SYNTHESIS OF FLUORINE ANALOGS OF PROTOPORPHYRIN POTENTIALLY USEFUL FOR DIAGNOSIS AND THERAPY OF CANCER PART 3.[1] SYNTHESIS OF (2,2-DIFLUOROVINYL)-TRIFLUOROVINYL- AND (1-CHLORO-2,2-DIFLUOROVINYL)-(2,2-DIFLUOROVINYL) DEUTEROPORPHYRIN

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This is dedicated to 73rd birthday of Professor Teruaki Mukaiyama.

Abstract – Wittig reaction of 3- and 8-formyl deuteroporphyrin dimethyl esters (**1** or **2**) with triphenylphosphonium difluoromethylide, generated *in situ* from sodium chlorodifluoroacetate and triphenylphosphine, gave 3- and 8-difluorovinyl compounds (**3** or **4**), which were iodinated to form corresponding 8- and 3-iodo compounds (**5** or **6**). Coupling reaction of these iodo compounds with our new bis(fluorovinyl)zinc reagents afforded the titled compounds (**7** to **10**) in moderate to good yields.

In the course of our study to prepare fluorine analogs of porphyrins potentially useful for diagnosis and therapy of cancer,[2] we have synthesized 3-(2,2-difluorovinyl)-8-vinyl (**A**), 8-(2,2-difluorovinyl)-3-vinyl-deuteroporphyrin (**B**) and 3,8-bis(2,2-difluorovinyl)deuteroporphyrin (**C**). Compound **B** was taken up by human stomach cancer, while **C** by rat liver cancer selectively.[3] As the extension of this research, a bis(trifluorovinyl) and a bis(1-chloro-2,2-difluorovinyl) analogs (**E** and **F**) of protoporphyrin were synthesized recently by the reaction of diiodo compound (**D**) with bis(trifluorovinyl)zinc or bis(1-chloro-2,2-difluorovinyl)zinc reagents in the presence of tetrakis(triphenylphosphine)palladium.[4] Here, we would like to report synthesis of new fluorine analogs of protoporphyrin (**G** and **H**), which have a 2,2-difluorovinyl, and a trifluorovinyl or 1-chloro-2,2-difluorovinyl groups on 3- or 8-position of the porphyrin ring

(see Figure 1).

