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# The Regioselective Synthesis of Bromochlorins Related to Chlorophyll-*a* from Methyl Pheophorbide-*a*

J.J. Wang*, J.Z. Li and F.G. Li
*Science and Engineering College of Chemistry and Biology, Yantai University, Yantai 264005, P. R. China*

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An efficient methodology has been developed for the regioselective synthesis of brominated chlorins related to chlorophyll-*a* from methyl pheophorbide-*a*. Several regioselective bromination reactions were accomplished by some particular reaction conditions and a series of conversion of functional group from methyl pheophorbide-*a* to synthesize mono-, bis- and tri-brominated chlorines. The possible mechanisms for the debromination were tentatively proposed and the structures of all new chlorins were characterized by elemental analysis, IR, UV-Vis and $^1$H NMR spectra.

**Keywords:** Chlorophyll-*a*, Chlorin, Bromination, Regioselective synthesis, Photodynamic therapy (PDT)

## TRODUCTION

Chlorins and bacteriochlorins, occurred in natural systems as a class of tetrapyrrolic macrocyclic compounds, have gained many interests in recent years because of their unique optical and photochemical properties. They can be utilized as the second generation photosensitizers for photodynamic therapy (PDT) of cancer and as models for photosynthetic reaction centers [1]. Among the chlorophyll derivatives, pheophorbide, pyropheophorbide, purpurin and N-alkylimide of purpurin-18 have been reported as potent photosensitizers with significant anticancer activity [2]. These naturally occurring (bacterio)chlorophylls, such as the most common chlorophyll-*a*, have a nucleophilic vinyl group attached directly to its chlorin *p*-system at 3-position and a 20-*meso*-position abutted on reduced pyrrole ring also shown distinct electron-rich property. It was well known that these C=C at 3-position or C20-*meso*-H can be converted into diverse other substituents which characterize their structural and spectroscopic properties. From many earlier works about various chlorophyll-related compounds it has been shown that the presence and position of the substituents in the parent molecule make a remarkable difference in biological and physicochemical properties. For example, the conversion from vinyl group to formyl group at 3-position by oxidation causes a red shift of the Qy peak maxima from 662 to 688 nm in ether [3], the introduction of pyridine ring at 20-*meso* position exhibits ultrafast energy transfer within cyclic self-assembled chlorophyll tetramers [4]. Recently, we also have developed synthetic routes for constructing various aliphatic, alicyclic and heterocyclic structures at 3- or 20-position [5]. However, it has been a knotty problem to selectively introduce a bromine atom into the active regions of chlorophyll derivatives by an electeophilic addition for C3-vinyl group or electrophilic substitution for C20-*meso*-hydrogen. In normal conditions the bromination of methyl pyropheophorbide-*a* produced a complicated mixture (Scheme 1) [6]. To investigate systematically peripheral functionalization of chlorins related to chlorophyll-*a*, we wish to report herein the regioselective bromination for methyl pyropheophorbide and purpurin-18

*Corresponding author. E-mail: wjj1955@163.com

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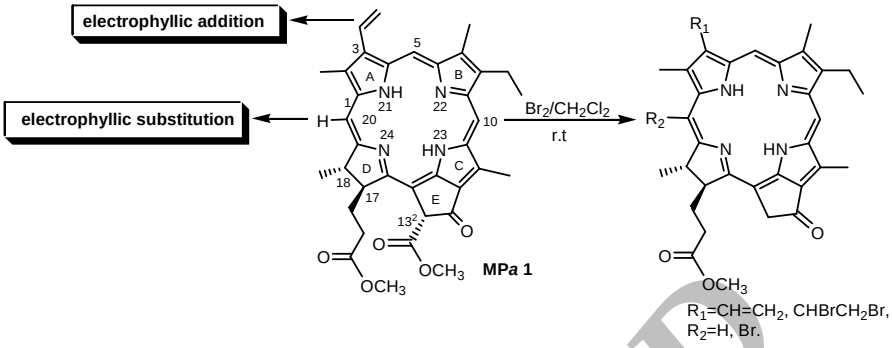


*Scheme 1*

ester by common electrophilic reactions.

