A Simple and Short Synthesis of Divinyl Chlorophyll Derivatives

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Introduction

For quite some time, one of the main objectives of our laboratory has been to prepare photosensitizers for photodynamic therapy (PDT) with long-wavelength absorptions at or near λ_{max} 800 nm,[1] since this wavelength is least attenuated in tissues and therefore may allow deeper necrosis of tumors undergoing PDT. We have recently reported[2] the preparation of certain bacteriopurpurins obtained by reacting the related 8-vinylchlorins with various dienophiles. Among these photosensitizers, the benzobacteriopurpurin obtained as the dimethylacetylene dicarboxylate (DMAD) adduct produced the long-wavelength absorption near λ_{max} 800 nm with good singlet oxygen yield (a requirement for effective photosensitizers). Unfortunately, due to its rapid clearance in serum and tissues (determined by in vivo reflection spectroscopy), it was found to be ineffective as a PDT photosensitizer in mice transplanted with RIF tumors.

Previously, in our efforts to establish the effect of various substituents on PDT activity, we have observed that lipophilicity plays an important role in the ability of the photosensitizer to localize in tumors.[3] We have shown that in porphyrin-based photosensitizers one of the simplest methods to alter the lipophilic characteristic is to introduce an alkyl ether side chain with variable carbon units at the peripheral position(s) of the molecule. In recent years, we have prepared a series of alkyl ether analogs of various chlorins,[4] including benzoporphyrin derivatives.[5] Among the compounds tested, the related hexyl ether derivatives of pyropheophorbide *a* and benzoporphyrin derivative were found to be most effective as in vivo photosensitizing agents.[4c,6] Thus, in order to investigate the effect(s) of such substituents in the benzobacteriochlorin series, we were interested in preparing and evaluating the biological activity of the related hexyl ether derivative.

Results and Discussion

For the synthesis of the desired benzobacteriochlorin, our aim was to prepare the 3-(1-hexyloxyethyl)-8-vinylchlorin e_6 trimethyl ester **4**. In our synthetic approach, methyl pheophorbide *a* obtained from *Spirulina pacifica* was converted into chlorin e_6 trimethyl ester **1** by following standard methodology.[7] The unstable bromo derivative obtained as an intermediate product by reacting **1** with 30% HBr/acetic acid was not characterized, and after removal of the solvents, it was immediately treated with 1-hexanol to afford the corresponding 3-(1-hexyloxyethyl)-3-devinyl analogue **2** in 70% yield. Reaction of **2** with OsO_4/H_2S[8] produced the corresponding *vic*-dihydroxybacteriochlorin **3** in 75% yield as a mixture of diastereomers. To our surprise, reaction of bacteriochlorin **3** in refluxing 1,2-dichlorobenzene did not produce the expected hexyl ether analogue **4**; instead, a mixture containing the 3,8-divinylchlorin e_6 trimethyl ester **6** and the corresponding porphyrin **5** was obtained, which was easily purified by column chromatography (Scheme 1). In the porphyrin series, this is the first example of such a tranformation. However, an extensive literature search revealed that similar types of pyrolysis in certain allylic ethers in solution at >160 °C have previously been reported by Cookson et al.[9] and Sarner and co-workers.[10]

The isolation of the divinyl chlorin-e_6 trimethyl ester **6** attracted our attention to the recent papers[11] that demonstrate the importance of such divinyl chlorins as intermediates in chlorophyll and bacteriochlorophyll biosynthesis. It is now believed that chlorophyll intermediates exist in monovinyl and divinyl forms, the divinyl intermediates containing vinyl side groups at rings A and B, whereas monovinyl forms have vinyl groups at ring A and ethyl groups at ring B. Bauer and co-workers[11d] have shown that the ratio of the accumulated monovinyl to divinyl intermediates was altered by physiological and environmental factors. However, it is not yet clear as to the significance of having pools of monovinyl and divinyl intermediates as monovinyl chlorophyll *a* is the final product. In any event, the analysis of the photosynthetic pigments is important in

