Pergamon

Tetrahedron 57 (2001) 8085–8094

TETRAHEDRON

Syntheses of chiral fluorine analogs of hematoporphyrin

Masaaki Omote, Akira Ando, Kazuyuki Sato and Itsumaro Kumadaki*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata 573-0101, Japan

Received 9 May 2001; accepted 27 July 2001

Abstract—Four chiral fluorine analogs of hematoporphyrin, (*R*,*R*)-, (*R*,*S*)-, (*S*,*R*)-, and (*S*,*S*)-3,8-bis(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrins, were synthesized starting from pyrroles with a chiral 2,2,2-trifluoro-1-hydroxyethyl (TFHE) group. This chiral TFHE group was obtained by asymmetric reduction of a trifluoroacetyl group. Among these chiral analogs of hematoporphyrin, the (*S*,*S*)-isomer showed higher affinity for cancer cells than other stereoisomers. © 2001 Elsevier Science Ltd. All rights reserved.

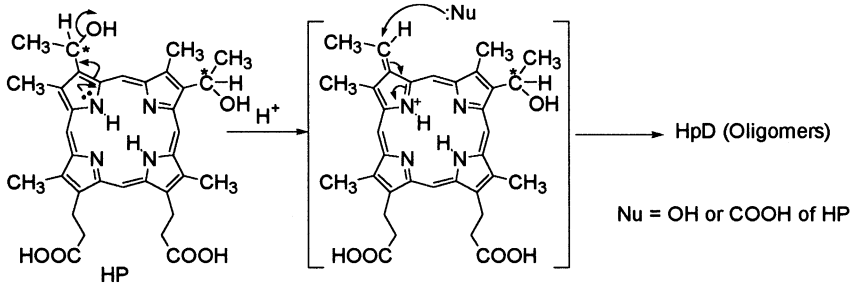
1. Introduction

Recently, photodynamic therapy (PDT) using porphyrin derivatives as a photosensitizer have attracted much attention in the field of diagnosis and therapy of cancer.[1] Many research groups, especially in Europe and Asia, have been engaged in this field and a lot of photosensitizers for PDT have been developed.[2] Among these photosensitizers, hematoporphyrin derivatives (HpD) obtained by treating hematoporphyrin (HP) with sulfuric acid in hot acetic acid still have been most widely used, although its composition is changeable case by case.[3] This difficulty might be due to the labile structure of HP: HP has two chiral centers, and commercial HPs have different composition of diastereomers. Further, owing to a strong electron-donating effect of the porphyrin ring, the hydroxyl groups of HP are eliminated easily to form cationic intermediates. This makes isomerization of the chiral centers occur easily, and the resulting cationic species produces oligomers through ether or ester bonds formation. One of the possible transformation of HP when treated with an acid is shown in Scheme 1.

HP itself is a mixture of stereoisomers, and its treatment with an acid gives a complex mixture of oligomers through ether or ester bond-formation and some of the dehydration products of the hydroxyethyl group to a vinyl group. We have been engaged in synthesizing new porphyrin photosensitizers that could be used for PDT as a substitute for HpD.[4] In the course of this research, we realized two interesting phenomena. First, affinity of porphyrins for a tumor tissue depends on the configuration of the substituents on the porphyrin ring. Second, the porphyrins were stabilized considerably by introducing fluorine atoms at a proper position of the substituent. From these phenomena, our attention was turned to a synthesis of fluorinated porphyrins.

We have already synthesized hematoporphyrin derivatives having achiral mono and bis-(2,2,2-trifluoro-1-hydroxyethyl) (TFHE) group(*S*) at 3- and/or 8-positions by the reaction of deuteroporphyrin dimethyl ester (DPDME) with trifluoroacetaldehyde in the presence of a Lewis acid (Scheme 2).[5]

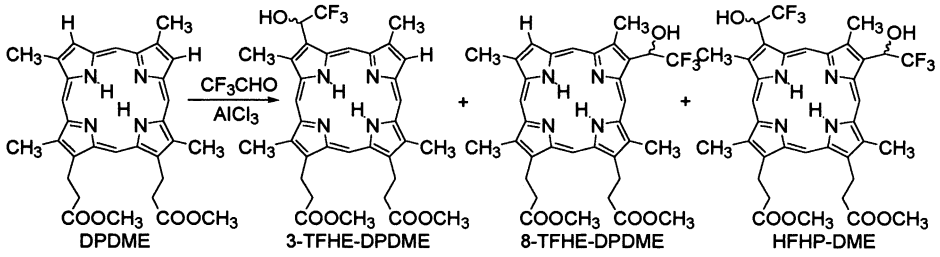
The hydroxyl groups of these fluorine analogs are very stable to heating, acidic and basic conditions and very difficult to be eliminated. This high stability of a TFHE group is



Scheme 1.

Keywords: hematoporphyrin; pyrrole; stereoisomers; fluorine; trifluoromethyl.
* Corresponding author. Tel.: +81-72-866-3140; fax: +81-72-850-7020; e-mail: kumadaki@pharm.setsunan.ac.jp

0040–4020/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(01)00780-3



Scheme 2.

in an outstanding contrast with that of the labile hydroxyethyl groups of HP. To investigate the affinity of these TFHE-porphyrins, each sodium salt was added to a culture medium of human liver cancer cells, JTC-16, and incubated for 48 h. The cells were washed with buffer solution and extracted with diisopropylamine–methanol.[6] The intensity of fluorescence of this extract was measured. From the results shown in Fig. 1, the cancer cells affinity of the three were obviously different and the bis substituted compounds, HFHPNa, showed the highest affinity. The affinity of porphyrins increased by introduction of the TFHE groups and was influenced by their positions on the porphyrin ring.

Racemic porphyrins are used for the experiments so far. A chiral compound would show different biological activity from its enantiomer. Thus, we thought that investigation using enantiometrically pure HPs was essential to understand biological activity of HP. However, HP itself is not stereochemically stable, since the hydroxyethyl groups of HP loses the hydroxyl group easily in the presence of a very weak acid through the mechanism shown in Scheme 1.

We decided to use fluorine analogs of HP as model compounds for investigation of biological properties of HP, namely, a fluorine atom is as small as a hydrogen atom. Replacement of hydrogen atoms with fluorine atoms does not change the form of the original compound so large, and the fluorine analog behaves similarly in an organism as the non-fluorinated one. A TFHE group is very stable, and its chirality is reserved through many steps of reactions. Bis-TFHE-DP, hexafluoro analog of HP (HFHP), seemed to be the best model compound for investigation of HP. Achiral HFHP was found to show high affinity for cancer cells, as shown above. If it were synthesized in a chiral form, the chirality would be stable due to the effect of fluorine atoms. The chiral and stable model compound will be useful in understanding the mechanism of the affinity of HP for tumor tissue at the molecular level.

This paper discusses enantioselective syntheses of fluorine analogs of four stereoisomers of hematoporphyrin and also briefly their affinity to cancer cells.

2. Results and discussion

Our strategy for the syntheses of the chiral porphyrins is similar to the previous route to dimethyl ethers of HFHP-DME.[7] A pyrrole with a chiral TFHE group was obtained by