## EXPERIMENTAL

Melting points were determined with an Electrothermal 9100 apparatus and uncorrected. IR spectra were measured with a Shimadzu FT IR 8300 spectrophotometer. The UV-Vis spectra were taken with a Unicam SP 800 spectrophotometer. The $^1$H NMR spectra were recorded on a Beucker ARX-400 using TMS as internal standard. The elemental analyses were performed on a Perkin-Elmer 240 microanalyer. All chemical reagents were commercially available and purified by using standard methods. Solvents were dried in routine ways and redistilled. Methyl pheophorbide-*a* (MPa) **1** was obtained according to Smith's method [7].

### 3$^1$(*R*/*S*)-Methyl-3-(1,2-dibromoethyl)-3-devinylpheophorbide-*a* (2)

To a dichloromethane solution (20 ml) of methyl pheophorbide-*a* **1** (186 mg, 0.307 mmol), 85 mg bromine (0.531 mmol) in 2 ml of dichloromethane were slowly added at -30 °C. After stirring for 3 h at the same temperature, the resulted mixture was poured into iced water and extracted with dichloromethane (3 × 20 ml). The combined extract was dried over $Na_2SO_4$, and the solvent was evaporated under vacuum. The residue was chromatographed with a silica gel column (eluent:hexane/ethyl acetate, 3:1) to give 113 mg **2** (0.147 mmol, 3$^1$-*R*/*S* = 1:1) as a dark-green powder in 48% yield. m.p.: 217-220 °C; UV-Vis ($CHCl_3$) $\lambda_{max}$: 412 (relative intensity, 1.00), 473 (0.05), 507 (0.13), 537 (0.12), 610 (0.10), 670 (0.60) nm; $^1$H NMR ($CDCl_3$) $\delta$: 0.02, -2.02 (each br s, each 1H, NH), 1.72 (1.48) (3H, d, J = 7.2 Hz, 18-$CH_3$), 1.79 (3H, t, J = 7.6 Hz, 8-$CH_3$), 2.48-2.65, 2.16-2.35 (all 4H, each m, 17a+17b-H), 3.89 (3.88), 3.62 (3.61), 3.60 (3.59), 3.40, 3.21 (3.20) (each 3H, each s, each $CH_3$+$OCH_3$), 3.62 (2H, q, J = 7.6 Hz, 8a-H), 4.14-4.21 (1H, m, 18-H), 4.47 (1H, q, J = 7.0 Hz, 17-H), 4.89 (4.88) (1H, d, J = 13.4 Hz, 3b-H), 5.43 (5.41) (1H, dd, J = 13.4, 5.6, Hz, 3b-H), 6.20 (6.16) (1H, s, 13$^2$-H), 6.85 (6.83) (1H, dd, J = 13.4, 3.4, 3a-H), 8.58 (8.59), 9.44 (9.45), 9.53 (9.54) (each 1H, each s, *meso*-H). IR (KBr) v: 3465 (O-H), 3323 (N-H), 2956, 2920, 2850 (C-H), 17357-1697 (C=O) 1605 (C=C), 1502 (chlorin skeleton), 1458, 1444, 1263, 1189, 1083, 1043 cm$^{-1}$; Anal. Calcd. for $C_{36}H_{38}Br_2N_4O_5$: C, 56.41; H, 5.00; N, 7.31; found: C, 56.23; H, 5.20; N, 7.11.

### 3$^1$-(*R*/*S*)-Methyl-3-(1,2-dibromoethyl)-20-bromo-3-devinylpheophorbide-*a* (3)

150 mg of NBS was partialy added to a solution of MPa **5** (200 mg, 0.330 mmol) in methylene chloride (50 ml), and the reaction mixture was stirred for 5 h under nitrogen in the dark. The resulting solution was then poured into 200 ml of iced water and extracted with methylene chloride (3 × 100 ml). The combined extracts was washed with 10% aqueous $NaHCO_3$, water and dried over $Na_2SO_4$ and evaporated to dryness. The residue was chromatographed on silica gel (eluent:hexane/ethyl acetate, 2:1) to afford 237 mg chlorin **3** (0.281 mmol, 3$^1$-*R*/*S* = 1:1) as dark-red solid in 85% yield. m.p.: 241-244 °C; UV-Vis ($CHCl_3$) $\lambda_{max}$: 415 (relative intensity, 1.00), 520 (0.11), 554 (0.21), 626 (0.08), 685 (0.84) nm; $^1$H NMR ($CDCl_3$) $\delta$: -1.74, -1.94 (each br s, each 1H, NH), 1.60 (3H, d, J = 7.0 Hz, 18-$CH_3$), 1.69 (3H, t, J = 7.6 Hz, 8-$CH_3$), 2.47-2.62, 2.43-2.45, 2.08-2.30 (all 4H, each m, 17a+