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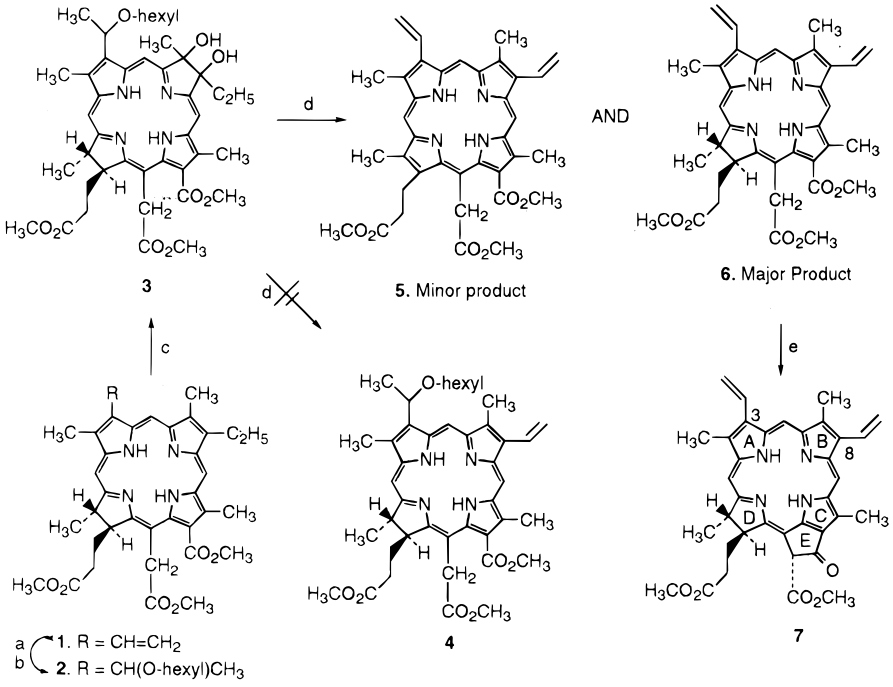
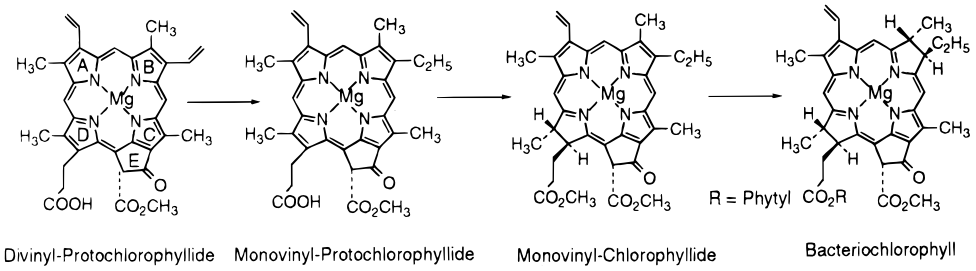
Scheme 1[a]

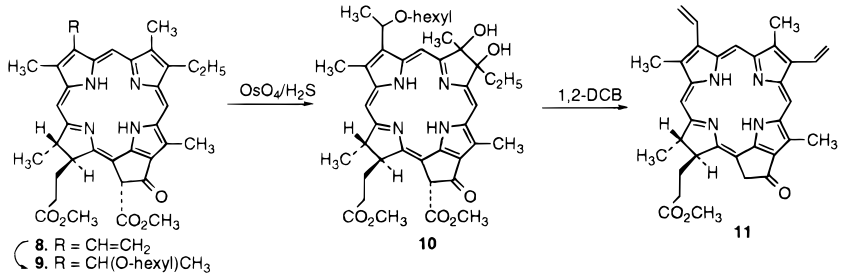


[a] Reagents: (a) HBr/AcOH; (b) 1-hexanol; (c) OsO_4/H_2S; (d) 1,2-dichlorobenzene; (e) PPh_3, $NaN(TMS)_2$.

Scheme 2. Pathway of Bacteriochlorophyll Biosynthesis in *R. capsulatus*



Scheme 3



the study of the photosynthetic apparatus, especially biogenesis of both plants and algae. Thus, in order to understand more about the biosynthesis of chlorophyll *a* and bacteriochlorophyll *a*, it is necessary to have the availability of the biosynthetic intermediates. See Scheme 2.

