Synthesis of Formyl(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrins and Their Derivatization to Porphyrin Derivatives with Elongated Side-Chains[1)]

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We previously synthesized 3- and 8-mono-, and 3,8-bis(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl esters (2—4) by Friedel–Crafts reaction of deuteroporphyrin dimethyl ester (1) with trifluoroacetaldehyde, and trifluorohematoporphyrin analogs (5 and 6) by acetylation of 2 and 3 followed by reduction. These fluorine analogs of natural porphyrins have interesting biological properties; some of them accumulate selectively in certain tumor cells. In order to introduce larger substituents at the 8- or 3-position of 2 and 3, 2 and 3 were converted in several steps to 8- and 3-formyl derivatives (13 and 14), respectively. These were treated with vinylmagnesium bromide to give 8- or 3-(1-hydroxy-2-propenyl) derivatives (15 or 16). Further, reaction of 7 or 8 with the enol ether of 2-octanone gave the 8- or 3-(3-oxo-1-nonenyl) compounds (17 or 18). The affinities of the porphyrin derivatives, obtained by hydrolysis of the above porphyrin esters, for tumor tissues were examined. Among them, the porphyrin obtained by hydrolysis of 16 was found to accumulate in liver cancer transplanted in nude mice to a greater extent than hematoporphyrin.

Key words porphyrin; fluorine; trifluorohydroxyethyl; cancer; diagnosis; formyl

With the aim of obtaining a porphyrin derivative useful for diagnosis and therapy of cancer, we have synthesized porphyrins with fluorine substituents at the 3- and/or 8-position, since biologically important porphyrins have characteristic substituents at these positions. We reported the synthesis of 3- and/or 8-(2,2-difluorovinyl) analogs of protoporphyrin[2)] and 3- and/or 8-(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin (**2**—**4**) by Friedel–Crafts reaction of deuteroporphyrin dimethyl ester (**1**),[3)] as well as the synthesis of trifluoro analogs of hematoporphyrin (**5** and **6**).[4)] These reactions are shown in Chart 1.

Some of these fluorine analogs accumulate specifically in certain tumor cells. Here we report synthesis of porphyrin derivatives with a larger substituent at the 3- or