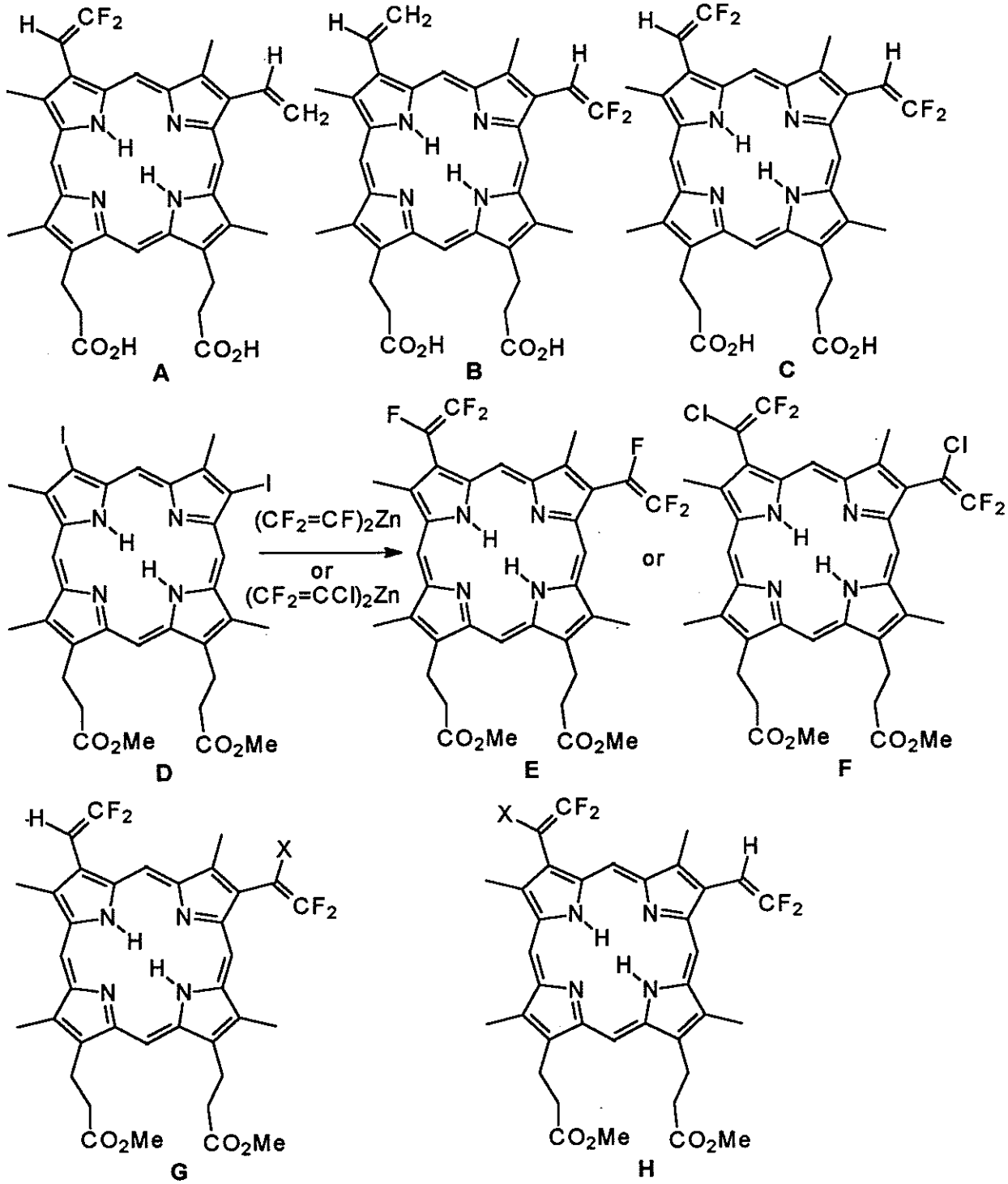
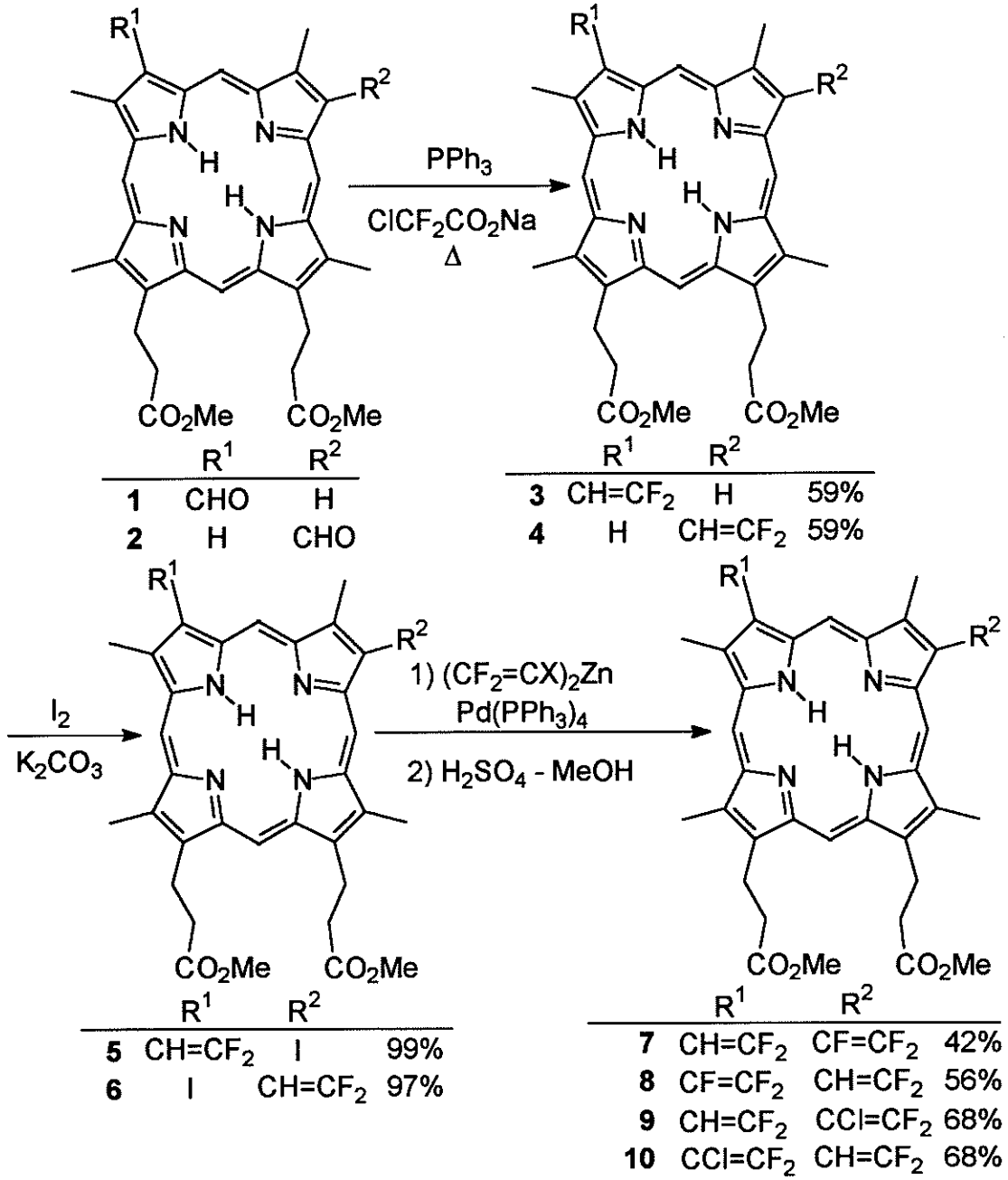


