

AN EFFICIENT ROUTE TO FORMYLDEUTEROPORPHYRINS AND THEIR WITTIG REACTION

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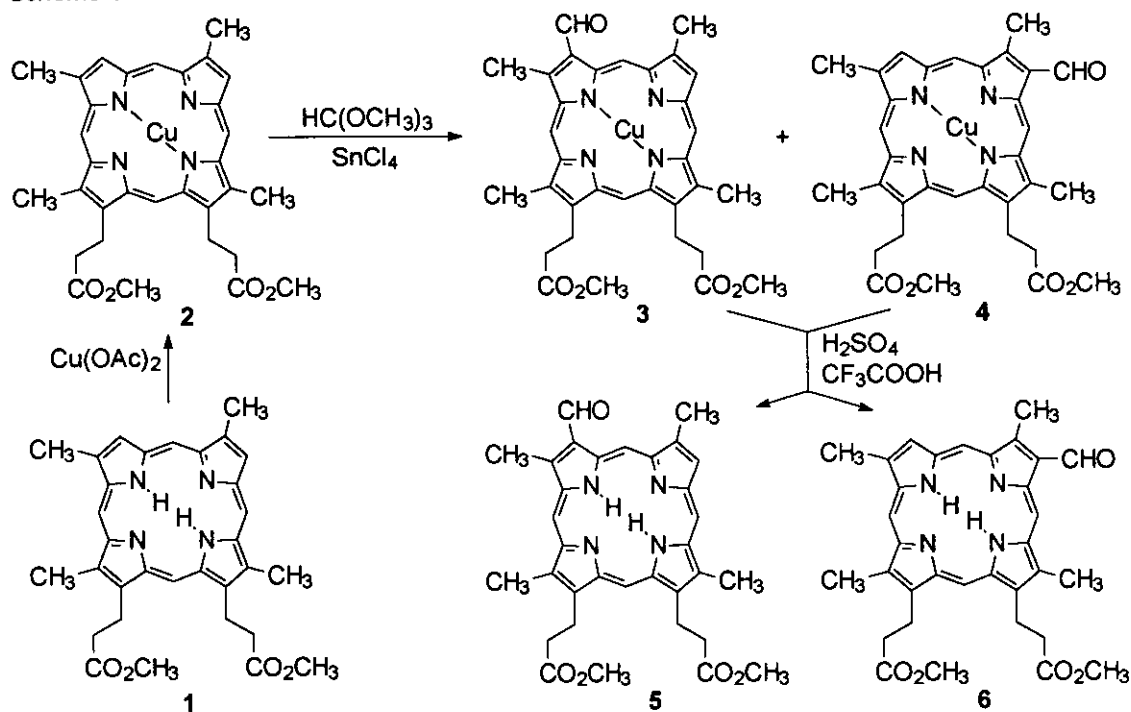
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Abstract - Copper complex of deuteroporphyrin dimethyl ester (**2**) was formylated with trimethyl orthoformate in the presence of tin(IV) chloride, followed by demetallation with $\text{H}_2\text{SO}_4\text{-CF}_3\text{COOH}$ and separation by column chromatography to give 3- (**5**) and 8-formyl compounds (**6**) in 46 and 47% yields, respectively. The Wittig reaction of these formylporphyrins gave highly functionalized 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 protohemin² and a good starting material for porphyrin derivatives. During functionalization 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.

