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Convenient peripheral aroyloxylation reactions of porphyrins and chlorophyll-*a*-based chlorins with benzoyl peroxide

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ABSTRACT

A practical and efficient methodology for the formation of C–O bonds on the porphyrin/chlorin periphery was developed. The aroyloxy-substituted porphyrins and chlorins related to chlorophyll-*a* at the β- and *meso*-positions, respectively, were conveniently synthesized by the free radical substitution reaction with benzoyl peroxide and its homologs.

Much effort has been devoted to the synthesis of porphyrins bearing carbon–heteroatom bonds, such as C–O, C–S, C–N, and C–P bonds, attached to β- and *meso*-positions.[1] The introduction of heteroatom-linked functional groups into the porphyrin periphery can modulate the properties of the porphyrin macrocycle and provides access to several new, potentially useful porphyrins by providing reaction sites for further transformations. The porphyrins and metalloporphyrins with attached aryloxy and alkoxy groups have been shown to have interesting properties.[2] Therefore, the formation of C–O bonds on the tetrapyrrole macrocycle periphery has received much attention, and considerable progress has been made recently.[3] However, in contrast to the large number of synthetic porphyrins with carbon-based peripheral substituents, only a few porphyrins with oxygen-based peripheral substituents, such as aryloxy, alkoxy, hydroxy, and acyloxy moieties, have been reported.[2a,e,g,4] In addition to the multistep and low-yield synthesis of β-alkoxyporphyrins from alkoxypyrroles, porphyrins bearing oxygen-based peripheral substituents have been mainly obtained by nucleophilic substitution and metal-catalyzed C–O bond formation reactions.[1b,3a,c] Although the nucleophilic substitution and metal-catalyzed cross-coupling reactions involve difficult reaction condition and expensive reagents, it is necessary to develop more convenient and economical methods for the direct construction of C–O bonds on the porphyrin periphery without additional steps, such as introduction of functional groups and metal complexation, in advance.

Although the metal-catalyzed aryloxylation and alkoxylation of halogenated porphyrins have emerged as a powerful approach for the formation of C–O bonds on porphyrin periphery, the corresponding acyloxylation, particularly aroyloxylation has not been systematically explored besides that reported by Iturraspe and Esdaile.[5] To extend the synthetic strategy to C–O bond formation on porphyrin/chlorin periphery, herein, we report a new approach for the synthesis of β- or *meso*-aroyloxy-substituted porphyrins and chlorins using benzoyl peroxide (BPO) and its homologs.

In this study, the free radical substitution of tetraphenylporphyrin **1** (TPP) was carried out by reacting it with BPO in toluene at 90 °C for 5 h to afford two main products, β-benzoyloxy-TPP **2** and β,β′-dibenzoyloxy-TPP **3** in 23% and 15% yields, respectively (Scheme 1). In this reaction, 1 mol equiv of BPO was used as the aroyloxylation reagent rather than as the initiator. The reaction temperature was required to be higher than 70 °C that corresponds to the pyrolysis temperature of BPO; otherwise, the reaction did not occur, indicating a free radical substitution reaction. The structures of products **2** and **3** were established by their ^{1}H NMR, UV–visible, and mass spectral analyses.[6] This simple and convenient aroyloxylation method motivated us to extend its application to other types of porphyrins.

Next, chlorophyll-*a* derivatives were used to investigate the C–O bond formation on the chlorin periphery because their 20-*meso*-position possesses special reactivity, such as high regioselectivity, for various electrophilic substitutions.[7] Methyl

