



Synthesis of A Fluorine Analog of Hematoporphyrin by Ring Closure

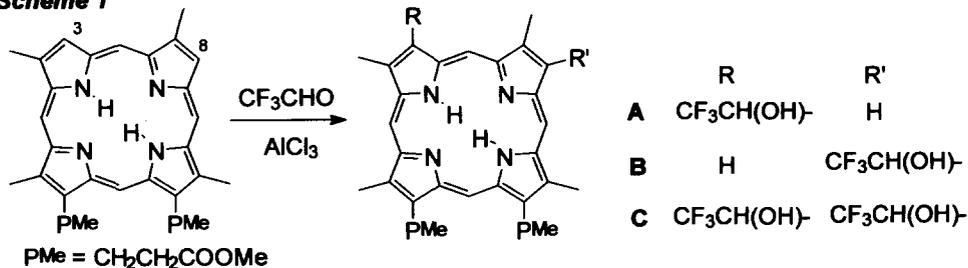
Masaaki Omote, Akira Ando, Toshiyuki Takagi, Mayumi Koyama, and Itsumaro Kumadaki*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-01, JAPAN

Abstract: Benzyl 3,5-dimethyl-2-pyrrolecarboxylate (1) was converted to 4-(2,2,2-trifluoro-1-hydroxyethyl) derivative (2) on treatment with trifluoroacetaldehyde ethyl hemiacetal in the presence of zinc chloride. After protection of the hydroxyl group with a methyl group, 2 was converted to benzyl 4-methyl-3-(2,2,2-trifluoro-1-methoxyethyl)-2-pyrrolecarboxylate (9) and benzyl 5-acetoxymethyl-3-methyl-4-(2,2,2-trifluoro-1-methoxyethyl)-2-pyrrolecarboxylate (10). Both esters were condensed to dipyrromethane compound 11, which was debenzylated, decarboxylated, and condensed with a bottom half of the porphyrin to give hexafluorohematoporphyrin derivative 14, potentially useful for photodynamic therapy of cancer. Copyright © 1996 Elsevier Science Ltd

It is well known that hematoporphyrin derivative (HPD) localizes to a tumor tissue. The localized HPD emits fluorescence on irradiation. Further, active oxygen is liberated by excitation with laser irradiation, and this active oxygen destroys the tumor tissues. Due to this property, HPD has been used in the diagnosis and therapy of cancer. It is called photodynamic therapy (PDT).¹ However, the HPD that has been used for the PDT is a mixture of several porphyrins, so it is difficult to obtain a fixed composition of medicine. To circumvent this problem, we planned to synthesize another porphyrin derivative which would localize preferentially to a tumor tissue. We expected that introduction of fluorine substituent to a porphyrin would give additional stability and lipophilicity.² If we could synthesize a fluorinated porphyrin derivative that localizes to a tumor tissue, it could be used as a tracer on ¹⁹F-NMR imaging, besides the conventional uses.² One of our approaches is synthesis of fluorinated hematoporphyrin derivatives, where 2,2,2-trifluoro-1-hydroxyethyl (TFHE) groups are introduced in the place of 1-hydroxyethyl groups at positions 3 or 8 on hematoporphyrin.

