# OPTICAL RESOLUTION AND ASYMMETRIC SYNTHESIS OF BENZYL 3,5-DIMETHYL-4-(2,2,2-TRIFLUORO-1-HYDROXYETHYL)-PYRROLE-2-CARBOXYLATE

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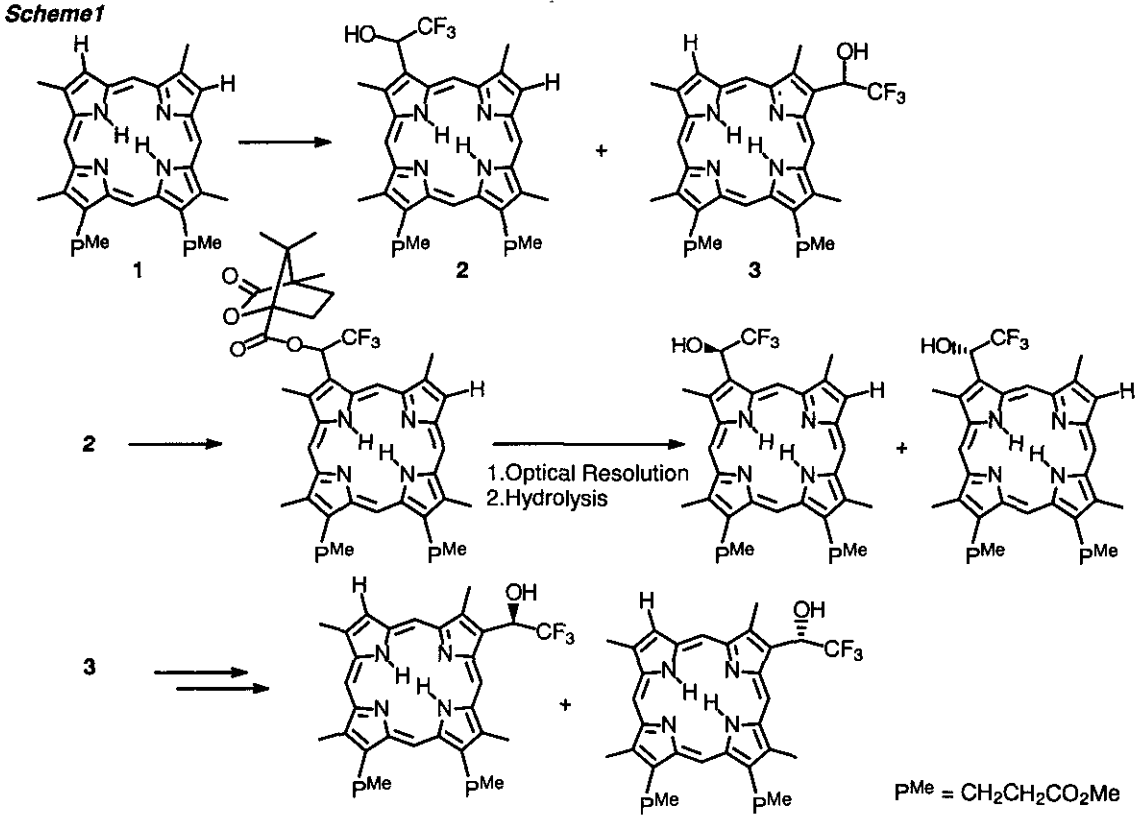
*Dedicated to Professor Koji Nakanishi on the Occasion of His 75th Birthday.*

Abstract - For the total synthesis of 3- and 8-(2,2,2-trifluoro-1-hydroxyethyl)-deuteroporphyrin dimethyl esters (**2**, and **3**) in a large scale by ring closure, the camphanyl ester (**5**) of the titled ester (**4**) was resolved, but hydrolysis of the resolved **5** was unsuccessful. Oxidation of **4** with Dess-Martin reagent gave 3-trifluoromethylcarbonyl compound (**6**), which was reduced with catecholborane in the presence of a chiral catalyst to a chiral isomer of **4** in a high enantiomeric excess.

Some of porphyrin derivatives were found to accumulate to tumor tissues.[1] These porphyrins emit fluorescence by irradiation by laser. This fluorescence is used for diagnosis of the tumor. Further, the porphyrins work as photosensitizer and liberate active oxygen. The active oxygen gives damage to the tumor. This is the basis for therapy of the tumor and is called photodynamic therapy (PDT). Now, "hematoporphyrin derivative" (HpD), which is obtained by treating hematoporphyrin with sulfuric acid in acetic acid, is used for this purpose, but HpD is a complex mixture of porphyrins of uncertain composition. Therefore, if a single porphyrin would accumulate to a tumor tissue and could be used as a photosensitizer, PDT would develop effectively. In the course of our study to find porphyrin derivatives useful for photodynamic therapy,[1] we have resolved 3- and 8-(2,2,2-trifluoro-1-hydroxyethyl)deutero-