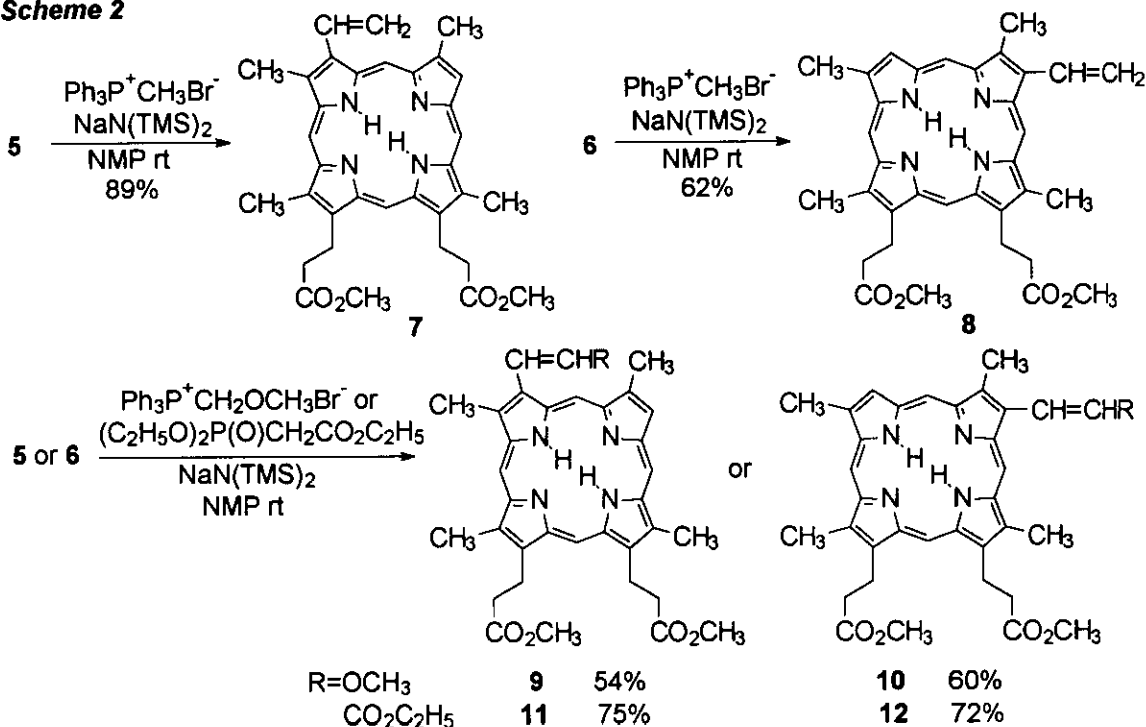
Scheme 1



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 show 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 deuterioporphyrin and develop a facile method for the Wittig reaction of the formylporphyrins.

Experimental

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

Formylation of Deuterioporphyrin Dimethyl Ester Cu-Complex. To a solution of deuterioporphyrin dimethyl ester Cu-complex⁶ (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 $\text{CF}_3\text{COOH-H}_2\text{SO}_4$ (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 $217.5\text{--}219.5^\circ\text{C}$ (lit., $220\text{--}221^\circ\text{C}$).⁷ MS (*m/z*) 564 (M^+). High resolution MS Calcd for $\text{C}_{34}\text{H}_{36}\text{N}_4\text{O}_4$: 564.274. Found: 564.274. $^1\text{H-NMR}$ (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-vinyldeuteroporphyrin dimethyl ester (**8**, 16 mg, 62%). **8**: Violet crystals. mp $209\text{--}210^\circ\text{C}$ (lit., $213\text{--}214^\circ\text{C}$).⁷ MS (*m/z*) 564 (M^+). High resolution MS Calcd for $\text{C}_{34}\text{H}_{36}\text{N}_4\text{O}_4$: 564.274. Found: 564.274. $^1\text{H-NMR}$ (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 μ L, 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 ^1H -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 $\text{C}_{35}\text{H}_{38}\text{N}_4\text{O}_5$: 594.284. Found: 594.283. ^1H -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 μ L, 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 $\text{C}_{35}\text{H}_{38}\text{N}_4\text{O}_5$: 594.284. Found: 594.284. ^1H -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 μ L, 0.126 mmol) in *N*-methylpyrrolidinone (3 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 112 μ L, 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 $\text{C}_{37}\text{H}_{40}\text{N}_4\text{O}_6$: 636.295. Found: 636.295. ^1H -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 μ L, 0.252 mmol) in *N*-methylpyrrolidinone (6 mL) was added sodium bis(trimethylsilyl)amide (1.0 *M* solution in THF, 224 μ L, 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. $^1\text{H-NMR}$ (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).

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