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Progress on the syntheses of fluorine analogs of natural porphyrins potentially useful for the diagnosis and therapy of certain cancers

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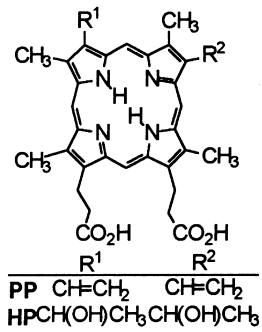
Abstract

Hematoporphyrin derivative (HpD) or photofrin II is used as a photosensitizer of photodynamic therapy (PDT) of cancer. However, these are complex mixtures of porphyrin derivatives. We have synthesized fluorine analogs of naturally important porphyrin derivatives, such as protoporphyrin (PP) and hematoporphyrin (HP) for application for the diagnosis and therapy of cancer. Some of these fluorine analogs were found to localize to tumor tissues and/or be taken up selectively by tumor cells. In this review, our former results are outlined briefly, then our recent studies on synthesis of chiral fluorine analogs of HP and synthesis of fluorine analogs of PP using our new zinc reagents will be discussed.

Keywords: Fluorine analogs; Photodynamic therapy; Protoporphyrin; Hematoporphyrin

1. Introduction

Porphyrins are planar macrocycles, consisting of four pyrrole rings joined by four methine bridges. This macrocycle is highly conjugated and its main absorption bands have very high extinction coefficients. The intense 'Soret' band, found around 400 nm, is a characteristic of these systems [1]. Furthermore, porphyrins show a characteristic red fluorescence on irradiation with ultraviolet light. Porphyrin derivatives have been investigated for application to various fields using their structural and spectroscopic properties. One of the recent investigations in these fields is the application of hematoporphyrin derivatives (HpD) to the diagnosis and therapy of certain tumors (concerning chemistry and biochemistry of HpD, see [2]). However, HpD, which was obtained by treatment of hematoporphyrin (HP) with sulfuric acid and acetic acid and found to localize to tumor tissues effectively, is a complex mixture of porphyrins. Therefore, HpD has some difficulties in clinical use, namely its low purity and uncertain photosensitivity. Photofrin II, obtained from HpD and used as a low photosensitivity drug, is thought to consist of the bis-hematoporphyrin ester or ether as a main component, but the composition is not constant. It is ambiguous which of the ester or ether is medically effective, because photofrin II is not of constant composition and not pure [3], as mentioned in our previous review [4]. Therefore, on searching for a more effective photosensitizer than photofrin II, syntheses and applications of phthalocyanines, chlorines [5], hematoporphyrin oligomers (HPO) [6], Ga-complexes of porphyrin dyes [7], and pheophorbide derivative (PH-1126) [8,9] are being actively investigated.



	R^1	R^2
PP	$CH=CH_2$	$CH=CH_2$
HP	$CH(OH)CH_3$	$CH(OH)CH_3$

We previously synthesized sodium salts of 3-(1-methoxyethyl)-8-vinyldeuteroporphyrin (**2**), 8-(1-methoxyethyl)-3-vinyldeuteroporphyrin (**3**) and 3,8-bis(1-methoxyethyl)-

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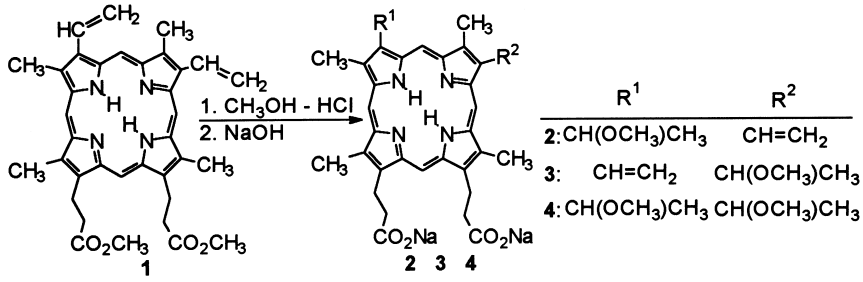


Scheme 1

deuteroporphyrin (**4**) by treatment of protoporphyrin (PP) dimethyl ester (PPDMe, **1**) with HCl gas in CH_3OH, followed by alkaline hydrolysis [10], as shown in Scheme 1.

Investigation of the localization of each CH_3OH-adduct to human gastric cancer (GCA-1) showed that **2** localized specifically to gastric cancer, but did not to human hepatocellular carcinoma (HCC-1), while **3** and **4** localize little to either cancers. Compound (**2**) showed a similar photodynamic effect to JTC-16 cells on irradiation by laser as does HpD [11]. These results suggest that some porphyrins might localize selectively to a specific tumor tissue and could be a specific sensitizer for particular tumors.

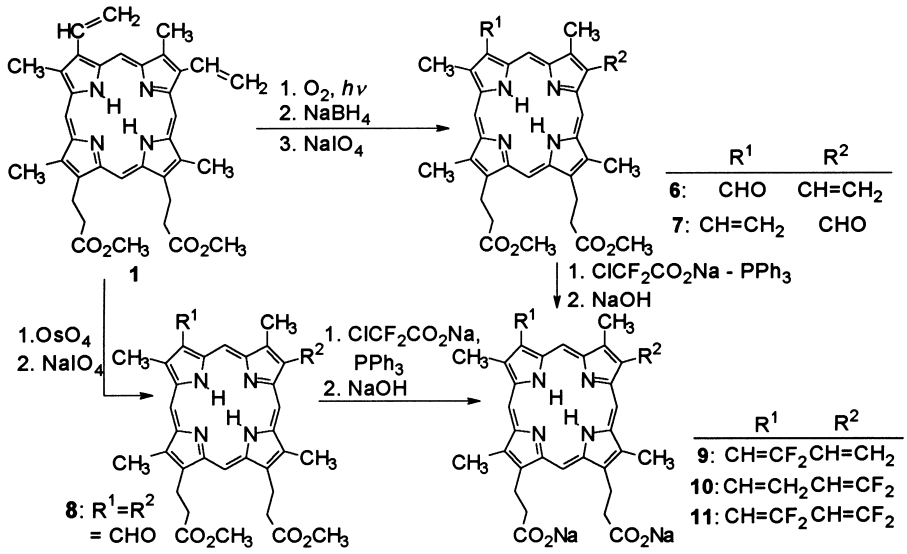
Since this work, we have been investigating syntheses of fluorine analogs of naturally occurring porphyrin derivatives which will localize selectively to specific tumor tissues. The reason we chose fluorine analogs are: (1) A fluorine atom is of similar size as a hydrogen atom, and incorporation of a fluorine atom does not change the shape of the original porphyrin, and will then be taken up as the unsubstituted derivative. (2) Usually, fluorine compounds are very stable, but some are very reactive and these reactivities are believed to induce important biological effects. Some fluorine analogs were expected to react with biological components (concerning the biological effects of fluorine compounds, see [12,13]) and to show anti-tumor effects. (3) Fluorine compounds are quite few in biological systems. Therefore, if a fluorine analog localized to tumor tissues, it would be detected by ^{19}F NMR imaging.

In this review, we overview the synthesis of fluorine analogs of PP and HP, described in the previous review, and then discuss synthesis of chiral analogs of HP by ring closure and of new fluorine analogs of PP using new fluorovinyl zinc reagents obtained recently by us.