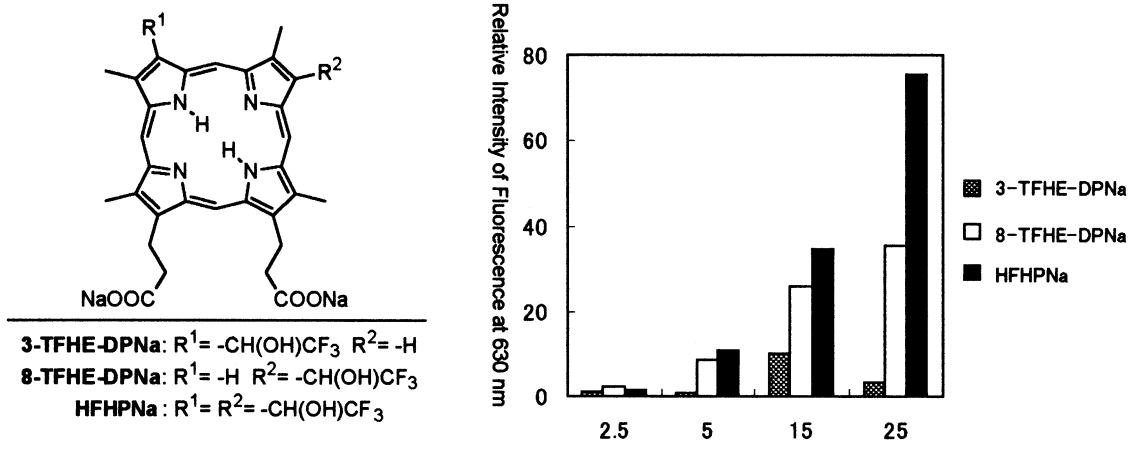
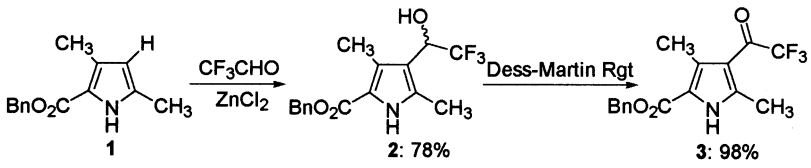
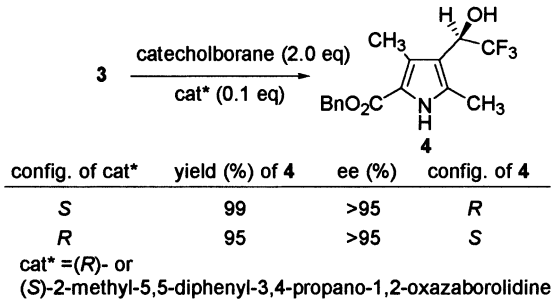


Figure 1.



Scheme 3.



config. of cat*	yield (%) of 4	ee (%)	config. of 4
S	99	>95	*R*
R	95	>95	*S*

cat* =(*R*)- or (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,2-oxazaborolidine

Scheme 4.

enantioselective reduction of a trifluoroacetyl group.[8] This pyrrole compound was transformed to the A and B rings of porphyrin, and these were converted to the desired chiral porphyrin derivatives by the MacDonald condensation.

Thus, trifluoroacetylpyrrole **2** was obtained by the oxidation of the pyrrole **1** with Dess–Martin reagent[9] in 98% yield, as shown in Scheme 3.

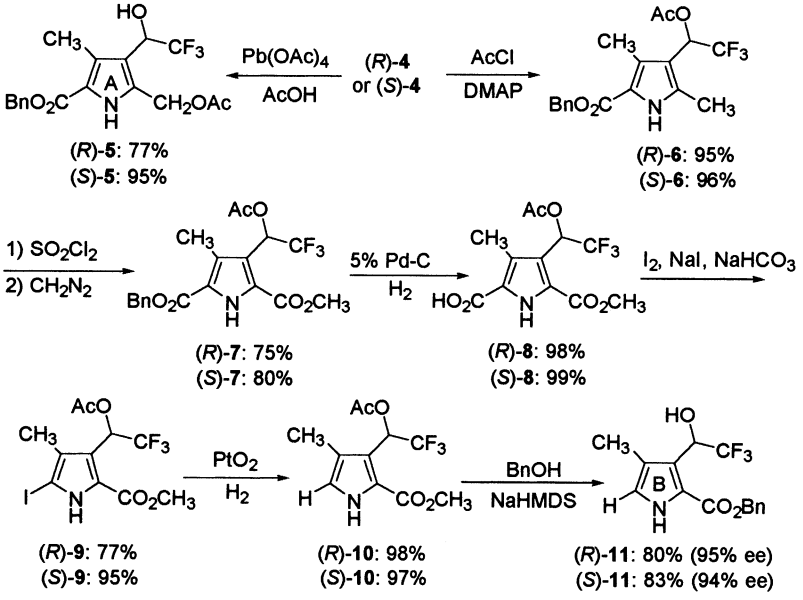
The enantioselective reduction proceeded effectively using Corey's oxazaborolidine catalyst (Scheme 4). High enantioselectivity was attained by using bulkier catecholborane[10] in the place of BH_3–THF.[11] When the (*S*)-catalyst was used, (*R*)-TFHE product (**4**) was obtained with more than 95% ee in a yield of 99%. Similarly, the enantiomer of **4** with (*S*) configuration was obtained quantitatively and more than 95% ee using the catalyst of the opposite configuration (Scheme 4). The configurations of both products were determined by X-ray analysis of (1*S*)-camphanyl esters of (*S*)-**4**.[8]

Now, we carried out the transformation of (*R*)- and (*S*)-**4**, obtained in high enantiomeric excesses, to the suitable chiral TFHE-pyrroles for synthesis of the ring A and B of HP. The strategy that we used for this transformation was similar to our previous route[7] with achiral pyrroles except that we had used methylated TFHE-pyrroles, while an acetyl group, which is much easier to remove, was used for protection of the hydroxyl group of the TFHE group (Scheme 5).

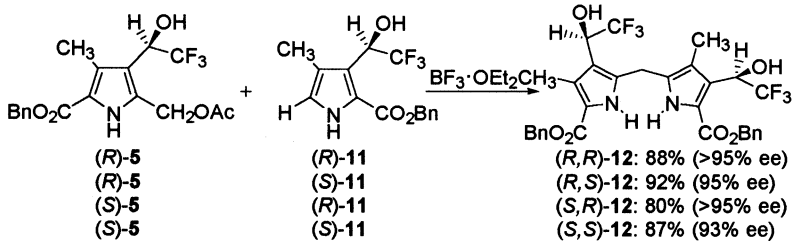
The methyl group at position 5 of compound **4** was oxidized to an acetoxymethyl group with lead(IV) acetate to give compound (*R*)- and (*S*)-**5** in 77 and 95% yields, respectively, without any decrease of enantiomeric excess. Compound **5** corresponds to the ring A of the desired porphyrin.

On the other hand, the hydroxyl group of compound (*R*)-**4** was acetylated with acetyl chloride in the presence of 4-dimethylaminopyridine to give an acetate (*R*)-**6** in a 95% yield. The methyl group at position 5 of (*R*)-**6** was oxidized by the reaction with sulfuryl chloride, followed by hydrolysis to give carboxylic compound in 99% yield. Esterification of the carboxyl group with diazomethane gave benzyl methyl ester (*R*)-**7** in 75% yield. Hydrogenolysis of the benzyl ester with 5% palladium on activated carbon gave the corresponding carboxylic acid (*R*)-**8** quantitatively. Reaction of **8** with iodine, sodium iodide and sodium hydrogen carbonate gave an iodide (*R*)-**9** in 77%. The iodine of compound (*R*)-**9** was removed by Adams catalyst to give α-unsubstituted pyrrole (*R*)-**10** in a 98% yield. Finally, the methyl ester of compound **10** was converted to a benzyl ester by transesterification with sodium bis(trimethylsilyl)-amide in benzyl alcohol. Simultaneous deacetylation took place to give compound (*R*)-**11** in an 80% yield. Compound **11** corresponds to the ring B of the desired porphyrin. By the same procedure, (*S*)-**11** was obtained from (*S*)-**4**. The yield in each step is shown in Scheme 5. Decrease in enantiomeric excess was not observed at all through these transformations. This suggested that the TFHE group was so stable through these transformations and that any precautions to avoid the racemization of the chiral TFHE groups were not required in further transformations.

Pyrroles (*R*)-**5** and (*R*)-**11** were condensed effectively to a dipyrrylmethane (*R*,*R*)-**12** in a 88% yield as shown in



Scheme 5.



Scheme 6.

Scheme 6. Diastereomeric excess of (*R*,*R*)-**12** was found to be very high by the NMR analysis of its MTPA ester. The enantiomeric excess of (*R*,*R*)-**12** was higher than expected from the ees of (*R*)-**5** and (*R*)-**11**. This might be due to the removal of other isomers during purification by column chromatography. Other dipyrrylmethanes ((*R*,*S*)-, (*S*,*R*)- and (*S*,*S*)-**12**) were also obtained in high diastereomeric excesses by the same method, as shown in Scheme 6.

HFHP-DME with both (*R*) configurations was synthesized from (*R*,*R*)-dipyrrylmethane **12**, as follows: (*R*,*R*)-**12** was hydrogenolyzed to dicarboxylic acid (*R*,*R*)-**13**. Decarboxylation of (*R*,*R*)-**13** proceeded effectively by heating a solution of (*R*,*R*)-**13** in ethanolamine to give α,α'-unsubstituted dipyrrylmethane, (*R*,*R*)-**14**, which was used for the next MacDonald condensation[12] without further purification. The ring closure proceeded under conventional condition of MacDonald condensation to give (*R*,*R*)-HFHP-DME (**16**) with a high enantiomeric excess (Scheme 7). (*R*,*S*)-, (*S*,*R*)- and (*S*,*S*)-HFHP-DME (**16**) were obtained in high enantiomeric excesses by the same method, as shown in Scheme 7.

