Synthesis of Fluorine Analogs of Protoporphyrin Potentially Useful for Diagnosis and Therapy of Cancer. IV.[1] Synthesis of (Trifluorovinyl)vinyl- and (1-Chloro-2,2-difluorovinyl)vinyldeuteroporphyrins

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Trifluoro or chlorodifluoro analogs of protoporphyrin, the compounds in the title, were synthesized for use in the diagnosis and therapy of cancer. 3- Or 8-acetyldeuteroporphyrin dimethyl esters (2 and 3) were iodinated with iodine in the presence of potassium carbonate to the corresponding iodo compounds (5 and 6). The iodo compounds (5 and 6) were treated with bis(trifluorovinyl)zinc in the presence of tetrakis(triphenylphosphine)-palladium to give trifluorovinyl derivatives (7 and 8) in good yields. Reduction of the acetyl group of 7 and 8 with sodium borohydride afforded the corresponding hydroxyethyl derivatives (9 and 10). Compounds (9 and 10) were dehydrated with methanesulfonyl chloride and triethylamine to give (trifluorovinyl)vinyldeuteroporphyrin dimethyl esters (11 and 12). Treatment of 5 and 6 with bis(1-chloro-2,2-difluorovinyl)zinc in the presence of tetrakis(triphenylphosphine)palladium, followed by similar reactions as above gave (1-chloro-2,2-difluorovinyl)-vinyldeuteroporphyrin dimethyl esters (17 and 18).

Key words fluorine; protoporphyrin analog; trifluorovinyl; chlorodifluorovinyl; zinc reagent; diagnosis and therapy of cancer

In the course of our attempt to prepare fluorine analogs of porphyrins potentially useful for the diagnosis and therapy of cancer,[2] we have paid attention to the peculiar structure of protoporphyrin, which is one of the most important porphyrins in biology and has two vinyl groups. These vinyl groups are very reactive and suffer from addition quite easily. Thus, we planned to modify the vinyl groups. First, we have synthesized 3-(2,2-difluorovinyl)-8-vinyl- (A), 8-(2,2-difluorovinyl)-3-vinyldeuteroporphyrin (B) and 3,8-bis(2,2-difluorovinyl)deuteroporphyrin (C). Compound B was taken up by human stomach cancer, and C by rat liver cancer, selectively.[3] These results suggest that the vinyl groups play an important role in biological fields. As an extension of this research, bis(trifluorovinyl) and bis(1-chloro-2,2-difluorovinyl) analogs of protoporphyrin (E and F) 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] Further, we synthesized 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 the 3- or 8-position of the porphyrin ring[5] (see Fig. 1).

Now, we would like to report the short synthesis of additional fluorine analogs of protoporphyrin, which have a trifluorovinyl or chlorodifluorovinyl group and a vinyl group.

To introduce the trifluorovinyl or chlorodifluorovinyl groups, we used our new reagents,[4] bis(trifluorovinyl)zinc or bis(1-chloro-2,2-difluorovinyl)zinc, and for construction of the vinyl group, we introduced an acetyl group to deuteroporphyrin. The acetyl group was reduced and dehydrated to a vinyl group.

Thus, deuteroporphyrin dimethyl ester was converted to a copper complex (**1**),[6] which was treated with acetyl chloride and zinc chloride, followed by demetallation with sulfuric acid and trifluoroacetic acid,[7] to give 3- (**2**), 8-acetyl- (**3**) and 3,8-diacetyldeuteroporphyrin dimethyl ester (**4**). Iodination[8] of **2** and **3** was more difficult than the other porphyrin derivatives, probably due to the electronic effect of the acetyl group, and proceeded only under reflux in methylene chloride. The iodo compounds (**5** and **6**) were treated with bis(trifluorovinyl)zinc[4] in the presence of tetrakis(triphenylphosphine)palladium to give the corresponding trifluorovinyl derivatives (**7** and **8**) in 70 and 70% yields, respectively. This result showed that the fluorovinylzinc reagent could be used in the presence of a carbonyl group. The acetyl groups of **7** or **8** were reduced with sodium borohydride to hydroxyethyl groups. The products (**9** and **10**) were treated with methanesulfonyl chloride in the presence of triethylamine to give (trifluorovinyl)vinyldeuteroporphyrin dimethyl esters (**11** and **12**) in 66 and 51% yields from **7** and **8**, respectively. All the transformations are shown in Chart 1.