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17b-H), 3.89, 3.69, 3.65, 3.54, 3.28 (each 3H, each s, each $CH_3$+$OCH_3$), 3.71 (2H, q, J = 7.6 Hz, 8a-H), 4.02 (4.07) (1H, dd, J = 10.1, 3.8 Hz, 3b-H), 4.14 (4.13) (1H, d, J = 8.5 Hz, 17-H), 4.40 (4,46) (1H, d, J = 10.1 Hz, 3b-H), 4.88 (1H, q, J = 7.0 Hz, 18-H), 6.47 (1H, dd, J = 10.1, 3.8 Hz, 3a-H), 6.23 (6.21) (1H, s, $13^2$-H), 9.60, 10.16 (10.11) (each 1H, each s, *meso*-H). IR (KBr) *v*: 3454 (N-H), 2961, 2867 (C-H), 1743, 1726-1703 (C=O), 1645, 1608 (C=C), 1535 (chlorin skeleton), 1461, 1402, 1309, 1143, 1074 $cm^{-1}$. Anal. Calcd. for $C_{36}H_{37}Br_3N_4O_5$: C, 51.14; H, 4.41; N, 6.63; found: C, 51.27; H, 4.60; N, 6.55.

### $3^1$-(*R*/*S*)-Methyl-3-(1-hydroxylethyl)-3-devinylpheophorbide-*a* (4)

MPa **1** (180 mg, 0.297 mol) was dissolved in 10 ml of a solution of 30% hydrogen bromide in acetic acid and then stirred for 3 h at 55 °C under nitrogen in dark. The solution was then poured into 100 ml of water and extracted with dichloromethane (3 × 25 ml). The combined extracts were washed with 100 ml of 10% aqueous sodium carbonate and then 100 ml of water and dried over $Na_2SO_4$. After evaporation, the residue was treated with excess ethereal diazomethane and evaporated, and the resulting solid was purified and cooled to -30 °C. To this solution was added 30 mg of NBS in portion-wise, the resulting solution was then stirred for 3 h and poured into 100 ml of water and extracted with 3 × 25 ml of methylene chloride. After removal of solvent the residue was treated with ethereal diazomethane and chromatography on silica gel (eluent:hexane/ethyl acetate, 4:1) to give 96 mg **4** (0.154 mmol, $3^1$-*R*/*S* = 1:1) as dark-green solid in the yield of 52%. m.p.: 257-269 °C; UV-Vis ($CHCl_3$) $\lambda_{max}$: 410 (relative intensity, 1.00), 505 (0.12), 536 (0.11), 604 (0.10), 661 (0.47) nm; $^1$H NMR ($CDCl_3$) $\delta$: -1.79, 0.35 (each br s, each 1H, NH), 1.67 (3H, t, J = 7.6 Hz, 8-$CH_3$), 1.79 (1.77) (3H, d, J = 7.0 Hz, 18-$CH_3$), 2.11 (3H, d, J = 6.0 Hz, 3a-$CH_3$), 2.16-2.37, 2.43-2.68 (each m, all 4H, 17a+17b-H), 3.21, 3.38 (3.37), 3.59 (3.58), 3.63, 3.87 (each 3H, each s, all 15H, $CH_3$+$OCH_3$), 3.65 (2H, q, J = 7.6 Hz, 8a-H), 4.12-4.21 (m, 1H, d, 17-H), 4.37-4.47 (1H, m, 18-H), 6.30-6.39 (m, 1H, 3a-H), 6.21 (6.18) (1H, s, $13^2$-H), 8.51 (8.49), 9.44, 9.64 (9.63) (each 1H, each s, *meso*-H). IR (KBr) *v*: 3408 (N-H), 2960, 2929 (C-H), 1726-1703 (C=O), 1646 (C=C), 1550 (chlorin skeleton), 1460, 1380, 1271, 1205, 1143, 1070 $cm^{-1}$. Anal. Calcd. for $C_{36}H_{40}N_4O_6$: C, 69.21; H, 6.45; N, 8.97; found: C, 69.44; H, 6.60; N, 8.79.

