OPTICAL RESOLUTION OF (2,2,2-TRIFLUORO-1-HYDROXYETHYL)DEUTEROPORPHYRINS

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Dedicated to the Memory of Professor Emeritus Shun-ichi Yamada.

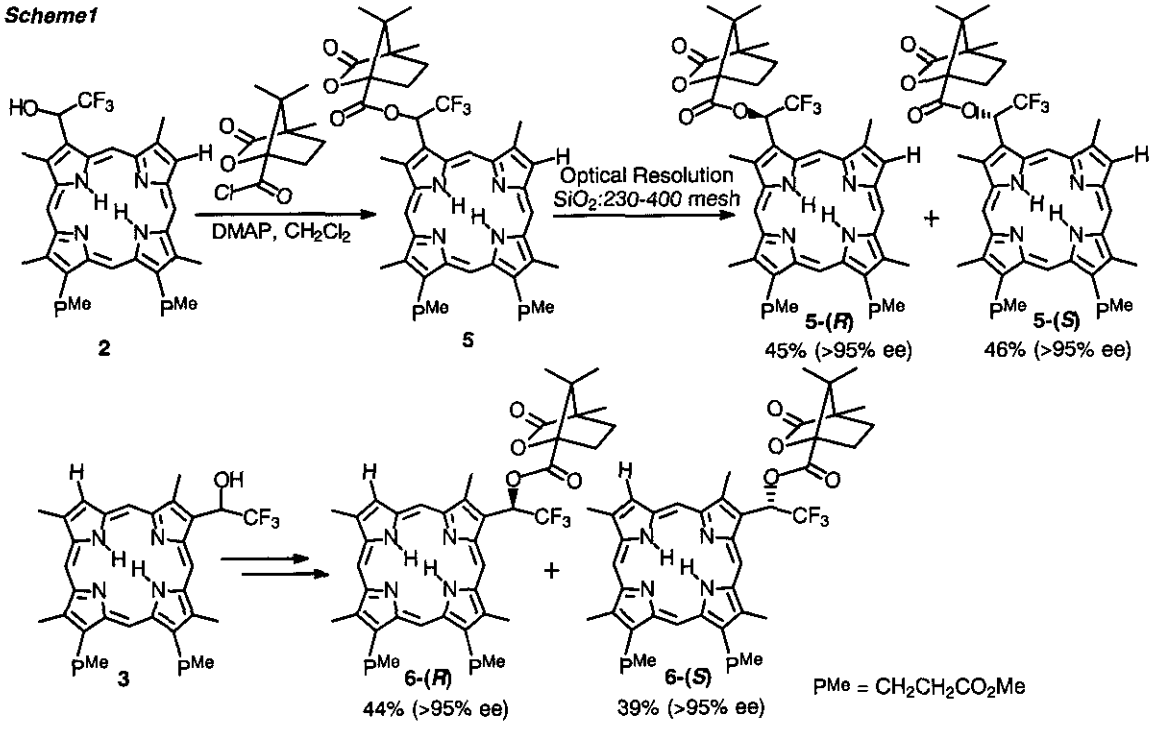
Abstract - Optical resolution of 3- and 8-(2,2,2-trifluoro-1-hydroxyethyl)-deuteroporphyrin dimethyl esters (**2** and **3**) were accomplished through their (1*S*)-camphanyl esters. Thus, these esters were easily resolved by column chromatography. Each camphanyl ester was cleaved with sodium bis(trimethylsilyl)amide - THF - MeOH. The resolved dimethyl esters were hydrolyzed by sodium hydroxide. The sodium salt of **2**-(*S*) was taken up by cancer cells about 15 times more than that of **2**-(*R*), while the salt of **3**-(*R*) was taken up more than that of **3**-(*S*).

