AN EFFICIENT ROUTE TO FORMYLDEUTEROPORPHYRINS AND THEIR WITTIG REACTION

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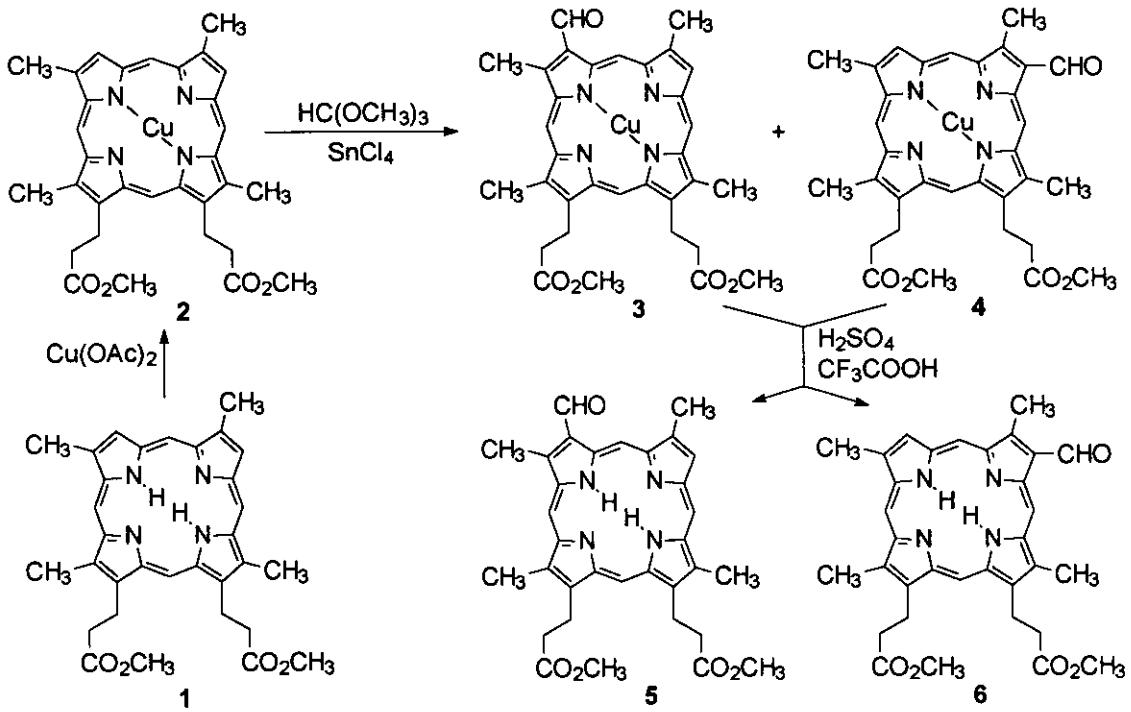
Abstract - Copper complex of deuteroporphyrin dimethyl ester (**2**) was formylated with trimethyl orthoformate in the presence of tin(IV) chloride, followed by demetallation with H_2SO_4-CF_3COOH and separation by column chromatography to give 3- (**5**) and 8-formyl compounds (**6**) in 46 and 47% yields, respectively. The Wittig reaction of these formylporphyrins gave highly functionallized derivatives of porphyrin.

Porphyrin derivatives are potentially useful as a sensitizer for photodynamic therapy (PDT),[1] and simple and efficient routes for their syntheses are required. Deuteroporphyrin dimethyl ester (**1**) is easily obtained from protohemin[2] and a good starting material for porphyrin derivatives. During functionallization of **1**, we found a much more efficient procedure for formylation of **1** than reported.[3] Thus, **1** was converted to copper complex (**2**), and this was treated with trimethyl orthoformate in the presence of tin (IV)chloride. Separation of the products by column chromatography gave a mixture of formylated products (**3** and **4**) with recovery of **1** in 10%. The mixture was demetallated with sulfuric acid in trifluoroacetic acid and separated by column chromatography to give 3- (**5**) and 8-formyldeuteroporphyrin dimethyl ester (**6**) in 46 and 47% yields based on reacted **2**, respectively. Montforts *et al.* reported formylation of **2** with trimethyl orthoformate in trifluoroacetic acid.[3] They recovered more than 30% of **2** and our total yield is much better than theirs. They isolated **3** and **4** by preparative MPLC, then demetallated with sulfuric acid. Therefore, reesterification with diazomethane is necessary to obtain the esters (**5** and **6**), while our method does not need reesterification. Further, we found that separation of **5** and **6** with column chromatography was much easier than that of **3** and **4**.