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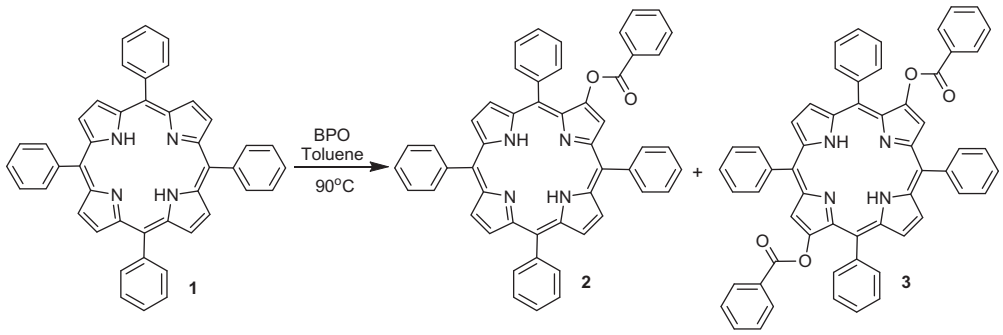
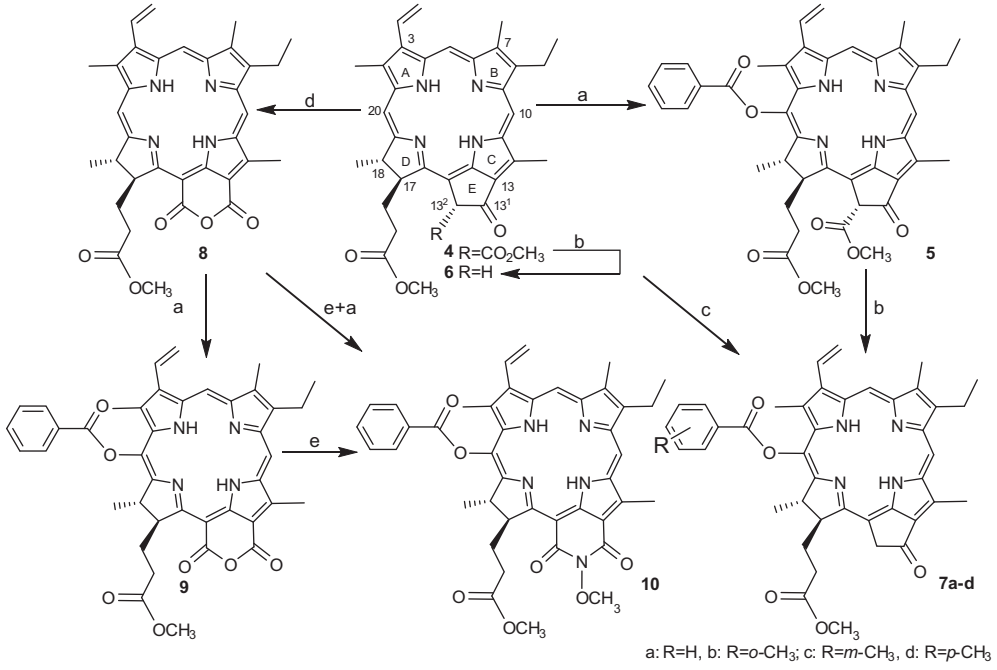


Scheme 1. Synthetic routes for β-aroyloxy-substituted tetraphenylporphyrins **2** and **3**.

pheophorbide-*a* (**4**, MPa), isolated from *Alga spirulina*,[8] was used as the starting material and reacted with BPO under the same reaction conditions for the reaction of **1** to smoothly afford 20-benzoyloxy-substituted chlorin **5**, as an unique product, in 56% yield (Scheme 2). The corresponding substitution reaction of methyl pyropheophorbide-*a* (**6**, MPPa), prepared by the thermal demethoxycarbonylation of **4** in refluxing acetic acid,[9] with BPO afforded methyl 20-benzoyloxy-pyropheophorbide-*a* **7a** in 58% yield.[6] Alternatively, **5** can also be converted into **7a** by refluxing in acetic acid in 88% yield, indicating that the C–O bond at the 20-position was quite stable under acidic conditions. Assuming that a bulky functional group at the 20-*meso* position may lead to atropisomerism, methyl-substituted benzoyl peroxides as the reactants, which were readily prepared by the reaction of methylbenzoyl chloride with hydrogen peroxide under basic conditions, reacted with **6** to afford the corresponding *ortho*-, *meta*-, and *para*-methylbenzoyloxy-substituted chlorins **7b**–**7d** in approximately equal yields, that is, 52%, 55%, and 53% yields, respectively. However, the aroyloxylations of the chlorins with a pyropheophorbide skeleton did not result in atropisomerism according to their ^{1}H NMR spectra. Even the 2-methyl group adjacent to the benzoyloxy group in chlorin **7b** did not restrict the rotation of the aromatic ring around the C–O bond attached to the 20-*meso*-position of the macrocycle periphery.

