

**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).

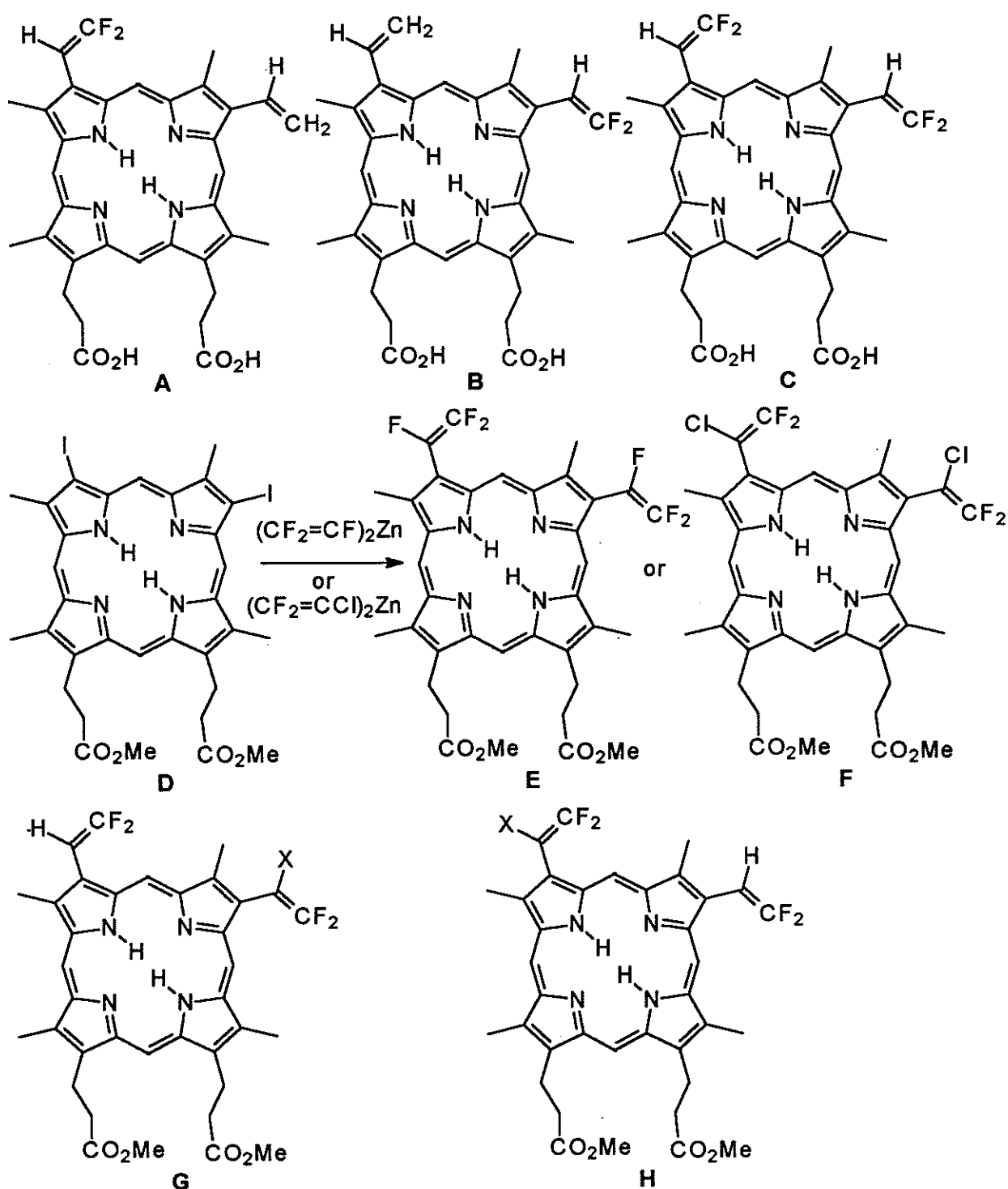
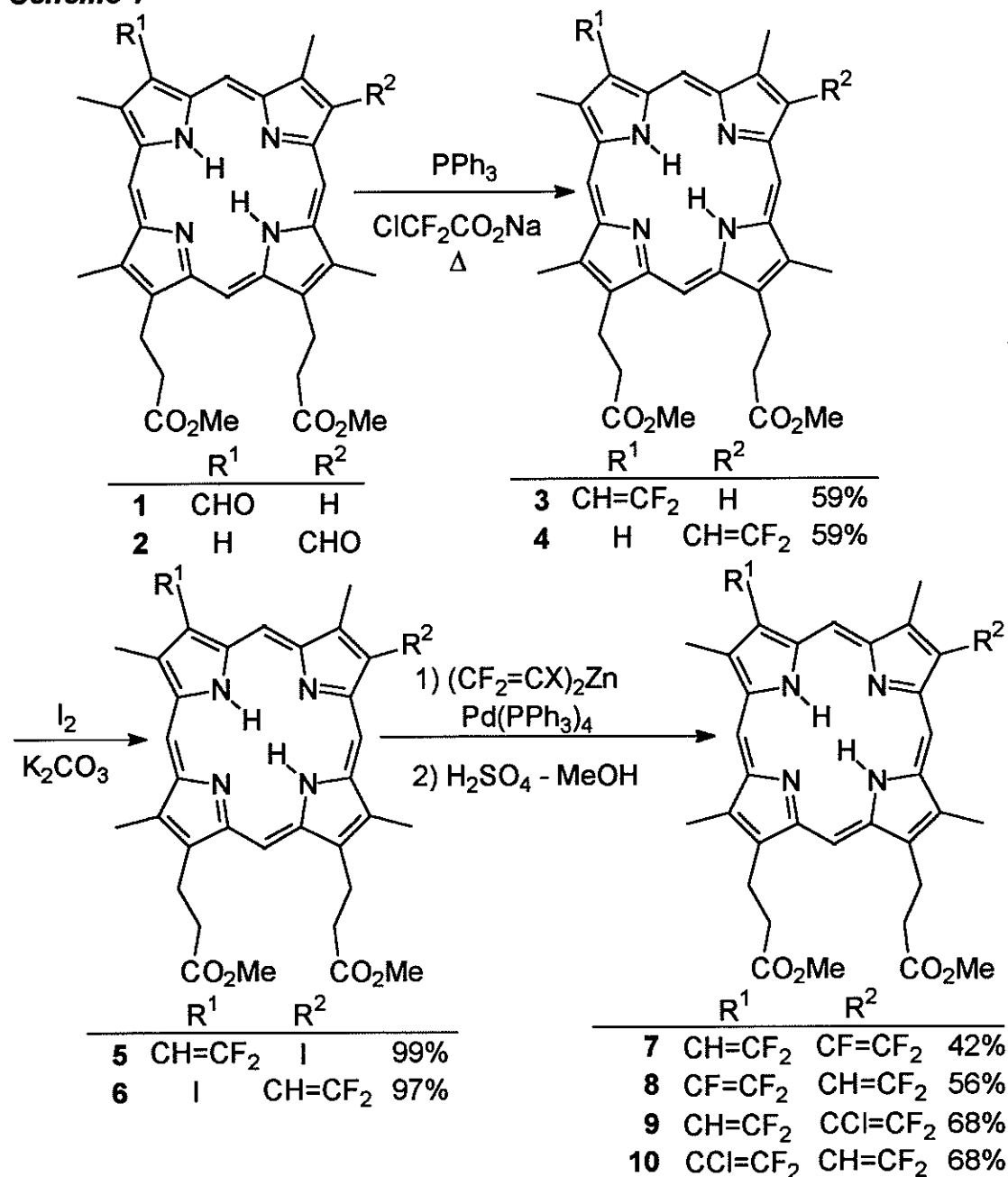


