

Thermolysis of *vic*-Dihydroxybacteriochlorins: A New Approach for the Synthesis of Chlorin–Chlorin and Chlorin–Porphyrin Dimers

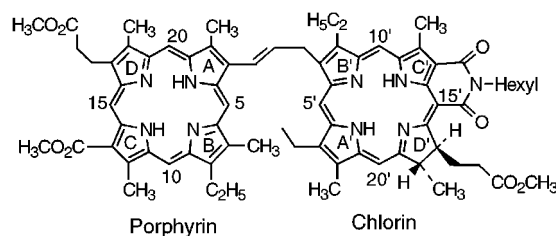
Andrei N. Kozyrev,[†] Gang Zheng,[†] Masayuki Shibata,[‡] James L. Alderfer,[‡]
Thomas J. Dougherty,[†] and Ravindra K. Pandey^{*,†,‡,§}

Chemistry Section, Photodynamic Therapy Center, Molecular and Cellular Biophysics,
and Department of Nuclear Medicine, Roswell Park Cancer Institute,
Buffalo, New York 14263

pdtctr@sc3103.med.buffalo.edu

Received July 2, 1999

ABSTRACT



A novel approach for the preparation of symmetrical (chlorin–chlorin), and unsymmetrical (chlorin–porphyrin) dimers joined with carbon–carbon linkages as models to study the “intramolecular” charge transfer is discussed.

The specific arrangement of chromophores in the bacterial photosynthetic reaction center has attracted considerable attention for its mimicking and functional studies over the past decade.¹ Many bis-chlorin model structures have been synthesized recently² to understand the key steps of the natural photosynthetic mechanism. Photophysical studies on the different model systems reveal that the 3D-structural arrangement of chromophore units is an important factor affecting electron and energy transfer properties.³ Along with

the “special pair”, a third pigment pair consisting of molecules of bacteriochlorophyll *Ba* and bacteriopheophytine Φa chromophore units is oriented in almost perpendicular arrangement.¹ This part of the photosynthetic array has been the subject of intensive studies for quite some time.⁴ Despite a large variety of reported models, we consider that co-

[†] Chemistry Section, Photodynamic Therapy Center.

[‡] Molecular and Cellular Biophysics.

[§] Department of Nuclear Medicine.

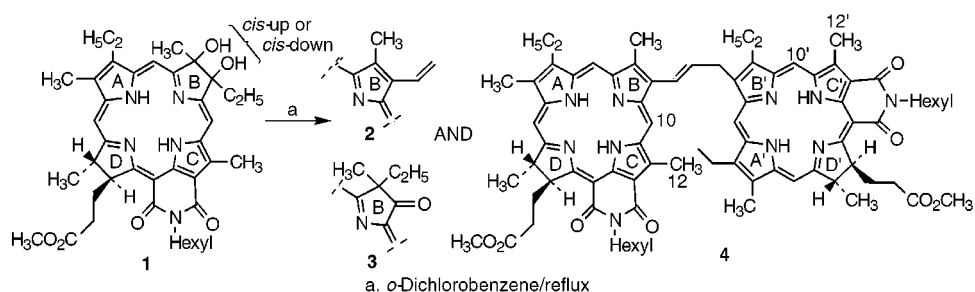
* Address correspondence to Dr. R. K. Pandey, Chemistry Division, Photodynamic Therapy Center, Roswell Park Cancer Institute, Buffalo, NY 14263. Phone: 716/845-3203. FAX: 716/845-8920. E-mail: rpandey@sc3103.med.buffalo.edu.

(1) (a) *The Photosynthetic Reaction Center*; Norris, J. R., Deisenhofer, J., Eds.; Academic Press: San Diego, 1993. (b) Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435 and references therein.