Some of porphyrin derivatives were found to accumulate to tumors.[1] These porphyrins emit fluorescence by irradiation. This fluorescence is used for diagnosis of tumor. Further, the porphyrins work as photosensitizer and liberate active oxygen. The active oxygen gives damage to the tumor. This is the basis for therapy of tumor and is called photodynamic therapy (PDT). Now, "hematoporphyrin derivative" (HpD), which is obtained by treating hematoporphyrin with sulfuric acid in acetic acid, is used for this purpose, but HpD is a complex mixture of porphyrins of uncertain composition. Therefore, if a single porphyrin could be used, PDT would develop effectively. In the course of our study to find a porphyrin derivative useful for photodynamic therapy,[1] we have reported the synthesis of 3- and 8-mono- and 3,8-bis(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrins (**2**, **3**, and **4**) by the reaction of deuteroporphyrin (**1**) with trifluoroacetaldehyde in the presence of aluminum chloride.[2] Bis compound

(**4**) was found to localize to tumor cells selectively.[2] The yield of **4** by the above method is unsatisfactorily low. Therefore, we have developed a total synthesis of **4** by ring closure.[3] Now, we would like to present optical resolution of **2** and **3**. The (*S*) isomer of **2** was found to be taken up by human gastric cancer cells about 15 times more than the (*R*) isomer.

For optical resolution, **2** and **3** were treated with (1*S*)-camphanyl chloride in the presence of dimethylaminopyridine (DMAP) to give corresponding esters (**5** and **6**) in good yields, respectively. The ester (**5**) was separated by column chromatography to give 3-((1*R*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)-deuteroporphyrin dimethyl ester (**5**-(*R*), 45%) and 3-((1*S*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)-deuteroporphyrin dimethyl ester (**5**-(*S*), 46%). The ester (**6**) was separated similarly to 8-((1*R*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester (**6**-(*R*), 44%) and 8-((1*S*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester (**6**-(*S*), 39%) as shown in Scheme 1.

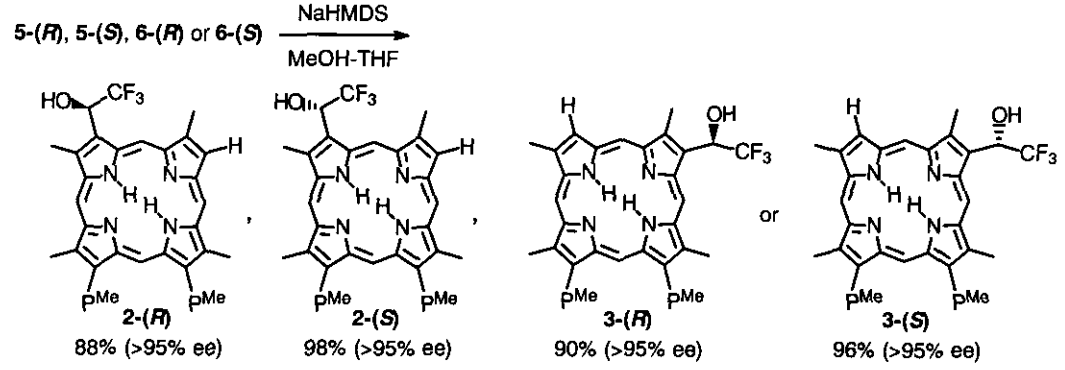
Scheme1



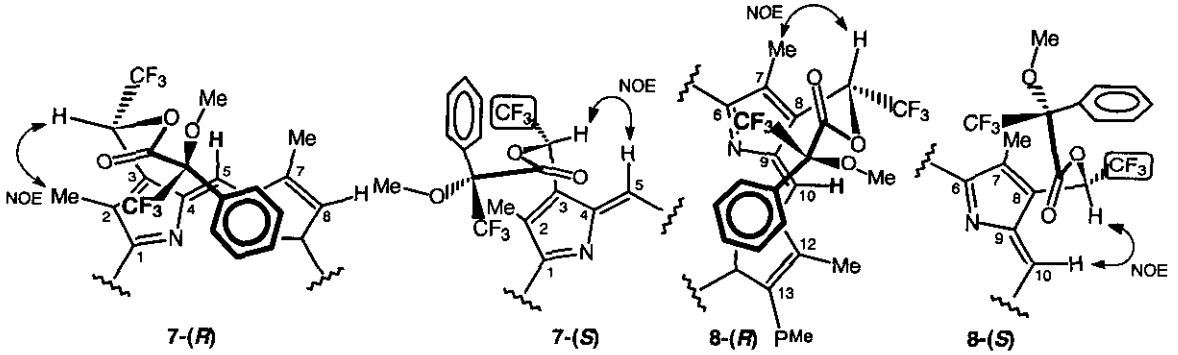
Each camphanyl ester was hydrolyzed with sodium bis(trimethylsilyl)amide in THF-MeOH to give **2**-(*R*), **2**-(*S*), **3**-(*R*), or **3**-(*S*) without decrease of the optical purity (see Scheme 2).