### $3^1$-(*R*/*S*)-Methyl-3-(1-hydroxylethyl)-20-bromo-3-devinylpyropheophorbide-*a* (5)

Chlorin **4** (98 mg, 0.157 mol) was dissolved in 15 ml of acetic acid and then refluxed for 3 h under nitrogen in dark. The solvent was removed to dryness under vacuum and then redissolved in 10 ml of methylene chloride. To this solution, 90 mg of NBS was partialy added, and the reaction mixture was stirred for 5 h under nitrogen in the dark. The resulting solution was then poured into 80 ml of iced water and extracted with methylene chloride (3 × 15 ml). The combined extracts was washed with 10% aqueous $NaHCO_3$, water and dried over $Na_2SO_4$ and evaporated to dryness. The residue was chromatographed on silica gel (eluent: hexane/ethyl acetate, 2:1) to afford 69 mg chlorin **5** (0.107 mmol, $3^1$-*R*/*S* = 1:1) as dark-red solid in 68% yield. m.p.: 251-254 °C; UV-Vis ($CHCl_3$) $\lambda_{max}$: 413 (relative intensity, 1.00), 478 (0.12), 537 (0.13), 616 (0.06), 673 (0.40) nm; $^1$H NMR ($CDCl_3$) $\delta$: -2.16 (-2.26), 0.59 (0.42) (each br s, each 1H, NH), 1.47 (1.40) (3H, d, J = 7.2 Hz, 18-$CH_3$), 1.67 (3H, t, J = 7.6 Hz, 8-$CH_3$), 1.87-2.08, 2.17-2.41, 2.54-2.66 (all 4H, each m, 17a+17b-H), 2.12 (2.15) (3H, J = 6.7 Hz, 3b-H), 3.25 (3.26), 3.52 (3.50), 3.62 (3.59), 3.65 (3.62) (each 3H, each s, each $CH_3$+$OCH_3$), 3.67 (3.66) (2H, q, J = 7.6 Hz, 8a-H), 4.82 (4.85) (1H, q, J = 7.2 Hz, 18-H), 4.08 (3.99) (1H, dd, J = 9.2, 2.8 Hz, 17-H), 4.89 (4.88) (1H, d, J = 13.4 Hz, 3b-H), 5.43 (5.41) (1H, dd, J = 13.4, 5.6, Hz, 3b-H), 5.01 (4.85) (1H, d, J = 19.8 Hz, $13^2$-H), 5.09 (5.00) (1H, d, J = 19.8 Hz, $13^2$-H), 6.45 (6.39) (1H, q, J = 6.7 Hz, 3a-H), 9.33 (9.29), 9.99 (10.09) (each 1H, each s, *meso*-H). IR (KBr) v: 3446 (N-H), 2960, 2927, 2858 (C-H), 1737-1704 (C=O), 1674 (C=C), 1542 (chlorin skeleton), 1523, 1458, 1398, 1174, 1068, 1051 $cm^{-1}$. Anal. Calcd. for $C_{34}H_{37}BrN_4O_4$: C, 63.25; H, 5.78; N, 8.68; found: C, 63.33; H, 5.60; N, 8.80.

### Methyl-20-bromopyropheophorbide-*a* (6)

Chlorin **5** (56 mg, 0.087 mmol) was dissolved in 25 ml of dried benzene containing 20 mg TsOH and stirred at 75 °C for 8 h. The resultant mixture was poured into 20 ml of iced water extracted with methylene chloride (3 × 15 ml). The combined extracts was washed with 10% aqueous $NaHCO_3$, water and dried over $Na_2SO_4$, sequently and evaporated to dryness. The



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residue was chromatographed on silica gel (eluent: hexane/ethyl acetate, 4:1) to afford chlorin **6** as red solid in 46% yield. Its analytical data was consistent with ones in the literature [6].