After achieving a successful synthesis of chlorophyll biosynthetic intermediate **6**, we extended this approach to investigate the utility of this method for the preparation of another biosynthetic intermediate, methyl 3,8-divinylpheophorbide *a* (**7**). Interestingly, the *vic*-dihydroxy-3-(1-hexyloxyethyl)methylpyropheophorbide *a* (**10**) obtained in two steps from methyl pheophorbide *a* (**8**) by refluxing in 1,2-dichlorobenzene also cleaved the methoxycarbonyl group present at position-13[2] (ring E) of the macrocycle, and the methyl 3,8-divinylpyropheophorbide *a* **11** was isolated as the sole product (Scheme 3). However, the biosynthetic intermediate **7** containing an isocyclic ring (ring E) was constructed in a single step by reacting divinylchlorin e_6 trimethyl ester with PPh_3/$NaN(TMS)_2$ as described by Smith and co-workers[12] (Scheme 2).

All new compounds were characterized by NMR and mass spectrometry. The NMR spectra of the 3,8-divinylchlorin e_6 trimethyl ester and the related dihydroxybacteriochlorin are shown in Figure 1. The multiple peaks in the NMR spectrum of *vic*-dihydroxybacteriochlorin (**3**)

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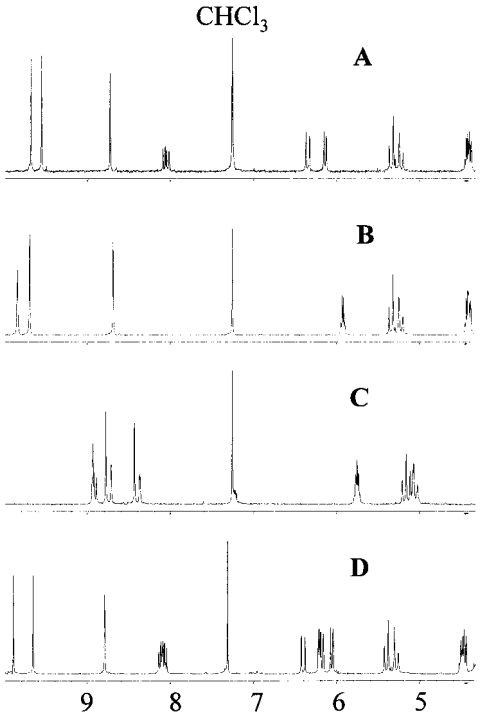

Figure 1. ^{1}H NMR spectra (Bruker 400 MHz, $CDCl_3$, δ ppm) of chlorin e_6 **1** (A), 3-(1-hexyloxyethyl)chlorin e_6 **2** (B), *vic*-dihydroxybacteriochlorin **3** (C), and 3,8-divinylchlorin e_6 **6** (D).

are due to the presence of a mixture of four possible diastereomers; the *cis*-hydroxy groups (ring B) are either up or down with respect to the trans-reduced ring D (in both *R* and *S* forms).

Recent reports from Smith's group[12] also deal with the elegant synthesis of similar analogues. However, it involves a multistep preparation. Though all the synthetic steps are high yielding, the overall yield is low and is certainly time consuming. The synthetic procedure developed by us provides the preparation of the target compound in the fewest steps possible, thus avoiding wasteful yield losses and minimizing synthesis time.

Experimental Section

Melting points are uncorrected. NMR spectra were obtained at 400 MHz on a Bruker instrument. All chemical shifts are reported in parts per million (ppm) relative to TMS. Mass spectrometry analyses were obtained from the Department of Molecular and Cellular Biophysics, RPCI, Buffalo.