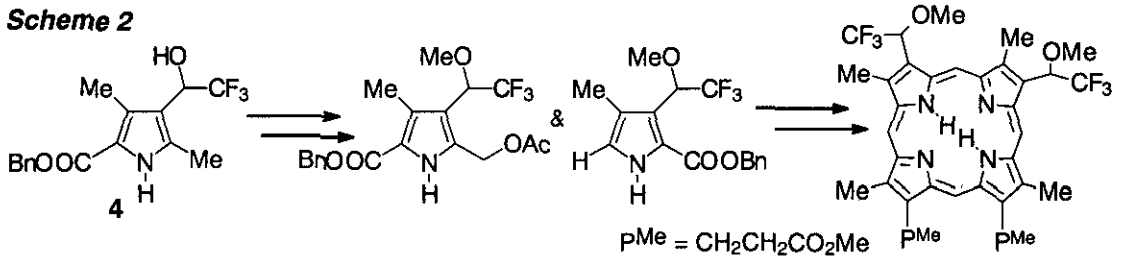
porphyrin dimethyl esters (**2**, and **3**), which were obtained by the Friedel-Crafts reaction of deuteroporphyrin (**1**). The resolved dimethyl esters were hydrolyzed by sodium hydroxide. The sodium salt from (*S*)-**2** was taken up by cancer cells about 15 times more than that from (*R*)-**2**, while the salt of (*R*)-**3** was taken up more than that of (*S*)-**3** (See Scheme 1).[2]

***Scheme1***




Further, we have reported the total synthesis of achiral hexafluorohematoporphyrin derivatives having 2,2,2-trifluoro-1-methoxyethyl groups starting from a pyrrole compound (**4**) (See Scheme 2).[3]

***Scheme 2***

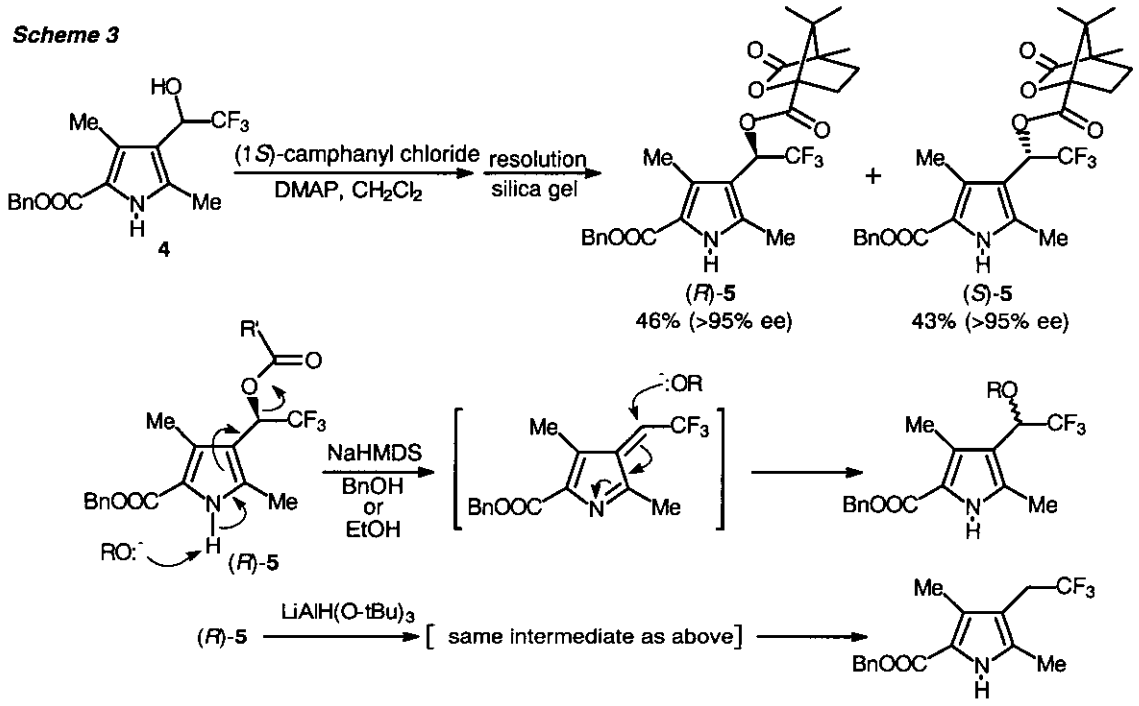



If a chiral isomer of **4** would be obtained, we could synthesize chiral porphyrin derivatives. These chiral porphyrins would help the development of PDT.

At first, **4** was converted to (1*S*)-camphanyl ester (**5**),[4] and the diasteremeric esters were resolved

successfully by column chromatography. Absolute configuration of (*S*)-**5** was determined by X-ray analysis, as shown in Figure 1. Unfortunately, removal of the camphanyl group from the resolved ester by hydrolysis under basic conditions resulted in the formation of racemic mixture of ethers. This can be explained a mechanism as shown in the middle of Scheme 3. Another attempt to remove the camphanyl group by reduction resulted in decamphanyloxylation probably through a similar intermediate as above (See the bottom of Scheme 3). These abnormal reactions might be explained by high stability of the intermediate due to the high electron density on the β-position of the pyrrole ring.

