SYNTHESIS OF A FLUORINE ANALOG OF HEMATOPORPHYRIN BY RING CLOSURE

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Dedicated with admiration and respect to Professor Emeritus Shigeru Oae on the occasion of his 77th birthday.

Abstract - Benzyl 3,5-dimethyl-2-pyrrolecarboxylate (**1**) was converted to 4-(2,2,2-trifluoro-1-hydroxyethyl) derivative (**2**) on treatment with trifluoroacetaldehyde ethyl hemiacetal in the presence of zinc chloride. After protection of the hydroxy group, **2** was converted to benzyl 4-methyl-3-(2,2,2-trifluoro-1-methoxyethyl)2-pyrrolecarboxylate (**9**) and benzyl 5-acetoxymethyl-3-methyl-4-(2,2,2-trifluoro-1-methoxyethyl)-2-pyrrolecarboxylate (**10**). Both esters were condensed to a dipyrrolomethane compound (**11**), which was debenzylated, decarboxylated, and condensed with a bottom half of the porphyrin to give a hexafluorohematoporphyrin derivative (**14**), potentially useful for photodynamic therapy of cancer.

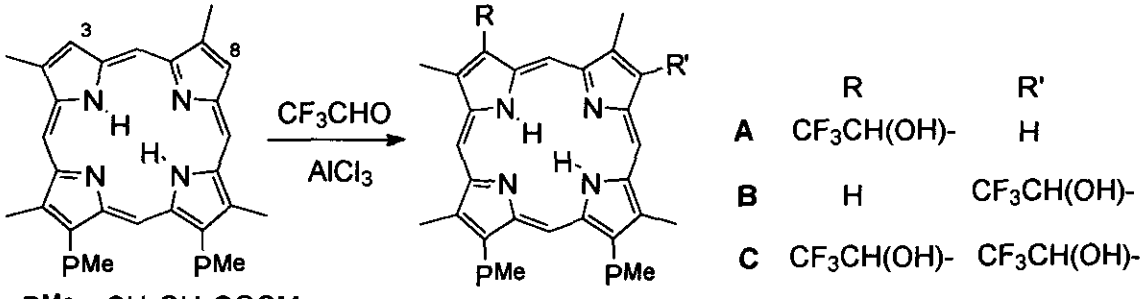
It is well known that hematoporphyrin derivative (HPD) localizes to a tumor tissue and liberates an active oxygen by excitation with laser irradiation that leads to a destruction of the tumor tissues. Due to this property, HPD has been used in the diagnosis and therapy of cancer. It is called photodynamic therapy (PDT).[1] However, the HPD that has been used for the PDT is a mixture of several porphyrins, so it is difficult to obtain a constant composition of medicine.

To circumvent this problem, we planned to synthesize another porphyrin derivative which localizes preferentially to a tumor tissue. We expected that fluorination of a porphyrin would give additional

stability and lipophilicity. If we could synthesize a fluorinated porphyrin derivative that localizes to a tumor tissue, it could serve as a tracer on ^{19}F-nmr imaging.[1] Thus, we have focused on synthesis of fluorinated hematoporphyrins which have a 2,2,2-trifluoro-1-hydroxyethyl group (TFHE group) instead of a 1-hydroxyethyl group at the positions 3 or 8 on hematoporphyrin.

We have already synthesized hematoporphyrin derivatives having mono and bis TFHE group(s), **A**, **B** and **C** by the reaction of deuteroporphyrin with trifluoroacetaldehyde in the presence of a Lewis acid. In this reaction, the mono substituted products **A** and **B** were obtained in a good yield but bis one (**C**) was in only poor yield.[2] (See Scheme 1)