Similar reactions of **5** and **6** with bis(1-chloro-2,2-difluorovinyl)zinc[4] in the presence of tetrakis(triphenylphosphine)palladium, as in the case of **7** and **8**, gave the corresponding 1-chloro-2,2-difluorovinyl compounds (**13** and **14**) in 59 and 78% yields, respectively. Reduction of the acetyl group on **13** and **14**, followed by dehydration as in the case of **11** and **12**, afforded (1-chloro-2,2-difluorovinyl)vinyl-deuteroporphyrin dimethyl esters (**17** and **18**) in overall yields of 66 and 53%, respectively (see Chart 2) .

In conclusion, using our new fluorovinyl zinc reagents, we were able to obtain four new fluorine analogs of protoporphyrin, which have either a trifluorovinyl or chlorodifluorovinyl group in the place of a vinyl group and are expected to work in the diagnosis and therapy of cancer. Biological behaviors are now under investigation and will be reported elsewhere.

Experimental

General Procedures ^{1}H-NMR were recorded on a JEOL-FX90Q and JNM-GX400 spectrometer. Tetramethylsilane was used as an internal standard. ^{19}F-NMR were recorded on Hitachi FT-NMR R-1500 and JEOL-FX90Q spectrometers. Trichlorofluoromethane was used as an internal standard. Mass spectra were obtained by JEOL JMS-DX-300. The melting points were measured on a Yanagimoto melting point apparatus, MP-S3, and

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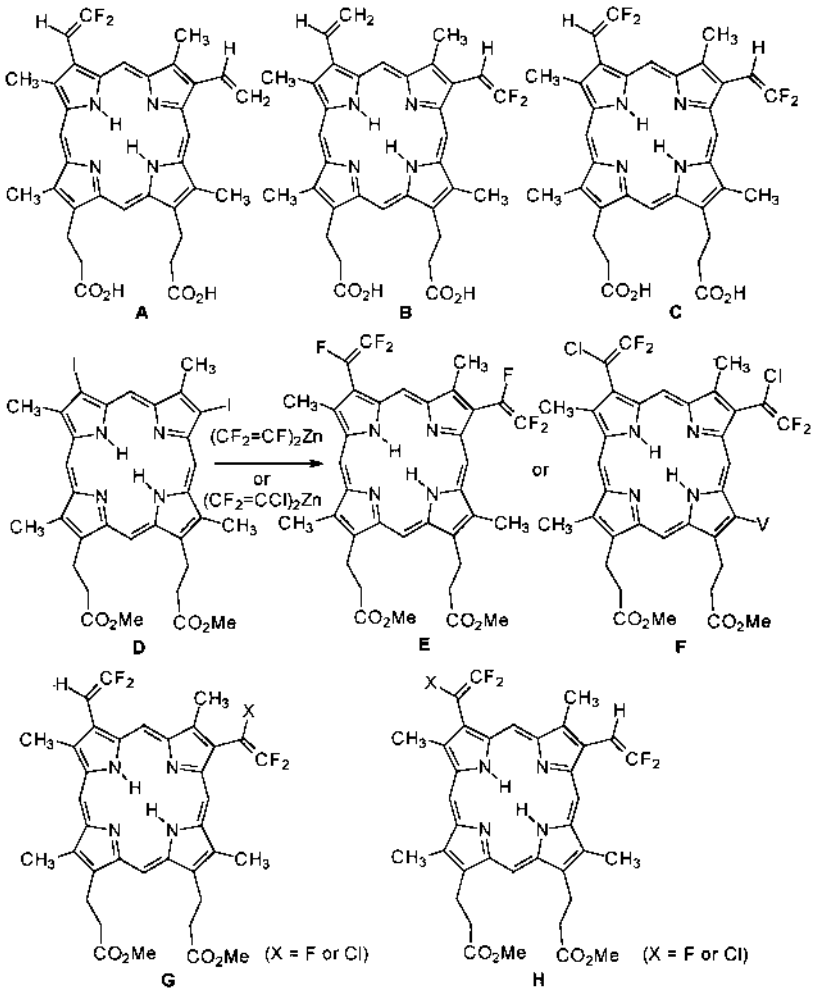

Fig. 1. Fluorovinyl Analogs of Protoporphyrin

are uncorrected. The purity of all the new compounds was confirmed by TLC, and analyzed by high resolution MS (HRMS).