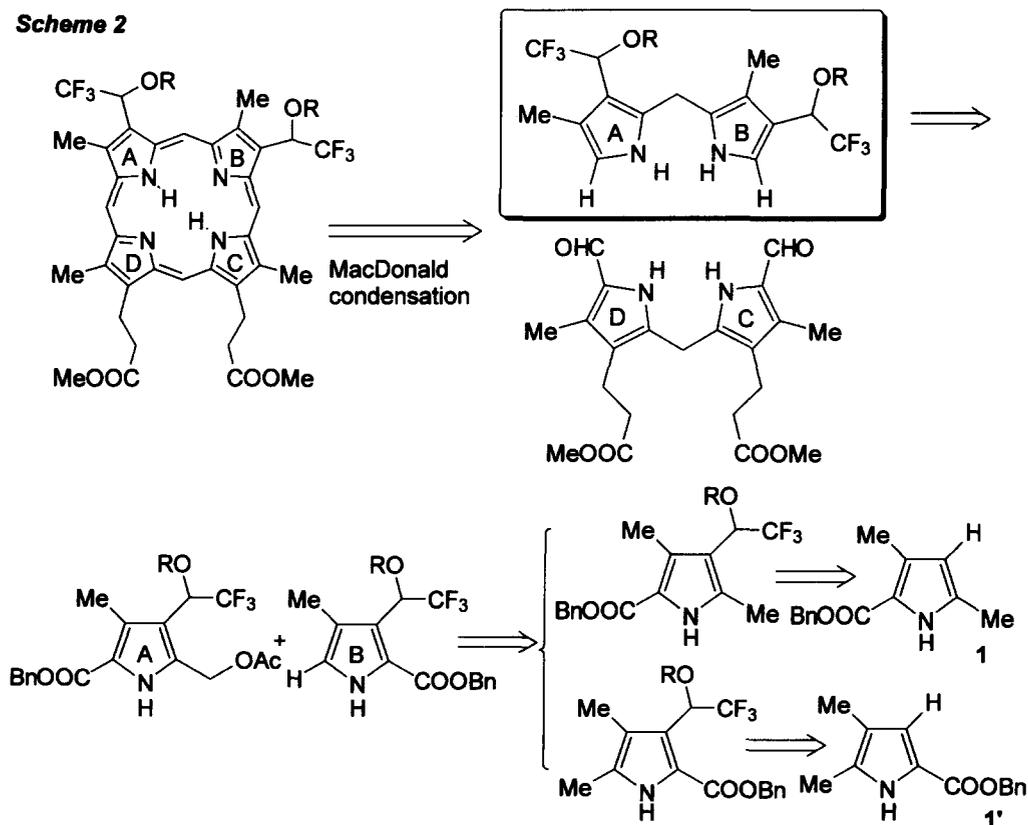
Scheme 1



As shown in Scheme 1, we have already synthesized hematoporphyrin derivatives having mono and bis TFHE group(s), A, B and C by the reaction of deuteroporphyrin with trifluoroacetaldehyde in the presence of a Lewis acid. In this reaction, the mono substituted products A and B were obtained in a good yield but the bis substituted one C was obtained only in a poor yield.³

Among the fluorinated porphyrin analogs shown above, the hexafluorohematoporphyrin (HFHP) derivative obtained by hydrolysis of C showed a high affinity for tumor cells in *in vitro* experiment.³ However, in the above route, C was obtained only in 6% yield. Further, the enantiomeric control for synthesis of chiral porphyrins seems to be difficult by this procedure. So our attention was turned to a total synthesis of a HFHP derivative by a ring closure method.

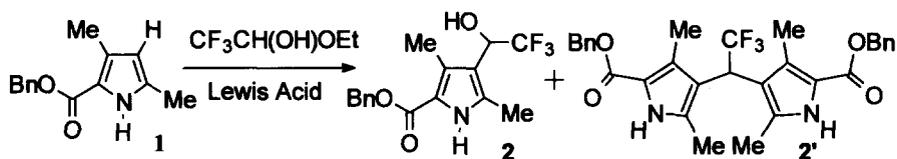
Our strategy is shown in Scheme 2. If a dipyrromethane with suitable fluorine substituent was synthesized, it could be coupled with the bisformyl compound by MacDonal condensation⁴ to give the objective HFHP derivative. Rings A and B of the dipyrromethane could be synthesized by trifluoro-hydroxyethylation of the two pyrroles, as shown in the last part of Scheme 2.



The trifluorohydroxyethylation of the first ester (**1**) was successfully carried out, but the same reaction of the latter (**1'**) did not proceed at all probably due to the strong electron attracting effect of the ester group at the alpha position.

Instead, the synthesis of the two pyrrole components for this strategy was accomplished as shown in Scheme 3. Namely, both rings with a trifluorohydroxyethyl group were synthesized from ester **1**, which was prepared by Battersby's method.⁵ The reaction of **1** with trifluoroacetaldehyde ethyl hemiacetal was examined in the presence of various Lewis acids. Objective compound **2** was produced most effectively with zinc chloride. A small amount of 3,3'-bis(pyrryl)methane derivative **2'** was isolated as shown in Table 1. With boron trifluoride etherate, **2'** was formed preferentially.