(2) (a) Jaquinod, L.; Nurco, D. J.; Medforth, C. J.; Pandey, R. K.; Forsyth, T. P.; Olmstead, M. M. and Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1013. (b) Jaquinod, L.; Senge, M. O.; Pandey, R. K.; Forsyth, T. P. and Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1840. (c) Kozyrev, A. N.; Alderfer, J. L.; Srikrishnan, T.; Pandey, R. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 837. (d) Zheng, G.; Alderfer, J. L.; Senge, M. O.; Shibata, M.; Dougherty, T. J. and Pandey, R. K. *J. Org. Chem.* **1998**, *6434*. (e) Johnson, C. K.; Dolphin, D. *Tetrahedron Lett.* **1998**, *39*, 4753. (f) Krattinger, B.; Nurco, D. J.; Smith, K. M. *Chem. Commun.* **1998**, 757.

(3) (a) Hunter, C. A.; Hyde, R. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1936. (b) Knapp, S.; Vasudevan, J.; Emge, T. J.; Arison, B. H.; Potenza, J. A.; Schugar, H. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2368. (c) Paolesse, R.; Pandey, R. K.; Forsyth, T. P.; Jaquinod, L.; Gerzevske, K. R.; Nurco, D. L.; Senge, M. O.; Licoccia, S.; Boschi, T. and Smith, K. M. *J. Am. Chem. Soc.* **1996**, *118*, 3869.

Scheme 1



valently linked bis-chlorin and porphyrin–chlorin model systems could provide valuable information on the electron transfer (ET) process in designing molecular photonic devices.

We report here a first synthesis of bis-chlorin systems by following a simple thermal dehydration of the corresponding 7,8-*vic*-dihydroxybacteriochlorin **1** [*cis*-hydroxy up or down relative to ring D (*trans*-reduced)]. This methodology has certain advantages for the construction of model photosynthetic systems and was also successfully used for the preparation of the novel porphyrin–chlorin heterodimer (Scheme 1).

In our recent attempts to synthesize bacteriopurpurins via the Diels–Alders approach, we developed a new procedure for the preparation of 8-vinylchlorins using thermolysis of the corresponding 7,8-*vic*-dihydroxybacteriochlorins.⁵ When mesopurpurin *N*-hexylimide was used as a substrate, the related 8-vinyl chlorin **2** was obtained in a moderate yield (50–55%).⁶ In addition, two other products were also isolated by preparative chromatography. The minor component was characterized as 8-ketobacteriochlorin **3** (9–12%). The other product obtained in 25–30% by mass spectrometry analysis gave a molecular ion peak at m/z 1322.7 ($M + 1$) indicating the formation of a dimeric structure.

We have previously shown that porphyrins containing (1-hydroxyethyl) substituents can be converted into the corresponding carbon–carbon linked dimers on reaction with triflic acid.⁷ Initially, we anticipated the formation of a similar bridge structure [EnDash–CH=CH–CH(CH₃)–] for the new purpurin *N*-hexylimide dimer.⁸ However, the ¹H NMR data were not consistent for a dimeric structure with such a carbon–carbon linkage. For example, the signal for the 8b-hydrogen appeared as a doublet of triplets at $\delta = 7.11$ ppm,

showed coupling with a signal observed at δ 4.93 ppm as a doublet, and integrated for two protons (Figure 1). In

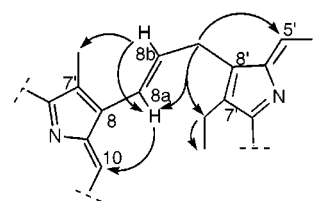


Figure 1. Selected NOE connectivities for dimer **4**.

addition, the methyl region (3.2–3.9 ppm), which was anticipated to have eight methyl signals, exhibited the resonances for only seven methyl groups. These results indicated that one of the methyl groups is certainly involved in the formation of a carbon–carbon bridge joining the two chlorin units. On the basis of these observations, we tentatively assigned this structure as bis purpurin *N*-hexylimide **4**. The detailed ¹H NMR/ROESY studies further confirmed the proposed structure and revealed a number of noteworthy features. For example, most of the signals of the individual chlorin units differ from each other, and interestingly, this difference was more prominent for the *meso* protons and methyl groups substituted at the peripheral positions. This distinctive resolution of the NMR signals facilitated a full assignment of the each chlorin resonances from their through-space interactions and coupling patterns obtained by 2D/ROESY and COSY experiments (Figure 1). The difference between the two chlorin units' resonances in dimer **4** were quite significant. Compared to the 12'-methyl resonances, the 12-methyl group showed an upfield shift ($\Delta\delta = -0.7$ ppm), accompanied by a similar shift ($\Delta\delta = -0.35$ ppm) of the corresponding neighboring *meso* proton. These data clearly indicate that one part of the vinyl-bearing chlorin unit is affected by the magnetic ring current of the other chlorin's π -system. A reasonable explanation of this observation can be attributed to the special arrangement of chromophores where one chlorin plane is located above another unit.⁹