Acetyldeuteroporphyrin Dimethyl Esters (2, 3 and 4) In an atmosphere of Ar, CH_3COCl (0.85 ml, 11.9 mmol) was added dropwise to a solution of deuteroporphyrin dimethyl ester copper complex (**1**, 470 mg, 0.78 mmol) and $ZnCl_2$ (1.79 g, 13.2 mmol) in CH_2Cl_2 (75 ml) under ice cooling, and the mixture was refluxed for 2 h. After the mixture was cooled, 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 under a vacuum. The residue was stirred in a mixture of trifluoroacetic acid and sulfuric acid (10 : 1) for 2 h. This mixture was poured into ice water, then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under a vacuum. The residue was separated by column chromatography (SiO_2, CH_2Cl_2–Et_2O, 100 : 0 to 95 : 5), and each fraction was recrystallized from CH_2Cl_2–hexane to give **2** (125 mg, 27%), **3** (77 mg, 17%) and **4** (123 mg, 25%).[7]

3-Acetyl-8-iododeuteroporphyrin Dimethyl Ester (5) A mixture of **2** (415 mg, 0.718 mmol), I_2 (1.81 g, 7.18 mmol) and K_2CO_3 (1.35 g, 9.77 mmol) in CH_2Cl_2 (50 ml) was refluxed for 1 h.[8] After the mixture was cooled, it was treated with 5% $Na_2S_2O_3$, then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under a vacuum. 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** (490 mg, 97%). **5**: Dark violet crystals. mp 263—264 °C. MS *m/z*: 706 (M^+). HRMS *m/z*: Calcd for $C_{34}H_{35}IN_4O_5$: 706.165 (M^+). Found: 706.166. ^{1}H-NMR ($CDCl_3$) δ: 10.48 (1H, s), 9.81 (1H, s), 9.79 (1H, s), 9.74 (1H, s), 4.30 (2H, t, J=7.8 Hz), 4.28 (2H, t, J=7.8 Hz), 3.77 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.56 (3H, s), 3.55 (3H, s), 3.49 (3H, s), 3.26 (3H, s), 3.20 (2H, t, J=7.8 Hz), 3.19 (2H, t, J=7.8 Hz), −4.23 (2H, br s).

8-Acetyl-3-iododeuteroporphyrin Dimethyl Ester (6) A mixture of **3** (140 mg, 0.242 mmol), I_2 (571 mg, 2.3 mmol) and K_2CO_3 (429 mg, 3.2 mmol) in CH_2Cl_2 (30 ml) was refluxed for 1 h, then it was worked up as in the case of **5** to give **6** (169 mg, 99%). **6**: Dark violet crystals. mp 199—201 °C (CH_2Cl_2–hexane). MS *m/z*: 706 (M^+). HRMS *m/z*: Calcd for $C_{34}H_{35}IN_4O_5$: 706.165 (M^+). Found: 706.164. ^{1}H-NMR ($CDCl_3$) δ: 10.34 (1H, s), 9.53 (1H, s), 9.41 (1H, s), 9.27 (1H, s), 4.24 (2H, t, J=7.8 Hz), 4.21 (2H, t, J=7.8 Hz), 3.65 (3H, s), 3.63 (3H, s), 3.56 (3H, s), 3.50 (3H, s), 3.35 (6H, s), 3.21 (3H, s), 3.16 (2H, t, J=7.8 Hz), 3.13 (2H, t, J=7.8 Hz), −4.96 (2H, br s).