Table 1. Reaction of Compound (1) with Trifluoroacetaldehyde Ethyl Hemiacetal.

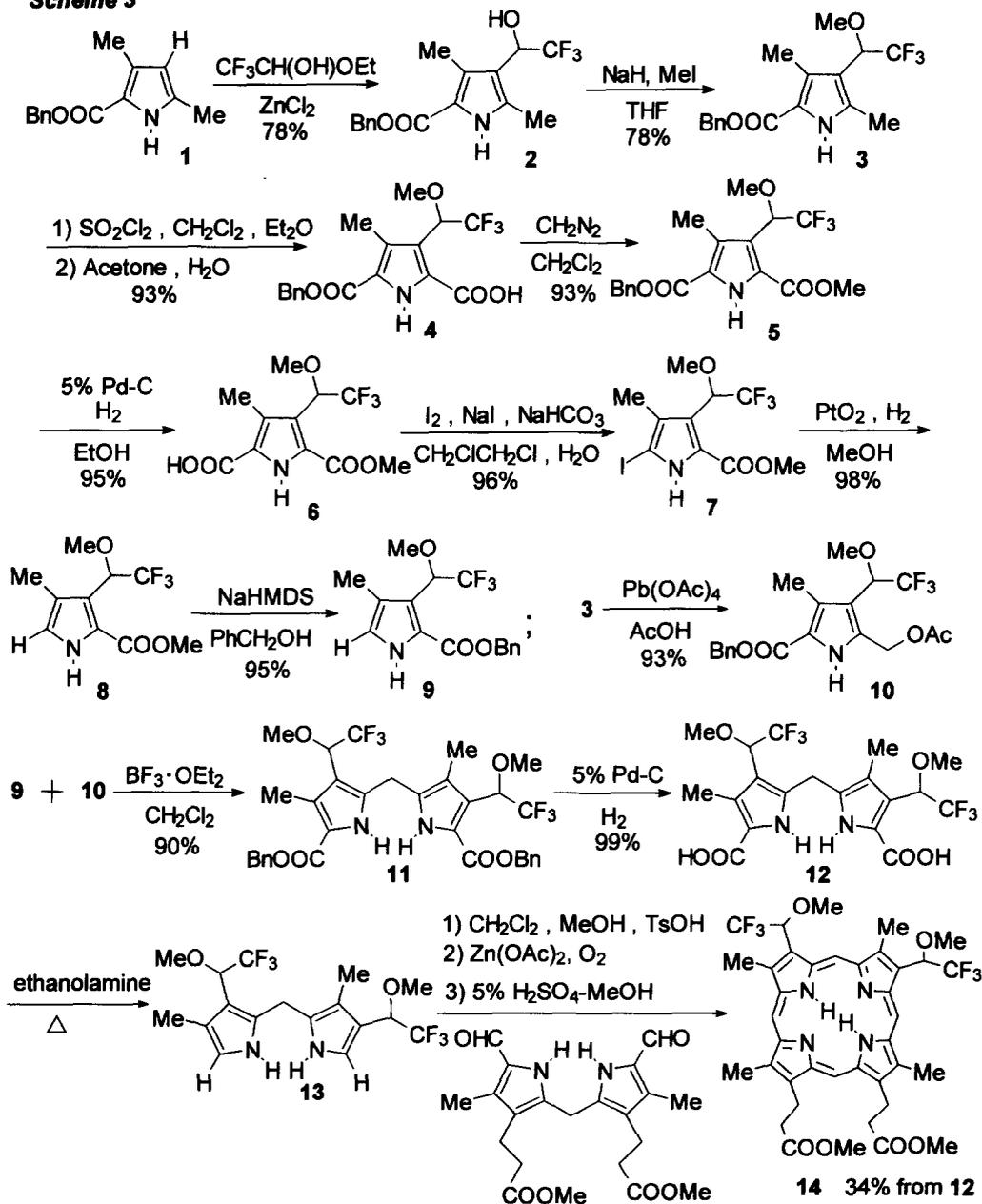


Run	Lewis Acid (eq)	Temp. (°C)	Time (h)	Yield (%)		Recovered (%)
				2	2'	
1	AlCl ₃ (1.3)	room temp.	15	—	—	—
2	MeAlCl ₂ (1.3)	room temp.	15	18	—	58
3	Me ₂ AlCl (1.3)	room temp.	15	33	—	20
4	Me ₃ Al (1.3)	room temp.	15	5	—	65
5	BF ₃ ·OEt ₂ (1.3)	room temp.	15	8	78	—
6	ZnCl ₂ (1.3)	room temp.	15	78	22	—
7	TiCl ₄ (1.3)	0 → r. t.	17	48	—	—
8	Ti(OisoPr) ₄ (1.3)	room temp.	17	—	—	94
9	SnCl ₄ (1.3)	0 → r. t.	19	—	25	—

