Total Synthesis of 17-nor-Deoxophylloerythroetioporphyrin

Shinya Nomoto,*[1] Junya Asano,[1] Kenta Asahina,[1] Hajime Mita,[2] and Yuichiro Kashiyama[3]

[1]Department of Chemistry, University of Tsukuba, Tsukuba 305-8571

[2]Department of Life, Environment and Materials Science, Fukuoka Institute of Technology, Higashi-ku, Fukuoka 811-0295

[3]Institute of Biogeosciences, Japan Agency for Marine-Earth Science and Technology, Natsushima-cho, Yokosuka 237-0061

Received February 8, 2010
E-mail: nomoto@chem.tsukuba.ac.jp

Synthesis of 17-nor-deoxophylloerythroetioporphyrin, a sedimentary nor-porphyrin, was performed through a bilene-*b* route in a reasonable total yield. The porphyrin prepared here can potentially be used as a biological marker for chlorophyll *c*-producing algae.

Sediments and petroleum commonly contain porphyrins, which are principally derived from chlorophylls and are usually found as complex mixtures with various substituents on their pyrrole rings due to chemical modification in sediments.[1] In previous work, several nor-porphyrins, which lack an alkyl side chain at 3-, 7-, 8-, 13-, or 17-positions, have been isolated from geological samples and identified (Figure 1).[2] The absence of side chains of nor-porphyrins has been attributed to defunctionalization of a vinyl, an acyl, and a carboxyvinyl group of chlorophylls at the early stage of the degradation in sediments. The individual nor-porphyrins therefore, can potentially be used as biological markers for specific photoautotrophs.[2h] Since these compounds may be of diagnostic value, there is a need for synthetic standards for spectroscopic and chromatographic studies. We report here the first synthesis of 17-nor-deoxophylloerythroetioporphyrin (17-nor-DPEP, **1**).

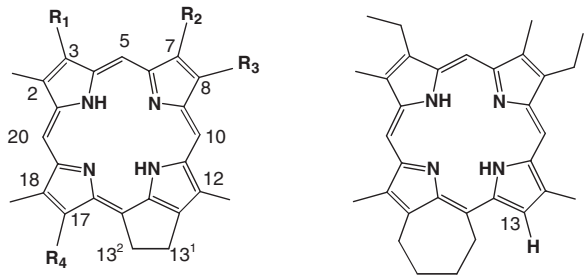
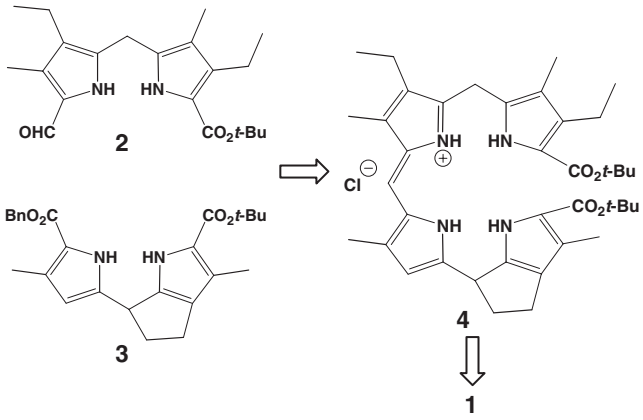
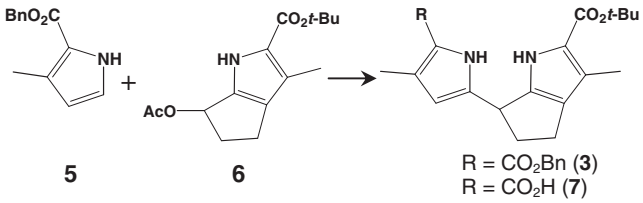


Figure 1. Sedimentary nor-porphyrins.



Scheme 1.



Scheme 2.

In the synthetic path shown in Scheme 1, we adopted a bilene-*b* route, since syntheses of DPEP porphyrins via biladienes-*a*,*c* have been known to result in significant lowering of cyclization yields due to destabilization of linear tetrapyrroles caused by the fused cyclopentene rings.[3] Bilene-*b* **4** containing *t*-butyl esters was prepared through the condensation of dipyrrolylmethane aldehyde **2** with dipyrrolylmethane **3** with mixed ester protective groups. The bilene-*b* was cyclized using orthoformate.