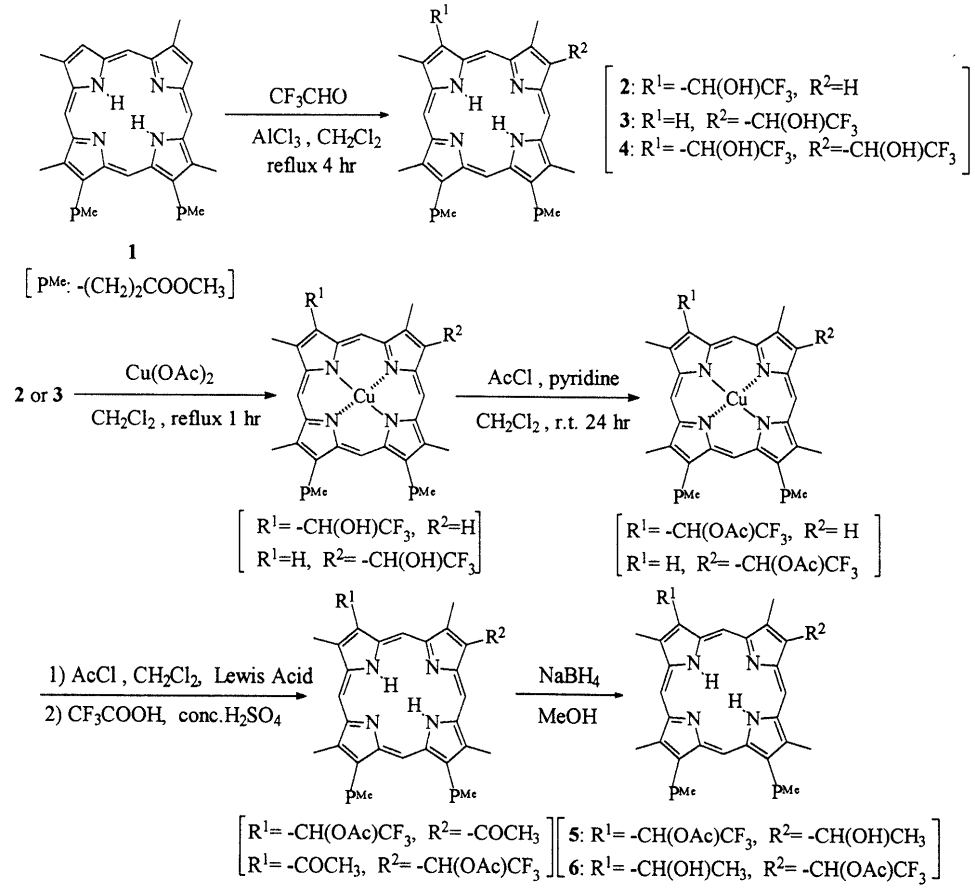

Chart 1

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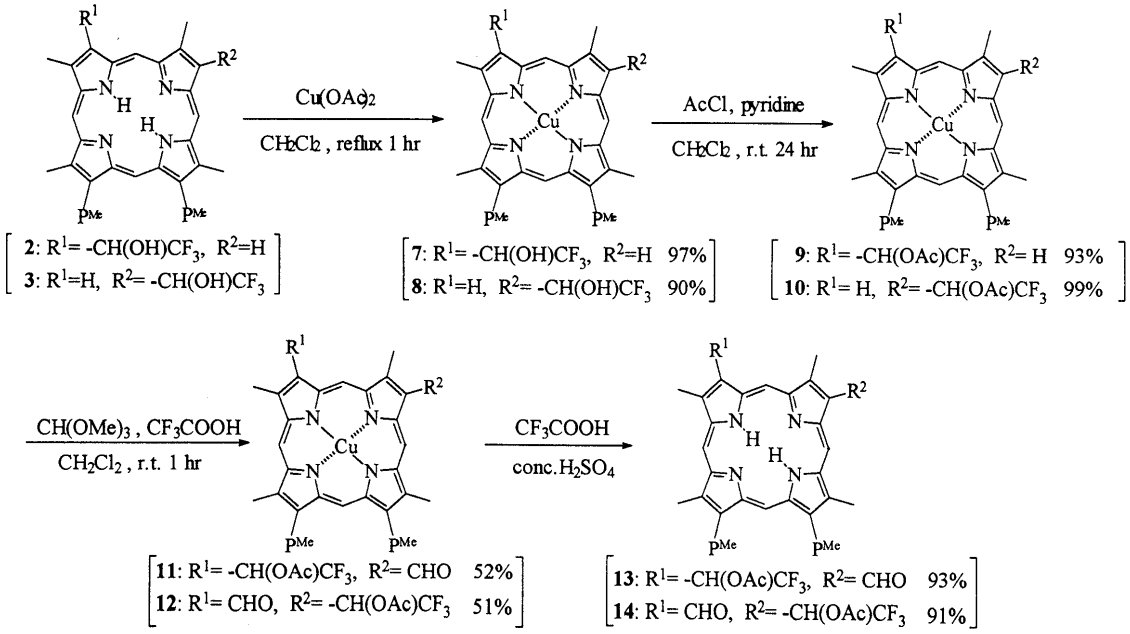
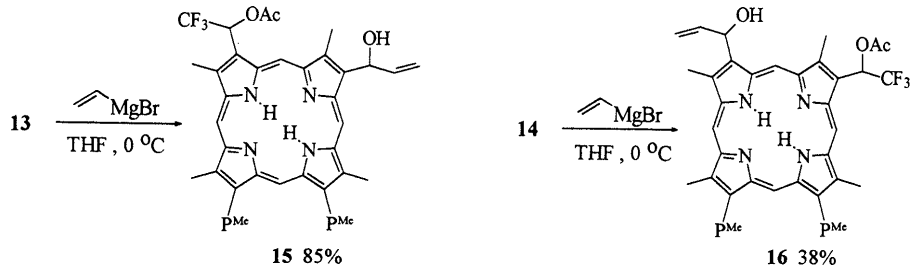