***Scheme 3***




Chiral isomers of **4** could not be obtained by optical resolution. Next, we planned an asymmetric synthesis of chiral **4**. For this purpose, racemic **4** was oxidized with the Dess-Martin reagent to a trifluoroacetyl compound (**6**), and enantioselective reduction of this compound was attempted. Compound (**6**) has one ester group and one carbonyl group. Therefore, a high chemoselective condition with a high enantioselectivity must be chosen. Reduction of **6** with borane in the presence of a catalytic amount of (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine at -60°C gave (*S*)-**4** in the yield of 99% and

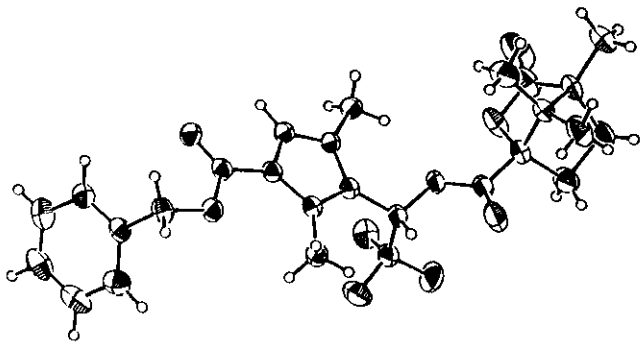
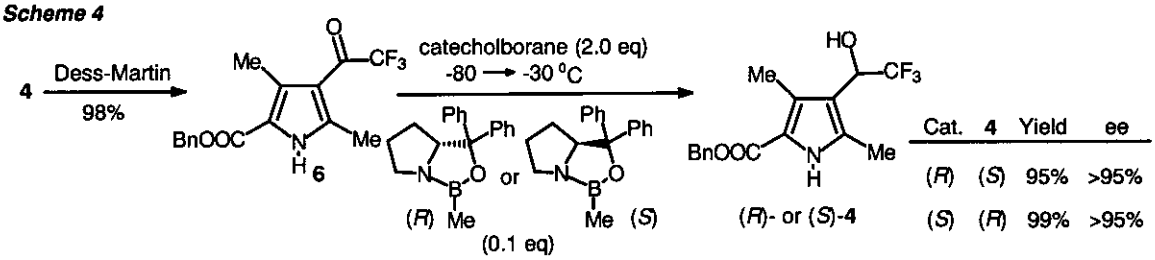


Figure 1 X-ray analysis of (*S*)-**5**

73% ee. When catecholborane was used in the place of borane, ee was improved to more than 95%.[5] The enantiomer ((*R*)-**4**) was obtained similarly using catecholborane in the presence of (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine, as shown in Scheme 4. Compound (*S*)-**4** was converted to the camphanyl ester ((*S*)-**5**) and identified with the authentic sample.

***Scheme 4***




In conclusion, both enantiomers of **4** are now available. These will be useful for synthesis of chiral (trifluorohydroxyethyl)porphyrins, which might be useful for photodynamic therapy of cancer. These syntheses of chiral porphyrins will be published in near future.

## REFERENCES AND NOTES

1. Concerning photodynamic therapy using compounds related to porphyrins, see "Advances in Experimental Medicine and Biology", **160**, "Porphyrin Photosensitization", D. Kessel and T. J. Dougherty (eds), Plenum, New York, 1983, and our review. A. Ando and I. Kumadaki, *Heterocycles*, 1996, **42**, 885. See also the references therein.
2. M, Omote, T, Matsumoto, A, Ando, T, Takagi, M. Koyama, I. Kumadaki, Submitted to *Heterocycles*.
3. M. Omote, A. Ando, T. Takagi, M. Koyama, and I. Kumadaki, *Heterocycles*, 1997, **44**, 89.
4. All the new compounds were identified by high resolution mass spectra, mass spectra, $^{1}$H- and $^{19}$F-NMR spectra.
5. A typical experiment of asymmetric reduction is as follows. Catecholborane (1.95 mL, 18.3 mmol) was added to a suspension of (*R*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine (270 mg, 0.974 mmol) in anhydrous THF (30 mL) at rt in an atmosphere of Ar and the mixture was stirred for another 30 min. To the mixture was added a solution of **6** (3.0 g, 9.23 mmol) in anhydrous THF (30 mL) over 75 min at -80°C and the mixture was stirred for 37 h at -30°C. The reaction was quenched with an alkaline $H_2O_2$ solution and worked up as usual. The crude product was separated by column chromatography ($SiO_2$, $Et_2O$-$CH_2Cl_2$, 5:95) and the eluate was recrystallized from hexane-$CH_2Cl_2$ to give benzyl 3,5-dimethyl-4-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrole-2-carboxylate ((*S*)-**4**, 2.87 g, 95%, >95% ee).

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