3-(1-Hexyloxy)ethylchlorin e_6 Trimethyl Ester 2 (as a Diastereomeric Mixture). Chlorin e_6 trimethyl ester **1** (140 mg) (prepared from methyl pheophorbide *a* by following the literature procedures[13]) was dissolved in 30% HBr in acetic acid (2.5 mL), and the reaction mixture (the reaction flask was sealed by a rubber septum) was stirred at room temperature for 3 h. After the acids were evaporated under high vacuum, the residue was dissolved in dry dichloromethane (10 mL). 1-Hexanol (3 mL) and anhydrous potassium carbonate (40 mg) were added immediately, and the reaction mixture was stirred under nitrogen atmosphere for 1 h. It was then diluted with dichloromethane (200 mL). The dichloromethane layer was separated, dried (Na_2SO_4), and filtered. Evaporation of the filtrate gave a residue that was chromatographed over a Grade II alumina column with 25% hexanes/dichloromethane. The major fraction was collected and evaporated to afford a sticky solid. After crystallization from hexanes/water, the title compound was obtained in 70% yield (114 mg). ^{1}H NMR (400 MHz, 3 mg/1 mL of $CDCl_3$, δ ppm): 9.85 and 9.84 (splitting s, 1H, 5-H); 9.70 (s, 1H, 10-H); 8.70 (s, 1H, 20-H); 5.93 (q, J = 6.6, 6.1 Hz, 1H, 3^1-H); 5.29 (ABX, J = 18.8 Hz, 2H for 15^2-H); 4.44 (q, J = 7.3 Hz, 1H, 18-H); 4.40 (d, J = 9.9 Hz, 1H for 17H); 4.26, 3.77, 3.63, 3.58 and 3.31 (each s, 3H, 5 × CH_3); 3.79 (q, J = 7.9 Hz, 2H, 8^1CH_2); 3.64 (m, 2H, O-CH_2-$CH_2CH_2CH_2CH_2CH_3$); 3.43 and 3.42 (splitting s, 3H, 1 × CH_3); 2.54 and 2.19 (each m, total for 4H, for 2 × 17^{1}H and 2 × 17^{2}H); 2.12 (m, 3H, 3^1-CH_3); 1.74 (d, J = 7.2 Hz, 3H, 18CH_3); 1.71 (t, J = 8.0 Hz, 3H, 8^2CH_3); 1.41−1.24 (m, total for 8H, $OCH_2CH_2CH_2CH_2CH_2$-CH_3); 0.78 (t, 3H, $OCH_2CH_2CH_2CH_2CH_2CH_3$); −1.30 and −1.47 (each br s, 1H, 2NH). UV−vis (in CH_2Cl_2, λ_{max} (ϵ): 400 (126 000), 499 (10 600), 601 (4500), 660 (37 900). HRMS: calcd for $C_{43}H_{56}N_4O_7$ 741.4227 (M + 1), found 741.4217 (M + 1).

7,8-Dihydroxy-3-(1-hexyloxy)ethylchlorin e_6 Trimethyl Ester 3 (as a Diastereomeric Mixture). The hexyl ether derivative of chlorin e_6 **2** (80 mg) was dissolved in dichloromethane (20 mL). Pyridine (15 drops) along with osmium tetraoxide (100 mg) and ether (3 mL) were added, and the reaction mixture was stirred in a sealed flask overnight. The reaction was monitored by analytical TLC and spectrophotometrically. H_2S gas was bubbled through the solution for 5 min. The reaction mixture was filtered. The filtrate was evaporated, and the residue was chromatographed over a silica column, eluting first with 5% acetone/dichloromethane to remove the unreacted starting material and then 10% acetone/dichloromethane. The slow-moving fraction was evaporated, and the residue so obtained was crystallized from dichloromethane/hexanes in 75% yield (62.5 mg).

^{1}H NMR (400 MHz, 3 mg/1 mL $CDCl_3$, δ ppm): 8.95, 8.94, 8.93, and 8.90 (each s, total 4H, *meso*-H); 8.79 and 8.72 (each s, total 4H, *meso*-H); 8.44, 8.38, and 8.37 (each s, total 4H, *meso*-H); 5.76 (m, J = 7.7 and 6.1 Hz, 4H, 3^1-H); 5.12 (ABX, J = 19.0 Hz, 8H for 15^2-H); 5.10 (d, J = 12.4 Hz, 4H, 17-H); 4.22 (q, J = 7.0 Hz, 4H, 18-H); 4.20 and 4.19 (each s, total 12H, 4 × CH_3); 3.75 and 3.74 (each s, total 12H, 4 × CH_3); 3.64 (s, 12H, 4 × CH_3); 3.35, 3.32, 3.31, and 3.29 (each s, total 24H, 8 × CH_3); 3.60 (m, 8H, $OCH_2CH_2CH_2CH_2CH_2CH_3$); 3.52 (m, 8H, 8^1$CH_2$); 2.48, 2.38, and 2.21 (each m, total 16H, 8 × 17^1-H and 8 × 17^2-H); 2.16 (s, 12H, 4 × CH_3); 2.01 (m, 12H, 3^1-CH_3); 1.66 (m, total 24H, 18CH_3 and 8^2-CH_3); 1.40−1.25 (m, total 32H, $OCH_2CH_2CH_2$-$CH_2CH_2CH_3$); 0.82 (m, 12H, $OCH_2CH_2CH_2CH_2CH_3$); −0.52, −0.73, −0.78 and −0.94 (each br s, total 8H, 8-NH). MP: 130−132 °C. UV−vis (in CH_2Cl_2, λ_{max} (ϵ)): 375 (67 000), 480 (4900), 510 (1990), 660 (6670), 723 (36 000). HRMS: calcd for $C_{43}H_{58}N_4O_9$ 774.4203, found 774.4200.

