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PRELIMINARY NOTE

Synthesis of Fluorine Analogues of Protoporphyrin

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SUMMARY

With intention of obtaining a porphyrin derivative useful for diagnosis and therapy of cancer, fluorine analogues of protoporphyrin, in which the vinyl group(s) were replaced by difluorovinyl group(s), were synthesized by the reaction of the formylporphyrins with sodium chlorodifluoroacetate in the presence of triphenylphosphine

It is well known that some porphyrin derivatives are localized by a tumor tissue and now photoradiation therapy using appropriate instruments of laser ray attracts the interests of clinical side [1] Thus, the localized porphyrin sensitizes the excitation of oxygen with laser The excited oxygen is believed to destroy the tumor cells On the other hand, the excited porphyrin emits a red fluorescence and it can be used for the diagnosis of cancer For these purposes, 'Hematoporphyrin derivative' (HpD), which is obtained by treating hematoporphyrin by acidic condition, is widely investigated [2] It was found to be a mixture of more than five porphyrin derivatives The main component of HpD which local-

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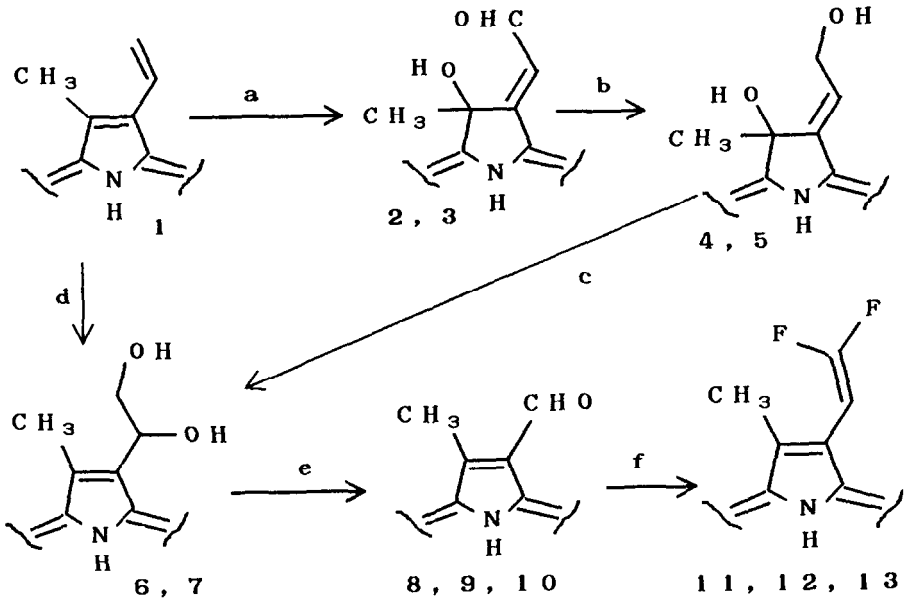
ızes ın tumor was reported to be a dımer of hematoporphyrın [3] However, the structure of thıs dımer was not fully ıdentifıed Thus, ıf a pure porphyrın derıvatıve, whıch ıs localızed by specıal tumor cells, ıs dıscovered, ıt wıll be very useful for the dıagnosıs and therapy of cancer We have already reported that methanol adducts of protoporphyrın, 3-(1-methoxy)ethyl-8-vınyldeuteroporphyrın, obtaıned by treatıng protoporphyrın wıth hydrogen chlorıde ın methanol [4] showed ınterestıng physıologıcal property, thıs compound showed a sımılar photodynamıc effect to JTC-16 cells on ırradıatıon of laser as HpD [5] On the other hand, the photo-ırradıatıon method ıs only useful when the lıght reaches to tumor tıssues Therefore, ıf other method could be used to determıne where a porphyrın ıs localızed, dıagnosıs usıng porphyrın derıvatıves would have a much more wıde applıcabılıty From thıs stand of vıew, new fluorıne derıvatıves of protoporphyrın were synthesızed Namely, ıf these compounds are localızed by a tumor tıssue, they wıll be followed not only by the laser ray but also by ^{19}F-NMR and help fındıng an early stage of cancer