Dipyrrolylmethane **2**[3b] was prepared from *t*-butyl 3-ethyl-4-methylpyrrole-2-carboxylate[2g] and benzyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate[4] in a total yield of 52%. Scheme 2 shows the synthesis of another dipyrrolylmethane **3**, which was obtained by the coupling of 5-free pyrrole **5**[5] with acetoxypyrrole **6**[6] in the presence of a catalytic amount of *p*-toluenesulfonic acid in 63% yield. Cleavage of the benzyl ester of **3** by hydrogenolysis gave the corresponding carboxylic acid **7** in a quantitative yield.

Decarboxylation and condensation of **7** with **2** was accomplished simultaneously by the action of 3 equivalents of *p*-toluenesulfonic acid, and linear tetrapyrrole hydrochloride **4** was isolated as red crystals in 89% yield. Cleavage of the *t*-butyl esters of **4** and decarboxylation of the resultant tetrapyrrole carboxylic acid was performed using trifluoroacetic acid, and the resulting defunctionalized tetrapyrrole was cyclized with triethyl orthoformate. Since it had been reported that poor results were obtained using DDQ as an oxidant, the cyclization product was air oxidized in the presence of zinc acetate for 2 days. After demetalation by trifluoroacetic acid and purification by chromatography, the desired 17-nor-DPEP (Figure 2) was obtained as violet crystals in 19% yield.

Published on the web June 24, 2010; doi:10.1246/bcsj.20100033

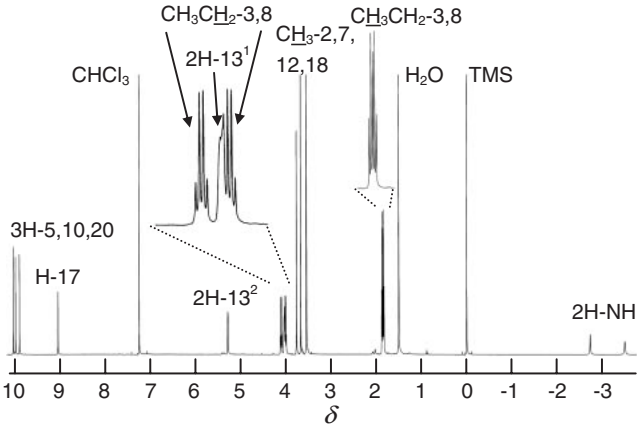


Figure 2. ^{1}H NMR spectrum of synthetic 17-nor-DPEP.

In the present study, we have shown that 17-nor-DPEP, a sedimentary nor-porphyrin found and identified in geological samples, can be synthesized through a bilene-*b* route in a reasonable total yield. Since it is possible to consider that chemical transformation in sediments generated 17-nor-DPEP from chlorophyll *c* by defunctionalization of the carboxyvinyl group at the C-17 position,[2h] the authentic sample prepared here has the important potential use as a biomarker for chlorophyll *c*-producing algae.

Experimental

Synthesis of Dipyrrolylmethane 3. *t*-Butyl 6-acetoxy-1,4,5,6-tetrahydro-3-methylcyclopenta[*b*]pyrrole-2-carboxylate[6] (2.46 g, 8.81 mmol) and benzyl 3-methylpyrrole-2-carboxylate[5] (1.88 g, 8.73 mmol) were dissolved in acetic acid (125 mL) and stirred in the presence of *p*-toluenesulfonic acid monohydrate (185 mg, 0.973 mmol) for 18 h at room temperature. The reaction mixture was diluted with chloroform (100 mL) and washed with water (500 mL). The aqueous layer was extracted with chloroform (200 mL), and the combined organic layer was washed with 10% aqueous sodium carbonate solution and dried with magnesium sulfate. The oil obtained after evaporation of the solvent was chromatographed (eluted with dichloromethane) on silica gel to afford **3** after recrystallization from ethanol in 63% yield (2.39 g). The product turns dark yellow in air.