3-Acetyl-8-(trifluorovinyl)deuteroporphyrin Dimethyl Ester (7) Under atmosphere of Ar, a solution of $(CF_2=CF)_2Zn$ in Et_2O (6.8 ml, 1.4 mmol) was added slowly to a solution of **5** (100 mg, 0.14 mmol) and $Pd(PPh_3)_4$ (33 mg, 20 mol%) in CH_2Cl_2 (10 ml) at room temperature. After the whole mixture was stirred for 18 h at room temperature, it was treated with 10% HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, then concentrated under a vacuum. The residue was stirred in 5% H_2SO_4–MeOH (15 ml) for 1 h. This mixture was poured into ice water, then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under a vacuum. The residue was separated by column chromatography (SiO_2, CH_2Cl_2–Et_2O, 97 : 3 to 90 : 10) and recrystallized from CH_2Cl_2–hexane to give **7** (65 mg, 69%). **7**: Dark violet crystals. mp 167—169 °C. MS *m/z*: 660 (M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}F_3N_4O_5$: 660.256 (M^+). Found: 660.256. ^{1}H-NMR ($CDCl_3$) δ: 10.79 (1H, s), 9.96 (1H, s), 9.94 (1H, s), 9.89 (1H, s), 4.34 (2H, t, J=8.3 Hz), 4.32 (2H, t, J=8.3 Hz), 3.84 (3H, s), 3.68 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.58 (3H, s), 3.54 (3H, s), 3.31 (3H, s), 3.25 (2H, t, J=12.2 Hz), 3.23 (2H, t, J=12.2 Hz), −3.64 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −92.77 (1F, dd, J=24, 73 Hz), −108.68 (1F, dd, J=73, 117 Hz), 148.05 (1F, dd, J=24, 117 Hz).

8-Acetyl-3-(trifluorovinyl)deuteroporphyrin Dimethyl Ester (8) In an atmosphere of Ar, a solution of $(CF_2=CF)_2Zn$ in Et_2O (4 ml, 0.15 mmol) was added to a solution of **6** (20 mg, 0.028 mmol) and $Pd(PPh_3)_4$ (6 mg, 20

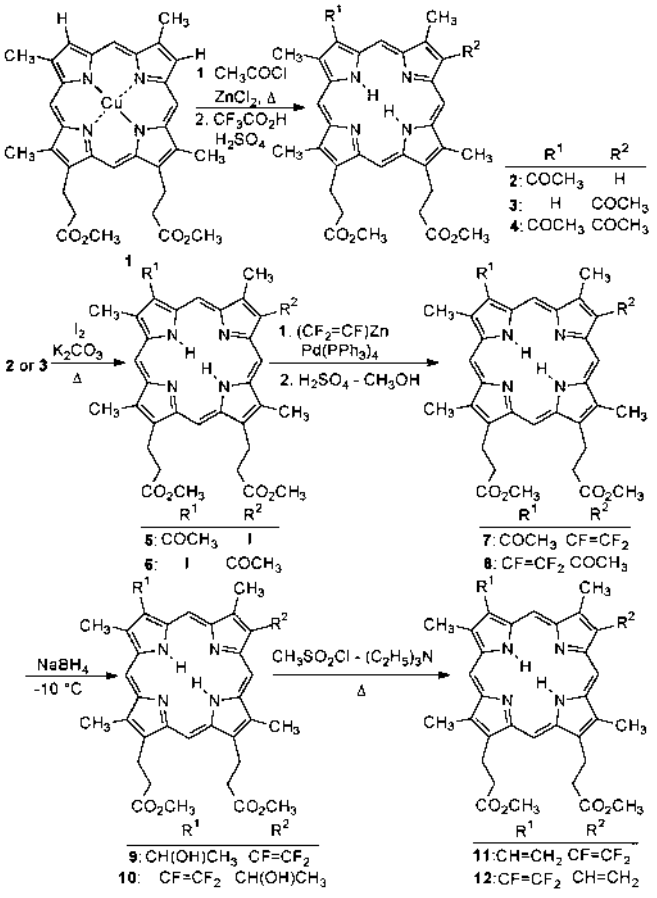

Chart 1

mol%) in CH_2Cl_2 (5 ml) at room temperature. After the whole mixture was stirred at room temperature for 17.5 h, it was worked up as in the case of **7** to give **8** (13 mg, 70%). **8**: Dark violet crystals. mp 197—199 °C (CH_2Cl_2–hexane). MS *m/z*: 660 (M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}F_3N_4O_5$: 660.256 (M^+). Found: 660.256. ^{1}H-NMR ($CDCl_3$) δ: 10.69 (1H, s), 10.14 (1H, s), 9.99 (1H, s), 9.92 (1H, s), 4.34 (2H, t, J=7.3 Hz), 4.33 (2H, t, J=7.3 Hz), 3.92 (3H, s), 3.66 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.58 (3H, s), 3.54 (3H, s), 3.35 (3H, s), 3.25 (2H, t, J=7.3 Hz), 3.23 (2H, t, J=7.3 Hz), −3.58 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −93.04 (1F, dd, J=24, 68 Hz), −108.60 (1F, dd, J=68, 117 Hz), −147.80 (1F, dd, J=24, 117 Hz).