The chlorophyll-*a* derivatives, purpurin-18 methyl ester (**8**) and purpurinimides (e.g., compound **10**), possess a bulkier six-membered ring E; therefore, they can occupy more space and the carbonyl group at the 15-position could push the substituted groups and hydrogen atoms on the ring D closer to the 20-substituent by the interatomic repulsion. To evaluate the effect of the change in the exocyclic E-ring on the atropisomerism, **4** was converted to **8** in 68% yield by the reaction in tetrahydrofuran (THF) containing LiOH in an open system in dark followed by the acidification with AcOH and methylation with ethereal diazomethane.[10] The substitution reaction of **8** with BPO afforded 20-benzoyloxy-substituted chlorin **9** (52% yield); its imidation with excess hydroxylamine in pyridine and methylation with diazomethane afforded 20-benzoyloxy-substituted purpurin-18 *N*-methoxyl imide **10** in 90% yield. This compound can also be obtained in 48% yield by a sequential conversion using hydroxylamine and PBO from **8**.[11]

As expected, both chlorins **9** and **10** exist as atropisomers based on their ^{1}H NMR spectra (Fig. 1A and B). For chlorins **9** and **10**, the ratios of the two atropisomers were similar (~5:2), and the chemical shifts of all their methyl groups and hydrogen atoms at the 18-position exhibited obvious differences. When the 17-H and 18-Me groups were on the same side as the 20-benzoyloxy group (atropisomer **b**), large upfield shifts were observed in the ^{1}H NMR



Scheme 2. Synthetic routes for 20-*meso*-aroyloxy-substituted chlorophyll-*a* derivatives; reagents and conditions: (a) BPO/toluene/90 °C; (b) AcOH/110 °C; (c) $(CH_3PhCO_2)_2O$/toluene/90 °C; (d) LiOH/THF/O_2; (e) (1) NH_2OH/pyridine, (2) CH_2N_2; BPO: benzoyl peroxide; THF: tetrahydrofuran.

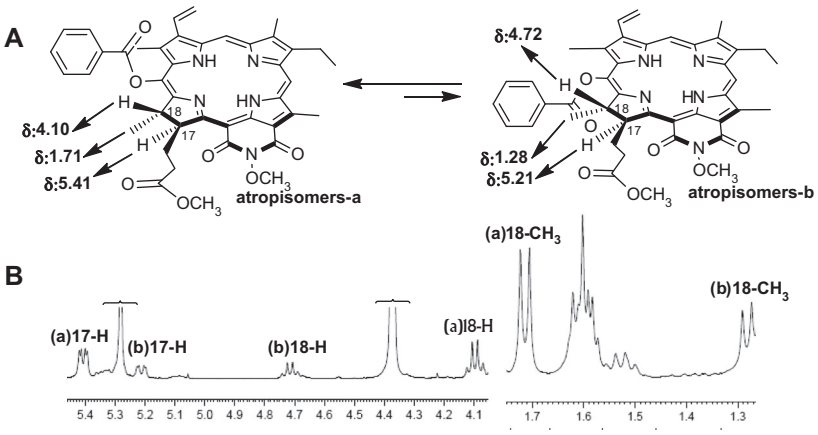


Figure 1. Equilibrium of the atropisomers of chlorin **10** (**A**) and chemical shifts of protons on the D-ring (**B**).

spectra, probably because of the shielding effect derived from the conjugated system of the aromatic ring, including the C=O bond attached to the 20-position in the chlorin chromophore, whereas for the same moiety in the opposite side with the 20-benzoyloxy group (atropisomer **a**), the chemical shifts were less affected. The reason for the atropisomerism in chlorins **9** and **10** can be attributed to their stereochemical structures around the 20-benzoyloxy group. Compared to the five-membered ring E in (pyro)pheophorbides **5** and **7**, the six-membered exocyclic ring E in chlorins **9** and **10** occupied more space, and the carbonyl group at the 15-position could push the substituted groups and hydrogen atoms on the D-ring closer to the 20-benzoyloxy group by the interatomic repulsion. The crowded atmosphere around the 20-*meso* position in chlorins **9** and **10** restricted the C–O single bond rotation of the C20-benzoyloxy group and resulted in the atropisomerism. The ^{1}H NMR spectrum of chlorin **10** indicated that atropisomer **a** is the preferred conformation because the benzoyloxy group is not extremely crowded with the adjacent substituents, whereas atropisomer **b** is strongly strained with the identically orientated C18-methyl group. The atropisomers of chlorins **9** and **10** showed closely overlapped bands in the TLC plate, and they could not be separated by high-performance liquid chromatography (HPLC).