All these stereoisomers **16** were hydrolyzed to sodium salts of sterically pure HFHPs. Detailed studies on biological behaviors of these isomers are now going on, but their preliminary tests showed that the (*S*,*S*)-isomer was most effectively taken up by human gastric cancer cells, KATO III. This suggests that chiral centers of HpD must play an important role in biological activity.

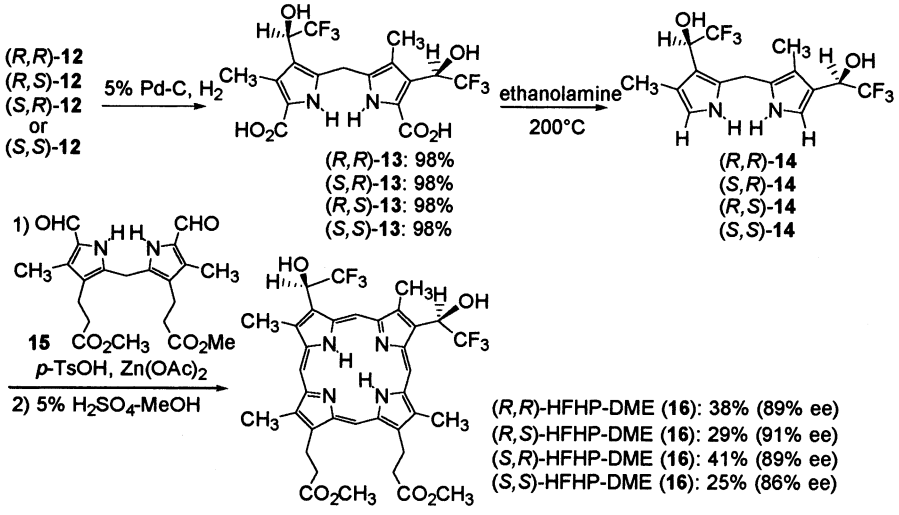
3. Conclusion

A chiral (2,2,2-trifluoro-1-hydroxyethyl)pyrrole (**4**) was obtained in high enantiomeric excess in a quantitative yield by reduction of a trifluoroacetylpyrrole in the presence of Corey's oxazaborolidine catalyst with catecholborane. An absolute configuration of **4** was determined by X-ray analysis of its (1*S*)-camphanyl ester. Both (*R*)- and (*S*)-**4** were transformed to corresponding precursors (*R*)- and (*S*)-**5** (A ring of porphyrin) and (*R*)- and (*S*)-**11** (B ring of porphyrin) without loss of enantiomeric excesses. Reaction of the chiral pyrrole (*R*)- or (*S*)-**5** with the another chiral pyrrole (*R*)- or (*S*)-**11** gave four dipyrrylmethanes (*R*,*R*)-, (*R*,*S*)-, (*S*,*R*)- and (*S*,*S*)-**12**. Decarboxylation of these dipyrrylmethanes followed by MacDonald condensation gave (*R*,*R*)-, (*R*,*S*)-, (*S*,*R*)- and (*S*,*S*)-HFHP-DME with high enantiomeric excesses. Preliminary tests of biological assay showed that the (*S*,*S*)-isomer was most effectively taken up by cancer cells of four isomers. This is the first experiment showing enantioselective recognition of porphyrin derivatives. We are convinced that these chiral porphyrins will help understanding of biological activities of porphyrins in PDT and other fields.

4. Experimental

4.1. General procedure

Melting points were measured on a micro melting point apparatus, Model MP (Yanagimoto, Kyoto, Japan) and a



Scheme 7.

melting point apparatus (Ishii Shoten, Tokyo, Japan) without correction. Optical rotations were measured on JASCO DIP-140 digital polarimeter. ^{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; bs, broad singlet; q, quartet. Mass spectra were recorded on a JEOL JMS-DX300.

4.1.1. Benzyl 3,5-dimethyl-4-(trifluoroacetyl)pyrrole-2-carboxylate (3). In a stream of Ar, a solution of benzyl 3,5-dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)pyrrole-2-carboxylate (**2**, 10 g, 30.6 mmol) in CH_2Cl_2 (20 mL) was added to a suspension of Dess–Martin reagent (20 g, 47.2 mmol) in anhydrous CH_2Cl_2 (20 mL) under ice-cooling. After stirring for 30 h at room temperature, the excess reagent was decomposed with saturated $Na_2S_2O_3$ and $NaHCO_3$ (7:1). The mixture was stirred for another 1 h and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O then dried over with anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2), and recrystallized from hexane–CH_2Cl_2 to give **3** (9.77 g, 98%). **3**: colorless crystals. Mp 125–127°C. MS (EI) *m/z*: 325 (M^+). HRMS $C_{16}H_{14}F_3NO_3$: 325.093 (M^+). Found: 325.093. IR (KBr) ν_{max} 3295, 1686, 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.75 (1H, bs), 7.39 (5H, m), 5.35 (2H, s), 2.56 (3H, s), 2.50 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −74.68 (3F, s).

4.1.2. Benzyl 3,5-dimethyl-4-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrole-2-carboxylate ((*R*)-4). In a stream of Ar, catecholborane (1.95 mL, 18.3 mmol) was added to a solution of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (270 mg, 0.97 mmol) in anhydrous THF (30 mL) at room temperature and the mixture was stirred for another 30 min. To the mixture was added a solution of **3** (3.00 g, 9.23 mmol) in anhydrous THF (30 mL) over 30 min at −80°C and the mixture was stirred for 24 h at −30°C. The reaction was quenched with an alkaline H_2O_2 solution (10% NaOH–30% H_2O_2=1:1, 40 mL) and the mixture was stirred for 1 h at room temperature. The whole was extracted with CH_2Cl_2, and the CH_2Cl_2 layer was washed with H_2O and 5% aqueous NaOH, then 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, 5:95), and recrystallized from hexane–CH_2Cl_2 to give (*R*)-**4** (3.00 g, 99%, >95% ee). (*R*)-**4**: colorless crystals. Mp 109–110°C. $[\alpha]_D^{20}$=−27.6° (*c* 2.14, CH_2Cl_2). MS (EI) *m/z*: 327 (M^+). HRMS $C_{16}H_{16}F_3NO_3$: 327.108 (M^+). Found: 327.109. IR (KBr) ν_{max} 3529, 3256, 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.92 (1H, bs), 7.37 (5H, m), 5.29 (2H, s), 5.05 (1H, qd, *J*=7.3, 4.0 Hz), 2.56 (1H, d, *J*=4.0 Hz), 2.35 (3H, s), 2.32 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −73.77 (3F, d, *J*=7.3 Hz).

4.1.3. Benzyl 3,5-dimethyl-4-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrole-2-carboxylate ((*S*)-4). In a stream of Ar, catecholborane (1.95 mL, 18.3 mmol) was added to a solution of (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (270 mg, 0.97 mmol) in anhydrous THF (30 mL) at room temperature and the mixture was stirred for another 30 min. To the mixture was added a solution of **3** (3.0 g, 9.23 mmol) in anhydrous THF (30 mL) over 75 min at −80°C and the mixture was stirred for 37 h at −30°C. After the mixture was worked up as in the case of (*R*)-**4**, the crude product was separated by column chromatography (SiO_2, Et_2O–CH_2Cl_2, 5:95), and recrystallized from hexane–CH_2Cl_2 to give (*S*)-**4** (2.87 g, 95%, >95% ee). (*S*)-**4**: colorless crystals (CH_2Cl_2–hexane). Mp 109–110°C. $[\alpha]_D^{20}$=+27.6° (*c* 2.07, CH_2Cl_2). MS (EI) *m/z*: 327 (M^+). HRMS $C_{16}H_{16}F_3NO_3$: 327.108 (M^+). Found: 327.108.