Pyrrole **2** was treated with sodium hydride and methyl iodide in THF to give methyl ether **3**. When DMF was used as a solvent in this reaction, *N,O*-dimethyl compound was formed in a large amount. Thus, choice of the solvent is essential for *O*-methylation. Compound **3** was treated with sulfonyl chloride, followed by hydrolysis to give half ester **4** of a dicarboxylic acid. Successive protection and deprotection gave another half ester **6**, which was converted to mono ester **8** through iodo compound **7**. Finally, the methyl ester was changed to benzyl ester **9**, which corresponded to the B ring of the porphyrin. The methyl group of **3** was oxidized by lead tetraacetate to 5-acetoxymethyl compound **10**, which corresponded to the

A ring of the porphyrin.

Scheme 3



Condensation of 9 and 10, successive transformation of the dipyrromethane, and MacDonald condensation are shown at the bottom of Scheme 3. The condensation of 9 and 10 was carried out successfully in the presence of a catalytic amount of boron trifluoride etherate, while this type of

condensation of 2-(acetoxymethyl)pyrroles with pyrroles has been reported to proceed effectively in the presence of *p*-toluenesulfonic acid as a catalyst. The dipyrromethane **11** was debenzylated with hydrogen in the presence of Pd-C, followed by decarboxylation to give the objective dipyrromethane **13**. This was condensed with the bottom-half dipyrromethane⁵ in the presence of *p*-toluenesulfonic acid, and the product was oxidized by air to a zinc complex of the porphyrin in the presence of zinc acetate *in situ*.⁶ Finally, the product was treated with sulfuric acid to eliminate the zinc, affording objective product **14** as a 1:1 mixture of diastereomers.

In conclusion, we have succeeded in the synthesis of a hexafluorohematoporphyrin derivative by a ring closure. This method could be applied for the synthesis of chiral porphyrins using chiral pyrrole compounds. Recently, we have succeeded in the optical resolution of racemic trifluoroethoxymethylated porphyrins and chiral synthesis of trifluoroethylated pyrroles. The biological test of **14** is now in progress. Synthesis of chiral compounds and biological activities will be published in the near future.

Experimental Section

General Procedures. Melting points were measured on a micro melting point apparatus, Model MP (Yanagimoto, Kyoto, Japan) and a melting point apparatus (Ishii Shoten, Tokyo, Japan) without correction. ¹H-NMR spectra were recorded on JEOL FX90Q and JNM-GX400 spectrometers. ¹⁹F-NMR spectra were measured on Hitachi R-1500 and JEOL FX90Q spectrometers. Trichlorofluoromethane was used as an internal standard and the lower field is shown by +. Abbreviations are: s, singlet; d, doublet; m, multiplet; bs, broad singlet; q, quartet. Mass spectra were recorded on a JEOL JMS-DX300.

Benzyl 3,5-Dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)pyrrole-2-carboxylate (2).

ZnCl₂ (7.54 g, 55.3 mmol), dehydrated by melting under vacuum, was suspended in anhydrous CH₂Cl₂ (170 ml) in a stream of Ar. To this mixture, a solution of benzyl 3,5-dimethylpyrrole-2-carboxylate⁵ (**1**, 10.0 g, 43.7 mmol) in CH₂Cl₂ (30 ml) was added at room temperature, then a solution of trifluoroacetaldehyde ethyl hemiacetal (6.2 ml, 53.4 mmol) in anhydrous CH₂Cl₂ (10 ml) was added. The whole mixture was stirred at room temperature for 28 h, then treated with saturated NH₄Cl, and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-Et₂O, 97:3), and recrystallized from CH₂Cl₂-hexane to afford **2** (11.2 g, 78%). **2**: Mp 122-123°C. MS *m/z*: 327 (M⁺). HRMS Calcd C₁₆H₁₆F₃NO₃ (M⁺): 327.107. Found: 327.108. ¹H-NMR (CDCl₃) δ: 8.99 (1H, s), 7.36 (5H, m), 5.28 (2H, s), 5.04 (1H, q-d, J=7.3, 4.4 Hz), 2.65 (1H, d, J=4.4 Hz), 2.34 (3H, s), and 2.30 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -78.66 (3F, d, J=7.3 Hz).