The stereochemistries of the trifluorohydroxyethyl groups were determined as follows. These alcohols were converted to (*R*)-methoxy(trifluoromethyl)phenylacetyl (MTP) esters (**7** and **8**) with (*S*)-(MTP) chloride in the presence of DMAP. The most stable conformation of each ester was estimated based on the NOE correlation using COSMIC on Nemesis as shown in Figure 1.

Scheme 2



Thus, 7-(*R*) showed NOE correlation between the methyl hydrogens at 2-position and the 3α hydrogen, while 7-(*S*) did between the 5-hydrogen and the 3α hydrogen. The 5-hydrogen of 7-(*R*) must be observed at higher field than that of 7-(*S*) due to the anisotropic effect of the benzene ring. Similarly, the peak of trifluoromethyl group of the trifluorohydroxyethyl (TFHE) group of 7-(*S*) must be observed at a higher field than that of 7-(*R*). The trifluoromethyl group of the MTP group of 7-(*R*) is over the porphyrin ring and should be observed at a higher field than that of 7-(*S*). The chemical shifts shown in Figure 1 are consistent with the expectation as above. The stereochemistries of 8-(*R*) and 8-(*S*) were estimated similarly, as shown in Figure 1.



	chemical shift (ppm)	
	7-(*R*)	7-(*S*)
5-H	10.09	10.37
TFHE-CF_3	-73.41	-73.88
MTP-CF_3	-72.31	-71.61

	chemical shift (ppm)	
	8-(*R*)	8-(*S*)
10-H	10.08	10.34
TFHE-CF_3	-73.36	-73.86
MTP-CF_3	-72.28	-71.64

Figure 1 Estimated Conformations of MTP Esters and Comparison of Chemical Shifts.

Each chiral dimethyl ester was hydrolyzed with sodium hydroxide and the sodium salt was incubated with human gastric cancer cells for 24 h. After cells were washed with buffer solution, the porphyrin taken up by cells was extracted with diisopropylamine-methanol and its amount was estimated by fluorometry. Relative intensity of fluorescence from 2-(*S*) was about 15 times stronger than that from

2-(*R*), while that from **3-(*R*)** was a little stronger than **3-(*S*)**, as shown in Table 1.

Table 1. Relative Intensities of Fluorescence of Chiral (2,2,2-Trifluoro-1-hydroxyethyl)deuteroporphyrins

Porphyrins	**2-(*R*)**	**2-(*S*)**	**3-(*R*)**	**3-(*S*)**
Relative Intensities	0.79	11.81	1.69	1.27

We believe that this is the first observation of differences between chiral porphyrin derivatives on taken-up by cancer cells.

EXPERIMENTAL

General Procedure. 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. Tetramethylsilane was used as an internal standard. ^{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; br s, broad singlet; q, quartet. Mass spectra were recorded on a JEOL JMS-DX300.

3-((1*R*)- and (1*S*)-1-(1*S*)-Camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin Dimethyl Esters (5-(*R*) and (*S*)). --- *A solution of DMAP (0.67 g, 5.50 mmol) in anhydrous* CH_2Cl_2 *(20 mL) was added to* a solution of **2** (1.00 g, 1.57 mmol) and (1*S*)-camphanyl chloride (0.41 g, 1.89 mmol) in anhydrous CH_2Cl_2 (80 mL) under ice-cooling and the mixture was stirred for 10 min at rt. The whole was poured into ice-water and neutralized with 10% aqueous HCl, 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, Et_2O-CH_2Cl_2, 3:97) to give 3-((1*R*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester (**5-(*R*)**, 0.57 g, 45%) and 3-((1*S*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester (**5-(*S*)**, 0.59 g, 46%). **5-(*R*)**: mp 218-219°C (CH_2Cl_2-hexane). MS *m/z*: 816 (M^+). HRMS Calcd $C_{44}H_{47}N_4O_8F_3$ (M^+): 816.335. Found: 816.335. ^{1}H-NMR ($CDCl_3$) δ: 10.56 (1H, s), 10.20 (1H, s), 10.04 (1H, s), 10.01 (1H, s), 9.16 (1H, s), 7.89 (1H, q, *J* = 7.3 Hz), 4.45 (2H, t, *J* = 7.8 Hz), 4.33 (2H, t, *J* = 7.8 Hz), 3.86 (3H, s), 3.82 (3H, s), 3.69 (3H, s), 3.66 (3H, s), 3.63 (3H, s), 3.55 (3H, s), 3.29 (2H, t, *J* = 7.8 Hz), 3.27 (2H, t, *J* = 7.8 Hz), 2.43 (1H, ddd, *J* = 16.0, 12.5, 4.0 Hz), 1.94 (1H, dd, *J* = 12.5, 4.0 Hz), 1.91 (1H, dd, *J* = 12.5, 4.0 Hz), 1.67 (1H, ddd, *J* = 16.0, 12.5, 4.0 Hz), 1.24 (3H, s), 1.19 (3H, s), 1.12 (3H, s), -3.80 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -74.09 (3F, d, *J* = 7.3 Hz). **5-(*S*)**: mp 215-216°C (CH_2Cl_2-hexane). MS *m/z*: 816 (M^+).