2. Synthesis of fluorine analogs of protoporphyrin

Protoporphyrin (PP) is a constituent of hemoglobin and one of the most important porphyrins in biology. We supposed that the vinyl groups must play an important role in its biological effects. Thus, we planned to introduce difluorovinyl group(s) in the place of the vinyl group(s) of PP. For this purpose, PPDMe (**1**) was transformed to formyl derivatives (**6**, **7** and **8**) by photochemical or chemical oxidation, as shown in Scheme 2.

The formyl compounds (**6**, **7** and **8**) were heated with sodium chlorodifluoroacetate in the presence of triphenylphosphine gave the corresponding (2,2-difluorovinyl) derivatives. Use of *N*-methylpyrrolidone (NMP) as solvent is essential. Diglyme, which is commonly used for this type of reaction, did not give a good result. The methyl esters were



Scheme 2

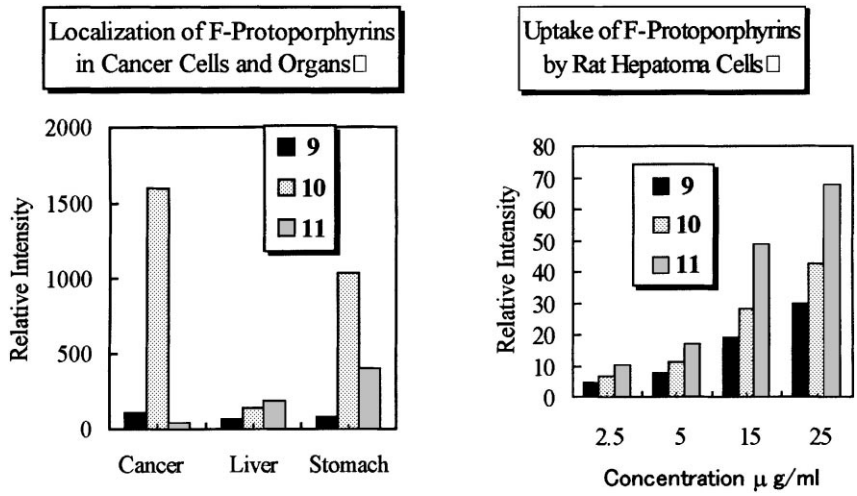


Fig. 1. (a) Localization of F-protoporphyrins in cancer cells and organs, and (b) uptake of F-protoporphyrins by rat hepatoma cells.

hydrolyzed by sodium hydroxide to sodium salts (**9**, **10** and **11**), for biological tests (see Scheme 2).

Each sodium salt was subjected to preliminary test of uptake by rat implanted with human gastric cancer (MKN-45). The results are shown in Fig. 1. This figure shows that 8-FPPN (**10**) has a high localizability to cancer cells and stomach, and localized specifically to gastric cancer cells. When these were contacted to rat ascite hepatoma cells, 3,8-FPPN (**11**) was taken up most efficiently [14,15]. These facts suggested that a special cancer took up a special porphyrin.

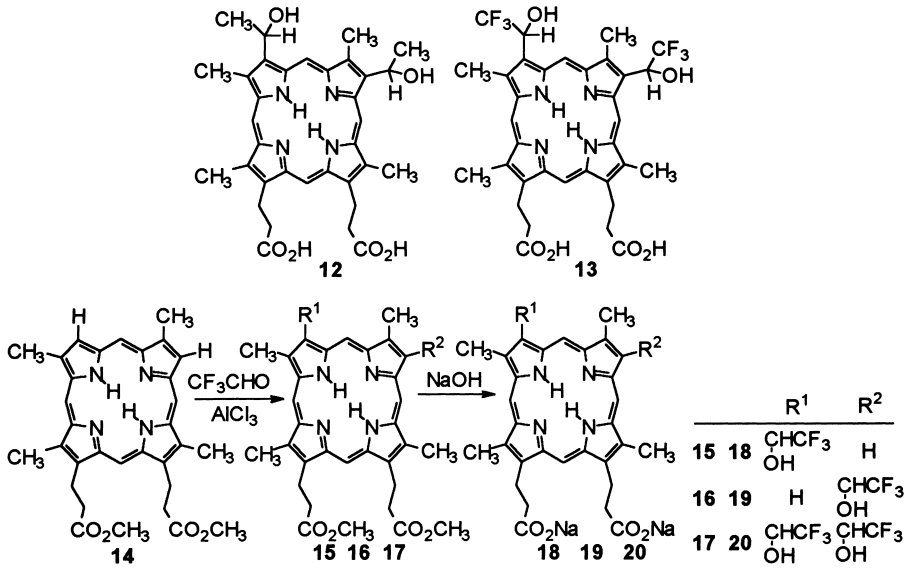
3. Fluorine analogs of hematoporphyrin

*3.1. Trifluorohydroxyethylation of deuteroporphyrin (**14**)*

Hematoporphyrin derivative (HpD), which has been used as a photosensitizer of PDT, was derived from HP (**12**). This compound has two 1-hydroxyethyl groups. The center carbons of these groups are chiral. Therefore, **12** has four stereo isomers, but commercial products are mixture of these isomers, and compositions are different depending on the providers. Further, the hydroxyethyl group is very unstable and liable to substitution and oxidation. On the other hand, a 2,2,2-trifluoro-1-hydroxyethyl (TFHE) group is quite stable. Thus, we planned the synthesis of bis(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin (**13**), an analog of HP, which has TFHE groups in the places of hydroxyethyl groups.

Treatment of deuteroporphyrin dimethyl ester (DPDMe **14**) with trifluoroacetaldehyde in the presence of $AlCl_3$ gave 3-(**15**), 8-mono-(**16**) and 3,8-bis-TFHE-DPDMe (**17**) in yields of 27%, 23% and 8%, respectively. These are hydrolyzed to sodium salts (**18**, **19** and **20**) (see Scheme 3).

Each sodium salt was added to a culture medium of human liver cancer cells, JTC-16, and incubated for 48 h.



Scheme 3

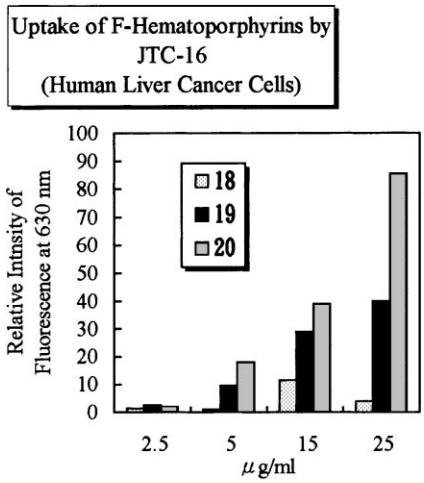


Fig. 2. Uptake of F-hematoporphyrins by JTC-16 (human liver cancer cells).

The cells were washed with buffer solution and extracted with diisopropylamine-methanol [16]. The intensity of fluorescence of this extract was measured. Interestingly, **20** was found to be taken up more strongly than other two compounds, as shown in Fig. 2. Of the two mono-TFHE compounds, **19** was taken up more strongly [17].