These chemistries are summarized in Scheme 1.

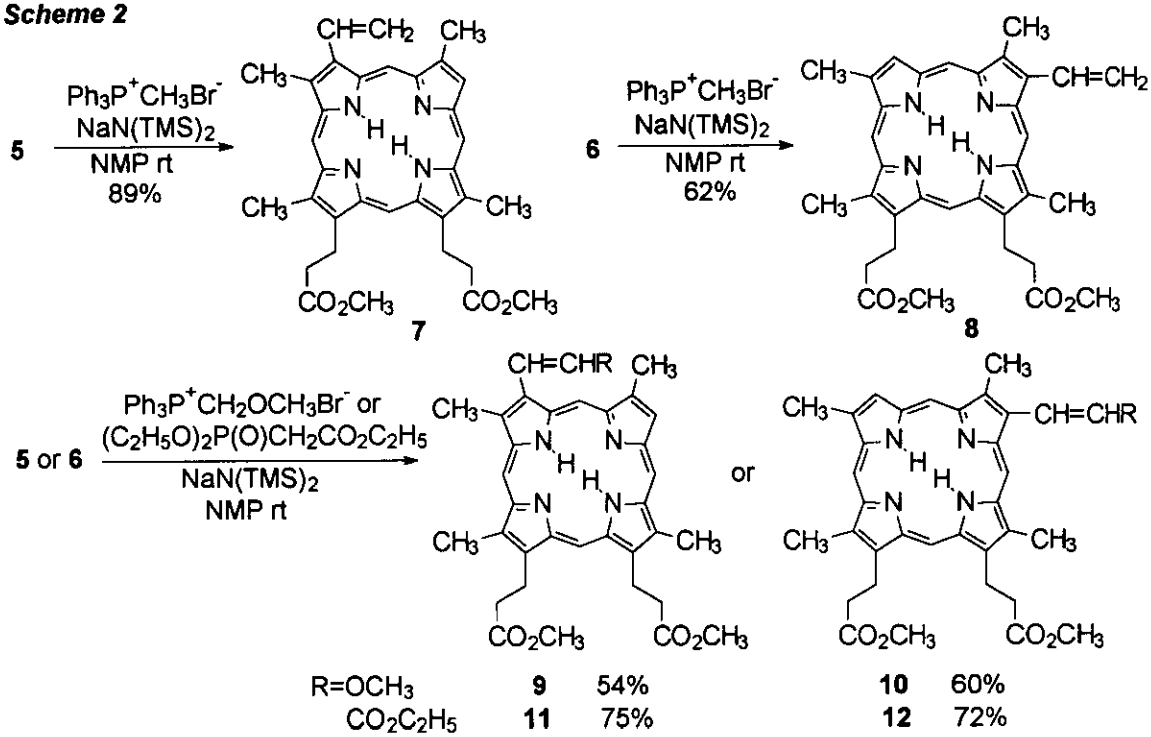
Scheme 1



Next, we planned derivatization of **5** or **6** to porphyrins with biologically important functional groups. For this purpose, we chose monovinyldeuteroporphyrin and examined its synthesis by the Wittig reaction. Malinen *et al.* reported that the Wittig reaction of **5** did give its vinyl derivative, but the ester groups were also converted to propenyl groups.[4] Tamiaki *et al.* reported that a formyl group on a porphyrin did not react with triphenylphosphonium methylide, while the benzylide gave a phenylvinyl derivative.[5] We examined the reaction of **5** with triphenylmethylphosphonium bromide in the presence of sodium bis(trimethylsilyl)amide in THF, but only low yield of vinyl compound was obtained. We examined the solvent effect, and found that *N*-methylpyrrolidinone (NMP) worked as a good solvent and gave 3-vinyldeuteroporphyrin dimethyl ester (**7**) in 89% isolation yield. Crucial point is that a solution of sodium bis(trimethylsilyl)amide was added to a solution of **3** and the phosphonium methylide under slow stirring at room temperature. We believe that a small evolution of heat by reaction of the phosphonium salt with the amide promoted the Wittig reaction. A vigorous stirring scatters the heat, and gives **7** in only poor yield. A similar reaction of **6** gave 8-vinyl compound (**8**) in 62% yield. These results shows that the Wittig reaction of formylporphyrins, which were reported to proceed hardly, is successfully carried out using NMP as a solvent and slow stirring during addition of the base.