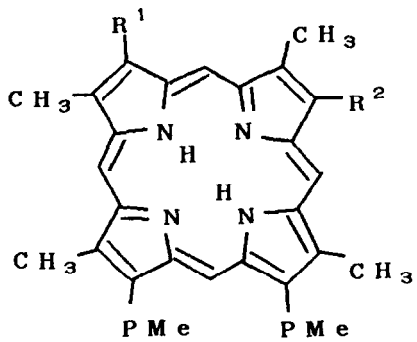
Our synthetıc procedure ıs shown ın Chart 1 Protoporphyrın (**1**) was photooxıdızed by whıte lıght ın the presence of oxygen to so-called photoporphyrıns, whıch was separated by column chromatography to compounds (2) and (3) These compounds were converted to 3-formyl-8-vınyl- (8) and 8-formyl-3-vınyl-deuteroporphyrın (9) by reductıon followed by rearrangement and glycol fıssıon accordıng to the lıterature [6] wıth some modıfıcatıons, sınce the yıelds of formyl compounds were much lower than reported Thus, reductıon of **2** and **3** wıth $NaBH_4$ was carrıed out at room temperature ınstead of heatıng on a steam bath, sınce formatıon of tarry substances was ınevıtable at a hıgher temperature Although the dıol compounds (**6** and 7), whıch were obtaıned after acıdıfıcatıon of the reactıon mıxture followed by extractıon wıth CH_2Cl_2, were reported to be too unstable to be purıfıed by a column chromatography, both compounds were ısolated on an SiO_2 column ın 82 and 81 % yıeld, respectıvely Compounds **6** and **7** are only slıghtly soluble ın benzene-CH_2Cl_2 Therefore, the ısolatıon yıelds of **8** and **9** by the oxıdatıon wıth $NaIO_4$-H_2SO_4 ın thıs

solvent (two-phase reaction) were much lower than reported The oxidation with HIO_4-$2H_2O$ in dioxane improved the isolation yields of **8** and **9** to 79 and 82 %, respectively The dialdehyde compound **10** was prepared by oxidation of protoporphyrin by OsO_4 followed by $NaIO_4$ [7]



a hν, O_2, in CH_2Cl_2 b $NaBH_4$, rt, 0 5 h c H^+, rt
d OsO_4, rt, 24 h e HIO_4 or $NaIO_4$, rt, 15 min - 2 h
f $CClF_2COONa$-Ph_3P, 160°C, 0 5 h

Chart 1



	R^1	R^2
8	-CHO	-CH=CH$_2$
9	-CH=CH$_2$	-CHO
10	-CHO	-CHO
11	-CH=CF$_2$	-CH=CH$_2$
12	-CH=CH$_2$	-CH=CF$_2$
13	-CH=CF$_2$	-CH=CF$_2$

PMe = $CH_2CH_2COOCH_3$

Fig 1

Physicochemical Data of 11, 12, and 13

11: Dark red crystals, mp 203.5-205.5°C.

Mass m/z: 626 (M^+).

High Resolution Mass Calcd. for $C_{36}H_{36}N_4O_4F_2$: 626.2703. Found: 626.2702.

IR (KBr) cm^{-1}: 3324 (N-H), 1738 (C=O), 1198, 1176 (C-F),

^{1}H-NMR (400MHz, $CDCl_3$): 9.99 (1H, s), 9.89 (1H, s), 9.87 (1H, s), 9.66 (1H, s), 8.18 (1H, d-d, J=17Hz, 11Hz), 6.47 (1H, d, J_{H-F}=25Hz), 6.33 (1H, d-d, J=17Hz, 1.4Hz), 6.17 (1H, d-d, J=11Hz, 1.4Hz), 4.45 (4H, m), 3.66 (3H, s), 3.65 (3H, s), 3.55 (6H, s), 3.52 (3H, s), 3.46 (3H, d, J=2.4Hz), 3.23 (4H, m), - 4.09 (2H, b).

^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): -82.14 (1F, d-d, J_{H-F}=25Hz, J_{F-F}=26Hz), -83.76 (1F, d, J=26Hz)

12: Dark red crystals, mp 204.0-205.5°C.