3,8-Divinylchlorine e_6 Trimethyl Ester 6. *vic*-Dihydroxybacteriochlorin **3** (35 mg) was dissolved in *o*-dichlorobenzene (10 mL) and heated at 165 °C for 5 h under nitrogen. After the solvent was removed under high vacuum, the residue was chromatographed on a silica gel column, eluting with acetone/dichloromethane (2−5% acetone). The major fraction (slow moving band) so obtained was evaporated and crystallized from dichloromethane/hexanes to afford the title compound in 60% yield (17 mg).

^{1}H NMR (400 MHz, 3 mg/1 mL $CDCl_3$, δ ppm): 9.90, 9.66, and 8.80 (each s, 1H, 5-H, 10-H, and 20-H); 8.11 and 8.09 (each dd, J = 17.8, 11.9 Hz, 1H, 3^1-CH=CH_2 and 8^1-CH=CH_2); 6.41 and 6.19 (each d, J = 17.8 Hz, 1H, *trans*-3^2-CH=CH_2 and *trans*-8^2-CH=CH_2); 6.21 and 6.06 (each d, J = 11.9 Hz, 1H, *cis*-3^2-CH=CH_2 and *cis*-8^2-CH=CH_2); 5.35 (ABX, J = 17.0 Hz, 2HY for 15^2-H); 4.50 (q, J = 7.1 Hz, 1H, 18-H); 4.46 (d, J = 9.9 Hz, 1H for 17-H); 4.31, 3.83, 3.69, 3.62, 3.53, and 3.47 (each s, 3H, 6 x CH_3); 2.63, 2.28, and 2.19 (each m, total for 4H, for 2 x 17^{1}H and 2 x 17^{2}H); 1.81 (d, J = 7.1 Hz, 3H, 18CH_3); −1.38 (br s, 2H, 2NH). MP: 200−201 °C. UV−vis (in CH_2Cl_2, λ_{max} (ϵ)): 408 (155 000), 507 (11 400), 606 (3120), 660 (42 000). HRMS: calcd for $C_{37}H_{40}N_4O_6$ 636.2948, found 636.2850.

3,8-Divinylprophyrin 5. The compound obtained as a minor fraction (fast-moving band) during the purification of the foregoing chlorin by column chromatography was identified as the title porphyrin.

Yield: 3.0 mg (10%). ^{1}H NMR (400 MHz, 3 mg/1 mL $CDCl_3$, δ ppm): 10.24, 10.09, and 10.04 (each s, 1H, 5-H, 10-H, and 20-H); 8.30 and 8.18 (each dd, J = 17.7, 11.9 Hz, 1H, 3^1-CH=CH_2 and 8^1-CH=CH_2); 6.45 and 6.33 (each d, J = 17.5 Hz, 1H, *trans*-3^2-CH=CH_2 and *trans*-8^2-(CH=CH_2); 6.29 and 6.16 (each d, J

(13) Smith, K. M., Ed. *Porphyrins and Metalloporphyrins*; Elsevier: New York, 1975.

= 11.7 Hz, 1H, *cis*-3^2-CH=CH2 and *cis*-8^2-CH=CH_2); 6.01 (s, 2H, 15^2-H); 4.32, 3.82, 3.74, 3.72, and 3.71 (each s, 3H, 5 × CH_3); 3.66 (s, 6H, 2 x CH_3); 3.45 and 3.12 (each t, J = 7.7 Hz, 2H, 2 × 17^1H and 2 × 17^2H); −1.10 (br s, 2H, 2NH). UV−vis (in CH_2Cl_2, λ_{max} (ϵ)): 414 (155 000), 513 (12 600), 549 (10 400), 585 (9000), 633 (5550). HRMS: (calcd for $C_{37}H_{38}N_4O_6$ 634.2991, found 634.2980.