4.1.4. Benzyl 5-acetoxymethyl-3-methyl-4-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrole-5-carboxylate ((*R*)-5). In a stream of Ar, lead(IV) acetate (1.00 g, 2.26 mmol) was added to a solution of (*R*)-**4** (300 mg, 0.92 mmol) in acetic acid (7.0 mL), and the mixture was stirred for 4 h at 65°C. After the excess of lead(IV) acetate was decomposed by ethylene glycol, the mixture was poured into ice-H_2O 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 purified by column chromatography (SiO_2, Et_2O–CH_2Cl_2, 5:95) to give (*R*)-**5** (350 mg, 99%, >95% ee by NMR analysis of Mosher's ester). (*R*)-**5**: colorless crystals (CH_2Cl_2–hexane). Mp 87–89°C. $[\alpha]_D^{20}$=−64.1° (*c* 0.948, CH_2Cl_2). MS (EI) *m/z*: 385 (M^+). HRMS $C_{18}H_{18}F_3NO_5$: 385.114 (M^+). Found: 385.114. IR (KBr) ν_{max} 3475, 3308, 1721, 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.32 (1H, bs), 7.43–7.32 (5H, m), 5.34 (1H, d, *J*=13.5 Hz), 5.32 (2H, s), 5.13 (1H, qd, *J*=7.0, 4.0 Hz), 5.08 (1H, d, *J*=13.5 Hz), 3.50 (1H, d, *J*=4.0 Hz), 2.35 (3H, s), 2.07 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −74.37 (3F, d, *J*=7.0 Hz).

4.1.5. Benzyl 4-((*R*)-1-acetoxy-2,2,2-trifluoroethyl)-3,5-dimethylpyrrole-2-carboxylate ((*R*)-6). In a stream of Ar, acetyl chloride (457 μL, 6.43 mmol) was added to a solution of (*R*)-**4** (0.96 g, 2.94 mmol) and 4-(dimethylamino)pyridine (0.78 g, 6.39 mmol) in anhydrous CH_2Cl_2 (44 mL) at room temperature, and the mixture was stirred for 1.5 h at the same temperature. After evaporation of the solvent under vacuum, the residue was separated by column chromatography (SiO_2, CH_2Cl_2) to give (*R*)-**6** (1.03 g, 95%) as a colorless syrup. (*R*)-**6**: $[\alpha]_D^{20}$=−57.1° (*c* 2.44, CH_2Cl_2). MS (EI) *m/z*: 369 (M^+). HRMS $C_{18}H_{18}F_3NO_3$: 369.119 (M^+). Found: 369.120. IR (KBr) ν_{max} 3307, 1761, 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.11 (1H, bs), 7.42–7.30 (5H, m), 6.17 (1H, q, *J*=7.6 Hz), 5.30 (2H, s), 2.39 (3H, s), 2.31 (3H, s), 2.14 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −71.39 (3F, d, *J*=7.6 Hz).

4.1.6. Benzyl 4-((*R*)-1-acetoxy-2,2,2-trifluoroethyl)-5-methoxycarbonyl-3-methylpyrrole-2-carboxylate ((*R*)-7). In a stream of Ar, sulfuryl chloride (0.93 mL, 11.6 mmol) was added to a solution of (*R*)-**6** (1.03 g, 2.79 mmol) in anhydrous CH_2Cl_2–Et_2O (6.7 mL, 10 mL) at room temperature, and the mixture was stirred for 1.5 h. The mixture was concentrated under vacuum, and the residue was dissolved in acetone (15 mL) and H_2O (3.1 mL). After the mixture was refluxed for 40 min, acetone was evaporated, and the residue was treated with ice-H_2O and hexane. The crystals, separated between two

layers, were collected by filtration. The crystals were dissolved in 2 M NH_4OH, then the solution was acidified by acetic acid to give a carboxylic compound (1.10 g, 99%). Colorless crystals (CH_2Cl_2–hexane). Mp 143–145°C. MS (EI) *m/z*: 399 (M^+). HRMS $C_{18}H_{16}F_3NO_6$: 399.093 (M^+). Found: 399.094. ^1H NMR ($CDCl_3$) δ: 9.98 (1H, bs), 9.75 (1H, bs), 7.54 (5H, s), 7.25 (1H, q, *J*=7.3 Hz), 5.45 (2H, s), 2.55 (3H, s), 2.20 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −70.83 (3F, d, *J*=7.3 Hz).

A solution of CH_2N_2 in Et_2O was added to a solution of the carboxylic acid obtained above (5.82 g, 14.6 mmol) in CH_2Cl_2 (50 mL) at room temperature. After the excess of CH_2N_2 was decomposed with AcOH, the mixture was poured into ice-H_2O 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 crude product was separated by column chromatography (SiO_2, CH_2Cl_2) to give (*R*)-**7** (4.54 g, 75%) as a colorless syrup. (*R*)-**7**: $[\alpha]_D^{20}=-10.5°$ (*c* 1.30, CH_2Cl_2). MS (EI) *m/z*: 413 (M^+). HRMS $C_{19}H_{18}F_3NO_6$: 413.109 (M^+). Found: 413.108. IR (KBr) ν_{max} 3307, 1757, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 9.67 (1H, bs), 7.45–7.35 (5H, m), 7.16 (1H, q, *J*=7.3 Hz), 5.34 (2H, s), 3.93 (3H, s), 2.47 (3H, s), 2.16 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −70.91 (3F, d, *J*=7.3 Hz).

4.1.7. 4-((*R*)-1-Acetoxy-2,2,2-trifluoroethyl)-5-methoxycarbonyl-3-methylpyrrole-2-carboxylic acid ((*R*)-8). A solution of (*R*)-**7** (4.46 g, 10.8 mmol) in THF (76 mL) was shaken in an atmosphere of H_2 in the presence of 5% Pd-C (365 mg) until absorption of H_2 was no longer observed. After the catalyst was filtered off, the solvent was evaporated under vacuum. The residue was dissolved in 2 M NH_4OH, then the solution was filtered and acidified with acetic acid to give colorless crystals of (*R*)-**8** (3.43 g, 98%). (*R*)-**8**: colorless crystals (CH_2Cl_2–hexane). Mp 184–186°C. MS (EI) *m/z*: 323 (M^+). HRMS $C_{12}H_{12}F_3NO_6$: 323.062 (M^+). Found: 323.062. ^1H NMR ($CDCl_3$) δ: 10.53 (1H, bs), 9.92 (1H, bs), 7.17 (1H, q, *J*=7.0 Hz), 4.01 (3H, s), 2.52 (3H, s), 2.24 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −70.88 (3F, d, *J*=7.0 Hz).

4.1.8. Methyl 4-((*R*)-1-acetoxy-2,2,2-trifluoroethyl)-2-iodo-3-methylpyrrole-5-carboxylate ((*R*)-9). A solution of I_2 (3.59 g, 14.1 mmol) and NaI (3.89 g, 26.0 mmol) in H_2O (20 mL) was added to a mixture of (*R*)-**8** (3.43 g, 10.6 mmol) and $NaHCO_3$ (2.76 g, 32.9 mmol) in CH_2ClCH_2Cl–H_2O (20 mL, 20 mL), and the mixture was refluxed for 40 min. After the excess of iodine was reduced 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), and recrystallized from hexane–CH_2Cl_2 to give (*R*)-**9** (3.30 g, 77%). (*R*)-**9**: colorless crystals. Mp 109–111°C. $[\alpha]_D^{20}=-10.2°$ (*c* 2.17, CH_2Cl_2). MS (EI) *m/z*: 405 (M^+). HRMS $C_{11}H_{11}F_3INO_4$: 404.969 (M^+). Found: 404.968. IR (KBr) ν_{max} 3308, 1772, 1696, 1448, 1398, 1384 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 9.26 (1H, bs), 7.13 (1H, q, *J*=7.6 Hz), 3.91 (3H, s), 2.17 (3H, s), 2.14 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −70.98 (3F, d, *J*=7.6 Hz).

4.1.9. Methyl 3-((*R*)-1-acetoxy-2,2,2-trifluoroethyl)-4-methylpyrrole-2-carboxylate ((*R*)-10). A solution of (*R*)-**9** (3.21 g, 7.93 mmol) in MeOH (39 mL) was stirred in an atmosphere of H_2 in the presence of platinum(IV) oxide (52 mg) and anhydrous sodium acetate (1.99 g, 24.3 mmol) until absorption of H_2 was no longer observed. After the catalyst was filtered off, H_2O was added to the mixture and the whole 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, Et_2O–CH_2Cl_2, 3:97) to give (*R*)-**10** (2.15 g, 97%). (*R*)-**10**: colorless crystals (CH_2Cl_2–hexane). Mp 139–140°C. $[\alpha]_D^{20}=-26.3°$ (*c* 2.54, CH_2Cl_2). MS (EI) *m/z*: 279 (M^+). HRMS $C_{11}H_{12}F_3NO_4$: 279.072 (M^+). Found: 279.071. IR (KBr) ν_{max} 3392, 1748, 1702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 9.05 (1H, bs), 7.17 (1H, q, *J*=7.6 Hz), 6.70 (1H, d, *J*=3.0 Hz), 3.89 (3H, s), 2.19 (3H, s), 2.17 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −71.15 (3F, d, *J*=7.6 Hz).