3.2. Synthesis of trifluorohematoporphyrins

Now, derivatization of the mono-TFHE-DPDMe (**15** and **16**) to mono(1-hydroxyethyl)-TFHE-DP; trifluoro analogs of HP, is discussed. Compounds **15** and **16** were converted to Cu complexes and then the hydroxyl groups were acetylated to give **21** and **22**. Treatment of **21** or **22** with acetyl chloride in the presence of a Lewis acid, followed by demetallation, gave ring-acetylated products **23** or **24**. In this acetylation, the Lewis acid played an important role. Tin(IV) chloride was effective for acetylation to **23**, but not for **24**. Titanium(IV) chloride was suitable for acetylation to **24**. The acetyl groups of **23** and **24** were reduced with sodium borohydride and the *O*-acetyl groups were removed by sodium hydroxide to give the desired sodium salts (**25** and **26**). These reactions are shown in Scheme 4.

These were found to be taken up by JTC-16 less than the hexafluoro analog **20** [18].

3.3. Modification of formyl-TFHE-deuteroporphyrins

To obtain fluorinated porphyrin derivatives that localize more selectively to a cancer, we formylated **21** and **22**, and introduced carbon substituents to the formyl groups. Thus, **21** and **22** were treated with trimethyl orthoformate in the presence of trifluoroacetic acid to give the corresponding formyl compounds (**27** and **28**), which were converted to 1-hydroxy-2-propen-1-yl (HPE) compounds or 3-oxo-1-nonenyl (ONE) compounds. These compounds were hydrolyzed to the corresponding sodium salts (**29–34**) [19]. These reactions are summarized in Scheme 5.

Distribution of these compounds and HpD to cancer and organs of nude mice transplanted with liver cancer are shown in Fig. 3 [19]. HpD was taken up by liver or kidney much more than our compounds, while most of our compounds, especially **32**, were distributed to cancer cells more

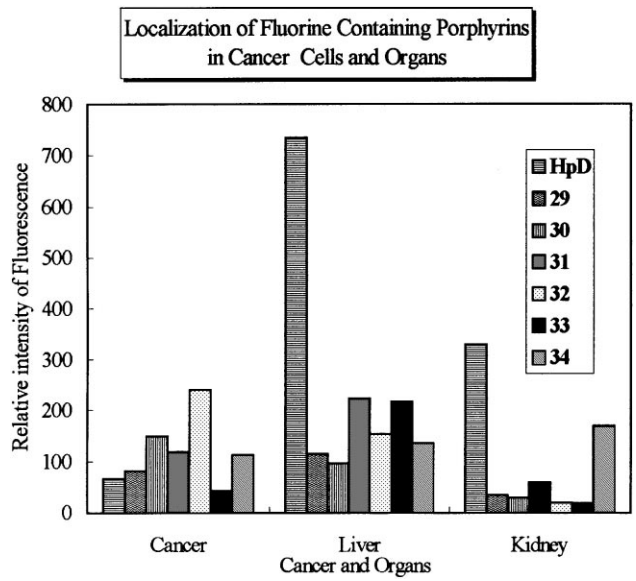
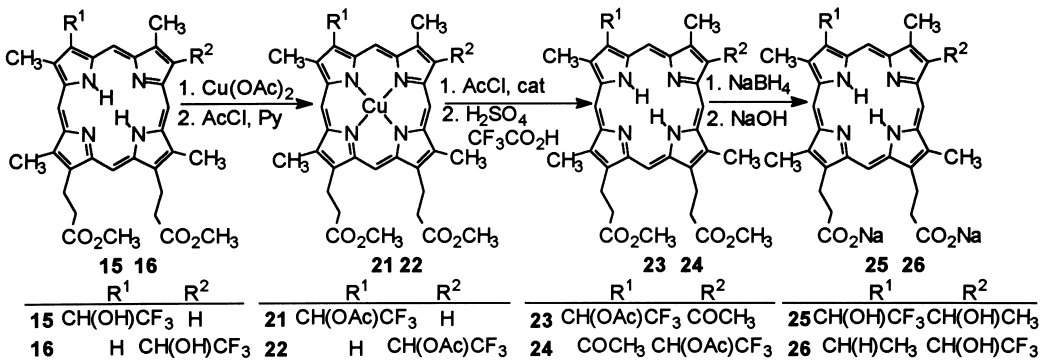
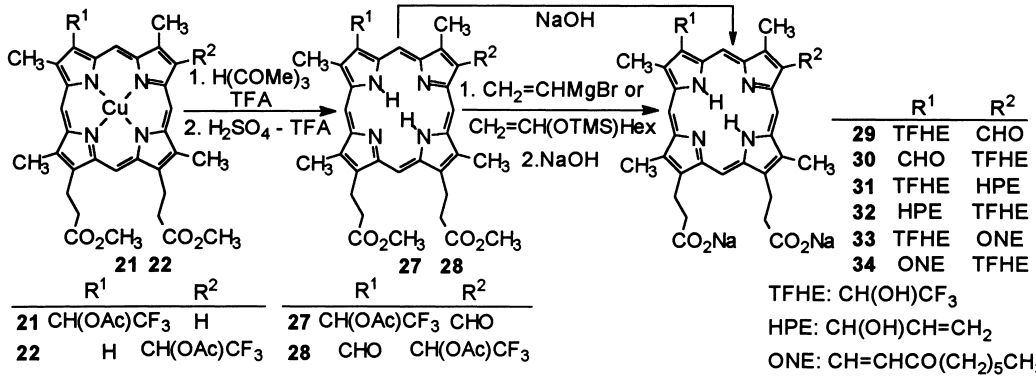


Fig. 3. Localization of fluorine-containing porphyrins in cancer cells and organs.



Scheme 4



Scheme 5

strongly than HpD. This suggested that fluorine analogs could be better sensitizers for PDT than HpD.

4. Synthesis of chiral fluorine analogs of hematoporphyrin

As mentioned before, the hydroxyethyl groups of HP have a chiral center, but all the commercial products are mixtures of diastereomers. Biological activities of most chiral compounds depend on their chirality. Thus, uptake of chiral fluorine analogs of HP by tumors must depend on the chirality. Thus, we planned to synthesize chiral fluorine analogs related to HP.

4.1. Optical resolution of mono-TFHE-deuteroporphyrin dimethyl esters

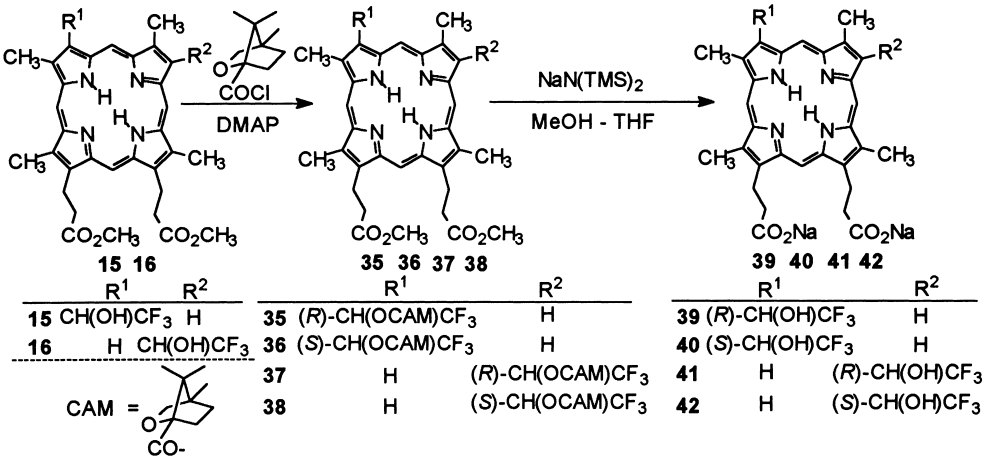
Optical resolution of bis-TFHE-DPMe (**17**) was attempted, but it contained four diastereoisomers, and we could not separate the mixture of diastereomeric esters. Next, we tried optical resolution of mono-TFHE-DPMe (**15** and **16**) derivatizing to (*S*)-camphanic esters. Diastereomeric esters of both isomers were separated efficiently using silica gel column chromatography. Separated esters (**35**–**38**) were hydrolyzed with sodium bis(trimethylsilyl)amide in MeOH-THF to sodium salts, 3-(*R*)-, 3-(*S*)-, 8-(*R*)-, and 8-(*S*)-TFHE-DP (**39**–**42**) (see Scheme 6) [20].

