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Synthesis of A Fluorine Analog of Hematoporphyrin by Ring Closure

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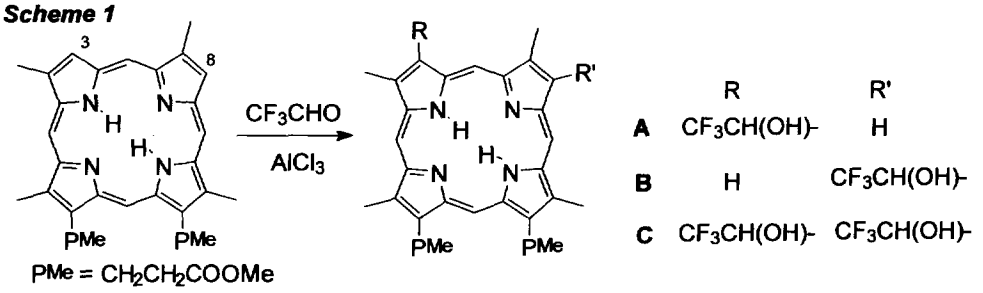
Abstract: Benzyl 3,5-dimethyl-2-pyrrolecarboxylate (**1**) was converted to 4-(2,2,2-trifluoro-1-hydroxyethyl) derivative (**2**) on treatment with trifluoroacetaldehyde ethyl hemiacetal in the presence of zinc chloride. After protection of the hydroxyl group with a methyl group, **2** was converted 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 dipyrrylmethane 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.

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 ^{19}F-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