### 20-Bromopurpurin-18-methyl Ester (7) and Purpurin-18-methyl Ester (8)

120 mg of potassium t-butoxide was partialy added to a solution of 120 mg chlorin **3** (0.143 mmol) in *t*-butaol (20 ml) at 0 °C, and the reaction mixture was stirred over night under nitrogen in the dark. After adding 5 ml of methanol the resulting solution was then poured into 200 ml of ice water and extracted with 3 × 100 ml of methylene chloride. The combined extracts was washed with 65% aqueous AcOH, water and dried over $Na_2SO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (eluent: hexane/ethyl acetate, 2:1) to afford 33 mg chlorin **7** (0.050 mmol) as red solid in 35% yield and 17 mg **8** (0.030 mmol) as red solid in 21% yield. **7**: m.p.: 235-237 °C; UV-Vis ($CHCl_3$) $\lambda_{max}$: 420 (relative intensity, 1.00), 493 (0.05), 561 (0.05), 663 (0.09), 713 (0.49) nm; $^1$H NMR ($CDCl_3$) $\delta$: 0.05, -1.50 (each br s, each 1H, NH), 1.50 (3H, d, J = 7.2 Hz, 18-$CH_3$), 1.66 (3H, t, J = 7.6 Hz, 8-$CH_3$), 2.75-2.84, 2.51-2.63, 2.28-2.41 (all 4H, each m, 17a+17b-H), 3.74, 3.57, 3.49, 3.15 (each 3H, each s, each $CH_3$+$OCH_3$), 3.62 (2H, q, J = 7.6 Hz, 8a-H), 4.83 (1H, q, J = 7.1 Hz, 18-H), 5.18 (1H, d, J = 8.9 Hz, 17-H), 6.10 (1H, dd, J = 17.8, 1.4 Hz, 3a-H), 6.27 (1H, dd, J = 11.4, 1.4 Hz, 3a-H), 7.78 (1H, dd, *J* = 17.8, 11.4 Hz, 3a-H), 9.52, 9.49 (each 1H, each s, *meso*-H). IR (KBr) v: 3469, 3350 (N-H), 2964, 2929, 2869 (C-H), 1747-1699 (C=O) 1606 (C=C), 1533 (chlorin skeleton), 1458, 1400, 1311, 1170, 1137, 1081, 1020 $cm^{-1}$. Anal. Calcd. for $C_{34}H_{33}BrN_4O_5$: C, 62.10; H, 5.06; N, 8.52; found: C, 62.23; H, 5.22; N, 8.76. The analytical data of compound **8** was consistent with ones in the literature [8].

### 3$^1$(*R/S*)-3-(1,2-Dibromoethyl)-20-bromopurpurin-18 methyl Ester (9)

150 mg of NBS was partialy added to a solution of purpurin-18 eater **8** (200 mg, 0.346 mmol) in methylene chloride (50 ml) at -30 °C, and the reaction mixture was stirred for 4 h at -5 °C under nitrogen in the dark. The resulting solution was then poured into 200 ml of iced water and extracted with methylene chloride (3 × 100 ml). The combined extracts was washed with 10% aqueous $NaHCO_3$, water and dried over $Na_2SO_4$ and evaporated to dryness. The residue was chromatographed on silica gel (eluent: hexane/ethyl acetate, 2:1) to afford 163 mg chlorin **9** (0.221 mmol, 3$^1$*R/S* = 1:1) as dark-red solid in 62% yield. m.p.: 246-249 °C; UV-Vis ($CHCl_3$) $\lambda_{max}$: 412 (relative intensity, 1.00), 480 (0.05), 545 (0.19), 647 (0.07), 707 (0.44) nm; $^1$H NMR ($CDCl_3$) $\delta$: -0.27, -0.15 (each br s, each 1H, NH), 1.76 (1.79) (3H, d, J = 6.9 Hz, 18-$CH_3$), 1.60 (1.61) (3H, t, J = 7.6 Hz, 8-$CH_3$), 1.93-2.04, 2.44-2.53, 2.71-2.83 (all 4H, each m, 17a+17b-H), 3.21, 3.42, 3.55 (3.57), 3.60 (3.61) (each 3H, each s, each $CH_3$+$OCH_3$), 3.56 (2H, q, J = 7.6 Hz, 8a-H), 4.44 (4.43) (1H, q, J = 7.2 Hz, 18-H), 4.67 (1H, dd, J = 10.5, 5.2 Hz, 3b-H), 4.90 (1H, td, J = 10.5, 4.0 Hz, 3b-H), 5.22 (5.20 (1H, d, J = 8.5 Hz, 17-H), 6.48-6.54 (1H, m, 3a-H), 8.68 (8.67), 9.41 (9.53), 9.57 (9.56) (each 1H, each s, *meso*-H). IR (KBr) *v*: 3446 (N-H), 2925, 2856 (C-H), 1741-1710 (C=O), 1610 (C=C), 1533 (chlorin skeleton), 1463, 1307, 1132, 1076, 1000 $cm^{-1}$. Anal. Calcd. for $C_{34}H_{34}Br_2N_4O_5$: C, 55.30; H, 4.64; N, 7.59; found: C, 55.23: H, 4.79: N, 7.76.