Figure 1 Fluorovinyl Analogs of Protoporphyrin

Recently, we have reported an effective formylation of deuteroporphyrin dimethyl ester,[5] and new bis(trifluorovinyl) and bis(1-chloro-2,2-difluorovinyl) reagents,[4] which were much more reactive than the corresponding fluorovinyl zinc chlorides prepared Normant's method.[6]

Compounds (**1** and **2**) were heated with sodium chlorodifluoroacetate in the presence of triphenylphosphine to give moderate yields of 2,2-difluorovinyl derivatives (**3** and **4**). These were iodinated with iodine and potassium carbonate to give iodo compounds (**5**) and (**6**) in quantitative yields (see Scheme 1).

Scheme 1



	R^1	R^2	
1	CHO	H	
2	H	CHO	
3	$CH=CF_2$	H	59%
4	H	$CH=CF_2$	59%
5	$CH=CF_2$	I	99%
6	I	$CH=CF_2$	97%
7	$CH=CF_2$	$CF=CF_2$	42%
8	$CF=CF_2$	$CH=CF_2$	56%
9	$CH=CF_2$	$CCl=CF_2$	68%
10	$CCl=CF_2$	$CH=CF_2$	68%

As shown in the previous paper,[4] reaction of chlorotrifluoroethene with *sec*-butyllithium in the presence of zinc chloride gave bis(trifluorovinyl)zinc, while reaction of trifluorovinyllithium, obtained by preliminary treatment of the ethene with *sec*-butyllithium, with zinc chloride produced trifluorovinylzinc chloride.[6] The former was found to be much more reactive than the latter.[4] Reaction of **5** and **6** with bis(trifluorovinyl)zinc in the presence of tetrakis(triphenylphosphine)palladium afforded (2,2-difluorovinyl)trifluorovinyldeuteroporphyrin dimethyl esters (**7**) and (**8**), respectively.

Similar reaction of 2-chloro-1,1-difluoroethene with *sec*-butyllithium in the presence of zinc chloride gave bis(1-chloro-2,2-difluorovinyl)zinc, which reacted with **5** and **6** similarly to produce corresponding (1-chloro-2,2-difluorovinyl)trifluorovinyldeuteroporphyrin dimethyl esters (**9**) and (**10**), respectively.

Biological behaviors of these compounds are under investigation and will be reported near future.

EXPERIMENTAL

General Procedures. ^{1}H-NMR spectra were recorded on JEOL FX90Q and JNM-GX400 spectrometers. MS spectra were recorded on a JEOL JMS-DX300. After purity of new compounds were confirmed by TLC, they were analyzed by HRMS.