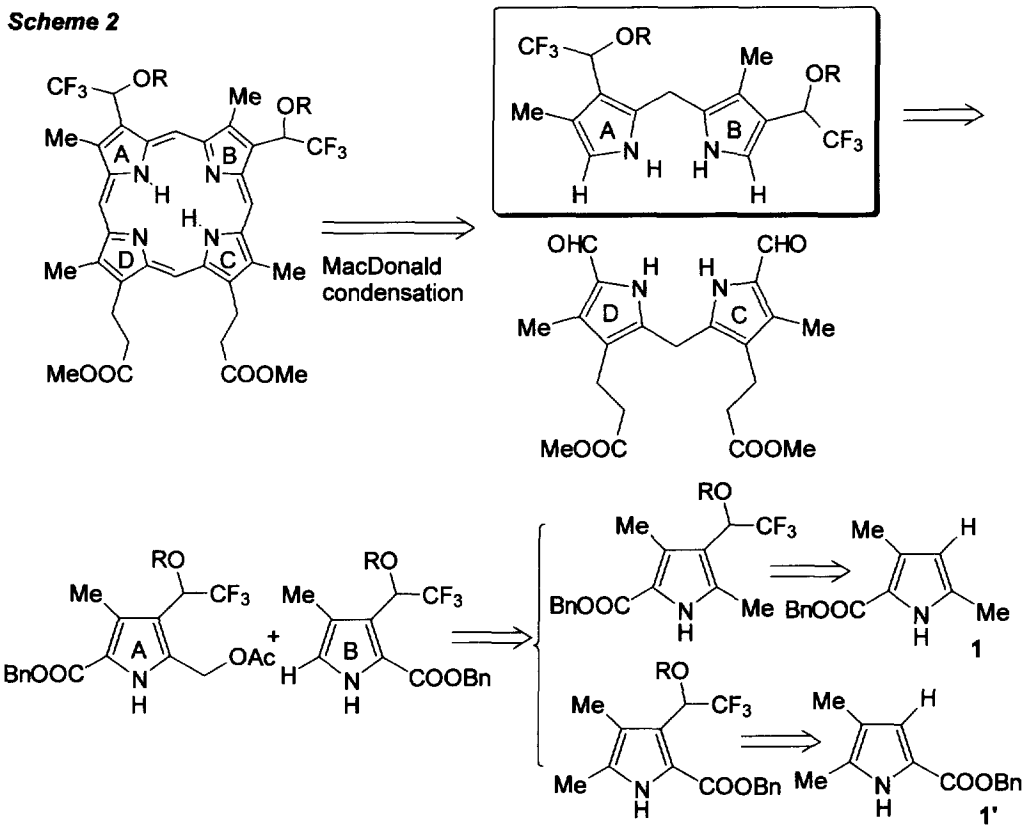
PMe = CH_2CH_2COOMe

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 dipyrrylmethane with suitable fluorine substituent was synthesized, it could be coupled with the bisformyl compound by MacDonald condensation[4] to give the objective HFHP derivative. Rings A and B of the dipyrrylmethane could be synthesized by trifluoro-hydroxyethylation of the two pyrroles, as shown in the last part of Scheme 2.

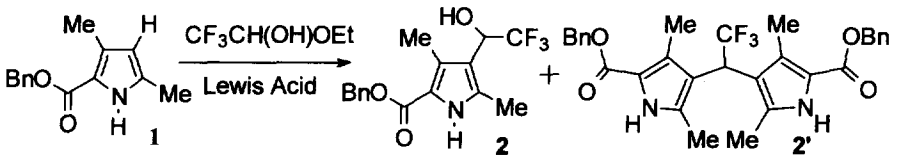
Scheme 2



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.