Benzyl 3,5-Dimethyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-2-carboxylate (3).

A solution of **2** (3.00 g, 9.17 mmol) in THF (10 ml) was added dropwise into a suspension of NaH (60% in oil, 92 mg, 27.6 mmol) in THF (50 ml) under ice-cooling in a stream of Ar, and the mixture was stirred at this temperature for 1 h, then MeI (684 μ l, 11.0 mmol) was added over another period of 25 min. After the mixture stirred for 2 h, it was treated with saturated NH₄Cl, neutralized with AcOH, and extracted with AcOH, and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, then dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-hexane, 9:1), and recrystallized from hexane to give **3** (2.45 g, 78 %). **3**: Mp 99-100°C. MS *m/z*: 341 (M⁺). HRMS Calcd C₁₇H₁₈F₃NO₃ (M⁺): 341.124. Found: 341.124. ¹H-NMR (CDCl₃) δ : 9.26 (1H, s), 7.37 (5H, m), 5.31 (2H, s), 4.56 (1H, q, J=7.3 Hz), 3.36 (3H, s), 2.34 (3H, s), and 2.27 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -76.81 (3F, d, J=7.3 Hz).

When DMF was used as a solvent, *O*- and *N*-alkylation of pyrrole ring proceeded competitively.

2-Benzyloxycarbonyl-3-methyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-5-carboxylic Acid (4).⁵

SO₂Cl₂ (2.17 ml, 27.0 mmol) was added dropwise to a solution of **3** (2.26 g, 6.63 mmol) in anhydrous CH₂Cl₂-Et₂O (15.8 ml, 25.0 ml) at room temperature in a stream of Ar, then the mixture was stirred for 1.5 h. The mixture was concentrated under vacuum, and the residue was dissolved in acetone (34 ml) and H₂O (6.8 ml). After the mixture was refluxed for 40 min, acetone was evaporated, and the residue was treated with ice-water and hexane. The crystals, which separated between two layers, were collected by filtration. The crystals were dissolved in 2M NH₄OH, then the solution was acidified by AcOH to give **4** (2.28 g, 93 %). **4**: Mp 162-163°C. MS *m/z*: 371 (M⁺). HRMS Calcd C₁₇H₁₆F₃NO₅ (M⁺): 371.098. Found: 371.098. ¹H-NMR (CDCl₃) δ : 9.92 (1H, s), 9.35 (1H, s), 7.40 (5H, s), 5.50 (1H, q, J=7.0 Hz), 5.36 (2H, s), 3.47 (3H, s), and 2.44 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -76.19 (3F, d, J=7.0 Hz).

Benzyl 5-Methoxycarbonyl-3-methyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-2-carboxylate (5).

A solution of diazomethane in Et₂O was added to a solution of **4** (1.56 g, 4.2 mmol) in CH₂Cl₂ (30 ml) at room temperature. After the excess of diazomethane was decomposed by AcOH, the mixture was poured into ice-water, then extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-hexane, 9:1), and recrystallized from hexane to give **5** (1.51 g, 93 %). **5**: Mp 69-70°C. MS *m/z*: 385 (M⁺). HRMS Calcd C₁₈H₁₈F₃NO₅ (M⁺): 385.114. Found: 385.113. ¹H-NMR (CDCl₃) δ : 9.64 (1H, s), 7.42 (5H, m), 5.64 (1H, q, J=7.3 Hz), 5.35 (2H, s), 3.90 (3H, s), 3.40 (3H, s), and 2.45 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -76.00 (3F, d, J=7.3 Hz).

5-Methoxycarbonyl-3-methyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-2-carboxylic acid (6).