4.1.10. Benzyl 4-methyl-3-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrole-2-carboxylate ((*R*)-11). In a stream of Ar, a solution of $NaN(Si(CH_3)_3)_2$ (1.0 M in THF, 1.0 mL) was added dropwise to a solution of (*R*)-**10** (100 mg, 0.36 mmol) in anhydrous $PhCH_2OH$ (1.0 mL) at 80°C, and the mixture was refluxed for 5 min at the same temperature. The mixture was poured into ice-H_2O and the whole 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, Et_2O–CH_2Cl_2, 5:95) to give (*R*)-**11** (90 mg, 80%). (*R*)-**11**: colorless crystals (CH_2Cl_2–hexane). Mp 99–100°C. $[\alpha]_D^{20}=-24.6°$ (*c* 1.93, CH_2Cl_2). MS (EI) *m/z*: 313 (M^+). HRMS $C_{15}H_{14}F_3NO_3$: 313.092 (M^+). Found: 313.092. IR (KBr) ν_{max} 3328, 3220, 1672, 1404, 1354, 1284 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 9.00 (1H, bs), 7.42–7.35 (5H, m), 6.81 (1H, d, *J*=11.6 Hz), 6.70 (1H, d, *J*=3.0 Hz), 5.34 (1H, d, *J*=12.2 Hz), 5.30 (1H, d, *J*=12.2 Hz), 5.06 (1H, dq, *J*=11.6, 7.3 Hz), 2.07 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −74.32 (3F, d, *J*=7.3 Hz).

4.1.11. Benzyl 5-acetoxymethyl-3-methyl-4-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrole-5-carboxylate ((*S*)-5). A solution of (*S*)-**4** (300 mg, 0.92 mmol) in acetic acid (7.0 mL) was treated similarly with $Pb(OAc)_4$, and the mixture was worked up similarly as in the case of (*R*)-**5** to give (*S*)-**5** (351 mg, 99%, >95% ee from NMR analysis of Mosher's ester). (*S*)-**5**: mp 90–91°C (CH_2Cl_2–hexane). $[\alpha]_D^{20}=+65.8°$ (*c* 1.16, CH_2Cl_2). MS (EI) *m/z*: 385 (M^+). HRMS $C_{18}H_{18}F_3NO_5$: 385.114 (M^+). Found: 385.114.

4.1.12. Benzyl 4-((*S*)-1-acetoxy-2,2,2-trifluoroethyl)-3,5-dimethylpyrrole-2-carboxylate ((*S*)-6). In a stream of Ar, acetyl chloride (435 μL, 6.12 mmol) was added to a solution of (*S*)-**4** (919 mg, 2.81 mmol) and 4-dimethylaminopyridine (739 mg, 6.05 mmol) in anhydrous CH_2Cl_2 (42 mL) at room temperature, and the mixture was stirred for 1.5 h at the same temperature. After the mixture was worked up as in the case of (*R*)-**6**, the crude product was separated by column chromatography (SiO_2, CH_2Cl_2) to give (*S*)-**6** (998 mg, 96%) as a colorless syrup. (*S*)-**6**: $[\alpha]_D^{20}=+56.9°$ (*c* 2.58, CH_2Cl_2). MS (EI) *m/z*: 369

(M^+). HRMS $C_{18}H_{18}F_3NO_4$: 369.119 (M^+). Found: 369.119.

4.1.13. Benzyl 4-((*S*)-1-acetoxy-2,2,2-trifluoroethyl)-5-methoxycarbonyl-3-methylpyrrole-2-carboxylate ((*S*)-7). In a stream of Ar, sulfuryl chloride (5.41 mL, 67.3 mmol) was added to a solution of (*S*)-**6** (5.99 g, 16.2 mmol) in anhydrous CH_2Cl_2–Et_2O (39.0 mL, 61.0 mL) at room temperature, and the mixture was stirred for 1.5 h. The mixture was concentrated under vacuum, and the residue was dissolved in acetone (84 mL) and H_2O (18 mL). A similar workup of the mixture as in the case of (*R*)-**7** gave the carboxylic compound (6.43 g, 99%). Coloress crystals (CH_2Cl_2–hexane). Mp 142–144°C. MS (EI) *m/z*: 399 (M^+). HRMS $C_{18}H_{16}F_3NO_6$: 399.093 (M^+). Found: 399.092.

Treatment of the carboxylic acid (6.43 g, 16.1 mmol) with CH_2N_2 and a similar workup as in the case of (*R*)-**7** gave (*S*)-**7** (5.39 g, 81%) as a colorless syrup. (*S*)-**7**: $[\alpha]_D^{20}=+7.48°$ (*c* 1.30, CH_2Cl_2). MS (EI) *m/z*: 413 (M^+). HRMS $C_{19}H_{18}F_3NO_6$: 413.109 (M^+). Found: 413.109.

4.1.14. 4-((*S*)-1-Acetoxy-2,2,2-trifluoroethyl)-5-methoxycarbonyl-3-methylpyrrole-2-carboxylic acid ((*S*)-8). A solution of (*S*)-**7** (622 mg, 1.51 mmol) in THF (13 mL) was shaken in an atmosphere of H_2 in the presence of 5% Pd-C (53 mg), and the mixture was worked up as in the case of (*R*)-**8** to give (*S*)-**8** (480 mg, 99%). (*S*)-**8**: colorless crystals (CH_2Cl_2–hexane). Mp 188–190°C. MS (EI) *m/z*: 323 (M^+). HRMS $C_{12}H_{12}F_3NO_6$: 323.062 (M^+). Found: 323.062.

4.1.15. Methyl 4-((*S*)-1-acetoxy-2,2,2-trifluoroethyl)-2-iodo-3-methylpyrrole-5-carboxylate ((*S*)-9). A solution of iodine (2.03 g, 8.00 mmol) and sodium iodide (2.20 g, 14.7 mmol) in H_2O (11 mL) was added to a mixture of (*S*)-**8** (1.94 g, 6.00 mmol) and anhydrous sodium bicarbonate (1.56 g, 18.6 mmol) in CH_2ClCH_2Cl–H_2O (11 mL, 11 mL), and the mixture was refluxed for 40 min. After the mixture was worked up as in the case of (*R*)-**9**, the crude product was separated by column chromatography (SiO_2, CH_2Cl_2), and recrystallized from hexane–CH_2Cl_2 to give (*S*)-**9** (2.31 g, 95%). (*S*)-**9**: colorless crystals. Mp 109–111°C. $[\alpha]_D^{20}=+10.1°$ (*c* 2.35, CH_2Cl_2). MS (EI) *m/z*: 405 (M^+). HRMS $C_{11}H_{11}F_3INO_4$: 404.969 (M^+). Found: 404.969.

4.1.16. Methyl 3-((*S*)-1-acetoxy-2,2,2-trifluoroethyl)-4-methylpyrrole-2-carboxylate ((*S*)-10). A solution of (*S*)-**9** (2.26 g, 5.58 mmol) in MeOH (28 mL) was stirred in an atmosphere of H_2 in the presence of PtO_2 (37 mg) and anhydrous NaOAc (1.40 g, 17.1 mmol), and the mixture was worked up as in the case of (*R*)-**10** to give (*S*)-**10** (1.51 g, 97%). (*S*)-**10**: mp 139–140°C. $[\alpha]_D^{20}=+28.2°$ (*c* 2.35, CH_2Cl_2). MS (EI) *m/z*: 279 (M^+). HRMS $C_{11}H_{12}F_3NO_4$: 279.072 (M^+). Found: 279.072.

4.1.17. Benzyl 4-methyl-3-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrole-2-carboxylate ((*S*)-11). In a stream of Ar, a solution of $NaN(Si(CH_3)_3)_2$ (1.0 M in THF, 6.0 mL) was added dropwise to a solution of (*S*)-**10** (607 mg, 2.18 mmol) in anhydrous $PhCH_2OH$ (6.0 mL) at 80°C, and the mixture was refluxed for 5 min. The mixture was worked up and separated as in the case of (*R*)-**11** to give (*S*)-**11** (566 mg, 83%). (*S*)-**11**: mp 99–100°C (CH_2Cl_2–hexane). $[\alpha]_D^{20}=+24.3°$ (*c* 2.39, CH_2Cl_2). MS (EI) *m/z*: 313 (M^+). HRMS $C_{15}H_{14}F_3NO_3$: 313.092 (M^+). Found: 313.093.