Mass m/z: 626 (M^+).

High Resolution Mass Calcd. for $C_{36}H_{36}N_4O_4F_2$: 626.2703. Found: 626.2702.

IR (KBr) cm^{-1}: 3324 (N-H), 1738 (C=O), 1194, 1170 (C-F),

^{1}H-NMR (400MHz, $CDCl_3$): 9.98 (1H, s), 9.87 (1H, s), 9.85 (1H, s), 9.63 (1H, s), 8.17 (1H, d-d, J=16Hz, 11Hz), 6.44 (1H, d, J_{H-F}=25Hz), 6.32 (1H, d, J=16Hz), 6.16 (1H, d, J=11Hz), 4.31 (4H, m), 3.66 (3H, s), 3.65 (3H, s), 3.55 (3H, s), 3.54 (3H, s), 3.51 (3H,s), 3.45 (3H, d, J=2.4Hz), 3.23 (4H, m), - 4.10 (2H, b).

^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$): -82.02 (1F, d-d, J_{H-F}=25Hz, J_{F-F}=26Hz), -83.64 (1F, d, J=26Hz)

13 Dark red crystals, mp 212-219 5°C

Mass m/z 662 (M^+)

High Resolution Mass Calcd for $C_{36}H_{34}N_4O_4F_4$ 662 2523 Found 662 2530

IR (KBr) cm^{-1} 3324 (N-H), 1736 (C=O), 1198, 1172 (C-F),

^{1}H-NMR (90MHz, $CDCl_3$) 9 92 (2H, s), 9 76 (2H, s), 6 65 (2H, d, J_{H-F}=26Hz), 4 33 (4H, d-d, J=7Hz, 7Hz), 3 66 (6H, s), 3 54 (6H, s), 3 48 (6H, s), 3 24 (4H, d-d, J=7Hz, 7Hz)

^{19}F-NMR ($CDCl_3$, ppm from $CFCl_3$) -81 86 (2F, d-d, J_{H-F}=26Hz, J_{F-F}=26Hz), -83 38 (2F, d, J=26Hz)

A solution of sodium chlorodifluoroacetate in N-methylpyrrolidone (NMP) was added to a solution of **8** and triphenylphosphine in NMP under argon atmosphere at 160°C and kept at this temperature for half an hour to give 3^2,3^2-difluoroprotoporphyrin dimethyl ester (**11**) in 55 % yield with recovery of **8** (26 %) ^{19}F-NMR of **11** showed presence of two kinds of vinyl fluorines at -82 14 and -83 76 ppm (internal standard $C\underline{F}Cl_3$) Similar reactions of **9** and **10** gave 8^2,8^2-difluoroprotoporphyrin dimethyl ester (**12**) and 3^2,3^2,8^2,8^2-tetrafluoroprotoporphyrin dimethyl ester (**13**) in 42 and 40 % yields, respectively The structures of compounds (**8**-**13**) are summarized in Fig 1

Compounds **11**, **12** and **13** were hydrolized with NaOH in toluene-MeOH to sodium salts of the protoporphyrins In a preliminary test, the Na salt from **11** was found to be localized by stomach cancer more selectively than by liver or stomach These biological results will be published elsewhere

1 W. Hausmann, Biochem. Z., 30 (1911) 276.

2 Concerning chemistry and biochemistry of HpD, see 'Advances in Experimental Medicine and Biology', **160**, 'Porphyrin Photosensitization', D. Kessel and T.J. Dougherty (eds.) Plenum, New York, 1983.

3 D. Kessel, Biochem. Pharmacology, 33 (1984) 1389.

4 H. Sato, M. Nishi, and I. Kumadaki, Chemistry Express, 3 (1988) 183.

5 H. Sato, R. Tsujimoto, I. Kumadaki, M. Nishi, K. Ido, and K. Kimura, J. Japan Soc. Laser Medicine, 6 (1986) 95.

6 H. H. Inhoffen, H. Brockmann Jr., and K.-M. Bliesener, Liebigs Ann. Chem., 730 (1969) 173.

7 F. Sparatore and D. Mauzerall, J. Org. Chem., 25 (1960) 1073.