A solution of **5** (1.51 g, 3.92 mmol) in EtOH (19 ml) was shaken in atmosphere of H₂ in the presence of 5% Pd-C (134 mg) until absorption of H₂ was completed. After the catalyst was filtered off, the solvent was evaporated under vacuum. The residue was dissolved in 2M NH₄OH, and the solution was acidified with AcOH to give the crystals of **6** (1.10 g, 95 %). **6**: Mp 184-186°C. MS *m/z*: 295 (M⁺). HRMS Calcd C₁₁H₁₂F₃NO₅ (M⁺): 295.067. Found: 295.067. ¹H-NMR (CDCl₃) δ: 9.76 (2H, s), 5.65 (1H, q, J=7.3 Hz), 3.94 (3H, s), 3.44 (3H, s), and 2.49 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -76.00 (3F, d, J=7.3 Hz).

Methyl 2-Iodo-3-methyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-5- carboxylate (7).

A solution of I₂ (1.35 g, 5.31 mmol) and NaI (1.46 g, 9.73 mmol) in H₂O (7 ml) was added to a mixture of **6** (1.10 g, 3.73 mmol) and anhydrous NaHCO₃ (1.04 g, 12.4 mmol) in CH₂ClCH₂Cl-H₂O (7 ml, 7 ml), then the whole mixture was refluxed for 40 min. After the excess of I₂ was decomposed by saturated NaHSO₃, the mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-hexane, 8:2), and recrystallized from hexane to afford **7** (1.39 g, 96 %). **7**: Mp 131-132°C. MS *m/z*: 377 (M⁺). HRMS Calcd C₁₀H₁₁F₃INO₃ (M⁺): 376.974. Found: 376.973. ¹H-NMR (CDCl₃) δ: 9.28 (1H, s), 5.59 (1H, q, J=7.3 Hz), 3.89 (3H, s), 3.40 (3H, s), and 2.12 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -75.97 (3F, d, J=7.3 Hz).

Methyl 3-Methyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-5-carboxylate (8).

A solution of **7** (1.39 g, 3.69 mmol) in MeOH (16 ml) was stirred in the atmosphere of H₂ in the presence of PtO₂ (20 mg) and anhydrous NaOAc (924mg, 11.3mmol), until absorption of H₂ was completed. After the catalyst was filtered off, H₂O was added to the mixture and the whole mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-hexane, 8:2), and recrystallized from hexane to give **8** (0.91 g, 98 %). **8**: Mp 90-92°C. MS *m/z*: 251 (M⁺). HRMS Calcd C₁₀H₁₂F₃NO₃ (M⁺): 251.077. Found: 251.076. ¹H-NMR (CDCl₃) δ: 9.05 (1H, s), 6.71 (1H, d, J=2.4 Hz), 5.63 (1H, q, J=7.3 Hz), 3.87 (3H, s), 3.41 (3H, s), and 2.16 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -76.08 (3F, d, J=7.3 Hz).

Benzyl 4-Methyl-3-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-2-carboxylate (9).

A solution of BnONa in anhydrous BnOH was added to a solution of **8** (0.93 g, 2.84 mmol) in anhydrous BnOH (4 ml) at 200°C, until evolution of MeOH was not observed. The mixture was poured into ice-water, then extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous

MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-hexane, 1:1) to give **9** (0.92 g, 76 %).

To improve the above procedure, a solution of sodium bis(trimethylsilyl)amide (1.0 M in THF, 1 ml) was added dropwise to a solution of **8** (100 mg, 0.40 mmol) in anhydrous BnOH at 80°C in a stream of Ar, and the mixture was refluxed at this temperature for 0.5 h. This was poured into ice-water, and the whole mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-hexane, 1:1) to give **9** (124 mg, 95 %). **9**: Mp 55-56°C. MS *m/z*: 327 (M⁺). HRMS Calcd C₁₆H₁₆F₃NO₃ (M⁺): 327.108. Found: 327.108. ¹H-NMR (CDCl₃) δ: 9.07 (1H, s), 7.37 (5H, m), 6.69 (1H, d, J=2.4 Hz), 5.65 (1H, q, J=7.3 Hz), 5.30 (2H, s), 3.37 (3H, s), and 2.15 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -75.97 (3F, d, J=7.3 Hz).