Chart 2



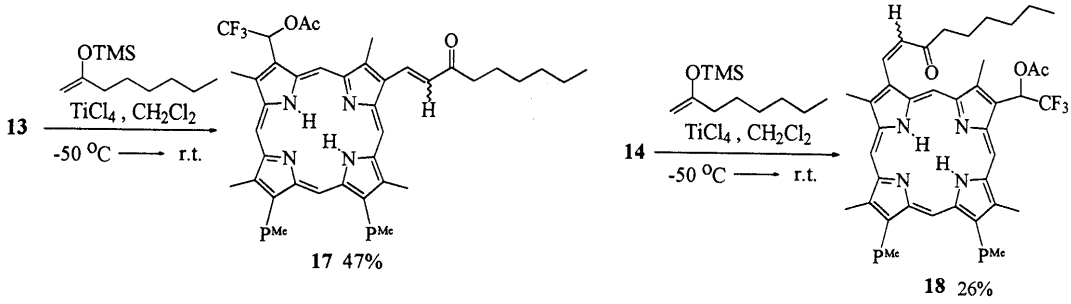


Chart 3

8-position. For this purpose, a formyl group was introduced into **2** and **3**, followed by modification of the formyl group with carbanion equivalents.

Since porphyrins are sensitive to a strong acidic condition, **2** and **3** were converted to copper complexes (**7** and **8**, respectively) by treatment with cupric acetate, as in the acetylation of porphyrin.[4] The hydroxyl group of **7** and **8** was acetylated to give the acetates (**9** and **10**), which were treated with trimethyl orthoformate in the presence of trifluoroacetic acid to afford the 8- and 3-formyl compounds (**11** and **12**) in the yields of 52% and 51%, respectively. These were demetalated with sulfuric acid and trifluoroacetic acid to give the copper-free compounds (**13** and **14**). Reaction of these formyl compounds with vinylmagnesium bromide gave the 8- and 3-(1-hydroxy-2-propenyl) compounds (**15** and **16**) in yields of 85% and 38%, respectively. Further, treatment of **13** and **14** with 2-(trimethylsilyloxy)-1-octene in the presence of titanium chloride gave the 8- and 3-(3-oxo-1-nonenyl) derivatives (**17** and **18**) in yields of 47% and 26%, respectively. These results are summarized in Charts 2 and 3.

Finally, compounds **13** through **18** were hydrolyzed with sodium hydroxide to the sodium salts (**19** to **24**). These salts were given to nude mice with liver cancer. Accumulation of these porphyrins in the tumor, liver and kidney was examined, using hematoporphyrin derivative (HPD) as a control. HPD accumulated more extensively than our porphyrins in liver and kidney, but some of our compounds were accumulated more highly in the tumor