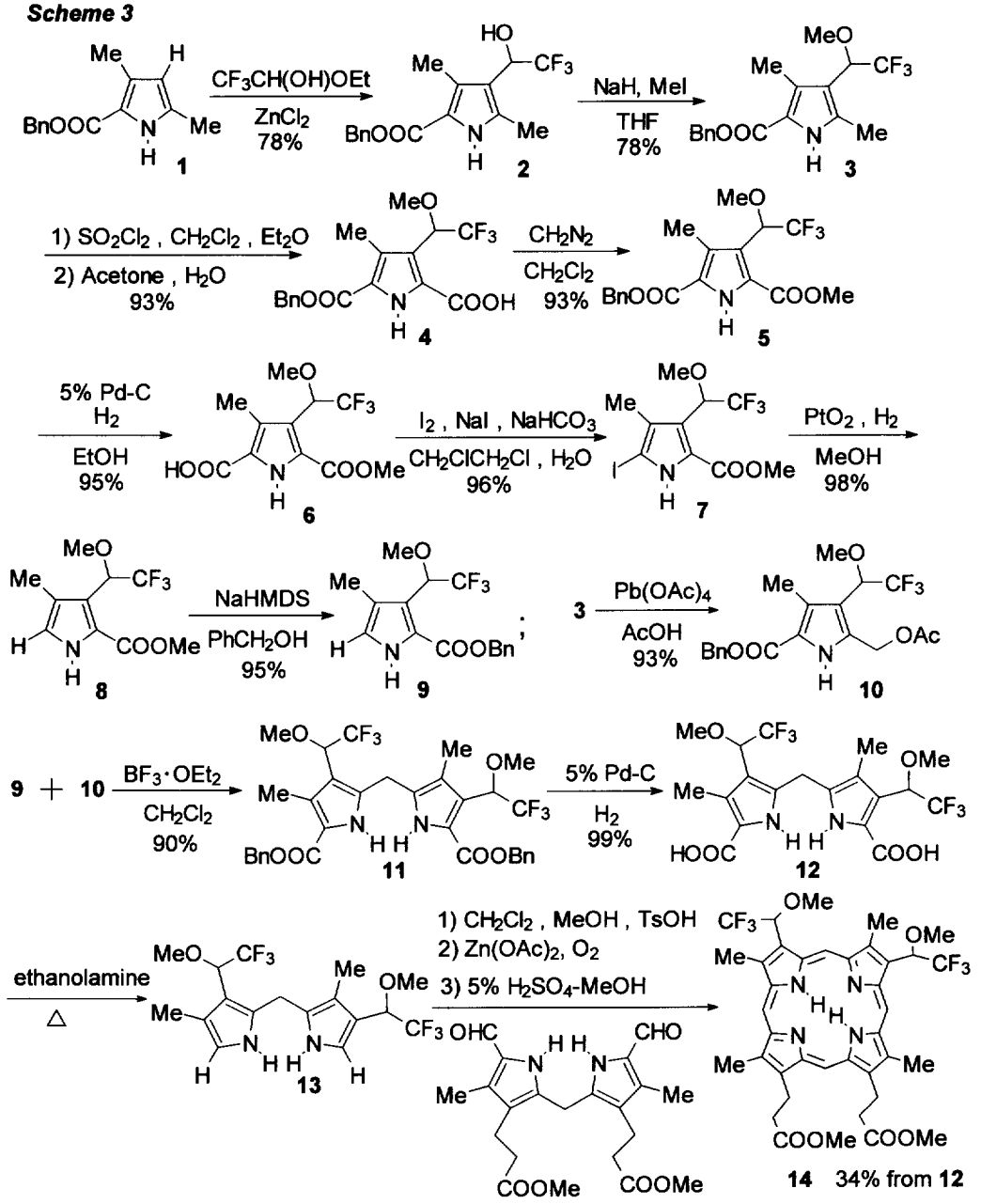


Run	Lewis Acid (eq)	Temp. (°C)	Time (h)	Yield (%)		Recovered (%)
				2	**2'**	
1	$AlCl_3$ (1.3)	room temp.	15	—	—	—
2	$MeAlCl_2$ (1.3)	room temp.	15	18	—	58
3	Me_2AlCl (1.3)	room temp.	15	33	—	20
4	Me_3Al (1.3)	room temp.	15	5	—	65
5	$BF_3 \cdot OEt_2$ (1.3)	room temp.	15	8	78	—
6	$ZnCl_2$ (1.3)	room 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 sulfuryl 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 dipyrrylmethane, 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 dipyrrylmethane **11** was debenzylated with hydrogen in the presence of Pd-C, followed by decarboxylation to give the objective dipyrrylmethane **13**. This was condensed with the bottom-half dipyrrylmethane[5] in the presence of *p*-toluenesulfonic acid, and the product was oxidizeed 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 trifluorohydroxyethylated 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. ^{1}H-NMR spectra were recorded on JEOL FX90Q and JNM-GX400 spectrometers. ^{19}F-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).

$ZnCl_2$ (7.54 g, 55.3 mmol), dehydrated by melting under vacuum, was suspended in anhydrous CH_2Cl_2 (170 ml) in a stream of Ar. To this mixture, a solution of benzyl 3,5-dimethylpyrrole-2-carboxylate[5] (**1**, 10.0 g, 43.7 mmol) in CH_2Cl_2 (30 ml) was added at room temperature, then a solution of trifluoroacetaldehyde ethyl hemiacetal (6.2 ml, 53.4 mmol) in anhydrous CH_2Cl_2 (10 ml) was added. The whole mixture was stirred at room temperature for 28 h, then treated with saturated NH_4Cl, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-Et_2O, 97:3), and recrystallized from CH_2Cl_2-hexane to afford **2** (11.2 g, 78%). **2**: Mp 122-123°C. MS *m/z*: 327 (M^+). HRMS Calcd $C_{16}H_{16}F_3NO_3$ (M^+): 327.107. Found: 327.108. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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 (50ml) under ice-cooling in a stream of Ar, and the mixture was stirred at this temperature for 1 h, then MeI (684 μl, 11.0 mmol) was added over another period of 25 min. After the mixture stirred for 2 h, it was treated with saturated NH_4Cl, neutralized with AcOH, and extracted with AcOH, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, then dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-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 $C_{17}H_{18}F_3NO_3$ (M^+): 341.124. Found: 341.124. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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]