To examine the scope and limitation of this methodology, we examined the Wittig reaction of **5** and **6** with electron rich and electron deficient ylides, triphenylphosphonium methoxymethylide and triethyl phosphonoacetate.

Scheme 2



These results show our methodology can be applied to both types of ylides, electron-deficient or excess. Compounds (**9**) and (**10**) were obtained as a mixture of *E/Z* isomers, while **11** and **12** were only *E* isomers. These are consistent with the fact that a stable ylide usually gives a stable olefin.

In conclusion, we could improve the method for introduction of a formyl group to deuteroporphyrin and develop a facile method for the Wittig reaction of the formylporphyrins.

Experimental

General Procedures. ^{1}H-NMR spectra were recorded on JEOL FX90Q and JNM-GX400 spectrometers. MS spectra were recorded on a JEOL JMS-DX300.

Formylation of Deuteroporphyrin Dimethyl Ester Cu-Complex. To a solution of deuteroporphyrin dimethyl ester Cu-complex[6] (4.50 g, 7.50 mmol) and trimethyl orthoformate (16.3 mL, 149 mmol) in CH_2Cl_2 (134 mL), tin tetrachloride (4.5 mL, 38.5 mmol) was added at 0°C. After the mixture was stirred

at rt for further 2.5 h, it was poured into ice-water, and extracted with CH_2Cl_2. The organic layer was combined, and washed with H_2O. After the solvent was removed under vacuum, the residue was separated by column chromatography (SiO_2, 4-10% Et_2O in CH_2Cl_2). The first red zone was DPDME-Cu (0.451 g, 10%). The second red zone was collected, and treated with CF_3COOH-H_2SO_4 (169 mL-16.9 mL) at 0°C. After the mixture was stirred at rt for 1.5 h, it was poured into ice-water, and then extracted with CH_2Cl_2. The organic layer was washed several times with H_2O until aqueous layer was neutral. After evaporation of the solvent under reduce pressure, the residue was separated by column chromatography (SiO_2, 4% Et_2O in CH_2Cl_2) to give 1.75 g (46%) of 3-formyldeuteroporphyrin dimethyl ester (**5**) and 1.77 g (47%) of 8-formyldeuteroporphyrin dimethyl ester (**6**). These were identified with the authentic samples obtained according to the literature.[3]

3-Vinyldeuteroporphyrin (Isopemptoporphyrin) Dimethyl Ester (7). To a solution of **5** (26 mg, 0.046 mmol) and methyltriphenylphosphonium bromide (84 mg, 0.235 mmol) in *N*-methylpyrrolidinone (6 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 225 μL, 0.225 mmol) at rt within several minutes under slow stirring. The mixture was stirred for 30 min at rt under argon, then poured into ice-water, and extracted with CH_2Cl_2 The extract was washed with water. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, 2% Et_2O in CH_2Cl_2) and the product was recrystallized from CH_2Cl_2-hexane to give 19 mg (73%) of 3-vinyldeuteroporphyrin dimethyl ester (7). 7: Violet crystals. mp 217.5-219.5°C (lit., 220-221°C).[7] MS (*m/z*) 564 (M^+). High resolution MS Calcd for $C_{34}H_{36}N_4O_4$: 564.274. Found: 564.274. ^{1}H-NMR ($CDCl_3$) δ:10.15 (s, 1H), 10.00 (s, 1H), 9.99 (s, 1H), 9.95 (s, 1H), 9.03 (q, *J*=0.9 Hz, 1H), 8.25 (dd, *J*=18.1, *J*=11.4 Hz, 1H), 6.33 (dd, *J*=11.4, *J*=1.8 Hz, 1H), 6.15 (dd, *J*=18.0, *J*=1.8 Hz, 1H), 4.38 (t, *J*=7.5 Hz, 2H), 4.37 (t, *J*=7.5 Hz, 2H), 3.70 (d, *J*=0.9 Hz, 3H), 3.66 (s, 6H), 3.64 (s, 3H), 3.60 (s, 3H), 3.58 (s, 3H), 3.26 (t, *J*=7.5 Hz, 4H), -3.88 (br s, 2H).