Benzyl 5-Acetylmethyl-3-methyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-2-carboxylate (10).

Pb(OAc)₄ (3.70 g, 8.35 mmol) was added to a solution of **3** (753 mg, 2.21 mmol) in acetic acid (25 ml) in the atmosphere of Ar, and the mixture was stirred at 65°C for 7 h. After the excess of Pb(OAc)₄ was decomposed by ethylene glycol, the mixture was poured into ice-water and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was recrystallized from MeOH to give **10** (823 mg, 93%). **10**: Mp 98-99°C. MS *m/z*: 399 (M⁺). HRMS Calcd C₁₉H₂₀F₃NO₅ (M⁺): 399.129. Found: 399.129. ¹H-NMR (CDCl₃) δ: 9.34 (1H, s), 7.38 (5H, m), 5.32 (2H, s), 5.15 (2H, s), 4.64 (1H, q, J=7.3 Hz), 3.41 (3H, s), 2.33 (3H, s), and 2.08 (3H, s). ¹⁹F-NMR (CDCl₃) ppm: -77.24 (3F, d, J=7.3 Hz).

Dibenzyl 3,4'-Bis(2,2,2-trifluoro-1-methoxyethyl)-4,3'-dimethyl-2,2'-dipyrrylmethane-5, 5'-dicarboxylate (11).

Method 1. A solution of **9** (120 mg, 0.37 mmol), **10** (148 mg, 0.37 mmol) and *p*-toluenesulfonic acid monohydrate (8 mg, 0.04 mmol) in anhydrous CH₂Cl₂ (8ml) was stirred at room temperature for 23 h in a stream of Ar, then the mixture was poured into water, and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-Et₂O, 99.5:0.5), and recrystallized from hexane to give **11** (185 mg, 76 %).

Method 2. A solution of **9** (120 mg, 0.37 mmol), **10** (148 mg, 0.37 mmol) and BF₃ · OEt₂ (15 μl, 0.122 mmol) in anhydrous CH₂Cl₂ (8 ml) was stirred at room temperature for 2 h in a stream of Ar, then the mixture was poured into water, and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by

column chromatography (SiO₂, CH₂Cl₂- Et₂O, 99.5:0.5), and recrystallized from hexane to give **11** (221 mg, 90 %). **11**: Mp 133-134°C. MS *m/z*: 666 (M⁺). HRMS Calcd C₃₃H₃₂F₆N₂O₆ (M⁺): 666.216. Found: 666.216. ¹H-NMR (CDCl₃) δ: 9.33 (1H, s), 9.02 (1H, s), 7.32 (10H, m), 5.63 (0.5H, q, J=7.3 Hz), 5.62 (0.5H, q, J=7.3 Hz), 5.26 (2H, s), 5.23 (2H, s), 4.56 (1H, q, J=7.3 Hz), 4.00 (1H, d, J=16.9 Hz), 3.86 (1H, d, J=16.9 Hz), 3.38 (1.5H, s), 3.37 (1.5H, s), 3.36 (3H, s), 2.32 (3H, s), and 2.13 (3H, s). ¹⁹F-NMR (CDCl₃) ppm : -75.82 (3F, d, J=7.3 Hz), and -76.20 (3F, d, J=7.3 Hz).

3,4'-Bis(2,2,2-trifluoro-1-methoxyethyl)-4,3'-dimethyl-2,2'-dipyrrylmethane-5,5'-dicarboxylic acid (12)

A solution of **11** (185 mg, 0.28 mmol) in THF (14 ml) was stirred in the atmosphere of H₂ in the presence of 5% Pd-C (74 mg) until absorption of H₂ was completed. After filtration of the catalyst and evaporation of the solvent, the residue was dissolved in 2M NH₄OH, and the solution was acidified with AcOH. The precipitate was collected by filtration to give **12** (133 mg, 99 %). This compound was unstable and did not show M⁺ on EI MS, and M⁺ was detected by FAB MS. **12**: MS *m/z*: 486 (M⁺). ¹H-NMR (CDCl₃) δ: 11.40 (1H, s), 10.98 (1H, s), 6.18 (2H, bs), 5.16 (1H, q, J=7.3 Hz), 4.60 (1H, q, J=7.3 Hz), 4.17 (1H, d, J=17.1 Hz), 3.87 (1H, d, J=17.1 Hz), 3.52 (3H, s), 3.24 (3H, s), 2.32 (3H, s), and 2.16 (3H, s).