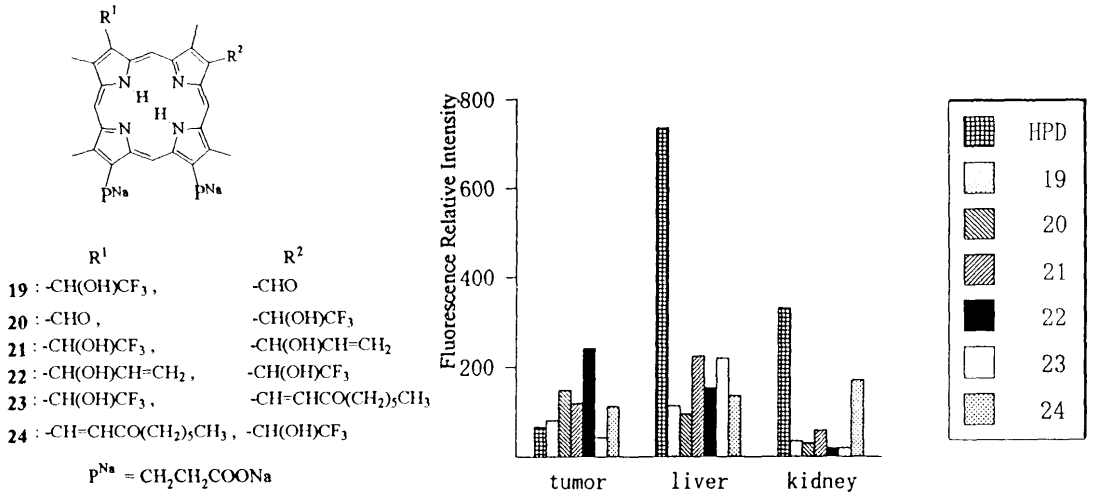


Fig. 1. Localization of Fluorinated Porphyrins in Tumor and Organs

than HPD. In particular, the porphyrin (**22**) obtained by hydrolysis of **16** accumulated in the tumor more than three times as effectively as HPD (Fig. 1). Thus, **22** seems greatly superior to HPD, since it accumulates selectively in the tumor and much less in the normal tissues. Namely, side effects of this compound on the normal organs should be much less than those of HPD. These results suggest that some fluorine analogs of porphyrin might accumulate in tumors more strongly and more selectively than HPD. Details of the biological experiment will be published elsewhere.

Experimental

3-(1-Acetoxy-2,2,2-trifluoroethyl)-8-formyldeuteroporphyrin Dimethyl Ester–Cu Complex (11) Trifluoroacetic acid (1.8 ml, 23.4 mmol) was added slowly to a solution of 3-(1-acetoxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester–Cu complex[4] (**9**, 300 mg, 0.41 mmol) and $CH(OMe)_3$ (1.5 ml, 13.7 mmol) in dry CH_2Cl_2 (6.0 ml) at room temperature under a stream of Ar, and the mixture was stirred for 1 h, then poured into ice-water. The whole was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over $MgSO_4$, and concentrated under vacuum. The residue was separated by column chromatography (SiO_2, CH_2Cl_2–ethyl acetate, 97 : 3—90 : 10) to give 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-formyldeuteroporphyrin dimethyl ester–Cu complex (**11**, 161 mg, 52%) and the starting material (12 mg, 42%).

3-(1-Acetoxy-2,2,2-trifluoroethyl)-8-formyldeuteroporphyrin Dimethyl Ester (13) Under ice-cooling, **11** (1.74 g, 2.27 mmol) was added to a mixture of trifluoroacetic acid (20.0 ml, 0.30 mol) and concentrated H_2SO_4 (2.0 ml), then the mixture was stirred for an hour, poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography (SiO_2, CH_2Cl_2–ethyl acetate, 95 : 5—70 : 30) to give 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-formyldeuteroporphyrin dimethyl ester (**13**, 1.49 g, 93%). **13**: Dark red crystals, mp 96—98 °C. MS *m/z*: 706 (M^+). HRMS $C_{37}H_{37}F_3N_4O_7$: 706.261 (M^+). Found: 706.261. IR (KBr): 3316 (>NH), 1764, 1740, 1670 (C=O), 1212, 1172 (C–F) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.41 (1H, s), 10.57 (1H, s), 10.45 (1H, s), 9.98 (1H, s), 9.64 (1H, s), 7.87 (1H, q, J=7.3 Hz), 4.19 (2H, t, J=7.8 Hz), 4.17 (2H, t, J=7.8 Hz), 3.96 (3H, s), 3.83 (3H, s), 3.63 (3H, s), 3.61 (3H, s), 3.50 (3H, s), 3.44 (3H, s), 3.18 (2H, t, J=7.8 Hz), 3.13 (2H, t, J=7.8 Hz), 2.48 (3H, s), −3.77 (2H, s). ^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): −74.23 (3F, d, J=7.32 Hz).

