dimethoxycarbonyl-4,7-ethano-2*H*-isoindole **6** in 72% overall yield starting from dimethyl acetylenedicarboxylate via six steps.

The reaction of **6** with aldehydes in the presence of TFA followed by oxidation with DDQ and metallation gave the zinc complexes of tetra(bicyclo)porphyrin with octaesters (**7a**,**b**). Porphyrins (**7a**,**b**) were converted into pure tetrabenzoporphyrins with octaester derivatives (**8a**,**b**) in 100% yields by heating at 200°C in vacuo for 10 min (Scheme 2).

The absorption spectra of **7a**,**b** and **8a**,**b** are shown in Fig. 1. Thus, the absorption spectra were dramatically changed by the formation of **8a**,**b**. The ester groups do not affect the electronic properties of **7a**,**b**, but do affect those of **8a**,**b**. The UV–vis spectra in $CHCl_3$ of **7a** [λmax/nm (ε): 405 (221,000), 529 (15,500), 564 (11,500)] and **7b** [λmax/nm (ε): 429 (264,000), 550 (28,600)] are similar to those of the zinc complexes of related porphyrins, which are not substituted with esters.[10] On the other hand, the UV–vis spectra of **8a** [λmax/nm (ε): 454 (413,000), 597 (19,200), 640 (103,000), 648 (115,000)] and **8b** [λmax/nm (ε): 485 (447,000), 621 (22,500), 667 (70,500)] are red-shifted by ca. 15–25 nm compared to those of the parent benzoporphyrins.[5] Furthermore, the intensity at the longest wavelength of **8a**,**b** is stronger than that of the parent. Thus, π-conjugation is highly extended by fused benzene rings substituted with ester functions. ^{1}H NMR spectral signals of **8a**,**b** were broad at room temperature, becoming sharp at high temperature. This may be due to the distortion of the porphyrin rings induced by poly-substitution. The purity of porphyrins **7a**,**b** and benzoporphyrins **8a**,**b** was confirmed by elemental analyses.[11] If pure porphyrins **7a**,**b** are heated, pure benzoporphyrins **8a**,**b** are obtained without purification. Contrary to the parent benzoporphyrin, the substituted benzoporphyrin **8a** is relatively soluble in organic solvents such as chloroform. Therefore, benzoporphyrin **8a** can be converted into various benzoporphyrins via chemical modification of the ester functions.

In conclusion, the present method based on Diels–Alder reactions, sulfonylation, Barton–Zard pyrrole syntheses, porphyrin syntheses, and retro Diels–Alder reactions provides a new strategy for the construction of functionalized tetrabenzoporphyrins.

Acknowledgements

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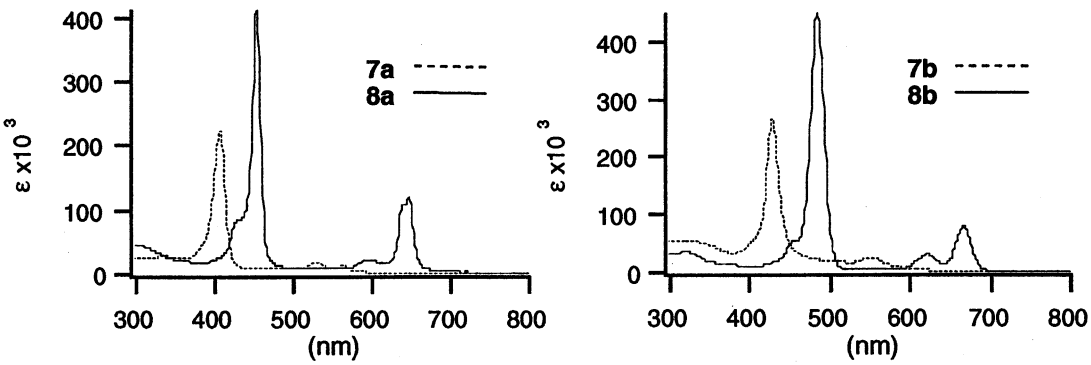

Figure 1. UV–vis spectra of **7** and **8** in $CHCl_3$.