8-Vinyldeuteroporphyrin (Pemptoporphyrin) Dimethyl Ester (8). To a solution of **6** (26 mg, 0.0459 mmol) and methyltriphenylphosphonium bromide (86 mg, 0.235 mmol) in *N*-methylpyrrolidinone (6 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 225 μL, 0.225 mmol) at rt within several minutes under slow stirring. The mixture was worked up as above to give 8-vinyl-deuteroporphyrin dimethyl ester (**8**, 16 mg, 62%). **8**: Violet crystals. mp 209–210°C (lit., 213–214°C).[7] MS (*m/z*) 564 (M^+). High resolution MS Calcd for $C_{34}H_{36}N_4O_4$: 564.274. Found: 564.274. ^{1}H-NMR ($CDCl_3$) δ: 10.12 (s, 1H), 10.02 (s, 1H), 10.0 (s, 2H), 9.04 (s, 1H), 8.25 (dd, *J*=18.0, *J*=11.4 Hz, 1H), 6.34 (dd, *J*=18.0, *J*=1.8 Hz, 1H), 6.15 (dd, *J*=11.4, *J*=1.8 Hz, 1H), 4.38 (t, *J*=7.0 Hz, 4H), 3.71 (s, 3H), 3.67 (s, 3H), 3.65 (s, 6H), 3.59 (s, 6H), 3.26 (t, *J*=7.0 Hz, 4H), -3.88 (br s, 2H).

3-[(2-Methoxy)vinyl]deuteroporphyrin Dimethyl Ester (9). To a solution of **5** (113 mg, 0.20 mmol)

and (methoxymethyl)triphenylphosphonium chloride (367 mg, 1.07 mmol) in *N*-methylpyrrolidinone (26 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 978 μL, 0.978 mmol) at rt within several minutes under slow stirring. After the mixture was stirred for 15 min at rt under argon, it was poured into ice-water, extracted with CH_2Cl_2, and the extract was washed with H_2O. After the evaporation of solvent, the residue was purified by column chromatography (SiO_2, 4% Et_2O in CH_2Cl_2), and product was recrystallized from CH_2Cl_2-hexane to give 3-[(2-methoxy)vinyl]deuteroporphyrin dimethyl ester (**9**, 64.3 mg, 54%, *E/Z* = 2:1, based on ^{1}H-NMR). **9**: Violet crystals. mp 188–199°C (this unsharpness might be due to the fact that this is a mixture of *E/Z* isomers). MS (*m/z*) 594 (M^+). High resolution MS Calcd for $C_{35}H_{38}N_4O_5$: 594.284. Found: 594.283. ^{1}H-NMR ($CDCl_3$) δ:10.05 (s, 1H), 9.98 (s, 2H), 9.95 (s, 1H), 9.02 (s, 1H), 7.50 (d, *J*=13.0 Hz, 0.67H), 7.21 (d, *J*=13.0 Hz, 0.67H), 6.83 (d, *J*=6.8 Hz, 0.33H), 6.72 (d, *J*=6.8 Hz, 0.33H), 4.37 (t, *J*=7.7 Hz, 4H), 4.14 (s, 2H), 3.99 (s, 1H), 3.71 (s, 3H), 3.65 (s, 6H), 3.62 (s, 3H), 3.59 (s, 3H), 3.26 (t, *J*=7.7 Hz, 4H), -3.81 (m, 2H, NH).