8-(1-Acetoxy-2,2,2-trifluoroethyl)-3-formyldeuteroporphyrin Dimethyl Ester–Cu Complex (12) 8-(1-Acetoxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester–Cu complex (**10**, 309 mg, 0.41 mmol) was treated with $CH(OMe)_3$ (1.6 ml, 14.6 mmol) in dry CH_2Cl_2 (6.0 ml) in the presence of trifluoroacetic acid (1.9 ml, 24.7 mmol), as in the case of **9**. 8-(1-Acetoxy-2,2,2-trifluoroethyl)-3-formyldeuteroporphyrin dimethyl ester–Cu complex (**12**, 162 mg, 51%) was obtained by work-up as above with a recovery of **10** (139 mg, 45%).

8-(1-Acetoxy-2,2,2-trifluoroethyl)-3-formyldeuteroporphyrin Dimethyl Ester (14) The copper complex (**12**, 1.51 g, 1.97 mmol) was treated with a mixture of trifluoroacetic acid (15.0 ml, 0.19 mol) and concentrated H_2SO_4 (1.5 ml) as in the case of **11**, and the mixture was worked up similarly to give 8-(1-acetoxy-2,2,2-trifluoroethyl)-3-formyldeuteroporphyrin dimethyl ester (**14**, 1.26 g, 91%). **14**: Dark red crystals, mp 171—173 °C. MS *m/z*: 706 (M^+). HRMS $C_{37}H_{37}F_3N_4O_7$: 706.261 (M^+). Found: 706.261. IR (KBr): 3320 (>NH), 1764, 1738, 1666 (C=O), 1214, 1174 (C–F) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.98 (1H, s), 10.66 (1H, s), 10.27 (1H, s), 9.71 (1H, s), 9.04 (1H, s), 7.89 (1H, q, J=7.3 Hz), 4.29 (2H, t, J=7.6 Hz), 4.15 (2H, t, J=7.6 Hz), 3.84 (3H, s), 3.69 (3H, s), 3.62 (3H, s), 3.61 (3H, s), 3.25 (2H, t, J=7.8 Hz), 3.18 (6H, s), 3.13 (2H, t, J=7.6 Hz), 2.51 (3H, s), −4.19 (2H, s). ^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): −74.15 (3F, d, J=7.33 Hz).

3-(1-Acetoxy-2,2,2-trifluoroethyl)-8-(1-hydroxy-2-propenyl)deuteroporphyrin Dimethyl Ester (15) A solution of vinylmagnesium bromide (1.0 M in hexane, 0.1 ml, 0.1 mmol) was added dropwise to a solution of **13** (50 mg) in tetrahydrofuran (THF) (1.5 ml) at 0 °C under an atmosphere of Ar, and the mixture was stirred for an hour, then saturated NH_4Cl was added. The organic phase was separated, and the aqueous solution was extracted with CH_2Cl_2. The combined organic phase were dried over $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography (SiO_2, CH_2Cl_2–ethyl acetate, 95 : 5—70 : 30) to give 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-(1-hydroxy-2-propenyl)deuteroporphyrin dimethyl ester (**15**, 44 mg, 85%, 1 : 1 mixture of diastereomers). **15**: Dark red crystals, mp 101—103 °C. MS *m/z*: 734 (M^+). HRMS $C_{39}H_{41}F_3N_4O_7$: 734.292 (M^+). Found: 734.292. IR (KBr): 3452 (O–H), 3324 (>NH), 1760, 1740 (C=O), 1218, 1176 (C–F) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.41 (1H*, s), 10.12 (0.5H, s), 10.09 (0.5H, s), 9.91 (0.5H, s), 9.90 (0.5H, s), 9.55 (1H*, s), 7.88 (0.5H, q, J=7.4 Hz), 7.87 (0.5H, q, J= 7.4 Hz), 6.68 (0.5H, ddd, J=17.0, 10.5, 5.0 Hz), 6.64 (0.5H, ddd, J=17.0, 10.5, 5.0 Hz), 6.60 (0.5H, d, J=5.0 Hz), 6.48 (0.5H, d, J=5.0 Hz), 5.61 (0.5H, dd, J=16.5, 1.5 Hz), 5.56 (0.5H, dd, J=16.5, 1.5 Hz), 5.35 (0.5H, dd, J=10.5, 1.5 Hz), 5.32 (0.5H, dd, J=10.5, 1.5 Hz), 4.13 (2H*, t, J=7.8 Hz), 3.97 (2H*, t, J=7.1 Hz), 3.80 (1.5H, s), 3.79 (1.5H, s), 3.63 (3H*, s), 3.60 (3H*, s), 3.59 (3H*, s), 3.40 (1.5H, s), 3.37 (1.5H, s), 3.35 (1.5H, s), 3.34 (1.5H, s), 3.12 (2H*, t, J=7.8Hz), 3.07 (2H*, t, J=7.1Hz), 2.62 (0.5H, bd, J=5.0 Hz), 2.51 (0.5H, bd, J=5.0 Hz), 2.47 (1.5H, s), 2.46 (1.5H, s), −4.08 (2H*, s). ^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): −74.12 (3F, d, J=7.33 Hz). (* shows peaks ascribed to both isomers.)