4.1.18. Dibenzyl (3*R*,4′*R*)-4,3′-dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylate ((*R*,*R*)-12). In a stream of Ar, boron trifluoride diethyl etherate (20 μL, 0.16 mmol) was added to a solution of (*R*)-**5** (62 mg, 0.16 mmol) and (*R*)-**11** (51 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (5.0 mL) under ice-cooling, and the mixture was stirred for 1 h at room temperature. The mixture was poured into ice-H_2O and the whole 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, Et_2O–CH_2Cl_2, 5:95) to give (*R*,*R*)-**12** (91 mg, 88%, >95% ee from NMR analysis of Mosher's ester). (*R*,*R*)-**12**: colorless crystals (CH_2Cl_2–hexane). Mp 80–82°C. $[\alpha]_D^{20}=-152.4°$ (*c* 1.01, CH_2Cl_2). MS (EI) *m/z*: 638 (M^+). HRMS $C_{31}H_{28}F_6N_2O_6$: 638.185 (M^+). Found: 638.186. ^{1}H NMR ($CDCl_3$) δ: 9.62 (1H, bs), 8.83 (1H, bs), 7.34 (5H, s), 7.33 (5H, s), 6.88 (1H, d, *J*=11.3 Hz), 5.27 (1H, d, *J*=12.2 Hz), 5.25 (1H, d, *J*=12.2 Hz), 5.23 (1H, d, *J*=12.2 Hz), 5.22 (1H, d, *J*=12.2 Hz), 5.11 (1H, q, *J*=7.0 Hz), 5.03 (1H, dq, *J*=11.3, 7.0 Hz), 4.10 (1H, d, *J*=16.5 Hz), 3.83 (1H, d, *J*=16.5 Hz), 3.19 (1H, bs), 2.29 (3H, s), 2.03 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −74.05 (3F, d, *J*=7.0 Hz), −74.15 (3F, d, *J*=7.0 Hz).

4.1.19. (3*R*,4′*R*)-4,3′-Dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylic acid ((*R*,*R*)-13). A solution of (*R*,*R*)-**12** (91 mg, 0.14 mmol) in THF (5.0 mL) was shaken in an atmosphere of H_2 in the presence of 5% Pd-C (26 mg) until absorption of H_2 was no more observed. After filtration of the catalyst and evaporation of the solvent, the residue was recrystallized from hexane–CH_2Cl_2 to give (*R*,*R*)-**13** (64 mg, 98%). (*R*,*R*)-**13**: colorless crystals. Mp 121–124°C. MS (EI) *m/z*: 458 (M^+). ^{1}H NMR ($CDCl_3$) δ: 10.75 (1H, s), 10.07 (1H, s), 8.27 (4H, bs), 5.13 (1H, q, *J*=7.3 Hz), 5.07 (1H, q, *J*=7.3 Hz), 4.22 (1H, d, *J*=16.0 Hz), 3.82 (1H, d, *J*=16.0 Hz), 2.29 (3H, s), 2.07 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −73.54 (3F, d, *J*=7.3 Hz), −73.96 (3F, d, *J*=7.3 Hz).

4.1.20. (3*R*,8*R*)-3,8-Bis(2,2,2-trifluoro-1-hydroxyethyl)-deuteroporphyrin dimethyl ester ((*R*,*R*)-HFHP-DME (*R*,*R*)-16). In a stream of Ar, (*R*,*R*)-**13** (64 mg, 0.14 mmol) was dissolved in degassed ethanolamine (2.7 mL) and stirred at 200°C for 30 min. The mixture was poured into ice-H_2O and the whole 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 used for the next step without further purification.

In a stream of Ar, a solution of *p*-toluenesulfonic acid monohydrate (86 mg, 0.45 mmol) in anhydrous MeOH (1.4 mL) was added to a solution of the above residue (51 mg, 0.14 mmol) and 5,5′-diformyl-3,3′-bis(2-methoxycarbonylethyl)-4,4′-dimethyl-2,2′-dipyrrylmethane[13] (**15**, 57 mg, 0.14 mmol) in anhydrous CH_2Cl_2–MeOH (14 mL, 1.4 mL) at room temperature, and the mixture was stirred

for 24 h. Further, a saturated solution of zinc acetate in anhydrous MeOH (1.4 mL) was added and the mixture was stirred for 24 h in air at room temperature. The mixture was concentrated under vacuum, and the residue was stirred with 5% sulfuric acid in MeOH at room temperature for 24 h. The mixture was poured into ice-H_2O and the whole 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, Et_2O–CH_2Cl_2, 15:85) to give (*R*,*R*)-HFHP-DME ((*R*,*R*)-**16**, 37 mg, 37%, 89% ee from NMR analysis of Mosher's ester). (*R*,*R*)-**16**: deep violet crystals (CH_2Cl_2–hexane). Mp 279–281°C. MS (EI) *m*/*z*: 734 (M^+). HRMS $C_{36}H_{36}F_6N_4O_6$: 734.254 (M^+). Found: 734.253. IR (KBr) ν_{max} 3472, 3315, 1738, 1725, 1268, 1163, 1129 cm^{-1}. UV (dichloromethane) λ (ε_{max}): 439 (31510), 525 (21306), 557 (12490), 599 (10776), 649 nm (5143). ^1H NMR ($CDCl_3$) δ: 10.56 (1H, s), 10.44 (1H, s), 9.91 (1H, s), 9.87 (1H, s), 6.99 (2H, m), 6.56 (1H, q, *J*=7.3 Hz), 6.50 (1H, q, *J*=7.3 Hz), 4.26 (2H, t, *J*=7.3 Hz), 4.24 (2H, t, *J*=7.3 Hz), 3.64 (3H, s), 3.60 (3H, s), 3.58 (3H, s), 3.56 (3H, s), 3.51 (3H, s), 3.46 (3H, s), 3.18 (2H, t, *J*=7.3 Hz), 3.16 (2H, t, *J*=7.3 Hz), −3.96 (2H, bs). ^{19}F NMR ($CDCl_3$) δ: −71.56 (6F, d, *J*=7.3 Hz).

4.1.21. Dibenzyl (3*R*,4′*S*)-4,3′-dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylate ((*R*,*S*)-12). In a stream of Ar, boron trifluoride diethyl etherate (32 μL, 0.26 mmol) was added to a solution of (*R*)-**5** (98 mg, 0.26 mmol) and (*S*)-**11** (80 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (8.0 mL) under ice-cooling, and then the mixture was stirred for 1 h at room temperature. Workup of the mixture similarly as in the case of (*R*,*R*)-**12** gave (*R*,*S*)-**12** (150 mg, 92%, 95% ee). (*R*,*S*)-**12**: colorless crystals (CH_2Cl_2–hexane). Mp 86–88°C. $[\alpha]_D^{20}$=−165.5° (*c* 0.989, CH_2Cl_2). MS (EI) *m*/*z*: 638 (M^+). HRMS $C_{31}H_{28}F_6N_2O_6$: 638.185 (M^+). Found: 638.184. ^1H NMR ($CDCl_3$) δ: 9.64 (1H, bs), 8.87 (1H, bs), 7.32 (5H, s), 7.30 (5H, s), 6.90 (1H, bd, *J*=11.3 Hz), 5.26 (1H, d, *J*=12.2 Hz), 5.24 (1H, d, *J*=12.2 Hz), 5.22 (1H, d, *J*=12.2 Hz), 5.19 (1H, d, *J*=12.2 Hz), 5.10 (1H, qd, *J*=7.3, 4.0 Hz), 4.97 (1H, dq, *J*=11.3, 7.3 Hz), 4.10 (1H, d, *J*=16.5 Hz), 3.84 (1H, d, *J*=16.5 Hz), 3.27 (1H, bd, *J*=4.0 Hz), 2.29 (3H, s), 2.01 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −74.07 (3F, d, *J*=7.3 Hz), −74.27 (3F, d, *J*=7.3 Hz).