The UV–visible spectra of **1** and **2** (Fig. 2A) indicate a strong bathochromic shift (48 nm) of the Qy band of **2** compared to that of **1**, and the full width at half maximum (FWHM) of the Soret band of **2** broadened dramatically (from 12 to 81 nm). These distinct changes in the optical property of **2** were attributed to the phenylacyloxy group at the 20-β-position; the steric and electronic effects of this group decreased the molecular symmetry and increased the molecular orbital division.

In the UV–visible spectra of chlorin and their 20-*meso*-benzoyloxy-substituted product (Fig. 2B), a slight bathochromic shift in the Qy band of chlorin **9** (6 nm) compared to its precursor **8** was observed. However, the introduction of the benzoyloxy group in pheophorbide **5** and pyropheophorbides **7a**–**d** scarcely affected their visible spectra. Only ~1–2 nm changes in the Qy bands were observed in the UV–visible spectra between the pre-and post-aroylation materials (Fig. 2B). These variations in the absorption spectra of chlorins indicated that the degree of difficulty and ease of the rotation of the phenylacyloxy group around the C–O bond attached to the 20-*meso*-position was an important factor influencing the spectroscopic properties, i.e., the more restricted the rotation of the substituted groups around the C–O bond attached to the macrocycle, the more effective is their interaction with the chlorin chromophore.

In conclusion, we successfully developed a practical and efficient methodology for the synthesis of β- or *meso*- benzoyloxy porphyrins and chlorins by the direct peripheral aroyloxylation

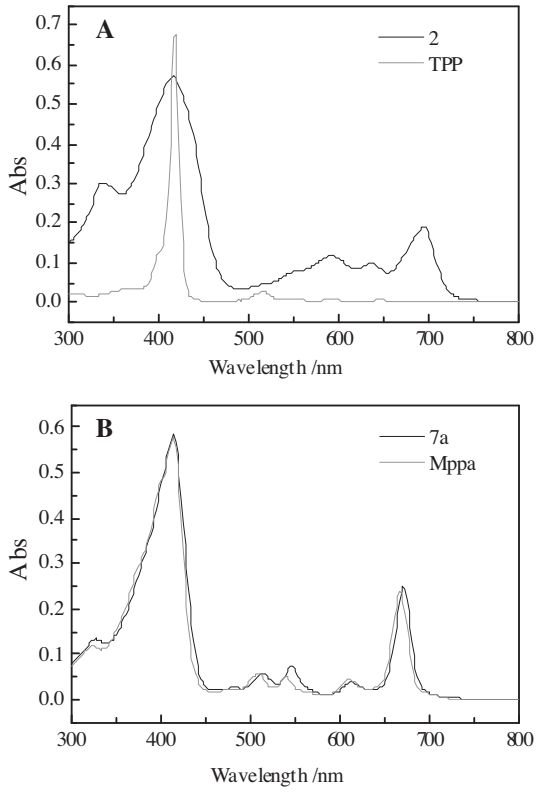


Figure 2. Electronic absorption spectra of aroyloxy-substituted chlorins.

reactions with BPO and its homologs. In this ligand-free and non-metal-catalyzed process, porphyrin or chlorins related to chlorophyll-*a* were directly used as the reaction substrates, without additional complicated steps such as metal complexation and halogenation. Because the reaction is simple and effective under mild conditions, it may allow the convenient preparation of various useful β- and *meso*-functionalized porphyrins and chlorins. Further studies on the application of the aroyloxy-substituted porphyrins, obtained in this study, are currently in progress.