Each salt was subjected to a preliminary test for uptake by human gastric cancer cells. Interestingly, 3-(*S*) compound (**40**) was taken up fifteen times more than 3-(*R*) isomer (**39**), while 8-(*R*) (**41**) was taken up a little more than 8-(*S*) isomer (**42**) [20].

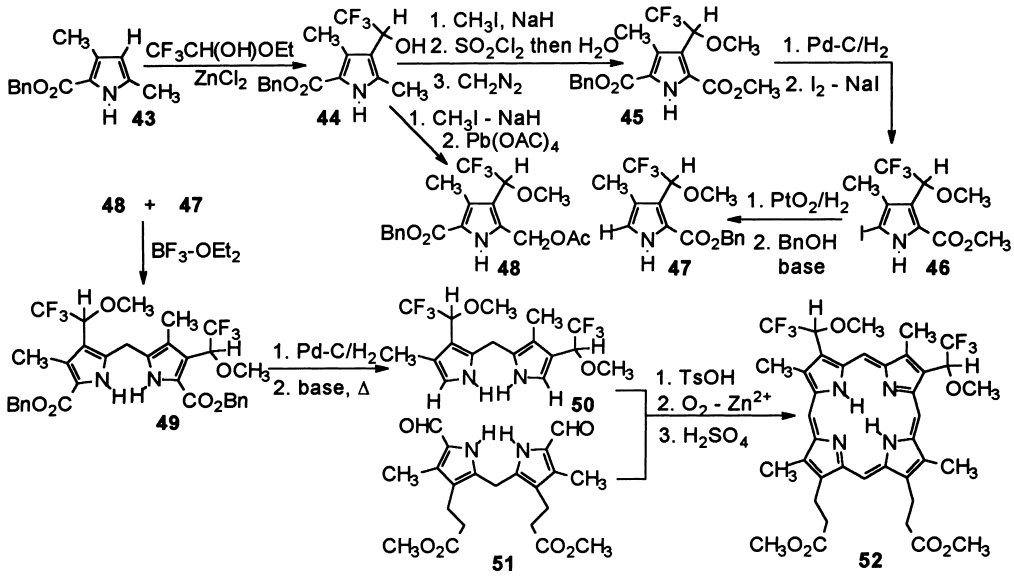
4.2. Model synthesis of TFHE-DP by ring closure

The above results suggested that the chirality of a TFHE group on porphyrin would play an important role in the uptake of porphyrins by cancer cells. Thus, we had interest in the difference between uptake of the diastereoisomers of the hexafluoro analog of HP (**20**). However, attempted isolation of the isomers was unsuccessful, as mentioned before. To solve this difficulty, we planned total synthesis of chiral analogs of HP by ring closure using a pyrrole derivative with a chiral TFHE group. First, we examined ring closure using non-chiral pyrrole derivatives.

Our strategy was: Benzyl 3,5-dimethylpyrrole-2-carboxylate (**43**) was treated with trifluoroacetaldehyde ethyl



Scheme 6



Scheme 7

hemiacetal in the presence of a Lewis acid to give a 4-TFHE derivative (**44**), which was derivatized to the ring A and B through several steps as shown in Scheme 7.

Thus, the hydroxyl group of the TFHE group of **44** was protected as a methyl ether, and the 5-methyl group was treated with sulfuryl chloride, followed by hydrolysis, to give the 5-carboxyl derivative. This was converted to a methyl ester (**45**) with diazomethane. The benzyl ester at 2-position was hydrogenolized, and *ipso*-iodination with simultaneous decarboxylation afforded the 2-iodo compound (**46**), which was hydrogenolized again to the 2-hydrogen compound (**47**). (Numbering of the pyrrole ring should be changed, but we kept that of **43**.) After *O*-methylation of **44**, the 5-methyl group was partially oxidized with lead tetraacetate to an acetoxymethyl compound (**48**). Condensation of **47** and **48** catalyzed by boron trifluoride etherate gave a bis(pyrrole)methane compound (**49**). The benzyl ester groups of **49** was hydrogenolyzed, and the carboxyl groups were removed by heating in ethanolamine to give **50**. MacDonald condensation of this compound with bottom half (**51**) obtained according to a reference gave the *O*,*O*-dimethyl analog of **17** (**52**) [21,22].

4.3. Synthesis of pyrrole compounds with a chiral TFHE group

We succeeded in the synthesis of a fluorine analog of HP by ring closure. If we could have a chiral form of the TFHE-pyrrole (**44**), we would be able to convert it to a chiral TFHE-DP.

First, **44** was derivatized to diastereomeric (*S*)-camphanic esters, and they were successfully resolved by silica gel column chromatography (>95% de). Absolute configuration of one ester (*S*)-53 was determined by X-ray analysis [23].

Unfortunately, however, hydrolysis of chiral **53** with sodium ethoxide or benzyloxide resulted in formation of racemic ethers (**54**) of **44**. (The mechanism must be fission of the alkyl carbon–oxygen bond due to the highly electron-donating effect of the pyrrole ring.) Attempted reductive deacylation with lithium tri-*tert*-butoxyaluminohydride gave a deacyloxylation product (**55**) probably through the same intermediate as above.

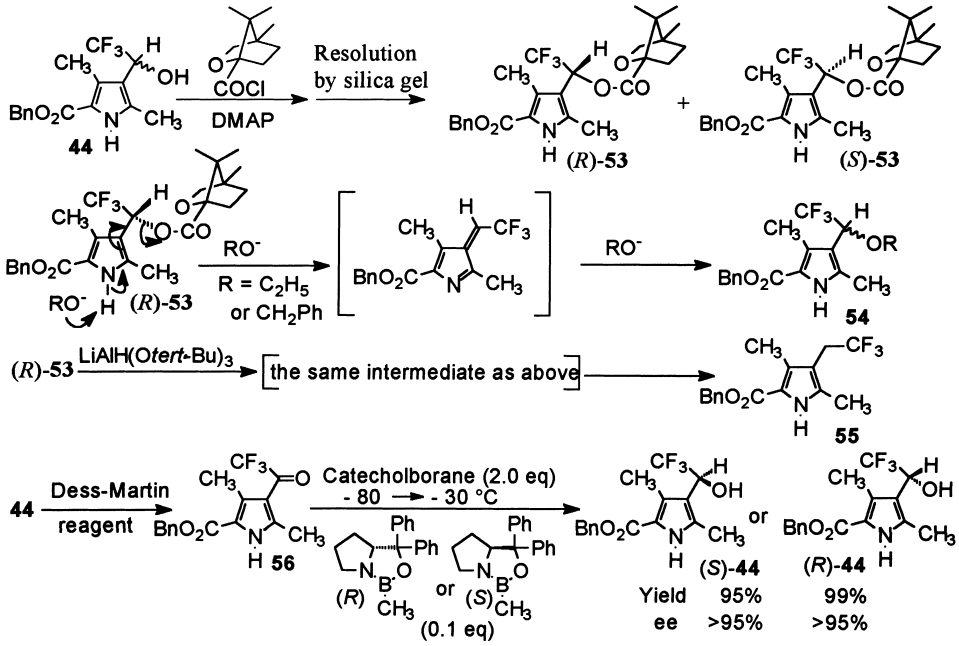
Finally, racemic **44** was oxidized with Dess–Martin reagent to a trifluoroacetyl-pyrrole compound (**56**), and its asymmetric reduction using Correy's oxazaborolidine catalyst and catecholborane gave high yields of (*R*)-and (*S*)-**44** in excellent enantiomeric excesses. All the reactions in this section are shown in Scheme 8 [23].