HRMS Calcd $C_{44}H_{47}N_4O_8F_3$ (M^+): 816.335. Found: 816.334. ^{1}H-NMR ($CDCl_3$) δ: 10.49 (1H, s), 10.19 (1H, s), 10.03 (1H, s), 9.99 (1H, s), 9.15 (1H, s), 7.91 (1H, q, *J* = 7.3 Hz), 4.43 (2H, t, *J* = 7.8 Hz), 4.31 (2H, t, *J* = 7.8 Hz), 3.83 (3H, s), 3.82 (3H, s), 3.68 (3H, s), 3.65 (3H, s), 3.62 (3H, s), 3.53 (3H, s), 3.28 (2H, t, *J* = 7.8 Hz), 3.25 (2H, t, *J* = 7.8 Hz), 2.68 (1H, ddd, *J* = 13.4, 10.6, 4.3 Hz), 2.21 (1H, ddd, *J* = 13.4, 9.1, 4.3 Hz), 1.99 (1H, ddd, *J* = 13.4, 10.6, 4.3 Hz), 1.77 (1H, ddd, *J* = 13.4, 9.1, 4.3 Hz), 1.11 (3H, s), 1.05 (3H, s), 0.56 (3H, s), -3.80 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -73.94 (3F, d, *J* = 7.3 Hz).

8-((1*R*)- and (1*S*)-1-(1*S*)-Camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin Dimethyl Ester (6-(*R*) and 6-(*S*)). --- **3** (0.98 g, 1.54 mmol) was treated similarly with DMAP (0.66 g, 5.41 mmol) and (1*S*)-camphanyl chloride (0.40 g, 1.85 mmol) and worked up as in the case of **2**. The products were separated by column chromatography (SiO_2, Et_2O-CH_2Cl_2, 3:97) to give 8-((1*R*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester (**6-(*R*)**, 0.55 g, 44%) and 8-((1*S*)-1-(1*S*)-camphanyloxy-2,2,2-trifluoroethyl)deuteroporphyrin dimethyl ester (**6-(*S*)**, 0.49 g, 39%). **6-(*R*)**: mp 198-199°C (CH_2Cl_2-hexane). MS *m/z*: 816 (M^+). HRMS Calcd $C_{44}H_{47}N_4O_8F_3$ (M^+): 816.335. Found: 816.335. ^{1}H-NMR ($CDCl_3$) δ: 10.54 (1H, s), 10.13 (1H, s), 10.09 (1H, s), 10.05 (1H, s), 9.17 (1H, s), 7.88 (1H, q, *J* = 7.3 Hz), 4.48 (2H, t, *J* = 7.8 Hz), 4.34 (2H, t, *J* = 7.8 Hz), 3.79 (3H, s), 3.78 (3H, s), 3.75 (3H, s), 3.67 (3H, s), 3.66 (3H, s), 3.56 (3H, s), 3.30 (2H, t, *J* = 7.8 Hz), 3.27 (2H, t, *J* = 7.8 Hz), 2.43 (1H, ddd, *J* = 14.5, 11.5, 4.5 Hz), 1.91 (2H, m), 1.66 (1H, ddd, *J* = 14.5, 10.5, 4.5 Hz), 1.25 (3H, s), 1.20 (3H, s), 1.13 (3H, s), -3.83 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -74.06 (3F, d, *J* = 7.3 Hz). **6-(*S*)**: mp 163-165°C (CH_2Cl_2-hexane). MS m/z: 816 (M^+). HRMS Calcd $C_{44}H_{47}N_4O_8F_3$ (M^+): 816.335. Found: 816.335. ^{1}H-NMR ($CDCl_3$) δ: 10.46 (1H, s), 10.14 (1H, s), 10.10 (1H, s), 10.07 (1H, s), 9.18 (1H, s), 7.92 (1H, q, *J* = 7.3 Hz), 4.49 (2H, dt, *J* = 7.8, 2.5 Hz), 4.35 (2H, t, *J* = 7.8 Hz), 3.79 (3H, s), 3.76 (3H, d, *J* = 2.5 Hz), 3.75 (3H, s), 3.67 (3H, s), 3.66 (3H, s), 3.58 (3H, s), 3.31 (2H, t, *J* = 7.8 Hz), 3.27 (2H, t, *J* = 7.8 Hz), 2.69 (1H, ddd, *J* = 13.5, 10.5, 4.5 Hz), 2.21 (1H, ddd, *J* = 13.5, 9.0, 4.5 Hz), 2.01 (1H, ddd, *J* = 13.5, 10.5, 4.5 Hz), 1.78 (1H, ddd, *J* = 13.5, 9.0, 4.5 Hz), 1.13 (3H, s), 1.08 (3H, s), 0.62 (3H, s), -3.81 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -73.97 (3F, d, *J* = 7.3 Hz).