3-(2,2-Difluorovinyl)deuteroporphyrin dimethyl ester (3)

A solution of $ClCF_2COONa$ (449 mg, 2.94 mmol) in *N*-methylpyrrolidone (NMP) (7 mL) was added drop by drop to a solution of 3-formyldeuteroporphyrin dimethyl ester (**1**, 70 mg, 0.123 mmol) and triphenylphosphine (746 mg, 2.84 mmol) in NMP (10 mL) at 150 °C. After the mixture was stirred at this temperature for 50 min, it was poured into ice-water, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was separated by column chromatography (SiO_2, CH_2Cl_2-Et_2O, 100:0 to 95:5), and recrystallized from CH_2Cl_2-hexane to give **3** (44 mg, 59%). **3**: Dark violet crystals. mp 192-193 °C. MS *m/z* 600 (M^+). HRMS Calcd $C_{34}H_{34}N_4O_4F_2$ (M^+): 600.255. Found: 600.255. ^{1}H-NMR ($CDCl_3$) δ: 9.78 (2H, s), 9.70 (1H, s), 9.60 (1H, s), 8.90 (1H, s), 6.36 (1H, d, J_{HF} = 26 Hz), 4.25 (4H, t, J = 7.5 Hz), 3.65 (3H, s), 3.62 (3H, s), 3.56 (3H, s), 3.47 (3H, s), 3.45 (3H, s), 3.36 (3H, s), 3.19 (4H, t, J = 7.9 Hz), – 4.69 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 82.27 (1F, dd, J_{FH} = 27, J_{FF} = 27 Hz), – 83.13 (1F, d, J_{FF} = 24 Hz).

8-(2,2-Difluorovinyl)deuteroporphyrin dimethyl ester (4)

8-Formyldeuteroporphyrin dimethyl ester (**2**, 100 mg, 0.176 mmol) in NMP (14 mL) was treated with PPh_3 (1.07 g, 4.08 mmol) and $ClCF_2COONa$ (641 mg, 4.20 mmol) in NMP (10 mL) as in the case of **3**, and worked up similarly to give **4** (62 mg, 59%). **4**: Dark violet crystals. mp 192-193 °C (CH_2Cl_2-hexane). MS *m/z* 600 (M^+). HRMS Calcd $C_{34}H_{34}N_4O_4F_2$ (M^+): 600.255. Found: 600.255. ^{1}H-NMR ($CDCl_3$) δ: 10.05 (1H, s), 10.03 (1H, s), 10.01 (1H, s), 9.89 (1H, s), 9.09 (1H, s), 6.18 (1H, d, J_{HF} = 26 Hz), 4.42 (2H, t, J = 7.6 Hz), 4.36 (2H, t, J = 7.6 Hz), 3.73 (3H, s), 3.66 (3H, s), 3.65 (3H, s), 3.62 (3H, s), 3.58 (3H, s), 3.55 (3H, d, J = 2 Hz), 3.27 (2H, t, J = 7.6 Hz), 3.26 (2H, t, J = 7.6 Hz), – 3.89 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 82.13 (1F, dd, J_{FH} = 24, J_{FF} = 27 Hz), – 83.79 (1F, d, J_{FF} = 27 Hz).

3-(2,2-Difluorovinyl)-8-iododeuteroporphyrin dimethyl ester (5)

A mixture of **3** (20 mg, 0.03 mmol), I_2 (75 mg, 0.3 mmol) and K_2CO_3 (41 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 90 min. After 5% $Na_2S_2O_3$ was added to the mixture, it was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was separated by column chromatography (SiO_2, CH_2Cl_2-Et_2O, 100:0 to 95:5), and recrystallized from CH_2Cl_2-hexane to give **5** (24 mg, 99%). **5**: Dark violet crystals. mp 219-220 °C. MS *m/z* 726 (M^+). HRMS Calcd $C_{34}H_{33}N_4O_4F_2I$ (M^+): 726.152. Found: 726.152. ^{1}H-NMR ($CDCl_3$) δ: 9.82 (1H, s), 9.75 (1H,

s), 9.71 (1H, s), 9.25 (1H, s), 6.18 (1H, d, J_{HF} = 26 Hz), 4.31 (2H, t, J = 7.8 Hz), 4.25 (2H, t, J = 7.8 Hz), 3.67 (3H, s), 3.64 (3H, s), 3.57 (3H, s), 3.48 (3H, s), 3.41 (3H, s), 3.35 (3H, s), 3.20 (4H, t, J = 7.8 Hz), – 4.69 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 81.72 (1F, dd, J_{FH} = 24, J_{FF} = 24 Hz), – 83.13 (1F, d, J_{FF} = 24 Hz).