Absolute configurations of **44** were determined by derivatizing to (*S*)-camphanic esters (**53**). The structure of (*S*)-**53** had been determined by X-ray analysis, as mentioned above.

4.4. Ring formation using chiral TFHE-pyrrole compounds

Now, we had chiral TFHE-pyrrole compounds in hand. Thus, the ring formation reactions in Section 4.2 were followed with a small modification.

Chiral **44** was acetylated and treated with sulfuryl chloride followed by hydrolysis to give a carboxylic acid, which was esterified with diazomethane to a methyl ester (*R*)-**57**. The benzyl ester at 2-position was hydrogenolized and the 2-carboxylic acid was subjected to *ipso*-iodination to give an iodo compound (**58**). This iodide was hydrogenolyzed to (*R*)-**59**, which was treated with sodium bis(trimethylsilyl)amide in benzyl alcohol to provide 5-carboxylic benzyl ester (*R*)-**60** with simultaneous deacetylation. Through these transformations, decrease of chirality was negligible. An



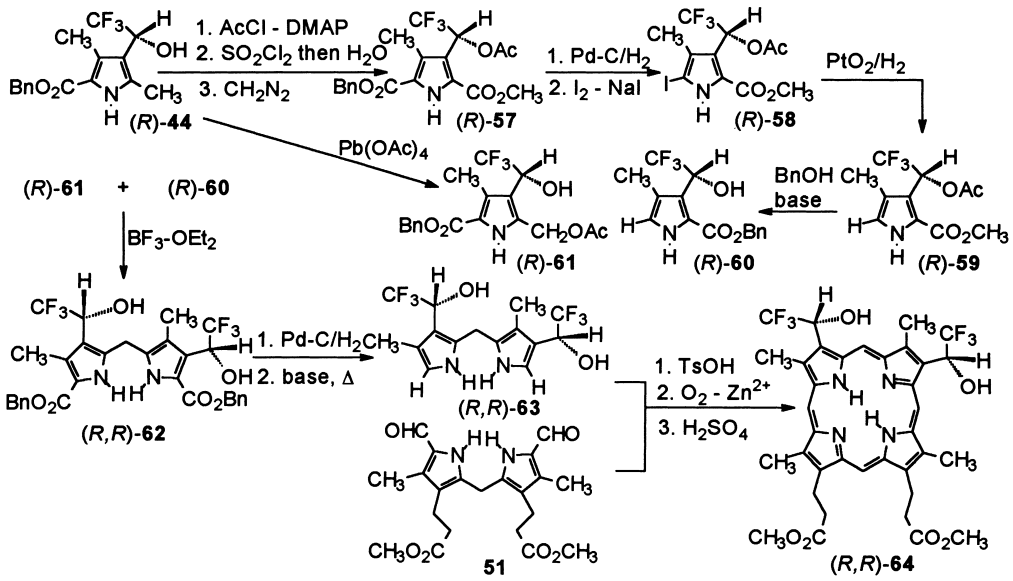
Scheme 8

especially interesting point is that hydrolysis of **59** proceeded without loss of the chirality, though the same reaction of chiral **53** had resulted in the complete racemization. The electron donating effect of the pyrrole ring may be overcome by the electron withdrawing effect of the 5-carboxylic ester group.

During these syntheses, a TFHE group was found to be quite stable. Thus, transformations hereafter were carried out without protection of the hydroxy group of the TFHE group.

Oxidation of (*R*)-**44** with lead tetraacetate was successfully carried out to give 5-acetoxymethyl compound (*R*)-**61** in high enantiomeric excess. Condensation of (*R*)-**60** and (*R*)-**61** in the presence of boron trifluoride etherate gave dipyrrolemethane compound (*R,R*)-**62** in a yield of 88% in more than 95% diastereomeric excess. The benzyl groups were removed by hydrogenolysis, and heating the dicarboxylic acid in ethanolamine gave (*R,R*)-**63**. Its condensation with the lower half (**51**), followed by oxidation and demetallation, provided (*R,R*)-**64** in a high diastereomeric excess. All the reactions shown above are summarized in Scheme 9.

Following the similar reactions from (*S*)-**44**, and combining (*R*)- or (*S*)-**60** with (*R*)- or (*S*)-**61**, we could obtain other three diastereo isomers, (*R,S*)-, (*S,R*)- and (*S,S*)-**64** in high diastereomeric excesses [24].



Scheme 9

Thus, we could obtain all the four diastereo isomers of hexafluoro analogs of HP. All these diastereomeric **64** were hydrolyzed to sodium salts. Detailed study of these isomers on biological behaviors are now going on, but their preliminary tests showed that the (*S*,*R*)-isomer was most effectively taken up by cancer cells. This suggests again that chiral centers of HpD must play an important role in biological activity, even when it is used as a mixture. The very high enantioselectivity in the reduction of a trifluoroacetyl group with catecholborane in the presence of Corey's oxazaborolidine catalyst is quite useful for synthesis of chiral 2,2,2-trifluoro-1-hydroxyethyl compounds. We will mention application of this reaction in Section 5 of this paper.

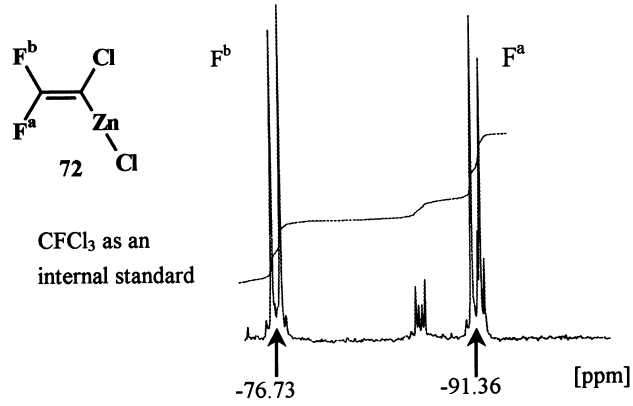


Fig. 4. Solution of **73** by Normant's procedure.

5. Synthesis of new fluorinated vinylzinc reagents and its application for synthesis of fluorine analogs of protoporphyrin

As mentioned in Section 2, analogs of protoporphyrins containing difluorovinyl group(s) in the place of vinyl group(s) showed particularly favorable behavior to cancer cells. As extension of this research, we planned synthesis of trifluorovinyl analogs of protoporphyrin by the reaction of iodoporphyrin with trifluorovinylzinc chloride reported by Normant's group [25]. At first, we followed their procedures, but we obtain the desired product only in poor yield. In the course of this study, modification of the procedure gave new fluorovinylzinc reagents, which were much more reactive than the former one. In Section 5.1 the synthesis of new fluorovinylzinc reagents is discussed, then their applications to synthesis of various fluorine analogs of protoporphyrin are presented.