3-((*R*)-2,2,2-Trifluoro-1-hydroxyethyl)deuteroporphyrin Dimethyl Ester (2-(*R*)). --- Sodium bis(trimethylsilyl)amide (1.0 M in THF, 7.55 ml, 7.55 mmol) was added to a solution of **5-(*R*)** (0.62 g, 0.76 mmol) in THF-MeOH (30 mL, 1:1, V/V) under ice-cooling, and the mixture was stirred for 15 min at rt. The whole was poured into ice-water and neutralized with 10% aqueous HCl, 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, Et_2O-CH_2Cl_2, 3:97-5:95) to give 3-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl ester (**2-(*R*)**, 0.42 g, 88%). **2-(*R*)**: mp 203-204°C (CH_2Cl_2-hexane). MS *m/z*: 636 (M^+). HRMS Calcd $C_{34}H_{35}N_4O_5F_3$ (M^+):

636.256. Found: 636.257. ^{1}H-NMR ($CDCl_3$) δ: 10.70 (1H, s), 10.12 (1H, s), 9.98 (1H, s), 9.93 (1H, s), 9.19 (1H, s), 6.96 (1H, dq, *J* = 7.3, 4.9 Hz), 6.65 (1H, d, *J* = 4.9 Hz), 4.22 (2H, t, *J* = 7.3 Hz), 4.20 (2H, t, *J* = 7.3 Hz), 3.77 (3H, s), 3.74 (3H, s), 3.60 (3H, s), 3.57 (3H, s), 3.50 (3H, s), 3.45 (3H, s), 3.19 (4H, t, *J* = 7.3 Hz), -4.13 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -75.41 (3F, d, *J* = 7.3 Hz).

3-((*S*)-2,2,2-Trifluoro-1-hydroxyethyl)deuteroporphyrin Dimethyl Ester (2-(*S*)). --- **5-(*S*)** (0.49 g, 0.60 mmol) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 6.00 mL, 6.00 mmol) and worked up as in the case of **5-(*R*)**. The product was purified by column chromatography (SiO_2, Et_2O-CH_2Cl_2, 3:97-5:95) to give 3-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl ester (**2-(*S*)**, 0.37 g, 98%). **2-(*S*)**: mp 203-204°C (CH_2Cl_2-hexane). MS *m/z*: 636 (M^+). HRMS Calcd $C_{34}H_{35}N_4O_5F_3$ (M^+): 636.256. Found: 636.256. ^{1}H-NMR ($CDCl_3$) δ: 10.71 (1H, s), 10.15 (1H, s), 10.01 (1H, s), 9.98 (1H, s), 9.21 (1H, s), 6.96 (1H, dq, *J* = 7.3, 4.9 Hz), 6.67 (1H, d, *J* = 4.9 Hz), 4.25 (2H, t, *J* = 7.3 Hz), 4.22 (2H, t, *J* = 7.3 Hz), 3.78 (3H, s), 3.74 (3H, s), 3.60 (3H, s), 3.58 (3H, s), 3.53 (3H, s), 3.47 (3H, s), 3.21 (4H, t, *J* = 7.3 Hz), -4.08 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -75.41 (3F, d, *J* = 7.3 Hz).