(4) (a) Wasielewski, M. R.; Johnson, D. G.; Niemczyk, M. P.; Gaines, G. L., III; O'Neil, M. P.; Svec, W. A. *J. Am. Chem. Soc.* **1990**, *112*, 6482. (b) Zheng, G.; Pandey, R. K.; Forsyth, T. P.; Kozyrev, A. N.; Dougherty, T. J.; Smith, K. M. *Tetrahedron Lett.* **1997**, *38*, 2409.

(5) (a) Zheng, G.; Kozyrev, A. N.; Dougherty, T. J.; Smith, K. M.; Pandey, R. K. *Chem. Lett.* **1996**, 1119. (b) Zheng, G.; Dougherty, T. J.; Pandey, R. K. *J. Org. Chem.* **1999**, *64*, 3751.

(6) Similar results were obtained for 7,8-*vic*-dihydroxy derivatives of chlorin *e*₆, chlorin *p*₆, mesopurpurin-18, and mesopyropheophorbide *a* methyl esters.

(7) Pandey, R. K.; Shiao, F.-Y.; Medforth, C. J.; Dougherty, T. J.; Smith, K. M. *Tetrahedron Lett.* **1990**, *31*, 789.

(8) Purpurin-imides are a class of compounds derived from purpurin-18. In this series, the six-membered exocyclic anhydride ring fused at the *meso* position is replaced by an imide ring system.

(9) (a) Sessler, J. L.; Johnson, M. R.; Creager, S. E.; Fettinger, J. C.; Ibers, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 6482 and references therein. (b) Harriman, A.; Sauvage, J. P. *Chem. Soc. Rev.* **1996**, 41.

Molecular modeling studies, using the observed NOEs and the changes in the chemical shifts ($\Delta\delta$) as a guide for the selection of the potential 3D structures,⁹ resulted in the energy-optimized structure of dimer **4** and is shown in Figure 2.¹¹ The two chlorin chromophores showed a “tilted”

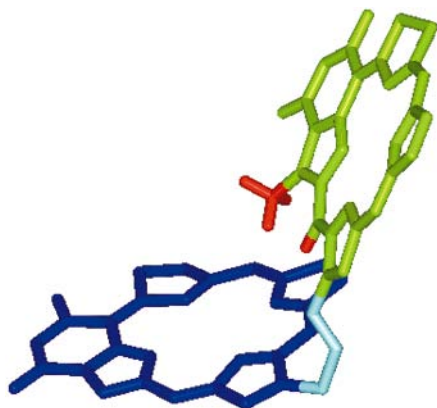


Figure 2. The 3D structure of the energy-optimized chlorin–chlorin dimer **4**. Each chromophore is shown in a different color. The 12-methyl and 10-*meso* protons (drawn in red) are pointing toward the opposing chlorin ring. For clarity, all other hydrogens as well as other substituents are not shown.

arrangement with an angle of about 134° . The 3D structural arrangement of dimer **4** showed a similarity to the geometrical arrangement of bacteriochlorophyll B_A and bacteriopheophytine F_A in the bacterial photosynthetic reaction center (RC) of *Rb. sphaeroides*,¹² which also possesses a tilted configuration with an angle of 115° between the two

(10) Gust, D.; Moore, T. A.; Bensasson, R. V.; Mathis, P.; Land, E. J.; Chachety, C.; Moore, A. L.; Liddell, P. A.; Nemeth, G. A. *J. Am. Chem. Soc.* **1985**, *107*, 3631.