Methyl 3-(1-Hexyloxyethyl)pheophorbide *a* 9 (as a Diastereomeric Mixture). Methyl pheophorbide *a* **8** (180 mg) was converted to the corresponding bromo derivative by reaction with 30% HBr/AcOH. The residue obtained after removal of the solvents was immediately reacted with 1-hexanol following the method discussed for the preparation of **2**. After the purification (Grade II alumina column, eluting solvents 25% hexanes/dichloromethane), the desired compound was obtained in 60% yield (125 mg) as a sticky solid.

^{1}H NMR (400 MHz, 3 mg/1 mL $CDCl_3$, δ ppm): 9.78, 9.54, and 8.82 (each s, 1H, 5-H, 10-H, and 20-H); 6.25 (s, 1H, 13^2-H); 5.89 (q, J = 7.0 Hz, 1H, 3^1-H); 4.45 (q, J = 6.8 Hz, 1H, 18-H); 4.20 (d, J = 8.3 Hz, 1H for 17-H); 3.88, 3.70, 3.57, 3.49, and 3.26 (each s, 3H, 5 × CH_3); 3.71 (q, 2H, 8^1CH_2); 3.67 (m, 2H, O$CH_2$$CH_2$$CH_2$$CH_2$$CH_2$$CH_3$); 2.63, 2.50, 2.33 and 2.21 (each m, total for 4H, for 2 × 17^1H and 2 × 17^2H); 2.11 (m, 3H, 3^1-CH_3); 1.80 (d, J = 7.0 Hz, 3H, 18CH_3); 1.71 (t, J = 7.6 Hz, 3H, 8^2CH_3); 1.41−1.27 (m, total for 8H, O$CH_2$$CH_2$$CH_2$$CH_2$$CH_2$$CH_3$); 0.77 (t, 3H, O$CH_2$$CH_2$$CH_2$$CH_2$$CH_3$); −1.64 (br s, 2H, 2NH). UV−vis (in CH_2Cl_2, λ_{max} (ϵ): 409 (92 000), 473 (3000), 505 (8700), 536 (8650), 605 (7200), 661 (38 000). HRMS: calcd for $C_{42}H_{52}N_4O_6$ 709.3946, found 709.3940.

Methyl 3,8-Divinylpyropheophorbide *a* 11. Compound **9** was reacted with osmium tetraoxide following the method discussed for the preparation of the foregoing bacteriochlorin **10**, and the resulting product without further purification was heated in *o*-dichlorobenzene for 3 h at 165 °C. After the solvent was removed under high vacuum, the residue was chromatographed on silica column, eluting with 2% methanol/dichloromethane to afford the title compound in 45% yield (35 mg).

^{1}H NMR (400 MHz, 3mg/1 mL $CDCl_3$, δ ppm): 9.68, 9.46, and 8.58 (each s, 1H, 5-H, 10-H, and 20-H); 8.02 and 7.93 (each dd, J = 17.8, 11.7 Hz, 1-H, 3^1-CH=CH_2 and 8^1-CH=CH_2); 6.30 and 6.16 (each d, J = 17.8 Hz, 1H, *trans*-3^2-CH=H_2 and *trans*-8^2-CH=CH_2); 6.20 and 6.00 (each d, J = 11.7 Hz, 1H, *cis*-3^2-CH=CH_2 and *cis*-8^2-CH=CH_2); 5.19 (ABX, J = 18.6 Hz, 2H for 13^2-H); 4.50 (q, J = 7.6 Hz, 1H, 18-H); 4.31 (m, 1H for 17-H); 3.67, 3.62, 3.43, and 3.38 (each s, 3H, 4 × CH_3); 2.71, 2.58, and 2.32 (each m, total for 4H, for 2 × 17^1H and 2 × 17^2H); 1.83 (d, J = 7.4 Hz, 3H, 18CH_3); −1.74 (br s, 2H, 2NH). Mp: 210−210 °C. UV−vis (in CH_2Cl_2, λ_{max} (ϵ)): 420 (130 000), 513 (13 500), 608 (9260), 666 (45 000). HRMS: calcd for $C_{34}H_{34}N_4O_3$ 546.2631, found 546.2628.

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Supporting Information Available: The ^{1}H NMR spectra of compounds **1**−**6**, **9**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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