***t*-Butyl 6-(2-Benzyloxycarbonyl-3-methyl-5-pyrrolyl)-1,4,5,6-tetrahydro-3-methylcyclopenta[*b*]pyrrole-2-carboxylate (3):** Pale orange solid; mp 178–180 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.55 (s, 9H), 2.26 (s, 3H), 2.31 (s, 3H), 2.53–2.67 (m, 2H), 2.77–2.88 (m, 2H), 4.21 (m, 1H), 5.29 (s, 2H), 5.84 (d, $J = 2.9$ Hz, 1H), 7.31–7.42 (m, 5H), 8.46 (br s, 1H), 8.58 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 11.71, 13.12, 23.23, 28.63, 37.67, 38.89, 65.78, 80.41, 110.31, 118.21, 122.47, 124.09, 128.05, 128.09, 128.56, 129.24, 130.50, 132.03, 136.44, 138.48, 138.78, 152.79, 161.31, 161.58; HRMS (ESI) m/z Calcd for $C_{26}H_{31}N_2O_4$: 435.2089 $[M + H]^+$, found: 435.2093 $[M + H]^+$; Anal. Found: C, 71.30; H, 7.13; N, 6.28%. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45%.

Synthesis of Dipyrrolylmethanecarboxylic Acid 7. A solution of dipyrrolylmethane diester **3** (510 mg, 1.17 mmol) in THF (75 mL) was stirred with 10% Pd–C under an atmosphere of hydrogen for 20 h at room temperature. The catalyst was filtered off and the solvent was removed under reduced pressure to afford **7** in a quantitative yield (431 mg). The product turns dark brown in air.

5-(2-*t*-Butoxycarbonyl-1,4,5,6-tetrahydro-3-methylcyclopenta[*b*]pyrrol-6-yl)-3-methylpyrrole-2-carboxylic Acid (7): White solid; mp 169–170 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.56 (s, 9H), 2.20 (s, 3H), 2.36 (s, 3H), 2.60–2.85 (m, 4H), 4.30 (m, 1H), 5.97 (d, $J = 2.8$ Hz, 1H), 10.3 (br s, 1H), 11.7 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 12.13, 13.35, 23.21, 28.58, 34.10, 36.65, 81.56, 109.04, 119.12, 122.99, 123.27, 128.63, 129.85, 141.81, 144.18, 164.00, 165.77; HRMS (ESI) m/z Calcd for $C_{19}H_{25}N_2O_4$: 345.1539 $[M + H]^+$, found: 345.1544 $[M + H]^+$; Anal. Found: C, 65.37; H, 7.22; N, 7.71%. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13%.

Synthesis of Bilene-*b* Hydrochloride 4. A methanol solution (0.3 mL) of *p*-toluenesulfonic acid monohydrate (37.1 mg, 0.195 mmol) was added to a solution of **2**[3] (20.8 mg, 0.0580 mmol) and **7** (20.4 mg, 0.0592 mmol) in dichloromethane (4 mL), and the reaction mixture was stirred under a nitrogen atmosphere in the dark for 2 h at room temperature. The solution was washed with 5% aqueous sodium hydrogen carbonate and water and dried over magnesium sulfate. After evaporation of the solvent the residual oil was dissolved in dichloromethane (5 mL), and HCl gas was bubbled into the solution for 10 s. The oily product obtained after evaporation of the solvent was triturated with ether to give **4** in 89% yield (35.1 mg).

1,19-Di-*t*-butoxycarbonyl-2,7-diethyl-3,8,12,18-tetramethyl-15,17-ethanobilene-*b* Hydrochloride (4): Red crystals; mp 170 °C (dec); ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.01 (t, $J = 7.6$ Hz, 3H), 1.08 (t, $J = 7.4$ Hz, 3H), 1.55 (s, 9H), 1.56 (s, 9H), 2.05 (s, 3H), 2.26 (s, 6H), 2.32 (s, 3H), 2.43–2.75 (m, 6H), 2.96–3.03 (m, 2H), 4.25 (s, 2H), 4.79–4.83 (m, 1H), 6.14 (s, 1H), 7.10 (s, 1H), 9.66 (br s, 1H), 10.5 (br s, 1H), 13.7 (br s, 1H), 14.0 (br s, 1H); HRMS (ESI) m/z Calcd for $C_{39}H_{53}N_4O_4$: 641.3977 $[M]^+$, found: 641.3979 $[M]^+$.