8-((*R*)-2,2,2-Trifluoro-1-hydroxyethyl)deuteroporphyrin Dimethyl Ester (3-(*R*)). --- **6-(*R*)** (0.50 g, 0.61 mmol) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 6.13 mL, 6.13 mmol) and worked up as in the case of **5-(*R*)**. The product was purified by column chromatography (SiO_2, Et_2O-CH_2Cl_2, 3:97-5:95) to give 8-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl ester (**3-(*R*)**, 0.35 g, 90%). **3-(*R*)**: mp 243-245°C (CH_2Cl_2-hexane). MS *m/z*: 636 (M^+). HRMS Calcd $C_{34}H_{35}N_4O_5F_3$ (M^+): 636.256. Found: 636.256. ^{1}H-NMR ($CDCl_3$) δ: 10.67 (1H, s), 10.17 (1H, s), 10.07 (1H, s), 9.92 (1H, s), 9.13 (1H, s), 6.96 (1H, dq, *J* = 7.3, 4.9 Hz), 6.67 (1H, d, *J* = 4.9 Hz), 4.38 (2H, t, *J* = 7.8 Hz), 4.22 (2H, t, *J* = 7.8 Hz), 3.75 (3H, s), 3.66 (3H, s), 3.61 (3H, s), 3.60 (3H, s), 3.59 (3H, s), 3.43 (3H, s), 3.29 (2H, t, *J* = 7.8 Hz), 3.21 (2H, t, *J* = 7.8 Hz), -4.09 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -75.42 (3F, d, *J* = 7.3 Hz).

8-((*S*)-2,2,2-Trifluoro-1-hydroxyethyl)deuteroporphyrin Dimethyl Ester (3-(*S*)). --- **6-(*S*)** (0.44 g, 0.54 mmol) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 5.39 mL, 5.39 mmol) and the mixture was worked up as in the case of **5-(*R*)**. The crude product was purified by column chromatography (SiO_2, Et_2O-CH_2Cl_2, 3:97-5:95) to give 8-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl ester (**3-(*S*)**, 0.33 g, 96%). **3-(*S*)**: mp 243-245°C (CH_2Cl_2-hexane). MS *m/z*: 636 (M^+). HRMS Calcd $C_{34}H_{35}N_4O_5F_3$ (M^+): 636.256. Found: 636.256. ^{1}H-NMR ($CDCl_3$) δ: 10.67 (1H, s), 10.18 (1H, s), 10.08 (1H, s), 9.92 (1H, s), 9.13 (1H, s), 6.96 (1H, dq, *J* = 7.3, 4.9 Hz), 6.67 (1H, d, *J* = 4.9 Hz), 4.38 (2H, t, *J* = 7.8 Hz), 4.22 (2H, t, *J* = 7.8 Hz), 3.76 (3H, s), 3.66 (3H, s), 3.61 (3H, s), 3.60 (3H, s), 3.59 (3H, s), 3.43 (3H, s), 3.29 (2H, t, *J* = 7.8 Hz), 3.21 (2H, t, *J* = 7.8 Hz), -4.09 (2H, br s). ^{19}F-NMR

($CDCl_3$) δ: -75.41 (3F, d, *J* = 7.3 Hz).

3-[(1*R*)-2,2,2-Trifluoro-1-((*R*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy)ethyl]deutero-porphyrin Dimethyl Ester (7-(*R*)). --- (*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (7 μL, 0.0374 mmol) was added to a solution of **2-(*R*)** (15 mg, 0.0236 mmol) and DMAP (9 mg, 0.0737 mmol) in CH_2Cl_2 (1 mL) at rt. After stirring for 10 min, the mixture was separated directly by column chromatography (SiO_2, Et_2O-CH_2Cl_2, 5:95) to give MTP ester (**7-(*R*)**, 19 mg, 95%). **7-(*R*)**: mp 138-140°C (CH_2Cl_2-hexane). MS *m/z*: 852 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.09 (1H, s), 10.05 (1H, s), 9.84 (1H, s), 9.82 (1H, s), 9.00 (1H, s), 8.02 (1H, br s), 7.22-7.13 (2H, m), 6.78-6.35 (3H, m), 4.28 (2H, t, *J* = 7.8 Hz), 4.20 (2H, t, *J* = 7.8 Hz), 3.79 (3H, s), 3.69 (3H, s), 3.64 (3H, s), 3.60 (3H, s), 3.53 (3H, s), 3.49 (3H, s), 3.42 (3H, s), 3.19 (4H, t, *J* = 7.8 Hz), -3.98 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -72.31 (3F, s), -73.41 (3F, d, *J* = 7.3 Hz).