(11) The SYBYL molecular modeling package version 6.03 (TRIPOS, St. Louis), running on the Evans & Sutherland ESV workstation, was used with the SYBYL standard geometry and force field parameters throughout this study. **Molecular Modeling Procedure:** Starting from the crystal structure of 2,3-dihydro-5,10-dimethyl-2,3,7,8,12,13,17,18-octaethylchlorin (Barkigia, K. M.; Thompson, M. A.; Fajer, J.; Pandey, R. K.; Smith, K. M.; Vincente, M. G. H. *New J. Chem.* **1992**, *16*, 599), the monomer unit was built and energy-optimized using the distance-dependent dielectric function and the Del Re *s* and Huckel *p* charges. Among four torsional angles in the C–C linker region, only one torsional angle around the double bond was determined to be in its *trans* configuration from the NMR data. The effect of three other dihedral angles in the linker upon the ¹H–¹H distances was carefully examined by using the model fragment (shown in Figure 1). Comparison of resulting ¹H–¹H distances with the NOE data indicated that the two end torsional angles can be in either plus (+) *gauche* or minus (–) *gauche* positions while the remaining middle torsional angle is likely to be in its *cis* configuration. The complete dimer was built from this linker fragment and the monomer unit by least-squares juxtaposition, and the energy minimizations were performed for all four conformers. The standard simulated annealing protocol (700 °C for 1000 cycles and an additional 1000 cycle for cooling to 200 °C) was used for 20 runs each for all four conformations without any distance constraints. Among 80 resulting structures, 10 structures were selected for the full energy optimization (0.05 kcal/mol/Å) on the basis of the relative orientation of the chromophores. The detailed distance map and distances between the appropriate ¹Hs and the ring system were examined. The structure that provided the best agreement with the observed NOEs and the changes in the chemical shifts was selected as the possible 3D structure of dimer **4**.

(12) Yeates, T. O.; Komiy, H.; Chirino, A.; Rees, D. C.; Allen, J. P.; Feher, G. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7993.

pigment planes. In comparison to the natural system in which the center-to-center distance was calculated to be 11.7 Å, the distance corresponding for dimer **4** was found to be 9.3 Å. Further, the 12-methyl substituent in dimer **4** is arranged in an identical fashion as observed for the methyl group for bacteriopheophytin *a* of the F_A–B_A pair.¹³ These data indicate that dimer **4** can be an interesting model for studying the ET processes.

The characterization of all the products obtained from the thermal dehydration gave a unique opportunity to propose a valid reaction mechanism for the formation of these species. First, in contrast to the pinacol–pinacolone rearrangement of the *vic*-dihydroxybacteriochlorin **1** (which produced both 7- and 8-keto analogues),¹⁴ we observed the formation of only 8-ketobacteriochlorin. This unambiguously indicated that the hydroxyl function at position-7 is leaving first to produce the carbocation **5**, which quickly rearranges to afford 8-keto-derivative **3**. Further elimination of the second hydroxyl group generates the thermodynamically favored benzylic-type carbocation **7b**, which on reaction with vinyl derivative **2**, obtained via intermediate **9**, would lead to the formation of novel dimer **4** (Scheme 2).

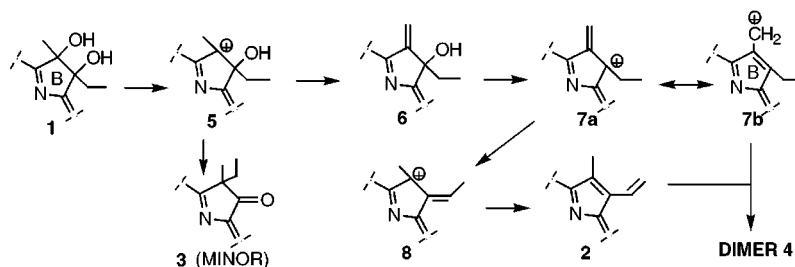
The proposed mechanism indicates that the carbocation **7b** might be a more stable reactive intermediate than others,

(13) Ivashin, N.; Kallebring, B.; Larsson, S.; Hansson, O. *J. Phys. Chem. B* **1998**, *102*, 5017.