SO_2Cl_2 (2.17 ml, 27.0 mmol) was added dropwise to a solution of **3** (2.26 g, 6.63 mmol) in anhydrous CH_2Cl_2-Et_2O (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 H_2O (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 NH_4OH, 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 $C_{17}H_{16}F_3NO_5$ (M^+): 371.098. Found: 371.098. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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 Et_2O was added to a solution of **4** (1.56 g, 4.2 mmol) in CH_2Cl_2 (30 ml) at room temperature. After the excess of diazomethane was decomposed by AcOH, the mixture was poured into ice-water, then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-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 $C_{18}H_{18}F_3NO_5$ (M^+): 385.114. Found: 385.113. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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 H_2 in the presence of 5% Pd-C (134 mg) until absorption of H_2 was completed. After the catalyst was filtered off, the solvent was evaporated under vacuum. The residue was dissolved in 2M NH_4OH, 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 $C_{11}H_{12}F_3NO_5$ (M^+): 295.067. Found: 295.067. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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 I_2 (1.35 g, 5.31 mmol) and NaI (1.46 g, 9.73 mmol) in H_2O (7 ml) was added to a mixture of **6** (1.10 g, 3.73 mmol) and anhydrous $NaHCO_3$ (1.04 g, 12.4 mmol) in CH_2ClCH_2Cl-H_2O (7 ml, 7 ml), then the whole mixture was refluxed for 40 min. After the excess of I_2 was decomposed by saturated $NaHSO_3$, the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-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 $C_{10}H_{11}F_3INO_3$ (M^+): 376.974. Found: 376.973. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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 H_2 in the presence of PtO_2 (20 mg) and anhydrous NaOAc (924mg, 11.3mmol), until absorption of H_2 was completed. After the catalyst was filtered off, H_2O was added to the mixture and the whole mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-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 $C_{10}H_{12}F_3NO_3$ (M^+): 251.077. Found: 251.076. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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 CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous

$MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-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 CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-hexane, 1:1) to give **9** (124 mg, 95 %). **9**: Mp 55-56°C. MS *m/z*: 327 (M^+). HRMS Calcd $C_{16}H_{16}F_3NO_3$ (M^+): 327.108. Found: 327.108. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) ppm: -75.97 (3F, d, J=7.3 Hz).

Benzyl 5-Acetoxymethyl-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 CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous $MgSO_4$. 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 $C_{19}H_{20}F_3NO_5$ (M^+): 399.129. Found: 399.129. ^{1}H-NMR ($CDCl_3$) d: 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). ^{19}F-NMR ($CDCl_3$) 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 CH_2Cl_2 (8ml) was stirred at room temperature for 23 h in a stream of Ar, then the mixture was poured into water, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-Et_2O, 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 $BF_3 \cdot OEt_2$ (15 μl, 0.122 mmol) in anhydrous CH_2Cl_2 (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 CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by

column chromatography (SiO_2, CH_2Cl_2- Et_2O, 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 $C_{33}H_{32}F_6N_2O_6$ (M^+): 666.216. Found: 666.216. ^{1}H-NMR ($CDCl_3$) 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). ^{19}F-NMR ($CDCl_3$) 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 H_2 in the presence of 5% Pd-C (74 mg) until absorption of H_2 was completed. After filtration of the catalyst and evaporation of the solvent, the residue was dissolved in 2M NH_4OH, 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^+). ^{1}H-NMR ($CDCl_3$) 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 CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and dried over anhydrous $MgSO_4$. 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'-dipyrrylmethane[5] (92mg, 0.23mmol) in anhydrous CH_2Cl_2-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 h[6]. The whole mixture was concentrated under vacuum, and the residue was stirred with 5 % H_2SO_4-MeOH at room temperature for 20 min. The mixture was poured into ice-water, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2-Et_2O, 98:2) and recrystallized from CH_2Cl_2-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 $C_{38}H_{40}F_6N_4O_6$ (M^+): 762.285. Found: 762.286. ^{1}H-NMR ($CDCl_3$) 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

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