8-(Trifluorovinyl)-3-vinyldeuteroporphyrin Dimethyl Ester (11) To a solution of **7** (65 mg, 0.10 mmol) in CH_2Cl_2–MeOH (13 ml, 3 ml), $NaBH_4$ (90 mg, 2.3 mmol) was added under ice cooling. After the mixture was stirred for another 2 h, it was treated with 10% HCl, then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under a vacuum. After Et_3N (200 μl) was added to a solution of the residue (unpurified **9**) in tetrahydrofuran (THF) (6 ml), MsCl (180 μl) was added to the mixture under ice cooling. After the whole mixture was refluxed for 1 h, it was poured into ice water, then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under a vacuum. The residue was separated by column chromatography (SiO_2, CH_2Cl_2–Et_2O, 97 : 3 to 95 : 5) and recrystallized from CH_2Cl_2–hexane to give **11** (42 mg, 66%). **11**: Reddish violet crystals. mp 102—104 °C. MS *m/z*: 644 (M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}F_3N_4O_4$: 644.265 (M^+). Found: 644.261. ^{1}H-NMR ($CDCl_3$) δ: 10.13 (1H, s), 10.02 (1H, s), 9.94 (1H, s), 9.92 (1H, s), 8.19 (1H, dd, J=11.2, 17.8 Hz), 6.37 (1H, dd, J=1.5, 17.5 Hz), 6.21 (1H, dd, J=1.5, 11.7 Hz), 4.42 (2H, t, J=7.3 Hz), 4.29 (2H, t, J=7.3 Hz), 3.66 (3H, s), 3.658 (3H, s), 3.652 (3H, s), 3.64 (3H, s), 3.62 (3H, s), 3.51 (3H, s), 3.27 (2H, t, J=7.3 Hz), 3.23 (2H, t, J=7.3 Hz), −3.91 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −93.91 (1F, dd, J=29, 73 Hz), −109.29 (1F, dd, J=73, 117 Hz), −146.90 (1F, dd, J=29, 117 Hz).

3-(Trifluorovinyl)-8-vinyldeuteroporphyrin Dimethyl Ester (12) To a solution of **8** (42 mg, 0.064 mmol) in CH_2Cl_2–MeOH (8 ml, 1.9 ml), $NaBH_4$ (90 mg, 2.3 mmol) was added at −10 °C. After the mixture was stirred for 2 h, it was worked up as in the case of **9**. In an atmosphere of Ar, MsCl