### 3-Cyclopropyl-3-devinylpyropheophorbide-*a* (10)

MPa **1** (230 mg, 0.379 mmol) was dissolved in 30 ml of acetic acid and then refluxed for 3 h under nitrogen in dark. The solvent was removed to dryness under vacuum, redissolved in 10 ml of methylene chloride, treated with ethereal diazomethane and stirred for 8 h. After evaporation the residue was dissolved in 5 ml of diphenyl ether and stirred at 180 °C for 1 h. The resulting solution was then poured into 80 ml of iced water and extracted with methylene chloride (3 × 15 ml). The combined extracts was washed with water and dried over $Na_2SO_4$ and evaporated. The residue was chromatographed on silica gel (eluent: hexane/ethyl acetate, 4:1) to afford 124 mg chlorin **9** (0.220 mmol) as green solid in 58% yield. The analytical data was consistent with ones in the literature [5c].

### 3-Cyclopropyl-20-bromo-3-devinylpyropheo-phorbide-*a* (11)

This compound **10** as a red solid was obtained in 71% yield from **9** by same method for preparing chlorin **3**. m.p.: 211-214 °C; UV-Vis ($CHCl_3$) $\lambda_{max}$: 415 (relative intensity, 1.00), 516 (0.08), 549 (0.10), 613 (0.06), 670 (0.42) nm; $^1$H



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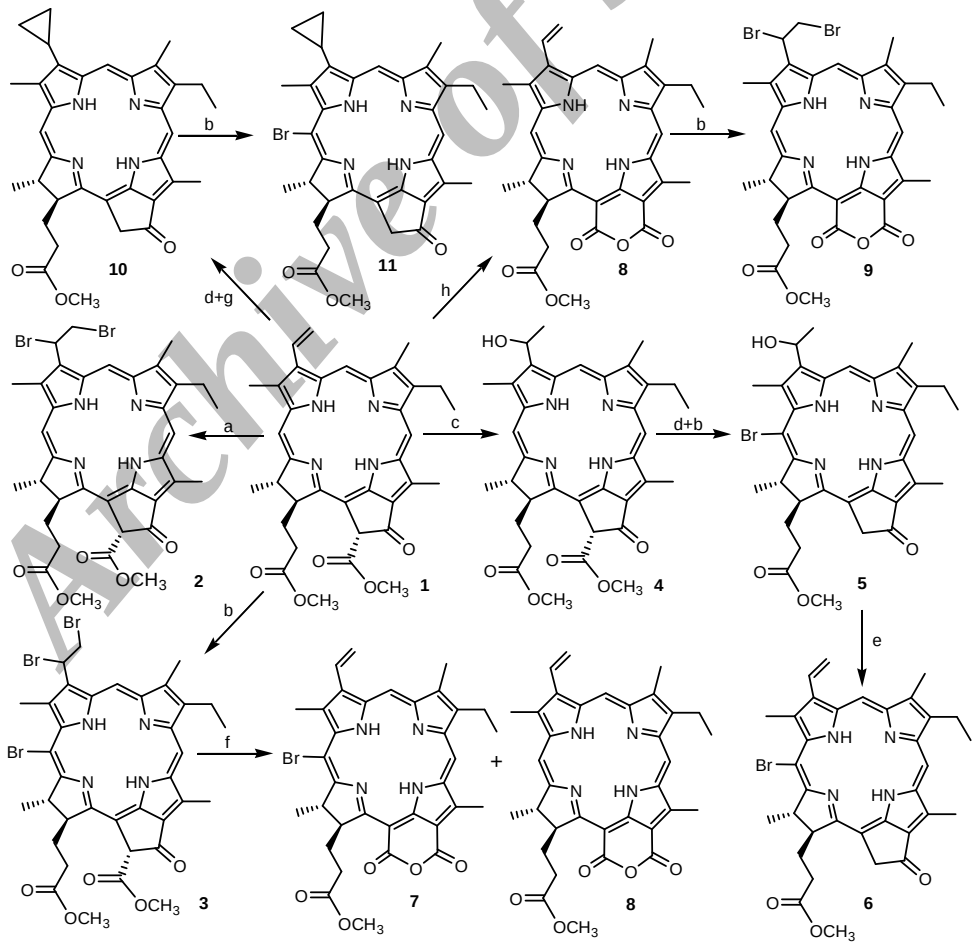
NMR ($CDCl_3$) $\delta$: -1.80, 0.87 (each br s, each 1H, NH), 1.25-1.34, 1.64-1.73 (all 4H, each m, 3(2')-H), 1.58 (3H, d, J = 6.9 Hz, 18-$CH_3$), 1.70 (3H, t, J = 7.6 Hz, 8-$CH_3$), 2.12-2.23, 2.46-2.61 (all 4H, each m, 17a+17b-H), 2.73-2.80 (1H, m, 3(1')-H), 3.30, 3.57, 3.66, 3.67 (each 3H, each s, each $CH_3$+$OCH_3$), 3.70 (2H, q, J = 7.6 Hz, 8a-H), 4.21 (1H, dd, J = 7.5, 3.3 Hz, 17-H), 4.55 (1H, q, J = 7.1 Hz, 18-H), 5.19 (1H, d, J = 19.9 Hz, $13^2$-H), 5.25 (1H, d, J = 19.9 Hz, $13^2$-H), 9.52, 9.91 (each 1H, each s, *meso*-H). IR (KBr) *v*: 3409, 3303 (N-H), 2960, 2929, 2866 (C-H), 1726-1703 (C=O), 1647 (C=C), 1550, 1460, 1380, 1271, 1205, 1143, 1070 $cm^{-1}$. Anal. Calcd. for $C_{35}H_{37}BrN_4O_3$: C, 65.52; H, 5.81; N, 8.73; found: C, 65.33; H, 5.72; N, 8.80.