Synthesis of 17-nor-DPEP (1). Bilene-*b* hydrochloride **4** (20.0 mg, 29.5 mmol) was dissolved in trifluoroacetic acid (2 mL) and the solution was stirred under a nitrogen atmosphere in the dark for 10 min at room temperature. After the solution was diluted with dichloromethane (30 mL), a dichloromethane solution (10 mL) of triethyl orthoformate (0.016 mL, 0.096 mmol) was added dropwise over a 30 min period and the mixture was stirred for 4 h. A saturated methanol solution (15 mL) of zinc acetate was added to the reaction mixture, which was stirred for 2 days. The solution was washed with water and dried with sodium sulfate. A black oil obtained by removal of the solvent was dissolved in trifluoroacetic acid and the solution was stirred for 5 min. The mixture was diluted with dichloromethane (10 mL), washed with 5% aqueous sodium hydrogen carbonate and water, and dried with magnesium sulfate. Removal of the solvent afforded an oil, which was chromatographed on neutral alumina (eluted with dichloromethane) to yield **1** in 19% yield (2.50 mg).

17-nor-DPEP (1): Violet crystals; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ −3.50 (s, 1H), −2.70 (s, 1H), 1.84 (t, $J = 7.8$ Hz, 3H), 1.87 (t, $J = 7.8$ Hz, 3H), 3.56 (s, 3H), 3.57 (s, 3H), 3.66 (s, 3H), 3.78 (s, 3H), 3.95–4.06 (m, 4H), 4.11 (q,

$J = 7.8$ Hz, 2H), 5.26–5.31 (m, 2H), 9.05 (d, $J = 1.0$ Hz, 1H), 9.90 (s, 1H), 9.99 (s, 1H), 10.0 (s, 1H); HRMS (ESI) m/z Calcd for $C_{30}H_{33}N_4$: 449.2622 $[M + H]^+$, found: 449.2621 $[M + H]^+$.

References

1 a) A. Treibs, *Angew. Chem.* **1936**, *49*, 682. b) W. W. Howe, *Anal. Chem.* **1961**, *33*, 255. c) J. Martin, E. Quirke, G. J. Shaw, P. D. Soper, J. R. Maxwell, *Tetrahedron* **1980**, *36*, 3261. d) K. Grice, P. Schaeffer, L. Schwark, J. R. Maxwell, *Org. Geochem.* **1997**, *26*, 677.

2 a) C. J. R. Fookes, *J. Chem. Soc., Chem. Commun.* **1983**, 1472. b) C. J. R. Fookes, *J. Chem. Soc., Chem. Commun.* **1983**, 1474. c) R. Ocampo, H. J. Callot, P. Albrecht, J. P. Kintzinger, *Tetrahedron Lett.* **1984**, *25*, 2589. d) M. I. Chicarelli, J. R. Maxwell, *Tetrahedron Lett.* **1984**, *25*, 4701. e) J. Verne-Mismer, R. Ocampo, H. J. Callot, P. Albrecht, *J. Chem. Soc., Chem. Commun.* **1987**, 1581. f) J. Verne-Mismer, R. Ocampo, H. J. Callot, P. Albrecht, *Tetrahedron Lett.* **1988**, *29*, 371. g) P. J. Clewlow, A. H. Jackson, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1925. h) Y. Kashiyama, M. Shiro, R. Tada, N. Ohkouchi, *Chem. Lett.* **2007**, *36*, 706.

3 a) B. Zhang, T. D. Lash, *Tetrahedron Lett.* **2003**, *44*, 7253. b) T. D. Lash, W. Li, D. M. Quizon-Colquitt, *Tetrahedron* **2007**, *63*, 12324.

4 A. W. Johnson, I. T. Kay, E. Markham, R. Price, K. B. Shaw, *J. Chem. Soc.* **1959**, 3416.

5 T. D. Lash, M. C. Hoehner, *J. Heterocycl. Chem.* **1991**, *28*, 1671.

6 D. M. Quizon-Colquitt, T. D. Lash, *J. Heterocycl. Chem.* **1993**, *30*, 477.