4.1.22. (3*R*,4′*S*)-4,3′-Dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylic acid ((*R*,*S*)-13). A solution of (*R*,*S*)-**12** (137 mg, 0.22 mmol) in THF (7.3 mL) was shaken in an atmosphere of H_2 in the presence of 5% Pd-C (38 mg) until absorption of H_2 was no more observed. The mixture was worked up as in the case of (*R*,*R*)-**13** to give (*R*,*S*)-**13** (98 mg, 99%). (*R*,*S*)-**13**: colorless crystals (CH_2Cl_2–hexane). Mp 121–125°C. MS (EI) *m*/*z*: 458 (M^+). ^1H NMR ($CDCl_3$) δ: 10.87 (1H, s), 10.10 (1H, s), 6.39 (4H, bs), 5.14 (1H, q, *J*=7.3 Hz), 4.97 (1H, q, *J*=7.3 Hz), 4.25 (1H, d, *J*=16.0 Hz), 3.85 (1H, d, *J*=16.0 Hz), 2.31 (3H, s), 2.07 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −73.49 (3F, d, *J*=7.3 Hz), −74.13 (3F, d, *J*=7.3 Hz).

4.1.23. (3*R*,8*S*)-3,8-Bis(2,2,2-trifluoro-1-hydroxyethyl)-deuteroporphyrin dimethyl ester ((*R*,*S*)-HFHP-DME (*R*,*S*)-16). In a stream of Ar, (*R*,*S*)-**13** (98 mg, 0.21 mmol) was dissolved in degassed ethanolamine (4.1 mL) and stirred at 200°C for 30 min. The mixture was poured into ice-H_2O and the whole 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 used for the next step.

In a stream of Ar, a solution of *p*-toluenesulfonic acid monohydrate (130 mg, 0.68 mmol) in anhydrous MeOH (2.2 mL) was added to a solution of the above residue (77 mg, 0.21 mmol) and **15** (86 mg, 0.21 mmol) in anhydrous CH_2Cl_2–MeOH (22 mL, 2.2 mL) at room temperature, and the mixture was stirred for 24 h. The mixture was treated with a saturated solution of zinc acetate in anhydrous MeOH (2.2 mL) similarly as in the case of (*R*,*R*)-**16**. After concentration under vacuum and treatment of the residue with 5% sulfuric acid in MeOH (30 mL) for 24 h at room temperature, the mixture was worked up as in the case of (*R*,*R*)-**16** to give (*R*,*S*)-HFHP-DME ((*R*,*S*)-**16**, 44 mg, 29%, 91% ee). (*R*,*S*)-**16**: deep violet crystals (CH_2Cl_2–hexane). Mp 236–238°C. MS (EI) *m*/*z*: 734 (M^+). HRMS $C_{36}H_{36}F_6N_4O_6$: 734.254 (M^+). Found: 734.254. IR (KBr) ν_{max} 3487, 3318, 1745, 1721, 1262, 1168, 1129 cm^{-1}. UV (dichloromethane) λ (ε_{max}): 435 (27959), 525 (12776), 560 (8000), 599 (7755), 648 nm (3918). ^1H NMR ($CDCl_3$) δ: 10.51 (1H, s), 10.40 (1H, s), 9.89 (1H, s), 9.87 (1H, s), 6.48 (2H, q, *J*=7.3 Hz), 6.40 (2H, bs), 4.30 (2H, t, *J*=7.8 Hz), 4.27 (2H, t, *J*=7.8 Hz), 3.66 (3H, s), 3.64 (3H, s), 3.63 (3H, s), 3.60 (3H, s), 3.54 (3H, s), 3.49 (3H, s), 3.23 (2H, t, *J*=7.8 Hz), 3.21 (2H, t, *J*=7.8 Hz), −4.01 (2H, bs). ^{19}F NMR ($CDCl_3$) δ: −71.78 (3F, d, *J*=7.3 Hz), −71.95 (3F, d, *J*=7.3 Hz).

4.1.24. Dibenzyl (3*S*,4′*R*)-4,3′-dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylate ((*S*,*R*)-12). In a stream of Ar, boron trifluoride diethyl etherate (20 μL, 0.16 mmol) was added to a solution of (*S*)-**5** (98 mg, 0.25 mmol) and (*R*)-**11** (80 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (5.0 mL) under ice-cooling, and then the mixture was stirred for 1 h at room temperature. Workup of the mixture as in the case of (*R*,*R*)-**12** gave (*S*,*R*)-**12** (130 mg, 80%, >95% ee). (*S*,*R*)-**12**: colorless crystals (CH_2Cl_2–hexane). Mp 81–83°C. $[\alpha]_D^{20}$=+128.08° (*c* 1.01, CH_2Cl_2). MS (EI) *m*/*z*: 638 (M^+). HRMS $C_{31}H_{28}F_6N_2O_6$: 638.185 (M^+). Found: 638.185. ^1H NMR ($CDCl_3$) δ: 9.65 (1H, bs), 8.84 (1H, bs), 7.34 (5H, s), 7.32 (5H, s), 6.91 (1H, bd, *J*=11.0 Hz), 5.27 (1H, d, *J*=12.2 Hz), 5.26 (1H, d, *J*=12.2 Hz), 5.23 (1H, d, *J*=12.2 Hz), 5.20 (1H, d, *J*=12.2 Hz), 5.11 (1H, q, *J*=7.3 Hz), 4.98 (1H, dq, *J*=11.0, 7.3 Hz), 4.11 (1H, d, *J*=16.5 Hz), 3.84 (1H, d, *J*=16.5 Hz), 3.21 (1H, bs), 2.29 (3H, s), 2.02 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −74.02 (3F, d, *J*=7.3 Hz), −74.24 (3F, d, *J*=7.3 Hz).

4.1.25. (3*S*,4′*R*)-4,3′-Dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylic acid ((*S*,*R*)-13). A solution of (*S*,*R*)-**12** (130 mg, 0.20 mmol) in THF (7.0 mL) was shaken in an atmosphere of H_2 in the presence of 5% Pd-C (36 mg) until absorption of H_2 was no more observed. The mixture was worked up as in the case of (*R*,*R*)-**13** to give (*S*,*R*)-**13** (92 mg, 98%). (*S*,*R*)-**13**: colorless crystals (CH_2Cl_2–hexane). Mp 120–124°C. MS (EI) *m*/*z*: 458 (M^+). ^1H NMR ($CDCl_3$) δ: 10.81 (1H,

s), 10.08 (1H, s), 8.29 (4H, bs), 5.15 (1H, q, J=7.3 Hz), 4.97 (1H, q, J=7.3 Hz), 4.26 (1H, d, J=16.7 Hz), (1H, d, J=16.7 Hz), 2.28 (3H, s), 2.06 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −73.51 (3F, d, J=7.3 Hz), −74.16 (3F, d, J=7.3 Hz).

4.1.26. (3*S*,8*R*)-3,8-Bis(2,2,2-trifluoro-1-hydroxyethyl)-deuteroporphyrin dimethyl ester ((*S*,*R*)-HFHP-DME (*S*,*R*)-16). In a stream of Ar, (*S*,*R*)-**13** (92 mg, 0.20 mmol) was dissolved in degassed ethanolamine (3.9 mL) and stirred at 200°C for 30 min. The mixture was poured into ice-H_2O and the whole 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 used for the next step.

In a stream of Ar, a solution of *p*-toluenesulfonic acid monohydrate (123 mg, 0.65 mmol) in anhydrous MeOH (2.0 mL) was added to a solution of the above residue (73 mg, 0.20 mmol) and **15** (82 mg, 0.20 mmol) in anhydrous CH_2Cl_2–MeOH (20 mL, 2.0 mL) at room temperature, and the mixture was stirred for 24 h. Further, a saturated solution of zinc acetate in anhydrous MeOH (2.0 mL) was added and the mixture was stirred for 24 h in air at room temperature. The whole mixture was concentrated under vacuum, and the residue was stirred with 5% sulfuric acid in MeOH (20 mL) for 24 h at room temperature. A similar workup of the mixture as in the case of (*R*,*R*)-**16** gave (*S*,*R*)-HFHP-DME ((*S*,*R*)-**16**, 59 mg, 41%, 89% ee). (*S*,*R*)-**16**: deep violet crystals (CH_2Cl_2–hexane). Mp 238–240°C. MS (EI) *m*/*z*: 734 (M^+). HRMS $C_{36}H_{36}F_6N_4O_6$: 734.254 (M^+). Found: 734.254. IR (KBr) ν_{max} 3479, 3319, 1741, 1721, 1262, 1162, 1129 cm^{-1}. UV (dichloromethane) λ (ε_{max}): 435 (27102), 525 (15347), 559 (9184), 599 (8041), 648 nm (3265). ^{1}H NMR ($CDCl_3$) δ: 10.38 (1H, s), 10.23 (1H, s), 9.83 (2H, s), 6.35 (2H, q, J=7.3 Hz), 5.98 (1H, bs), 5.91 (1H, bs), 4.28 (2H, t, J=7.8 Hz), 4.24 (2H, t, J=7.8 Hz), 3.66 (3H, s), 3.64 (3H, s), 3.54 (3H, s), 3.53 (3H, s), 3.50 (3H, s), 3.46 (3H, s), 3.22 (2H, t, J=7.8 Hz), 3.20 (2H, t, J=7.8 Hz), −4.08 (2H, bs). ^{19}F NMR ($CDCl_3$) δ: −71.77 (6F, d, J=7.3 Hz).