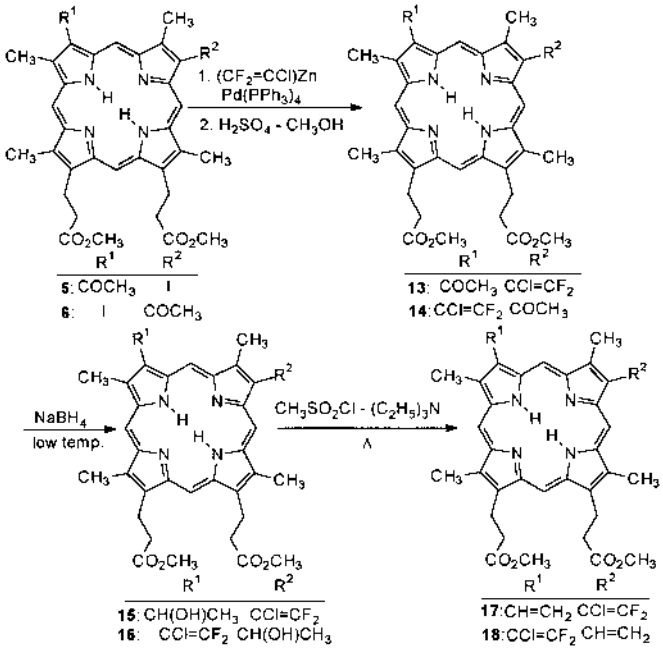

Chart 2

(90 μl) was added to a solution of the residue (unpurified **10**) and Et_3N (100 μl) in THF (3 ml) under ice cooling. The mixture was refluxed for 1 h, then worked up as in the case of **11** to give **12** (21 mg, 51%). **12**: Reddish brown crystals. mp 105—106 °C (CH_2Cl_2–hexane). MS *m/z*: 644 (M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}F_3N_4O_4$: 644.261 (M^+). Found: 644.260. ^{1}H-NMR ($CDCl_3$) δ: 10.02 (1H, s), 9.96 (1H, s), 9.94 (1H, s), 9.82 (1H, s), 8.19 (1H, dd, J=11.5, 17.7 Hz), 6.38 (1H, dd, J=1.5, 17.9 Hz), 6.20 (1H, dd, J=1.5, 11.5 Hz), 4.34 (2H, t, J=7.8 Hz), 4.24 (2H, t, J=7.8 Hz), 3.70 (3H, s), 3.65 (3H, s), 3.63 (3H, s), 3.56 (3H, s), 3.52 (3H, s), 3.47 (3H, s), 3.21 (2H, t, J=7.8 Hz), 3.19 (2H, t, J=7.8 Hz), −4.07 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −93.18 (1F, dd, J=29, 68 Hz), −108.76 (1F, dd, J=68, 117 Hz), −147.83 (1F, dd, J=29, 117 Hz).

3-Acetyl-8-(1-chloro-2,2-difluorovinyl)deuteroporphyrin Dimethyl Ester (13) In an atmosphere of Ar, a solution of $(CF_2{=}CCl)_2Zn$ in Et_2O (2.5 ml, 0.39 mmol) was added to a solution of **5** (55 mg, 0.078 mmol) and $Pd(PPh_3)_4$ (18 mg, 20 mol%) in CH_2Cl_2 (7 ml) at room temperature. After the mixture was stirred at room temperature for another 17 h, it was worked up as in the case of **7** to give **13** (31 mg, 59%). **13**: Dark violet crystals. mp 165—166 °C (CH_2Cl_2–hexane). MS *m/z*: 676 (M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}ClF_2N_4O_5$: 676.225 (M^+). Found: 676.225. ^{1}H-NMR ($CDCl_3$) δ: 10.85 (1H, s), 10.07 (1H, s), 10.02 (1H, s), 9.97 (1H, s), 4.36 (4H, t, J=7.3 Hz), 3.86 (3H, s), 3.70 (3H, s), 3.66 (3H, s), 3.65 (3H, s), 3.60 (3H, s), 3.59 (3H, s), 3.33 (3H, s), 3.26 (4H, t, J=7.3 Hz), −3.45 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −83.69 (1F, d, J=29 Hz), −86.87 (1F, d, J=29 Hz).

8-Acetyl-3-(1-chloro-2,2-difluorovinyl)deuteroporphyrin Dimethyl Ester (14) In an atmosphere of Ar, a solution of $(CF_2{=}CCl)_2Zn$ in Et_2O (3 ml, 0.93 mmol) was added slowly to a solution of **6** (20 mg, 0.0283 mmol) and $Pd(PPh_3)_4$ (7 mg, 19 mol%) in CH_2Cl_2 (5 ml) at room temperature. After the mixture was stirred at room temperature, it was worked up as in the case of **7** to give **14** (15 mg, 78%). **14**: Dark violet crystals. mp 220—222 °C (CH_2Cl_2–hexane). MS *m/z*: 676 (M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}ClF_2N_4O_5$: 676.225 (M^+). Found: 676.225. ^{1}H-NMR ($CDCl_3$) δ: 10.63 (1H, s), 10.19 (1H, s), 9.94 (1H, s), 9.80 (1H, s), 4.28 (2H, t, J=7.3 Hz), 4.26 (2H, t, J=7.3 Hz), 3.92 (3H, s), 3.67 (3H, s), 3.64 (3H, s), 3.63 (3H, s), 3.54 (3H, s), 3.52 (3H, s), 3.32 (3H, s), 3.20 (2H, t, J=7.8 Hz), 3.19 (2H, t, J=7.8 Hz), −3.67 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −83.19 (1F, d, J=29 Hz), −86.35 (1F, d, J=29 Hz).