Scheme 1



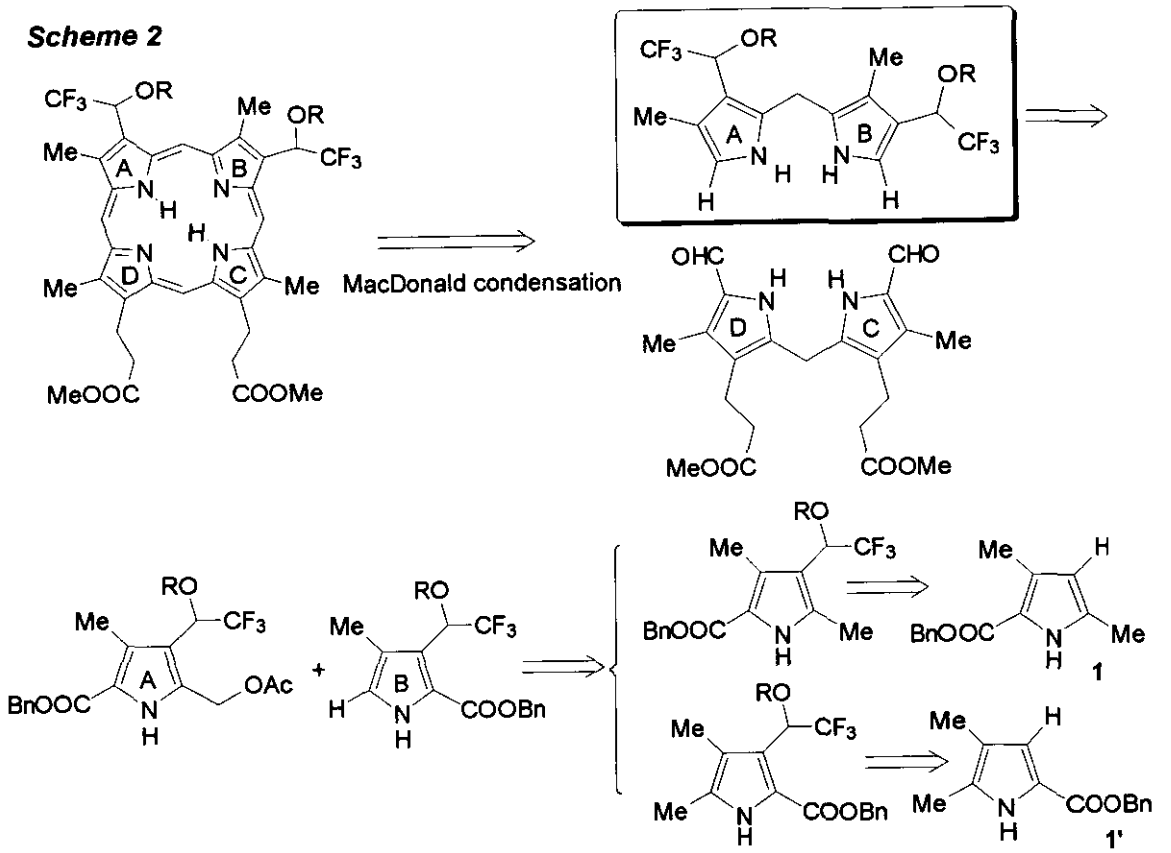
	R	R'
A	$CF_3CH(OH)$-	H
B	H	$CF_3CH(OH)$-
C	$CF_3CH(OH)$-	$CF_3CH(OH)$-

A high affinity of the hexafluorohematoporphyrin (HFHP) derivative obtained by hydrolysis of **C** for tumor cells was observed in *in vitro* experiment. However, in the above route, **C** was obtained in only 6% yield. Further, the enantiomeric control for synthesis of chiral porphyrins seems to be difficult by this procedure. Therefore, our attention was turned to a total synthesis of a HFHP derivative by a ring closure method.

Our strategy is shown in Scheme 2. If a dipyrrolomethane with a suitable fluorine substituent was synthesized, it could be coupled with a bisformyl compound by the MacDonald condensation[3] to give the objective HFHP derivative. Rings A and B of the dipyrrolomethane could be synthesized by trifluorohydroxyethylation of the two pyrroles (**1** and **1'**) shown in the last part of Scheme 2. The trifluorohydroxyethylation of **1** was successfully carried out, but the same reaction of **1'** did not proceed at all.

In fact, the synthesis of the two pyrrole components for this strategy was accomplished as shown in the top of Scheme 3. Namely, both rings with a trifluorohydroxyethyl group were synthesized from the ester (**1**), which was prepared by Battersby's method.[4] This ester was treated with trifluoroacetaldehyde hemiacetal in the presence of a Lewis acid to give a trifluorohydroxyethyl compound (**2**).[5] For this reaction, zinc chloride was most effective to give **2** in the yield of 78% with a small amount of a 3,3'-bis(pyrrolo)methane. When boron trifluoride etherate was used as a catalyst, the latter product was