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11. Selected spectroscopic data; **2**: colorless crystals; mp = 58–59°C; ^{1}H NMR (270 MHz, $CDCl_3$, *J* Hz) δ: 1.35 (m, 1H), 1.55 (m, 1H), 1.74 (m, 1H), 2.27 (m, 1H), 3.20 (q, *J* 6.5, 1H), 3.23 (q, *J* 6.5, 1H), 3.31 (dd, *J* 4.9 and *J* 2.3, 1H), 3.77 (m, 1H), 3.82 (s, 6H), 7.28–7.37 (m, 3H), 7.46–7.51 (m, 2H); *m*/*z* (EI) 367 (M^+); anal. calcd for $C_{18}H_{19}O_4SCl$: C, 58.93; H, 5.22. Found: C, 58.98; H, 5.25; **3**: colorless crystals; mp = 135–137°C; ^{1}H NMR (270 MHz, $CDCl_3$, *J* Hz) δ: 1.35–1.80 (m, 3H), 2.22 (m, 1H), 3.21 (m, 1H), 3.31 (dd, 1H, *J* 5.80 and *J* 1.83), 3.65 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 4.23 (m, 1H), 7.56–7.64 (m, 2H), 7.66–7.74 (m, 1H), 7.90–7.95 (m, 2H); *m*/*z* (EI) 398 (M^+); anal. calcd for $C_{18}H_{19}ClO_6S$: C, 54.20; H, 4.80. Found: C, 54.14; H, 4.87; **5**: colorless needles; mp = 117°C; ^{1}H NMR (270 MHz, $CDCl_3$, *J* Hz) δ: 1.4–1.8 (m, 4H), 1.58 (s, 9H), 3.78 (s, 3H), 3.79 (s, 3H), 4.28 (m, 1H), 4.78 (m, 1H), 6.61 (d, *J* 2.93, 1H), 8.47 (br s, 1H); *m*/*z* (EI) 361 (M^+); anal. calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.01; H, 6.50; N, 3.81; **7a** (mixture of four isomers): purple powder; ^{1}H NMR (270 MHz, $CDCl_3$–pyridine) δ: 2.16 (m, 8H), 2.47 (m, 8H), 3.98–4.02 (m, 24H), 6.23 (m, 8H), 10.46 (m, 4H); *m*/*z* (FAB) 1151 (M^++1); anal. calcd for $C_{60}H_{52}N_4O_{16}Zn{\cdot}2H_2O$: C, 60.74; H, 4.76; N, 4.72. Found: C, 60.86; H, 4.63; N, 4.66; **7b** (mixture of four isomers): purple powder; ^{1}H NMR (270 MHz, $CDCl_3$) broad signals were obtained at room temperature.; *m*/*z* (FAB) 1456 (M^++1); anal. calcd for $C_{84}H_{68}N_4O_{16}Zn{\cdot}5/2H_2O$: C, 67.27; H, 4.91; N, 3.73. Found: C, 67.20; H, 5.13; N, 3.92; **8a**: green powder; ^{1}H NMR (270 MHz, $CDCl_3$–pyridine); δ: 4.40 (s, 24H), 9.31 (s, 8H), 9.45 (s, 4H); *m*/*z* (FAB) 1039 (M^++1); anal. calcd for $C_{52}H_{36}N_4O_{16}Zn{\cdot}H_2O$: C, 59.13; H, 3.63; N, 5.30. Found: C, 59.22; H, 3.61; N, 5.14; **8b**: deep green powder; *m*/*z* (FAB) 1344 (M^++1); anal. calcd for $C_{76}H_{52}N_4O_{16}Zn{\cdot}H_2O$: C, 67.09; H, 4.00; N, 4.12. Found: C, 67.25; H, 4.23; N, 4.36.