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References and notes

1. (a) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432; (b) Gao, G.-Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 3261; (c) Takanami, T.; Hayashi, M.; Hino, F.; Suda, K. *Tetrahedron Lett.* **2003**, *44*, 7353; (d) Gao, G.-Y.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2004**, *6*, 1837; (e) Gao, G.-Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2004**, *69*, 8886; (f) Matano, Y.; Matsumoto, K.; Terasaka, Y.; Hotta, H.; Araki, Y.; Ito, O.; Shiro, M.; Sasamori, T.; Tokitoh, N.; Imahori, H. *Chem. Eur. J.* **2007**, *13*, 891.
2. (a) Murashima, T.; Uchihara, Y.; Wakamori, N.; Uno, H.; Ogawa, T.; Ono, N. *Tetrahedron Lett.* **1996**, *37*, 3133; (b) Wojaczyński, J.; Latos-Grażyński, L.; Hrycyk, W.; Pacholska, E.; Rachlewicz, K.; Szterenberg, L. *Inorg. Chem.* **1996**, *35*, 6861; (c) Crossley, J. M.; King, L. G.; Simpson, J. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3087; (d) Sibilia, S. A.; Czernuszewicz, R. S.; Crossley, M. J.; Spiro, T. G. *Inorg. Chem.* **1997**, *36*, 6450; (e) Kalish, H.; Camp, J. E.; Stepień, M.; Latos-Grażyński, L.; Balch, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 11719; (f) Kalish, H.; Camp, J. E.; Stepień, M.; Latos-Grażyński, L.; Olmstead, M. M.; Balch, A. L. *Inorg. Chem.* **2002**, *41*, 989; (g) Wojaczyński, J.; Stępień, M.; Latos-Grażyński, L. *Eur. J. Inorg. Chem.* **2002**, *2002*, 1806.
3. (a) Chen, Y.; Gao, G.-Y.; Peter Zhang, X. *Tetrahedron Lett.* **2005**, *46*, 4965; (b) Gao, G.-Y.; Ruppel, J. V.; Allen, D. B.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2007**, *72*, 9060; (c) Liu, C.; Shen, D.-M.; Chen, Q.-Y. *J. Org. Chem.* **2007**, *72*, 2732.
4. Agarwal, N.; Hung, C. H.; Ravikanth, M. *Tetrahedron* **2004**, *60*, 10671.
5. (a) Iturraspe, J.; Gossauer, A. *Photochem. Photobiol.* **1991**, *54*, 43; (b) Esdaile, L. J.; Senge, M. O.; Arnold, D. P. *Chem. Commun.* **2006**, 4192.
6. General procedure for the aroyloxylation of porphyrin and chlorin: To a toluene solution (10 ml) of substrate (0.10 mmol), 0.10 mmol benzoyl peroxide (1.0 equiv) was added. This mixture was stirred at 90 °C for 5 h, poured into 20 ml of cool water and then extracted with dichloromethane (3 × 15 ml). The combined extracts were washed with water, dried over anhydrous Na_2SO_4. After evaporation in vacuo, the residue was purified on chromatography on a silica gel column with hexane/ethyl acetate (5:1) to give the products as solid with moderate yields. Selected data: compound **2**: Yield: 23%. UV–vis ($CHCl_3$) λ_{max}: 417 (relative intensity, 1.00), 593 (0.28), 638 (0.23), 698 (0.40) nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 4.8 Hz, 1H, β-H), 8.87 (d, J = 4.8 Hz, 1H, β-H), 8.79 (d, J = 4.8 Hz, 1H, β-H), 8.71 (d, J = 4.8 Hz, 1H, β-H), 8.66 (s, 1H, β-H), 8.23 (d, J = 7.6 Hz, 4H, Ph-Ha), 8.20 (d, J = 7.6 Hz, 4H, Ph-Ha), 