3-[(1*S*)-2,2,2-Trifluoro-1-((*R*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy)ethyl]deutero-porphyrin Dimethyl Ester (7-(*S*)). --- **3-(*S*)** (15 mg, 0.0236 mmol) was treated with DMAP (9 mg, 0.0737 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (7 μL, 0.0374 mmol) at rt and worked up as in the case of **2-(*R*)** to give the MTP ester (**7-(*S*)**, 18 mg, 90%). **7-(*S*)**: mp 71-73°C (CH_2Cl_2-hexane). MS *m/z*: 852 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.37 (1H, s), 10.08 (1H, s), 9.80 (1H, s), 9.78 (1H, s), 9.00 (1H, s), 8.02 (1H, br s), 7.52-7.42 (2H, m), 7.12-6.83 (3H, m), 4.20 (2H, t, *J* = 7.8 Hz), 4.16 (2H, t, *J* = 7.8 Hz), 3.79 (3H, s), 3.62 (3H, s), 3.58 (3H, s), 3.54 (3H, s), 3.50 (3H, s), 3.39 (3H, s), 3.32 (3H, s), 3.13 (4H, t, *J* = 7.8 Hz), -4.02 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -71.61 (3F, s), -73.88 (3F, d, *J* = 7.3 Hz).

8-[(1*R*)-2,2,2-Trifluoro-1-((*R*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy)ethyl]deutero-porphyrin Dimethyl Ester (8-(*R*)). --- **3-(*R*)** (15 mg, 0.0236 mmol) was treated with DMAP (9 mg, 0.0737 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (7 μL, 0.0374 mmol) at rt and worked up as in the case of **2-(*R*)** to give the MTP ester (**8-(*R*)**, 19 mg, 95%). **8-(*R*)**: mp 112-114°C (CH_2Cl_2-hexane). MS *m/z*: 852 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.08 (1H, s), 9.98 (1H, s), 9.90 (1H, s), 9.82 (1H, s), 8.92 (1H, s), 7.92 (1H, br s), 7.28-7.15 (2H, m), 6.72-6.40 (3H, m), 4.32 (2H, t, *J* = 7.8 Hz), 4.20 (2H, t, *J* = 7.8 Hz), 3.80 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.50 (6H, s), 3.40 (3H, s), 3.39 (3H, s), 3.24 (2H, t, *J* = 7.8 Hz), 3.20 (2H, t, *J* = 7.8 Hz), -4.05 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -72.28 (3F, s), -73.36 (3F, d, *J* = 7.3 Hz).

8-[(1*S*)-2,2,2-Trifluoro-1-((*R*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy)ethyl]deutero-porphyrin Dimethyl Ester (8-(*S*)). --- **3-(*S*)** (15 mg, 0.0236 mmol) was treated with DMAP (9 mg, 0.0737 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (7 μL, 0.0374 mmol) and

worked up as in the case of **2-(*R*)** to give MTP ester (**8-(*S*)**, 17 mg, 85%). **8-(*S*)**: mp 62-64°C (CH_2Cl_2-hexane). MS *m/z*: 852 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.34 (1H, s), 9.99 (1H, s), 9.89 (1H, s), 9.63 (1H, s), 8.99 (1H, s), 8.00 (1H, br s), 7.52-7.44 (2H, m), 7.14-6.88 (3H, m), 4.35 (2H, t, J = 7.8 Hz), 4.12 (2H, t, J = 7.8 Hz), 3.77 (3H, s), 3.62 (3H, s), 3.48 (3H, s), 3.44 (6H, s), 3.33 (3H, s), 3.32 (3H, s), 3.22 (2H, t, J = 7.8 Hz), 3.16 (2H, t, J = 7.8 Hz), -4.10 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: -71.64 (3F, s), -73.86 (3F, d, J = 7.3 Hz).

REFERENCES AND NOTES

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