3,4'-Bis(2,2,2-trifluoro-1-methoxyethyl)-4,3'-dimethyl-2,2'-dipyrrylmethane (13)

In a stream of Ar, **12** (133 mg, 0.27 mmol) was dissolved in degassed ethanolamine (3 ml) and stirred at 200°C for 1 h. The mixture was poured into ice-water and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was used for the next step.

3, 8-Bis(2,2,2-trifluoro-1-methoxyethyl)deuteroporphyrin Dimethyl Ester (14)

In a stream of Ar, a solution of *p*-toluenesulfonic acid monohydrate (137 mg, 0.72 mmol) in anhydrous MeOH (2.3 ml) was added to a solution of **13** (91 mg, 0.23 mmol) and 5,5'-diformyl-3,3'-bis(2-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrylmethane⁵ (92mg, 0.23mmol) in anhydrous CH₂Cl₂-MeOH (23 ml, 2.3 ml) at room temperature, and the mixture was stirred for 15 h. Further, a saturated solution of Zn(OAc)₂ in MeOH (2.4 ml) was added and stirred in air at room temperature for 24 h⁶. The whole mixture was concentrated under vacuum, and the residue was stirred with 5 % H₂SO₄-MeOH at room temperature for 20 min. The mixture was poured into ice-water, and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, and dried over anhydrous MgSO₄. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO₂, CH₂Cl₂-Et₂O, 98:2) and recrystallized from CH₂Cl₂-hexane to give **14** as a mixture of diastereomers (1:1) (60 mg, 34 %). **14**: Mp 254-255°C. MS *m/z*: 762 (M⁺). HRMS Calcd C₃₈H₄₀F₆N₄O₆ (M⁺): 762.285. Found: 762.286. ¹H-NMR (CDCl₃) δ: 10.68

(0.5H, s), 10.66 (0.5H, s), 10.55 (0.5H, s), 10.53 (0.5H, s), 10.13 (1H, s), 9.99 (0.5H, s), 9.98 (0.5H, s), 6.24 (1H, q, J=7.3 Hz), 6.21 (1H, q, J=7.3 Hz), 4.40 (2H, t, J=7.5 Hz), 4.30 (2H, t, J=7.5 Hz), 3.87 (4.5H, s), 3.86 (1.5H, s), 3.84 (1.5H, s), 3.83 (1.5H, s), 3.82 (1.5H, s), 3.81 (1.5H, s), 3.72 (3H, s), 3.69 (3H, s), 3.68 (3H, s), 3.58 (3H, s), 3.24 (2H, t, J=7.5 Hz), 3.20 (2H, t, J=7.5 Hz), and -3.63 (2H, s). ^{19}F -NMR (CDCl_3) ppm : -74.80 (6F, d, J=7.3 Hz).

References and Notes

1. Concerning photodynamic therapy using compounds related to porphyrins, see review; Kessel, D.; Dougherty, T. J. 'Advances in Experimental Medicines and Biology', **160**, 'Porphyrin Photosensitization', Plenum, New York, 1983. Concerning fluorine analogs of porphyrins, see our review; Ando, A.; Kumadaki, I. *Heterocycles*, **1996**, 42, 885.
2. Concerning the biological effects of fluorine compounds, see Filler, R.; Kobayashi, Y. 'Biomedical Aspects of Fluorine Chemistry', Kodansha, Tokyo, 1983.
3. Ando, A.; Kitamura, T.; Aono, S.; Sato, H.; Omote, M.; Koyama, M.; Takagi, T.; Miki, T.; Kumadaki, I. *Heterocycles*, **1993**, 35, 1309.
4. Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.*, **1960**, 82, 4384.
5. Robinson, J. A.; McDonald, E.; Battersby, A. R. *J. Chem. Soc. Perkin Trans 1*, **1985**, 1699.
6. Lash T. D.; Denny, C. P. *Tetrahedron*, **1995**, 51, 59.

(Received in Japan 8 July 1996; accepted 17 September 1996)