8.10 (d, J = 7.0 Hz, 2H, Ph-Ha), 7.71–7.09 (m, 9H, Ph-Hb and Ph-Hc), 7.60 (t, J = 7.4 Hz, 1H, Ph-Hb and Ph-Hc), 7.44 (t, J = 7.7 Hz, 1H, Ph-Hb and Ph-Hc), 7.43 (t, J = 7.6 Hz, 1H, Ph-Hb or Ph-Hc), 7.42 (t, J = 7.6 Hz, 1H, Ph-Hb or Ph-Hc), 7.41 (t, J = 7.7 Hz, 1H, Ph-Hb or Ph-Hc), 7.28 (t, J = 7.4 Hz, 1H, Ph-Hb or Ph-Hc), −2.82 (br s, 2H, NH). Anal. Calcd for $C_{51}H_{34}N_4O_2$: C, 83.36; H, 4.66; N, 7.62. Found: C, 83.39; H, 4.68; N, 7.69. MS (ESI): $[M + H]^+$ 735.3. Compound **3**: Yield: 15%. UV–vis ($CHCl_3$) λ_{max}: 419 (relative intensity, 1.00), 594 (0.30), 640 (0.23), 701 (0.41) nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 4.9 Hz, 2H, β-H), 8.74 (s, 2H, β-H), 8.67 (d, J = 4.9 Hz, 2H, β-H), 8.66 (s, 1H, β-H), 8.12 (d, J = 7.1 Hz, 4H, Ph-Ha), 8.21 (d, J = 7.2 Hz, 2H, Ph-Ha), 8.20 (d, J = 7.7 Hz, 2H, Ph-Ha), 7.81 (d, J = 7.2 Hz, 4H, Ph-Ha), 7.80–7.71 (m, 10H, Ph-Hb and Ph-Hc), 7.54 (t, J = 7.5 Hz, 2H, Ph-Hb or Ph-Hc), 7.35 (t, J = 7.7 Hz, 2H, Ph-Hb or Ph-Hc), 7.33 (t, J = 7.8 Hz, 2H, Ph-Hb or Ph-Hc), 7.10 (t, J = 7.5 Hz, 1H, Ph-Hb or Ph-Hc), −2.89 (br s, 2H, NH). Anal. Calcd for $C_{58}H_{38}N_4O_4$: C, 81.48; H, 4.48; N, 6.55. Found: C, 81.53; H, 4.55; N, 6.58. MS (ESI): $[M+H]^+$ 855.3. Compound **7a**: Yield: 58%. UV–vis ($CHCl_3$) λ_{max}: 413 (relative intensity, 1.00), 473 (0.04), 513 (0.06), 545 (0.11), 611 (0.06), 669 (0.42) nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58, 9.57 (each s, each 1H, *meso*-H), 8.63 (dd, J = 8.3, 6.2 Hz, 2H, Ph-H), 7.87 (t, J = 7.9 Hz, 1H, Ph-H), 7.76 (t, J = 7.9 Hz, 2H, Ph-H), 7.92 (dd, J = 17.8, 11.5 Hz, 1H, 3^1-H), 6.21 (dd, J = 11.7, 1.5 Hz, 1H, 3^2-H), 6.16 (dd, J = 17.8, 1.5 Hz, 3^2-H), 5.31, 5.20 (each d, J = 19.9 Hz, 2H, 13^2-H), 4.28 (d, J = 8.0 Hz, 1H, 17-H), 4.25 (q, J = 7.3 Hz, 18-H), 3.71, 3.46, 3.27(×2) (each s, each 3H, OCH_3+CH_3), 3.73 (q, J = 7.6 Hz, 2H, 8^1-CH_2), 2.45–2.57, 2.27–2.38, 1.81–1.90 (each m, 4H, 17^1 + 17^2-CH_2), 1.70 (d, J = 7.1 Hz, 18-CH_3), 1.69 (t, 3H, J = 7.7 Hz, 8^2-CH_3), 0.45, −2.20 (each br s, each 1H, NH). Anal. Calcd for $C_{41}H_{40}N_4O_5$: C, 73.63; H, 6.03; N, 8.38. Found: C, 73.65; H, 6.08; N, 8.37. MS (ESI): $[M+H]^+$ 669.3.
7. (a) Wang, J. J. *Chin. J. Org. Chem.* **2005**, *25*, 1353; (b) Wang, J. J.; Li, J.; Yin, J. G.; Liu, Y. J. *Chin. J. Org. Chem.* **2008**, *28*, 693; (c) Wang, J.-J.; Liu, C.-L.; Li, J.-Z. *Synth. Commun.* **2012**, *42*, 487.
8. (a) Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4946; (b) Wang, J. J.; Li, J. Z.; Li, Y. W.; Jakus, J.; Shim, Y. K. *J. Porphyrins Phthalocyanines* **2010**, *14*, 859.
9. Li, J.-Z.; Cui, B.-C.; Wang, J.-J.; Shim, Y.-K. *Bull. Korean Chem. Soc.* **2011**, *32*, 2465.
10. Li, J. Z.; Li, L.; Kim, J. H.; Cui, B. C.; Wang, J. J.; Shim, Y. K. *J. Porphyrins Phthalocyanines* **2011**, *15*, 264.
11. Li, J. Z.; Wang, J. J.; Yoon, I.; Cui, B. C.; Shim, Y. K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1846.