8-[(2-Methoxy)vinyl]deuteroporphyrin Dimethyl Ester (10). To a solution of **6** (27 mg, 0.477 mmol) and (methoxymethyl)triphenylphosphonium chloride (85 mg, 0.248 mmol) in *N*-methylpyrrolidinone (6 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 225 μL, 0.225 mmol) at rt within several minutes under slow stirring. The mixture was worked up as above to give 8-[(2-methoxy)-vinyl]deuteroporphyrin dimethyl ester (**10**, 17 mg, 60%, *E/Z*=7:5) and **6** (9 mg, 33%), respectively. **10**: Violet crystals. mp 176–187°C (this unsharpness might be due to the fact that this is a mixture of *E/Z* isomers). MS (*m/z*) 594 (M^+). High resolution MS Calcd for $C_{35}H_{38}N_4O_5$: 594.284. Found: 594.284. ^{1}H-NMR ($CDCl_3$) δ: 9.95, 9.91, 9.89, 9.87, 9.84, 8.95, 8.94, 7.45 (d, *J*=13.2 Hz, 0.58H), 7.11 (d, *J*=13.2 Hz, 0.58H), 6.80 (d, *J*=6.4 Hz, 0.42H), 6.66 (d, *J*=6.4 Hz, 0.42H), 4.37 (t, *J*=7.5 Hz, 4H), 4.10 (s, OCH_3, 1.74H), 3.96 (s, OCH_3, 1.26H), 3.63 (s, 9H), 3.53 (s, 9H), 3.22 (t, *J*=7.5 Hz, 4H), -3.51 (br s, 2H, NH).

3-[(2-Ethoxycarbonyl)vinyl]deuteroporphyrin Dimethyl Ester (11). To a solution of **5** (13 mg, 0.023 mmol) and triethyl phosphonoacetate (25 μL, 0.126 mmol) in *N*-methylpyrrolidinone (3 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 112 μL, 0.112 mmol) at rt within several minutes under slow stirring. After the mixture was stirred for 30 min at this temperature under argon, it was poured into ice-water, and extracted with CH_2Cl_2. The extract was washed with H_2O. After the evaporation of the solvent, the residue was purified by column chromatography (SiO_2, 4% Et_2O in CH_2Cl_2), and the product was recrystallized from CH_2Cl_2-hexane to give 3-[(2-ethoxycarbonyl)vinyl]-deuteroporphyrin dimethyl ester (**11**, 11 mg, 75%). **11**: Red-violet crystals. mp 232–236°C. MS (*m/z*) 564 (M^+). High resolution MS Calcd for $C_{37}H_{40}N_4O_6$: 636.295. Found: 636.295. ^{1}H-NMR ($CDCl_3$) δ: 9.84

(s, 1H), 9.82 (s, 1H), 9.79 (s, 1H), 9.69 (s, 1H), 9.15 (d, *J*=16.3 Hz, 1H), 8.94 (s, 1H), 6.94 (d, *J*=16.3 Hz, 1H), 4.55 (q, *J*=7.0 Hz, 2H), 4.32 (br t, *J*=7.5 Hz, 2H), 4.28 (br t, *J*=7.0 Hz, 2H), 3.66 (s, 3H), 3.64 (br s, 3H), 3.63 (s, 3H), 3.50 (s, 9H), 3.21 (br t, *J*=7.5, 7.0 HZ, 2+2H), 1.57 (t, *J*=7.0 Hz, 3H), -4.34 (br, 2H, NH)

8-[(2-Ethoxycarbonyl)vinyl]deuteroporphyrin Dimethyl Ester (12). To a solution of **6** (26 mg, 0.0459 mmol) and triethyl phosphonoacetate (50 μL, 0.252 mmol) in *N*-methylpyrrolidinone (6 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 224 μL, 0.224 mmol) at rt within several minute under slow stirring. After the mixture was stirred for 1 h and 45 min at same temperature under argon, it was worked up as above to give 8-[(2-ethoxycarbonyl)vinyl]deuteroporphyrin dimethyl ester (**12**, 21 mg, 72%). **12**: Violet crystals. mp 226–229°C. MS (*m/z*) 564 (M^+). High resolution MS Calcd for $C_{37}H_{40}N_4O_6$: 636.295. Found: 636.2953. ^{1}H-NMR ($CDCl_3$) δ: 9.90 (s, 2H), 9.87 (s, 1H), 9.80 (s, 1H), 9.22 (d, *J*=16.3 Hz, 1H), 8.99 (br s, 1H), 7.00 (d, *J*=16.3 Hz, 1H), 4.55 (q, *J*=7.0 Hz, 2H), 4.36 (m, 2H), 4.30 (m, 2H), 3.69 (br s, 3H), 3.65 (s, 3H), 3.64 (s, 3H), 3.59 (s, 3H), 3.57 (s, 3H), 3.53 (s, 3H), 3.23 (t, *J*=7.4 Hz, 4H), 1.57 (t, *J*=7.0 Hz, 3H), -4.19 (br, 2H, NH).

RERERENCES AND NOTES

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