Figure 1 Fluorovinyl Analogs of Protoporphyrin

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



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 trifluorovinyl lithium, 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)trifluorovinyldeuterioporphyrin 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)trifluorovinyldeuterioporphyrin dimethyl esters (**9**) and (**10**), respectively.

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

EXPERIMENTAL

General Procedures. $^1\text{H-NMR}$ 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 $\text{ClCF}_2\text{COONa}$ (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 $\text{C}_{34}\text{H}_{34}\text{N}_4\text{O}_4\text{F}_2$ (M^+): 600.255. Found: 600.255. $^1\text{H-NMR}$ (CDCl_3) δ : 9.78 (2H, s), 9.70 (1H, s), 9.60 (1H, s), 8.90 (1H, s), 6.36 (1H, d, $J_{\text{HF}} = 26$ 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). $^{19}\text{F-NMR}$ (CDCl_3) ppm: -82.27 (1F, dd, $J_{\text{FH}} = 27$, $J_{\text{FF}} = 27$ Hz), -83.13 (1F, d, $J_{\text{FF}} = 24$ 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 $\text{ClCF}_2\text{COONa}$ (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 $\text{C}_{34}\text{H}_{34}\text{N}_4\text{O}_4\text{F}_2$ (M^+): 600.255. Found: 600.255. $^1\text{H-NMR}$ (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, $J_{\text{HF}} = 26$ 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). $^{19}\text{F-NMR}$ (CDCl_3) ppm: -82.13 (1F, dd, $J_{\text{FH}} = 24$, $J_{\text{FF}} = 27$ Hz), -83.79 (1F, d, $J_{\text{FF}} = 27$ 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% $\text{Na}_2\text{S}_2\text{O}_3$ 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 $\text{C}_{34}\text{H}_{33}\text{N}_4\text{O}_4\text{F}_2\text{I}$ (M^+): 726.152. Found: 726.152. $^1\text{H-NMR}$ (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 $\text{C}_{34}\text{H}_{33}\text{N}_4\text{O}_4\text{F}_2\text{I}$ (M^+): 726.152. Found: 726.152. ^1H -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 $(\text{CF}_2=\text{CF})_2\text{Zn}^4$ in Et_2O (6 mL, 0.07 mmol) was added drop by drop to a solution of 5 (20 mg, 0.028 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (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 $\text{C}_{36}\text{H}_{33}\text{N}_4\text{O}_4\text{F}_5$ (M^+): 680.243. Found: 680.241. ^1H -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 $\text{Pd}(\text{PPh}_3)_4$ (15 mg, 0.013 mol) in CH_2Cl_2 (12.5 mL) was treated with a solution of $(\text{CF}_2=\text{CF})_2\text{Zn}$ 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 $\text{C}_{36}\text{H}_{33}\text{N}_4\text{O}_4\text{F}_5$ (M^+): 680.243. Found: 680.242. ^1H -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, $J_{\text{FH}} = 24$, $J_{\text{FF}} = 24$ Hz), -82.68 (1F, d, $J_{\text{FF}} = 24$ 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 $(\text{CF}_2=\text{CCl})_2\text{Zn}^4$ in Et_2O (12 mL, 0.14 mmol) was added drop by drop to a solution of **5** (100 mg, 0.138 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (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 $\text{C}_{36}\text{H}_{33}\text{N}_4\text{O}_4\text{ClF}_4$ (M^+): 696.212. Found: 696.212. ^1H -NMR (CDCl_3) δ : 10.09 (1H, s), 9.97 (1H, s), 9.92 (1H, s), 9.89 (1H, s), 6.56 (1H, d, $J_{\text{HF}} = 25.2$ 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, $J_{\text{FH}} = 24$, $J_{\text{FF}} = 24$ Hz), -82.78 (1F, d, $J_{\text{FF}} = 24$ 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 $\text{Pd}(\text{PPh}_3)_4$ (20 mg, 12 mol %) in CH_2Cl_2 (15 mL) was treated with a solution of $(\text{CF}_2=\text{CCl})_2\text{Zn}$ 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 $\text{C}_{36}\text{H}_{33}\text{N}_4\text{O}_4\text{ClF}_4$ (M^+): 696.212. Found: 696.212. ^1H -NMR (CDCl_3) δ : 10.12 (1H, s), 10.04 (1H, s), 9.93 (1H, s), 9.80 (1H, s), 6.63 (1H, d, $J_{\text{HF}} = 26$ 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, $J_{\text{FH}} = 24$, $J_{\text{FF}} = 24$ Hz), -82.79 (1F, d, $J_{\text{FF}} = 24$ Hz), -83.35 (1F, d, $J = 29$ Hz), -86.35 (1F, d, $J = 29$ Hz).

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Received, 12th April, 1999