## RESULTS AND DISCUSSIONS

Because of the similar electron-rich properties of the C3-vinyl group and C20-*meso*-position, the multi-sites reactions of chlorins related to chlorophyll-*a* with bromine in dichloromethane lead to forming a complicated mixture, from which mono-, di, tri-brominated chlorins and other low yield of products have been separated in our previous works [6]. In order to selectively obtain brominated chlorophyll derivatives at C3- or C20-position, we choosed methyl pheophorbide-*a* **1** (**MPa**) as starting material, which is extracted from *Spirulina maxima* alga [7] and readily converted into dibromochlorin **2** in 48% yield by a electrophilic additional reaction with




a) $Br_2/CH_2Cl_2$.-30°C; b) NBS/$CH_2Cl_2$/r,t; c) 30%HBr in AcOH/40°C/$CH_2N_2$; d) AcOH/reflux; e) TsOH/$C_6H_6$/75°C; f) t-BuOH/t-BuOK/$CH_2N_2$; g )$CH_2N_2$/MeOH; h) KOH/$C_3H_7OH$/Acetone/$O_2$.

*Scheme 2*



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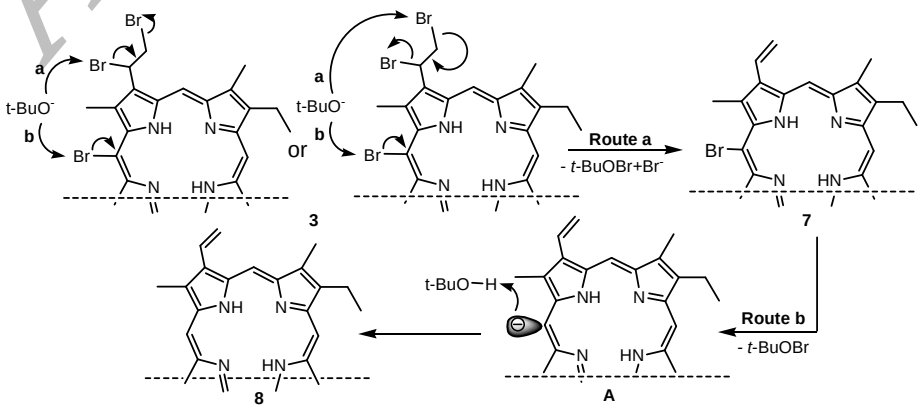
bromine in methylene chloride at -30 °C. On the treatment of MPa **1** with excess NBS in dichloromethane generated tribromochlorin **3** in excellent yield, which can be viewed as an applicable precursor for preparing brominated chlorin deu to its polybrominated structure and *β*-ketoester moiety on exocyclic ring. To avoid the competitive reaction from C3-vinyl group, this electron-rich C=C was converted into hydroxyethyl group in advance by reaction with hydrogen bromide in acetic acid to form chlorin **4** in 52% yield, whose demethyloxycarbonylation by refluxing in AcOH for 3 h and bromination with NBS for 1 h gave 20-bromochlorin **5** as a sole brominated product in 68% yield. Subsequent dehydration was accomplished by refluxing in benzene containing catalytic amount of TsOH for 2 h to produce 20-bromo-MPPa **6** in 46% yield. The treatment of **3** with potassium *t*-butoxide in *t*-butanol at 0 °C over rnight gave 20-bromopurpurin-18 **10** in 35% yield and purpurin-18 **3** in 21% yield after methylation with ethereal diazomethane. This reaction indicated that C20-bromine can also be removed under strong alkaline condition and *β*-ketoester moiety as an exocyclic ring was readily converted into six-membered cyclic anhydride by allomerization and rearrangement [9]. Because the structural alteration of exocyclic ring of chlorin would affect the density and distribution of ring current, it might enlarge the gap in electrophilic reaction between C3-vinyl group and C20-*meso*-hydrogen. The bromination of purpurin-18 **8** with NBS, readily prepared from MPa **1** according to the literature [8], proved the above-mentioned supposal in which dibromo-substituted purpurin **9** as an exclusive product was obtained in 62% yield. For same purpose to evade the interference of C3-vinyl group to the electrophilic bromination, chlorin **10**, obtained by one-pot method from MPa **1**, was used as a substrate and brominated with NBS to give high yield of mono- brominated chlorine **11**.