8-(1-Chloro-2,2-difluorovinyl)-3-vinyldeuteroporphyrin Dimethyl Ester (17) To a solution of **13** (31 mg, 0.046 mmol) in CH_2Cl_2–MeOH (6.0 ml, 1.4 ml), $NaBH_4$ (30 mg, 0.79 mmol) was added at −20 °C. After the mixture was stirred for 2 h, it was worked up as in the case of **9**. In an atmosphere of Ar, MsCl (66 μl) was added to a solution of the residue (unpurified **15**) and Et_3N (68 μl) in THF (3 ml) under ice cooling. After the mixture was refluxed for 1 h, it was worked up as in the case of **11** to **17** (20 mg, 66%). **17**: Dark violet crystals. mp 177—178 °C (CH_2Cl_2–hexane). MS *m/z*: 660

(M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}ClF_2N_4O_4$: 660.231 (M^+). Found: 660.230. ^{1}H-NMR ($CDCl_3$) δ: 10.22 (1H, s), 10.10 (1H, s), 10.02 (1H, s), 10.01 (1H, s), 8.25 (1H, dd, *J*=11.5, 17.8 Hz), 6.40 (1H, dd, *J*=1.3, 17.6 Hz), 6.22 (1H, dd, *J*=1.3, 11.2 Hz), 4.44 (2H, t, *J*=7.8 Hz), 4.32 (2H, t, *J*=7.8 Hz), 3.70 (3H, s), 3.68 (3H, s), 3.66 (3H, s), 3.65 (3H, s), 3.64 (3H, s), 3.55 (3H, s), 3.29 (2H, t, *J*=7.8 Hz), 3.26 (2H, t, *J*=7.8 Hz), −3.67 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −79.06 (1F, d, *J*=29 Hz), −81.79 (1F, d, *J*=29 Hz).

3-(1-Chloro-2,2-difluorovinyl)-8-vinyldeuteroporphyrin Dimethyl Ester (18) To a solution of **14** (25 mg, 0.037 mmol) in CH_2Cl_2–MeOH (5.4 ml, 1.2 ml), $NaBH_4$ (40 mg, 1.1 mmol) was added at −10 °C. After the mixture was stirred for 3 h, it was worked up as in the case of **9**. In an atmosphere of Ar, MsCl (80 μl) was added to a solution of the residue (unpurified **16**) and Et_3N (84 μl) in THF (3.0 ml) under ice cooling. After the mixture was refluxed for 1 h, it was worked up as in the case of **11** to give **18** (13 mg, 53%). **18**: Dark violet crystals. mp 183—184 °C (CH_2Cl_2–hexane). MS *m/z*: 660 (M^+). HRMS *m/z*: Calcd for $C_{36}H_{35}ClF_2N_4O_4$: 660.231 (M^+). Found: 660.232. ^{1}H-NMR ($CDCl_3$) δ: 10.13 (1H, s), 10.00 (2H, s), 9.86 (1H, s), 8.22 (1H, dd, *J*=12, 18 Hz), 6.39 (1H, dd, *J*=1.5, 18 Hz), 6.20 (1H, dd, *J*=1.5, 12 Hz), 4.34 (2H, t, *J*=7.6 Hz), 4.22 (2H, t, *J*=7.6 Hz), 3.74 (3H, s), 3.65 (6H, s), 3.62 (3H, s), 3.57 (3H, s), 3.47 (3H, s), 3.22 (2H, t, *J*=8.3 Hz), 3.20 (2H, t, *J*=8.3 Hz), −3.90 (2H, br s). ^{19}F-NMR ($CDCl_3$) ppm: −84.03 (1F, d, *J*=29 Hz), −86.94 (1F, d, *J*=29 Hz).

References and Notes

1) Part of this work was presented at the 119th Annual Meeting of the Pharmaceutical Society of Japan, Tokushima, March 1999. Part III. Shigeoka T., Kuwahara Y., Watanabe K., Sato K., Omote M., Ando A., Kumadaki I., accepted by *Heterocycles*.
2) Concerning our previous work, see a review: Ando A., Kumadaki I., *Heterocycles*, **42**, 885—899 (1996).
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8) For example, the iodination of mono(difluorovinyl)deuteroporphyrin dimethyl ester proceeded at room temperature. See ref. 4.