5.1. Synthesis of new fluorovinylzinc reagents and their application for synthesis of bis-(trifluorovinyl)- and bis(1-chloro-2,2-difluorovinyl)deuteroporphyrin dimethyl esters

Normant's group reported synthesis of trifluorovinylzinc chloride (**67**) by the reaction of chlorotrifluoroethene (**65**) with *sec*-butyllithium at −60°C, followed by addition of zinc chloride at −100°C, and its reaction with aryl iodide in the presence of tetrakis-(triphenyl)palladium to provide aryl trifluoroethene (**68**). First, we applied this method to 3,8-diiodo-DPDMe copper complex (**69**: Met = Cu), but it was quite difficult to control the temperature for the formation of the zinc reagent, and the solution of **67** was colored brown and was turbid. The yield of the 3,8-bis(trifluorovinyl)-DPDMe (**70**) was only 23%. A similar reaction of 2-chloro-1,1-difluoroethene (**71**) gave a moderate yield of 3,8-bis(1-chloro-2,2-difluorovinyl)-DPDMe (**74**).

The poor yield of **70** seemed to be due to the low stability of trifluorovinyllithium (**66**). Therefore, we modified the procedure. Our idea was if zinc chloride was present when **66** was formed, **66** would react with zinc chloride before decomposition to form **67**. Thus, we added *sec*-butyllithium to a solution of **65** in the presence of zinc chloride. The solution of zinc reagent thus formed was colorless and clear. Reaction of this solution with uncomplexed **69** (Met = H_2) gave a zinc complex of **70**, which was demetallated by treatment with sulfuric acid in methanol to give an excellent overall yield of **70**. By the same procedure as above, **71** gave **74** in 99% yield.

It was quite strange for us that these large differences in reactivities between the metal reagents originated only from methods of formation. Thus, we investigated the differences using ^{19}F NMR. Our zinc reagent from **64** showed a much more complex ^{19}F NMR spectrum than expected from **67**. A solution of **67** by Normant's method was turbid and we could not obtain a clear spectrum. A solution of **73** by Normant's procedure showed two doublets as expected (see Fig. 4), while a solution of the zinc reagent from **71** by our procedure showed two pairs of two doublets (Fig. 5). The chemical shifts of this spectrum is similar to those of **71**, but peak heights pattern is different from each other. We tentatively assigned this as a mixture of *cisoid*- and *transoid*-bis(1-chloro-2,2-difluorovinyl)-zinc (**76**), as shown in Fig. 5. We believe that our zinc reagent from **65** must be a similar mixture of bis(trifluorovinyl)zinc (**75**), which would show much more complex spectrum on ^{19}F NMR as observed (see Figs. 4 and 5).

All the results are shown in Scheme 10 [26].

As shown above, we could obtain much more reactive fluorovinylzinc reagents than those obtained by Normant's procedure. These would provide new methodology for synthesis of fluorine compounds.

5.2. Synthesis of fluorine analogs of protoporphyrin with a 2,2-difluorovinyl and (a trifluorovinyl or a 1-chloro-2,2-difluorovinyl) groups using bis(fluorovinyl)zinc

5.2.1. Reagents

A new methodology for introduction of a trifluorovinyl or a 1-chloro-2,2-difluorovinyl groups to a porphyrin ring was established as shown in the previous section. Formerly, we

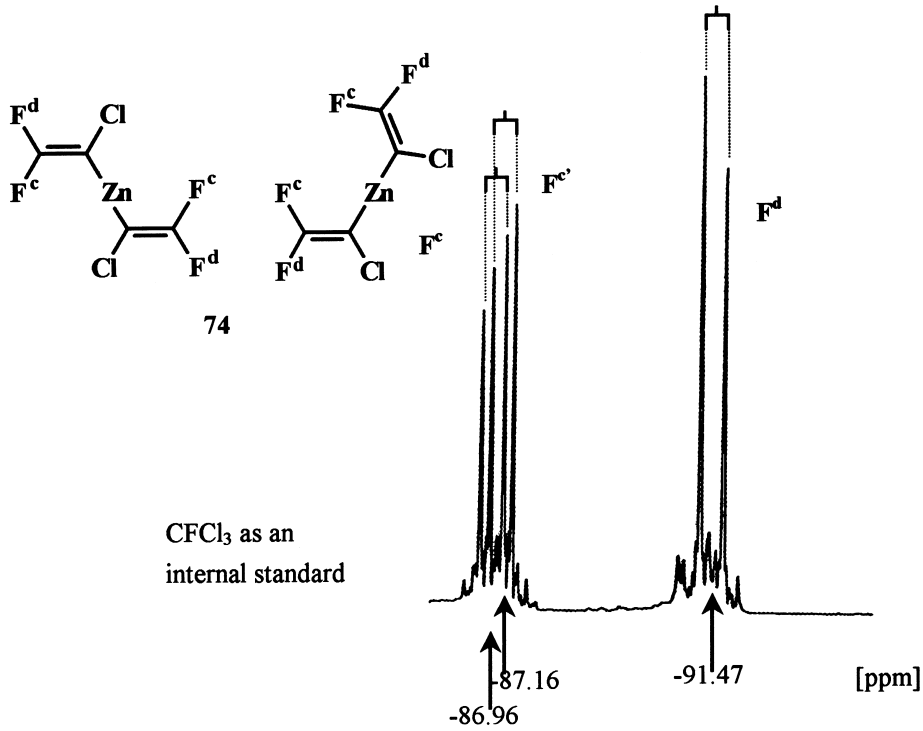
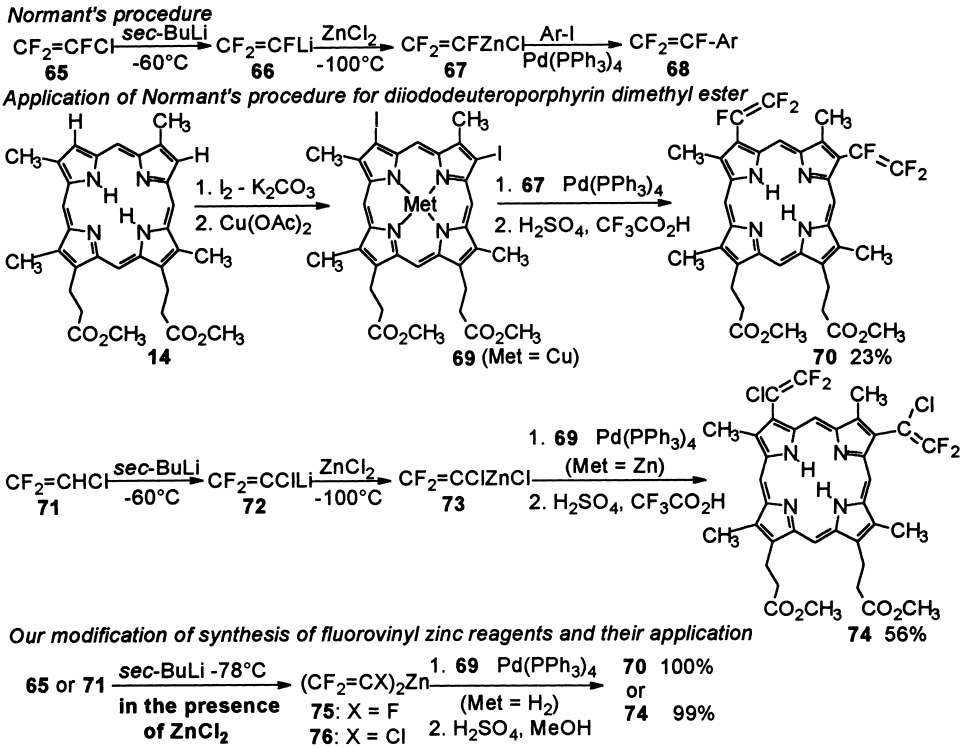


Fig. 5. A solution of the zinc reagent from **71** by our procedure.

had succeeded in the synthesis of difluorovinylporphyrins by the Wittig reaction as in Section 2. Now, introduction of both groups to DPDMe (**14**) by combination of both methodologies will be presented.