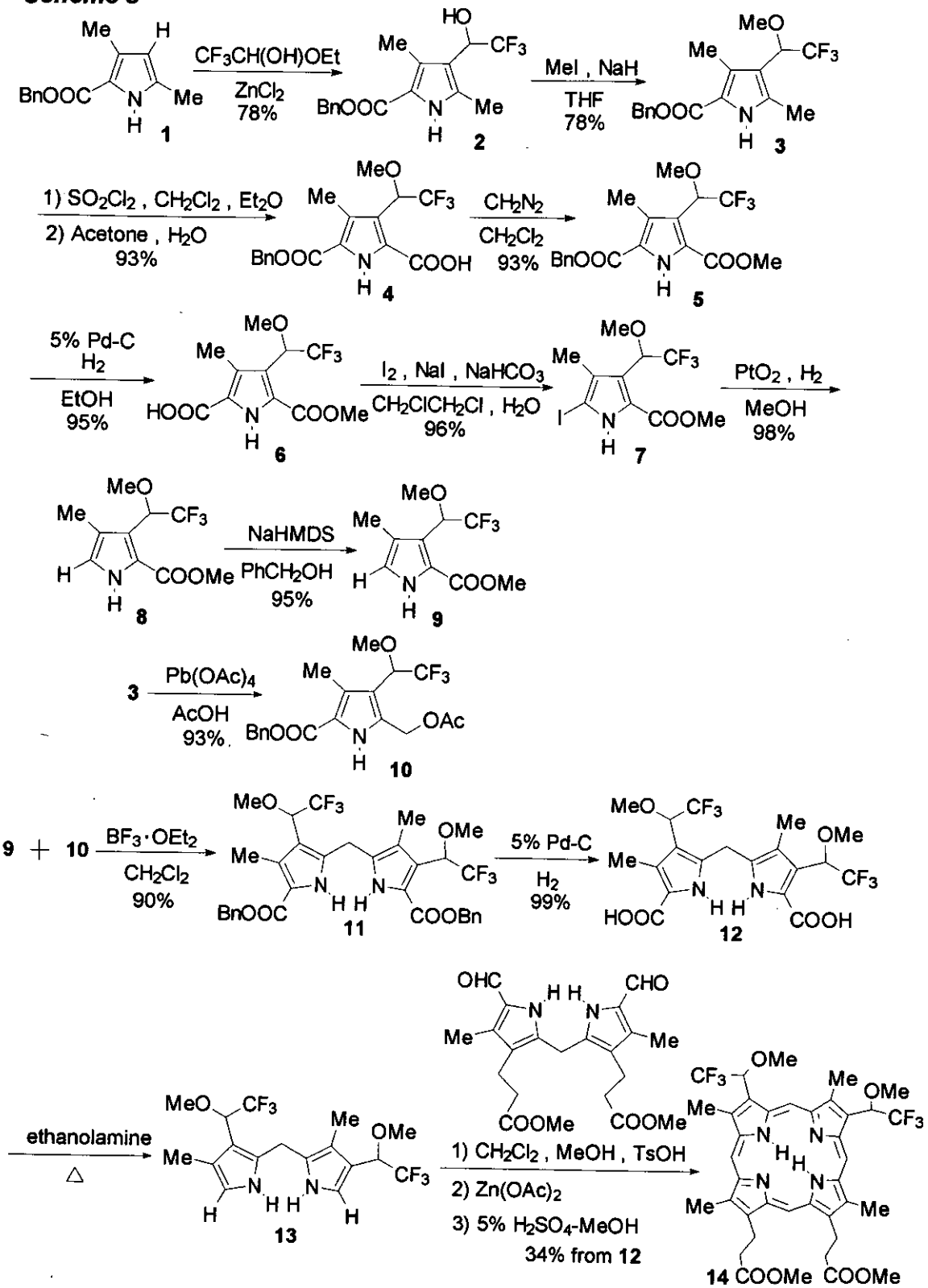
Scheme 2



obtained preferentially. After protection of the hydroxyl group, this was treated with sulfuryl chloride, followed by hydrolysis to give a half ester (**4**) of a dicarboxylic acid. Successive protection and deprotection gave another half ester (**6**), which was converted to a mono ester (**8**) through an iodo compound (**7**). Finally, the methyl ester was changed to a benzyl ester (**9**), which corresponds to the B ring of the porphyrin. The methyl group of the compound (**3**) was oxidized by lead tetraacetate to a 5-acetoxymethyl compound (**10**), which corresponds to the A ring of the porphyrin.

Condensation of **9** and **10**, successive transformation of the dipyrrolomethane, and the final MacDonald condensation were shown in the bottom of Scheme 3. Namely, the condensation of **9** and **10** was accomplished in the presence of a catalytic amount of boron trifluoride etherate, while this type of condensation of 2-(acetoxymethyl)pyrroles with pyrroles usually uses *p*-toluenesulfonic acid as a catalyst. The dipyrrolomethane (**11**) was debenzylated, followed by decarboxylation to give the objective dipyrrolomethane (**13**). This was condensed with the bottom-half dipyrrolomethane[4] in the presence of *p*-toluenesulfonic acid, and the product was oxidized to a zinc complex of the porphyrin in the presence of zinc acetate *in situ*.[6] Finally, the product was treated with sulfuric acid to eliminate the zinc affording the objective product (**14**).

Scheme 3


CF3CH(OH)OEt
ZnCl2
78%
MeI , NaH
THF
78%
1) SO2Cl2 , CH2Cl2 , Et2O
2) Acetone , H2O
93%
CH2N2
CH2Cl2
93%
5% Pd-C
H2
EtOH
95%
I2 , NaI , NaHCO3
CH2ClCH2Cl , H2O
96%
PtO2 , H2
MeOH
98%
NaHMDS
PhCH2OH
95%
Pb(OAc)4
AcOH
93%
BF3·OEt2
CH2Cl2
90%
5% Pd-C
H2
99%
ethanolamine
△
1) CH2Cl2 , MeOH , TsOH
2) Zn(OAc)2
3) 5% H2SO4-MeOH
34% from 12

We have succeeded in the synthesis of a hexafluorohematoporphyrin derivative by a ring closure. This method could be applied for the synthesis of a chiral porphyrin using a chiral pyrrole compound. Recently, we have succeeded in the separation of racemic trifluorohydroxyethyl pyrroles. The biological effect of **14** are now in progress.

REFERENCES AND NOTES

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