The regioselective electrophilic addition resulting from the reaction of **8** with NBS at room temperature has shown that the C3-vinyl group of purpurin-18 ester possessed more intense nucleophilic property in comparison with C20-*meso*-position. For pheophorbide-*a* **1**, the bromination with $Br_2$ at -30 °C also reflected that reactive activity of C3-vinyl group actually was slightly higher than that of C20-*meso*-position in this competitive reaction.

It was found that the normal dehydrobromination of C3-dibromoethyl group was not occurred, while elimination of all bromine atoms, attached to C3-position or C20-*meso*-position, took place by a halophilic reaction step. The steric hindrances of bromine atoms at C3-position and chlorin chromophore may obstruct the potassium *tert*-butoxide with bulky space from attacking protons, connected geminaly with the bromine atoms. The debromination of chlorin **3** gone through two different routes as shown in Scheme 3. Unlike nucleophile-induced halophilic reactions [10], the concerted debromination reaction at C3-position (route a) directly recovered the vinyl group without forming relevant carbanion *via* a bromophilic attacking toward C3a-bromine atom (or C3b-bromine atom) resulting from nucleophilic reagent to give 20-*meso*-brominated chlorine **7**, accompanied by leaveing a *t*-butyl hypbromorite and a bromonion. In route b, the attacking toward to the 20-bromine atom from t-BuOK firstly generated a carbanion intermediate **A**, and then abstracted a proton from




*Scheme 3*



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solvent to give purpurin-18 **8**. At the same time, the exocyclic five-membered rings of chlorine **3** smoothly convert into six-membered cyclic anhydride moiety by allomerization and arrangement [9].

In conclusion, an efficient methodology for the regioselective synthesis of brominated chlorins possessing basic skeleton of chlorophyll-*a* from methyl pheophorbide-*a* has been developed. Mono-bromination for C20-*meso*-position of methyl pyropheophorbide-*a* (MPPa) was accomplished by protecting C3-vinyl group. From easily accessible tribrominated precusor **8**, several regioselective brominated chlorins were obtained by debromination and relevant conversion of functional group. Introducing and removing bromine located on chlorin chromophore can widen conversion modes of chlorophyll homologues. These brominated chlorins may serve as versatile building blocks that allow for subsequent transformations into more complicated and applicable chlorophyll derivatives.

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