We have reported an efficient formylation of **14** [27]. **14** was converted to a copper complex (**77**). Treatment of **77** with trimethyl orthoformate in the presence of tin(IV) chloride, followed by demetallation with sulfuric acid



Scheme 10

and trifluoroacetic acid, gave 3- and 8-formyl compounds (**78** and **79**) in the yields of 46% and 47%, respectively.

Heating **78** or **79** with sodium chlorodifluoroacetate and triphenylphosphine in *N*-methylpyrrolidone afforded difluorovinyl compounds (**80** or **81**). Iodination of these compounds with iodine in the presence of potassium carbonate gave the corresponding iodo compounds (**82** and **83**) in high yields. When these transformations were carried out in reverse order, we did not obtain good results, namely iodination of **78** or **79** gave formyl iodo compounds, which were little soluble in any solvents and quite difficult to purify.

Coupling reactions of (difluorovinyl)iodo-DPDMe (**82** and **83**) with bis(trifluorovinyl)zinc (**75**) or bis(1-chloro-2,2-difluorovinyl)zinc (**76**) in the presence of tetrakis(triphenylphosphine)palladium provided DPDMe derivatives having a 2,2-difluorovinyl group and (a trifluorovinyl or a 1-chloro-2,2-difluorovinyl group) on 3- or 8-positions (**84** to **87**). All the reactions are shown in Scheme 11 [28].

These syntheses were accomplished recently, and investigation of biological behaviors is now in progress.

5.3. Synthesis of fluorine analogs of protoporphyrin with a trifluorovinyl or 1-chloro-2,2-difluorovinyl and a vinyl groups

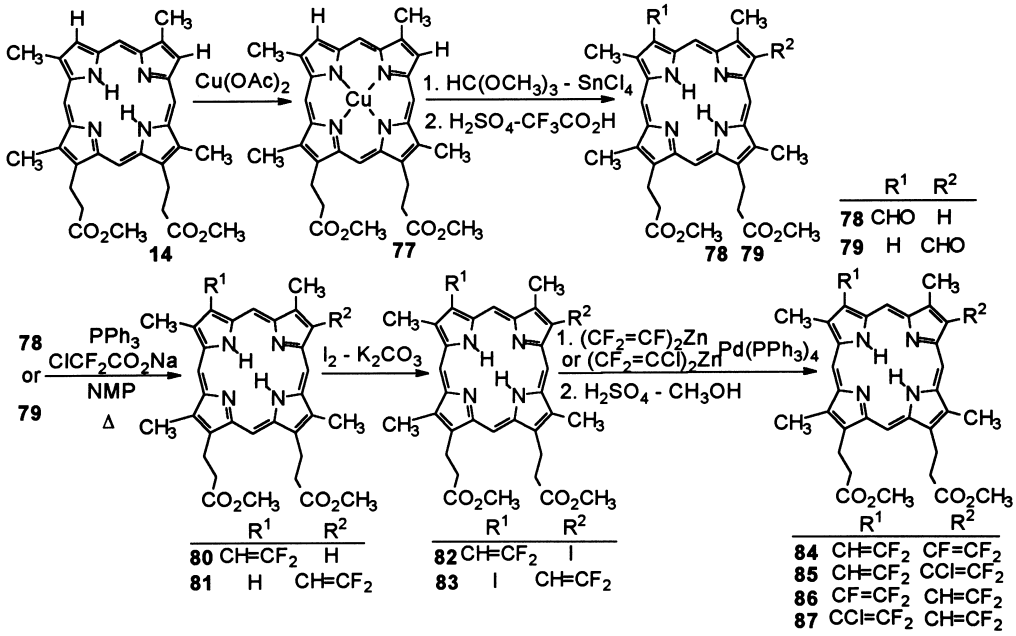
In Section 2, we discussed synthesis of difluoro analogs of protoporphyrin and their biological behavior to tumors. Now, syntheses of trifluoro and chlorodifluoro analogs of protoporphyrin will be presented. Our strategy was the following: introduction of trifluorovinyl or 1-chloro-2,2-difluorovinyl groups by coupling reaction using bis(fluorovinyl)zinc reagents, and formation of a vinyl group by introduction of an acetyl group, followed by its reduction and dehydration. All the reactions are shown in Scheme 12.

The copper complex of DPDMe (**77**) was acetylated with acetyl chloride in the presence of zinc chloride, followed by demetallation with sulfuric acid and trifluoroacetic acid, to give 3- and 8-mono-, and 3,8-diacetyl-DPDMe (**88**, **89** and **90**) in 27%, 17% and 25% yields, respectively.

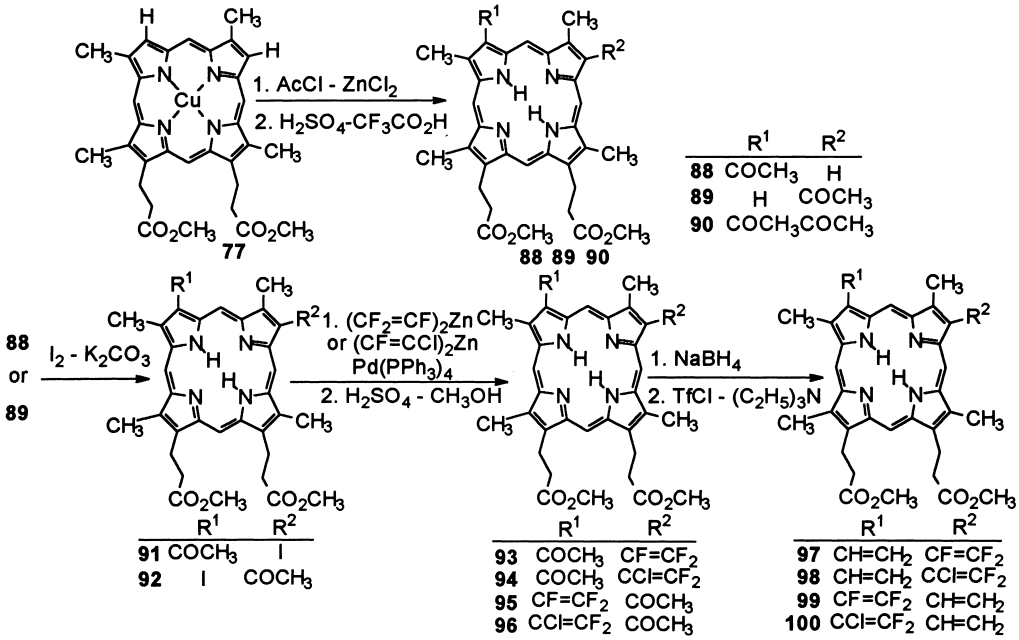
Since unsubstituted vinyl groups on 3- or 8-positions of porphyrin ring are highly reactive, we planned formation of these groups at the last stage of synthesis. Thus, **88** and **89** were iodinated with iodine and potassium carbonate. The acetyl groups deactivated their *ortho* positions for nucleophilic attack, and the reaction needed reflux for a long time, but gave high yields of iodo compounds (**91** and **92**). These iodo compounds were treated with the above mentioned bis(fluorovinyl)zinc reagents (**75–76**), followed by elimination of the complexed zinc with sulfuric acid in methanol, to provide DPDMe derivatives having one 1-chloro-2,2-difluorovinyl or trifluorovinyl group and an acetyl group (**93–96**). Reduction of the acetyl group of these compounds with sodium borohydride, followed by dehydration with trifluoromethanesulfonyl chloride and triethylamine afforded four desired compounds (**97–100**) in moderate to good yields [29]. Syntheses of these compounds were just accomplished, and study on their biological features is now in progress.