8-(1-Acetoxy-2,2,2-trifluoroethyl)-3-(1-hydroxy-2-propenyl)deuteroporphyrin Dimethyl Ester (16) A solution of **14** (100 mg) in THF (6.0 ml) was treated with vinylmagnesium bromide (1.0 M in hexane, 0.2 ml, 0.2 mmol) and worked up as in the case of **13** to give 8-(1-acetoxy-2,2,2-trifluoroethyl)-3-(1-hydroxy-2-propenyl)deuteroporphyrin dimethyl ester (**16**, 40 mg, 38%, a mixture of diastereomers). Dark red crystals, mp 91—92 °C. MS *m/z*: 734 (M^+). HRMS $C_{39}H_{41}F_3N_4O_7$: 734.291 (M^+). Found: 734.291. IR (KBr): 3480 (O–H), 3324 (>NH), 1762, 1740 (C=O), 1218, 1178 (C–F) cm^{-1}. ^{1}H-NMR ($CDCl_3$) (a mixture of diastereomers) δ: 10.35 (0.5H, s), 10.34 (0.5H, s), 10.19 (0.5H, s), 10.12 (0.5H, s), 9.52

(1H*, s), 9.50 (0.5H, s), 9.44 (0.5H, s), 7.88 (0.5H, q, J=7.4 Hz), 7.87 (0.5H, q, J=7.4 Hz), 6.45 (0.5H, ddd, J=17.0, 10.5, 5.0 Hz), 6.42 (0.5H, ddd, J=17.0, 10.5, 5.0 Hz), 6.13 (0.5H, d, J=5.0 Hz), 6.04 (0.5H, d, J=5.0 Hz), 5.40 (0.5H, dd, J=17.0, 1.5 Hz), 5.36 (0.5H, dd, J=17.0, 1.5 Hz), 5.21 (0.5H, dd, J=10.5, 1.5 Hz), 5.18 (0.5H, dd, J=10.05, 1.5 Hz), 4.16 (2H*, t, J=7.8 Hz), 3.86 (1H, t, J=7.1 Hz), 3.82 (1H, t, J=7.1 Hz), 3.73 (1.5H, s), 3.70 (1.5H, s), 3.64 (3H*, s), 3.63 (3H*, s), 3.60 (3H*, s), 3.20 (1.5H, s), 3.18 (1.5H, s), 3.15 (2H*, t, J=7.8 Hz), 3.13 (1.5H, s), 3.11 (1.5H, s), 3.02 (1H, t, J=7.1 Hz), 3.00 (1H, t, J=7.1 Hz), 2.48 (1.5H, s), 2.45 (1.5H, s), 2.34 (0.5H, br), 2.18 (0.5H, br), −4.23 (1H, s), −4.24 (1H, s). ^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): −74.03 (1.5F, d, J= 7.32 Hz), −74.06 (1.5F, d, J= 7.32 Hz). (* shows peaks ascribed to both isomers.)