4.1.27. Dibenzyl (3*S*,4′*S*)-4,3′-dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylate ((*S*,*S*)-12). In a stream of Ar, boron trifluoride diethyl etherate (24 μL, 0.20 mmol) was added to a solution of (*S*)-**5** (74 mg, 0.190 mmol) and (*S*)-**11** (60 mg, 0.190 mmol) in anhydrous CH_2Cl_2 (6.0 mL) under ice-cooling, and then the mixture was stirred for 1 h at room temperature. Workup of the mixture as in the case of (*R*,*R*)-**12** gave (*S*,*S*)-**12** (106 mg, 87%, 93% ee). (*S*,*S*)-**12**: colorless crystals (CH_2Cl_2–hexane). Mp 88–90°C. $[\alpha]_D^{20}$=+122.7° (*c* 1.20, CH_2Cl_2). MS (EI) *m*/*z*: 638 (M^+). HRMS $C_{31}H_{28}F_6N_2O_6$: 638.185 (M^+). Found: 638.185. ^{1}H NMR ($CDCl_3$) δ: 9.63 (1H, bs), 8.90 (1H, bs), 7.32 (5H, s), 7.29 (5H, s), 6.88 (1H, bd, J=11.3 Hz), 5.25 (1H, d, J=12.2 Hz), 5.22 (1H, d, J=12.2 Hz), 5.21 (2H, s), 5.11 (1H, qd, J=7.3, 3.4 Hz), 5.03 (1H, dq, J=11.3, 7.3 Hz), 4.08 (1H, d, J=16.5 Hz), 3.81 (1H, d, J=16.5 Hz), 3.25 (1H, bd, J=3.4 Hz), 2.29 (3H, s), 2.02 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −74.03 (3F, d, J=7.3 Hz), −74.14 (3F, d, J=7.3 Hz).

4.1.28. (3*S*,4′*S*)-4,3′-Dimethyl-3,4′-bis(2,2,2-trifluoro-1-hydroxyethyl)-2,2′-dipyrrylmethane-5,5′-dicarboxylic acid ((*S*,*S*)-13). A solution of (*S*,*S*)-**12** (191 mg, 0.30 mmol) in THF (10 mL) was shaken in an atmosphere of H_2 in the presence of 5% Pd-C (53 mg) until absorption of H_2 was no more observed. The mixture was worked up as in the case of (*R*,*R*)-**13** to give (*S*,*S*)-**13** (134 mg, 98%). (*S*,*S*)-**13**: colorless crystals (CH_2Cl_2–hexane). Mp 124–127°C. MS (EI) *m*/*z*: 458 (M^+). ^{1}H NMR ($CDCl_3$) δ: 10.78 (1H, s), 10.15 (1H, s), 8.77 (4H, bs), 5.10 (1H, q, J=7.3 Hz), 4.93 (1H, q, J=7.3 Hz), 4.15 (1H, d, J=16.0 Hz), 3.78 (1H, d, J=16.0 Hz), 2.21 (3H, s), 1.99 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −73.49 (3F, d, J=7.3 Hz), −73.95 (3F, d, J=7.3 Hz).

4.1.29. (3*S*,8*S*)-3,8-Bis(2,2,2-trifluoro-1-hydroxyethyl)-deuteroporphyrin dimethyl ester ((*S*,*S*)-HFHP-DME (*S*,*S*)-16). In a stream of Ar, (*S*,*S*)-**13** (134 mg, 0.29 mmol) was dissolved in degassed ethanolamine (5.7 mL) and stirred at 200°C for 30 min. The mixture was poured into ice-H_2O and the whole 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 used for the next step.

In a stream of Ar, a solution of *p*-toluenesulfonic acid monohydrate (180 mg, 0.95 mmol) in anhydrous MeOH (3.0 mL) was added to a solution of the above residue (107 mg, 0.29 mmol) and **15** (120 mg, 0.30 mmol) in anhydrous CH_2Cl_2–MeOH (30 mL, 3.0 mL) at room temperature, and the mixture was stirred for 24 h. Further, a saturated solution of zinc acetate in anhydrous MeOH (3.0 mL) was added and the mixture was stirred for 24 h in air at room temperature. The whole mixture was concentrated under vacuum, and the residue was stirred with 5% sulfuric acid in MeOH (20 mL) at room temperature for 24 h. A similar workup of the mixture as in the case of (*R*,*R*)-HFHP-DME gave (*S*,*S*)-HFHP-DME ((*S*,*S*)-**16**, 53 mg, 25%, 86% ee). (*S*,*S*)-**16**: deep violet crystals (CH_2Cl_2–hexane). Mp 275–277°C. MS (EI) *m*/*z*: 734 (M^+). HRMS $C_{36}H_{36}F_6N_4O_6$: 734.254 (M^+). Found: 734.253. IR (KBr) ν_{max} 3480, 3350, 1745, 1726, 1268, 1164, 1130 cm^{-1}. UV (dichloromethane) λ (ε_{max}): 439 (31224), 525 (18286), 559 (10898), 599 (9796), 649 nm (5020). ^{1}H NMR ($CDCl_3$) δ: 10.43 (2H, s), 9.93 (1H, s), 9.92 (1H, s), 6.57 (1H, bs), 5.54 (1H, q, J=7.3 Hz), 6.42 (1H, q, J=7.3 Hz), 6.33 (1H, bs), 4.33 (2H, t, J=7.3 Hz), 4.31 (2H, t, J=7.3 Hz), 3.67 (3H, s), 3.65 (3H, s), 3.60 (6H, s), 3.57 (3H, s), 3.51 (3H, s), 3.26 (2H, t, J=7.3 Hz), 3.24 (2H, t, J=7.3 Hz), −3.98 (2H, bs). ^{19}F NMR ($CDCl_3$) δ: −71.67 (3F, d, J=7.3 Hz), −71.75 (3F, d, J=7.3 Hz).

References

1. (a) Lipson, R. I.; Baldes, E. J.; Olsen, A. M. *J. Natl Cancer Inst.* **1961**, *26*, 1. (b) Diamond, I.; Granelli, S.; McDonagh, A. F.; Nielsen, S.; Wilson, C. B.; Jaenicke, R. *Lancet* **1972**, 1175. (c) Dougherty, T. J.; Grinsley, G.; Fiel, B. R. *J. Natl Cancer Inst.* **1975**, *55*, 115.
2. Bonnet, R. *Chem. Soc. Rev.* **1995**, 19.
3. (a) Becker, E.; Bradley, R.; Watson, C. *J. Am. Chem. Soc.* **1961**, *83*, 3743. (b) Dougherty, T. J. *Photochem. Photobiol.* **1987**, *45*, 879. (c) Mironov, A. F.; Nizhnik, A. N.; Nockel, A. Y. *J. Photochem. Photobiol. B* **1990**, *4*, 297.

4. (a) Ando, A.; Kumadaki, I. *Heterocycles* **1996**, *42*, 885. (b) Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **1999**, *100*, 135.
5. Ando, A.; Kitamura, T.; Aono, S.; Sato, H.; Omote, M.; Koyama, M.; Takagi, T.; Miki, T.; Kumadaki, I.; Sato, H. *Heterocycles* **1993**, *35*, 1309.
6. Sato, H.; Ido, K.; Kimura, K. *Clin. Chem.* **1994**, *40*, 1239.
7. Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I. *Tetrahedron* **1996**, *52*, 13961.
8. Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I.; Shiro, M. *Heterocycles* **1997**, *47*, 65.
9. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
10. (a) Corey, E. J.; Cheng, X.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835. (b) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431.
11. (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (b) Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429. (c) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 4141. (d) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.
12. Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384.
13. Robinson, J. A.; McDonald, E.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1699.