6. Conclusions

In the course of this study, we concentrated on the syntheses of fluorine analogs of naturally occurring porphyrins, especially having fluorine atoms on the 3- and 8-positions of protoporphyrin and hematoporphyrin. We have



Scheme 11



Scheme 12

synthesized many types of fluorine analogs of these porphyrins. Studies of these compounds as a sensitizer in photodynamic therapy are just going on, and preliminary tests gave promising results.

A trifluorohydroxyethyl [$CF_3CH(OH)$-] group was found remarkably to be more stable than a hydroxyethyl [$CH_3CH(OH)$-] group of hematoporphyrin, and hematoporphyrin analogs with that substituent were synthesized in optically pure forms. Studies on metabolism of these chiral compounds to elucidate the mechanism of their take-up by tumors are also in progress. These studies will provide insights into metabolism of porphyrins, since the hydroxyethyl group is unstable and difficult to study. We hope that "mimic effect" of fluorine atoms would help these studies.

During these syntheses, we established two general methodologies: (1) chiral reduction of a trifluoroacetyl group with catecholborane in the presence of Corey's catalyst, and (2) synthesis of new bis(fluorinated vinyl)zinc reagents (**75** and **76**). These are much more reactive than fluorinated vinylzinc chlorides reported previously, and their application to syntheses of various fluorine compounds are hopeful.

We summarized our recent study of syntheses of fluorine analogs of porphyrins, but some important methodologies established in this study will open new fluorine chemistry and/or non-fluorine chemistry.

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References

[1] K.M. Smith (Ed.), Porphyrins and Metalloporphyrins, Elsevier, Amsterdam, 1975.
[2] D. Kessel, T.J. Dougherty (Eds.), Advances in experimental medicine and biology, Porphyrin Photosensitization, vol. 160, Plenum Press, New York, 1983.
[3] R.K. Pandey, F.-Y. Shiau, T.J. Dougherty, K.M. Smith, Tetrahedron 47 (1991) 9571.
[4] A. Ando, I. Kumadaki, Heterocycles 42 (1996) 885.
[5] K. Aizawa, T. Okunaka, T. Ohtani, H. Kawabe, Y. Yasunaka, S. O'hata, H. Kato, Y. Hayata, T. Saito, Photochem. Photobiol. 46 (1987) 789.
[6] N. Miyoshi, A. Hirata, K. Kunimi, K. Sakurai, K. Sakamoto, N. Matumoto, H. Hisazumi, M. Fukuda, Lasers Med. Sci. 3 (1988) 185.
[7] S. Nakajima, H. Hayashi, K. Ohshima, K. Yamazaki, Y. Kubo, N. Samejima, Y. Kakiuchi, Y. Shindoh, H. Koshimizu, I. Sakata, H. Yamauchi, Photochem. Photobiol. 46 (1987) 783.
[8] R.K. Pandey, D.A. Bellnier, K.M. Smith, T.J. Dougherty, Photochem. Photobiol. 53 (1991) 65.
[9] S. Chernomorsky, C. Wong, R.D. Poretz, Photochem. Photobiol. 55 (1992) 205.
[10] H. Sato, M. Nishi, I. Kumadaki, Chem. Express 3 (1988) 183.
[11] H. Sato, R. Tsujimoto, I. Kumadaki, M. Nishi, K. Ido, K. Kimura, J. Jpn. Soc., Laser Med. 6 (1986) 95.
[12] R. Filler, Y. Kobayashi (Eds.), Biomedicinal Aspects of Fluorine Chemistry, Kodansha, Tokyo, 1983.
[13] R. Filler, Y. Kobayashi, L.M. Yagupolskii (Eds.), Organic Fluorine Compounds in Medicinal Chemistry and Biomedicinal Applications, Elsevier, Amsterdam, 1993.
[14] A. Ando, T. Shinada, S. Kinoshita, N. Arimura, M. Koyama, T. Nagai, T. Miki, I. Kumadaki, H. Sato, Chem. Pharm. Bull. 38 (1990) 2175.
[15] A. Ando, T. Shinada, S. Kinoshita, N. Arimura, T. Nagai, T. Miki, I. Kumadaki, J. Fluorine Chem. 42 (1989) 293.
[16] H. Sato, K. Ido, K. Kimura, Clin. Chem. 40 (1994) 1239.
[17] A. Ando, T. Kitamura, S. Aono, H. Sato, M. Omote, M. Koyama, T. Takagi, T. Miki, I. Kumadaki, H. Sato, Heterocycles 35 (1993) 1309.
[18] M. Omote, A. Ando, M. Koyama, T. Takagi, I. Kumadaki, Heterocycles 39 (1994) 381.

[19] M. Omote, A. Ando, T. Takagi, M. Koyama, I. Kumadaki, H. Sato, Chem. Pharm. Bull. 43 (1995) 1107.
[20] M. Omote, T. Matsumoto, A. Ando, M. Koyama, T. Takagi, I. Kumadaki, Heterocycles 46 (1997) 259.
[21] M. Omote, A. Ando, T. Takagi, M. Koyama, I. Kumadaki, Heterocycles 44 (1997) 89.
[22] M. Omote, A. Ando, T. Takagi, M. Koyama, I. Kumadaki, Tetrahedron 52 (1996) 13961.
[23] M. Omote, A. Ando, T. Takagi, M. Koyama, I. Kumadaki, M. Shiro, Heterocycles 47 (1997) 65.
[24] M. Omote, A. Ando, I. Kumadaki, Unpublished results.
[25] J.P. Gilet, R. Sauvêtre, J.F. Normant, Synthesis (1986) 538.
[26] T. Shigeoka, Y. Kuwahara, K. Watanabe, K. Sato, M. Omote, A. Ando, I. Kumadaki, J. Fluorine Chem., submitted for publication.
[27] A. Ando, M. Yamazaki, M. Komura, Y. Sano, N. Hattori, M. Omote, I. Kumadaki, Heterocycles 50 (1999) 913.
[28] T. Shigeoka, Y. Kuwahara, K. Watanabe, K. Sato, M. Omote, A. Ando, I. Kumadaki, Heterocycles, in press.
[29] T. Shigeoka, Y. Kuwahara, K. Watanabe, K. Sato, M. Omote, A. Ando, I. Kumadaki, Chem. Pharm. Bull. 47 (1999) 1326–1329.