3-(1-Acetoxy-2,2,2-trifluoroethyl)-8-(3-oxo-1-noneyl)deuteroporphyrin Dimethyl Ester (17) $TiCl_4$ (9.3 μl, 0.085 mmol) was added to a solution of **13** (50 mg, 0.071 mmol) in dry CH_2Cl_2 (2.0 ml) at −50 °C, then 2-(trimethylsilyloxy)-1-octene (30 mg, 0.15 mmol) was added dropwise at the same temperature. The mixture was stirred at the above temperature for 30 min, allowed to warm to 0 °C, and stirred for 3 h at this temperature. It was poured into ice-water, and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and dried over $MgSO_4$, then concentrated under vacuum. The residue was purified by column chromatography (SiO_2, CH_2Cl_2–ethyl acetate, 30:70—5:95) to give 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-(3-oxo-1-noneyl)deuteroporphyrin dimethyl ester (**17**, 27 mg, 47%). **17**: Dark red crystals, mp 169—171 °C. MS m/z: 816 (M^+). HRMS $C_{45}H_{51}N_3N_4O_7$: 816.372 (M^+). Found: 816.372. IR (KBr): 3320 (>NH), 1762, 1742 (C=O), 1218, 1176 (C–F) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.48 (1H, s), 10.08 (1H, s), 10.03 (1H, s), 9.90 (1H, s), 9.20 (1H, d, J=16.1 Hz), 7.85 (1H, q, J=7.4 Hz),7.45 (1H, d, J=16.1 Hz), 4.31 (2H, t, J=7.9 Hz), 4.29 (2H, t, J=7.9 Hz), 3.83 (3H, s), 3.81 (3H, s), 3.65 (3H, s), 3.63 (3H, s), 3.57 (3H, s), 3.52 (3H, s), 3.24 (2H, t, J=7.9 Hz), 3.23 (2H, t, J=7.9 Hz), 3.00 (2H, t, J=7.3 Hz), 1.96 (2H, quintet, J=7.3 Hz), 1.58 (2H, m), 1.40—1.53 (4H, m), 0.98 (3H, t, J=7.1 Hz), −3.63 (2H, s). ^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): −74.17 (3F, d, J= 7.32 Hz).

8-(1-Acetoxy-2,2,2-trifluoroethyl)-3-(3-oxo-1-noneyl)deuteroporphyrin Dimethyl Ester (18) A solution of **14** (50 mg, 0.071 mmol) in dry CH_2Cl_2 (3.5 ml) was treated with $TiCl_4$ (9.3 μl, 0.085 mmol) and 2-(trimethylsilyloxy)-1-octene (70 mg, 0.35 mmol) as in the case of **13**, and worked up as above to give 8-(1-acetoxy-2,2,2-trifluoroethyl)-3-(3-oxo-1-noneyl)-deuteroporphyrin dimethyl ester (**18**, 15 mg, 26%). **18**: Dark red crystals, mp 149—151 °C. MS m/z: 816 (M^+). HRMS $C_{45}H_{51}F_3N_4O_7$: 816.370 (M^+). Found: 816.370. IR (KBr): 3316 (>NH), 1764, 1740 (C=O), 1216, 1178 (C–F) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.35 (1H, s), 10.11 (1H, s), 9.88 (1H, s), 9.71 (1H, s), 9.06 (1H, d, J=15.6 Hz), 7.86 (1H, q, J=7.3 Hz), 7.32 (1H, d, J=16.1 Hz), 4,35 (2H, t, J=7.8 Hz), 4.23 (2H, t, J=7.3 Hz), 3.82 (3H, s), 3.66 (3H, s), 3.65 (3H, s), 3.63 (3H, s), 3.50 (3H, s), 3.41 (3H, s), 3.26 (2H, t, J=7.8 Hz), 3.20 (2H, t, J=7.3 Hz), 2.98 (2H, t, J=7.5 Hz), 2.46 (3H, s), 1.96 (2H, quintet, J=7.6 Hz), 1.53—1.62 (2H, m), 1.40—1.52 (4H, m), 0.99 (3H, t, J=7.1 Hz), −3.80 (2H, s). ^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): 74.06 (3F, d, J=7.32 Hz).

References and Notes

1) A part of this work was presented at the 2nd Porphyrin Symposium, October, 1994, Tokyo.
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