8-(2,2-Difluorovinyl)-3-iododeuteroporphyrin dimethyl ester (6)

4 (100 mg, 0.166 mmol) was treated with I_2 (376 mg, 2.96 mmol) and K_2CO_3 (206 mg, 1.49 mmol) in CH_2Cl_2 (25 mL) as in the case of **5**, and worked up similarly to give **6** (117 mg, 97%). **6**: Dark violet crystals. mp 215-217 °C (CH_2Cl_2-hexane). MS *m/z* 726 (M^+). HRMS Calcd $C_{34}H_{33}N_4O_4F_2I$ (M^+): 726.152. Found: 726.152. ^{1}H-NMR ($CDCl_3$) δ: 10.10 (1H, s), 9.98 (1H, s), 9.95 (1H, s), 9.85 (1H, s), 6.68 (1H, d, J_{HF} = 26 Hz), 4.41 (2H, t, J = 7.8 Hz), 4.33 (2H, t, J = 7.8 Hz), 3.67 (3H, s), 3.64 (3H, s), 3.62 (3H, s), 3.61 (3H, s), 3.55 (6H, s), 3.26 (2H, t, J = 7.8 Hz), 3.25 (2H, t, J = 7.8 Hz), – 4.00 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 81.71 (1F, dd, J_{FH} = 24, J_{FF} = 24 Hz), – 83.13 (1F, d, J_{FF} = 24 Hz).

3-(2,2-Difluorovinyl)-8-trifluorovinyldeuteroporphyrin dimethyl ester (7)

A solution of $(CF_2{=}CF)_2Zn$[4] in Et_2O (6 mL, 0.07 mmol) was added drop by drop to a solution of **5** (20 mg, 0.028 mmol) and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol) in CH_2Cl_2 (5 mL) at rt. After the mixture was stirred at this temperature for 40 h, it was treated with 10% HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was stirred in 5% H_2SO_4-MeOH at rt for 2 h, and poured into ice-water. The whole mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was separated by column chromatography (SiO_2, CH_2Cl_2-Et_2O, 100:0 to 95:5), and recrystallized from CH_2Cl_2-hexane to give **7** (8 mg, 42%). **7**: Reddish brown crystals. mp 176-177 °C. MS *m/z* 680 (M^+). HRMS Calcd $C_{36}H_{33}N_4O_4F_5$ (M^+): 680.243. Found: 680.241. ^{1}H-NMR ($CDCl_3$) δ: 10.06 (1H, s), 10.04 (1H, s), 9.96 (1H, s), 9.82 (1H, s), 6.64 (1H, d, J_{HF} = 24 Hz), 4.38 (2H, t, J = 7.8 Hz), 4.31 (2H, t, J = 7.8 Hz), 3.66 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.63 (3H, s), 3.61 (3H, s), 3.53 (3H, s), 3.25 (2H, t, J = 7.8 Hz), 3.23 (2H, t, J = 7.8 Hz), – 3.87 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 81.38 (1F, dd, J_{FH} = 24, J_{FF} = 24 Hz), – 82.68 (1F, d, J_{FF} = 24 Hz), – 99.83 (1F, dd, J = 68, 29 Hz), – 115.86 (1F, dd, J = 120, 68 Hz), – 156.59 (1F, dd, J = 120, 29 Hz).

8-(2,2-Difluorovinyl)-3-trifluorovinyldeuteroporphyrin dimethyl ester (8)

A solution of **6** (50 mg, 0.07 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.013 mol) in CH_2Cl_2 (12.5 mL) was treated with a solution of $(CF_2{=}CF)_2Zn$ in Et_2O (15 mL, 0.18 mmol) as in the case of **7**, and worked up similarly to give **8** (27 mg, 56%). **8**: Dark violet crystals. mp 182-184 °C (CH_2Cl_2-hexane). MS *m/z* 680 (M^+). HRMS Calcd $C_{36}H_{33}N_4O_4F_5$ (M^+): 680.243. Found: 680.242. ^{1}H-NMR ($CDCl_3$) δ: 10.01 (1H, s), 9.90 (1H, s), 9.87 (1H, s), 9.81 (1H, s), 6.53 (1H, d, J_{HF} = 24 Hz), 4.38 (2H, t, J = 7.8 Hz), 4.28 (2H, t, J = 7.8 Hz), 3.66 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.63 (3H, s), 3.52 (3H, s), 3.51 (3H, s), 3.25 (2H, t, J = 7.8

3.22 (2H, t, J = 7.8 Hz), – 4.04 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 81.43 (1F, dd, J_{FH} = 24, J_{FF} = 24 Hz), – 82.68 (1F, d, J_{FF} = 24 Hz), – 99.64 (1F, dd, J = 71, 29 Hz), – 115.87 (1F, dd, J = 117, 71 Hz), – 156.56 (1F, dd, J = 117, 29 Hz).

8-(1-Chloro-2,2-difluorovinyl)-3-(2,2-difluorovinyl)deuteroporphyrin dimethyl ester (9)

A solution of $(CF_2{=}CCl)_2Zn$[4] in Et_2O (12 mL, 0.14 mmol) was added drop by drop to a solution of **5** (100 mg, 0.138 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.017 mol) in CH_2Cl_2 (15 mL) at rt. After the mixture was stirred at this temperature for 40 h, it was worked up as in the case of **7** to give **9** (65 mg, 68%). **9**: Reddish brown crystals. mp 178-179 °C (CH_2Cl_2-hexane). MS *m/z* 696 (M^+). HRMS Calcd $C_{36}H_{33}N_4O_4ClF_4$ (M^+): 696.212. Found: 696.212. ^{1}H-NMR ($CDCl_3$) δ: 10.09 (1H, s), 9.97 (1H, s), 9.92 (1H, s), 9.89 (1H, s), 6.56 (1H, d, J_{HF} = 25.2 Hz), 4.40 (2H, t, J = 7.8 Hz), 4.30 (2H, t, J = 7.8 Hz), 3.66 (3H, s), 3.65 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.53 (6H, s), 3.27 (2H, t, J = 7.8 Hz), 3.24 (2H, t, J = 7.8 Hz), – 3.82 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 81.43 (1F, dd, J_{FH} = 24, J_{FF} = 24 Hz), -82.78 (1F, d, J_{FF} = 24 Hz), – 83.80 (1F, d, J = 29 Hz), – 86.75 (1F, d, J = 29 Hz).

3-(1-Chloro-2,2-difluorovinyl)-8-(2,2-difluorovinyl)deuteroporphyrin dimethyl ester (10)

A solution of **6** (100 mg, 0.138 mmol) and $Pd(PPh_3)_4$ (20 mg, 12 mol %) in CH_2Cl_2 (15 mL) was treated with a solution of $(CF_2{=}CCl)_2Zn$ in Et_2O (12 mL, 0.28 mmol) as in the case of **9**, and worked up as in the case of **7** to give **10** (65 mg, 68%). **10**: Reddish brown crystals. mp 199-201 °C (CH_2Cl_2-hexane). MS *m/z* 696 (M^+). HRMS Calcd $C_{36}H_{33}N_4O_4ClF_4$ (M^+): 696.212. Found: 696.212. ^{1}H-NMR ($CDCl_3$) δ: 10.12 (1H, s), 10.04 (1H, s), 9.93 (1H, s), 9.80 (1H, s), 6.63 (1H, d, J_{HF} = 26 Hz), 4.35 (2H, t, J = 7.8 Hz), 4.29 (2H, t, J = 7.8 Hz), 3.66 (3H, s), 3.65 (6H, s), 3.63 (3H, s), 3.58 (3H, s), 3.51 (3H, s), 3.24 (2H, t, J = 7.8 Hz), 3.22 (2H, t, J = 7.8 Hz), – 3.80 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: – 81.43 (1F, dd, J_{FH} = 24, J_{FF} = 24 Hz), – 82.79 (1F, d, J_{FF} = 24 Hz), – 83.35 (1F, d, J = 29 Hz), – 86.35 (1F, d, J = 29 Hz).

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