(14) Kozyrev, A. N.; Pandey, R. K.; Medforth, C. J.; Zheng, G.; Dougherty, T. J.; Smith, K. M. *Tetrahedron Lett.* **1996**, *37*, 747.

(15) **Representative Experimental Section: General Method for the Preparation of Homo- and Heterodimers.** The *vic*-dihydroxybacteriochlorin **1** (50 mg, 75 μmol) in 1,2-dichlorobenzene (30 mL) was refluxed for 1 h under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature and chromatographed on a silica column, eluting with 2% acetone/CH₂Cl₂ to produce the desired homodimer **4** in 55% yield. Under similar conditions, reaction of bacteriochlorin **1** with a 3-fold excess of rhodoporphyrin IX dimethyl ester **9** produced the heterodimer **10** in 31% yield. **Purpurin-18 hexylimide dimer (4):** UV/vis (CH₂Cl₂) λ_{max} (ε) = 414 (215 000), 510 (190 000), 546 (21 000), 636 (16 500), 699 (87 000); ¹H NMR (600 MHz, CDCl₃, δ ppm) 9.71 (s, 1H, 10'-H), 9.57 (s, 1H, 5'-H), 9.48 (s, 1H, 10-H), 9.09 (s, 1H, 5-H), 8.53 (s, 1H, 20'-H), 8.44 (s, 1H, 20-H), 7.78 (d, *J* = 16.1 Hz, 1H, 8a-H), 7.11 (dt, *J* = 16.1, 6.1 Hz, 1H, 8b-H), 5.43 (dd, *J* = 6.2 Hz, 17-H), 5.37 (dd, *J* = 6.2 Hz, 17'-H), 4.93 (d, *J* = 6.1, 2H, 7'-CH₂), 4.43 (m, 3H, N-CH₂ + 18'-H), 4.39 (t, 2H, N'-CH₂), 4.29 (dq, 1H, 18-H), 3.89 (q, *J* = 7.8 Hz, 2H, 8'a-CH₂), 3.82 (s, 3H, 12'-Me), 3.76 (q, *J* = 7.8 Hz, 2H, 2'a-CH₂), 3.69 (q, *J* = 7.8 Hz, 2H, 3a-CH₂), 3.61 (s, 3H, CO₂Me), 3.59 (s, 3H, CO₂Me), 3.18 (s, 6H, 2-Me, 2'-Me), 3.16 (s, 3H, 12-Me), 3.15 (s, 3H, 7-Me), 2.71 (m, 1H, 17'a-H), 2.69 (m, 1H, 17a-H), 2.43 (m, 4H, 17/17'-a',b), 2.02 (m, 6H, 17/17'-b', hexyl-b/b'-CH₂), 1.89 (m, 4H, hexyl-c/c'-CH₂), 1.83 (t, *J* = 7.6 Hz, 8'-Me), 1.78 (d, *J* = 6.2, 3H, 18'-Me), 1.72 (d, *J* = 6.2, 3H, 18-Me), 1.63 (t, *J* = 7.5 Hz, 3'-Me), 1.58 (t, *J* = 7.6 Hz, 3-Me), 1.56 (m, 8H, hexyl-CH₂), 0.98 (m, 6H, hexyl-Me), 0.12 (br s, 1H, NH), -0.04 (br s, 1H, NH), -0.08 (br s, 1H, NH), -0.18 (br s, 1H, NH); HRMS, calcd 1322.7243, C₈₀H₉₄N₁₀O₈ requires 1322.7255. **Porphyrim–purpurin N-hexylimide heterodimer (10):** UV/vis (CH₂Cl₂) λ_{max} (ε) = 414 (165 000), 420 (180 000), 510 (15 000), 546 (33 000), 588 (12 000), 636 (15 000), 699 (44 000); ¹H NMR (600 MHz, CDCl₃, δ ppm) porphyrin, 10.97 (s, 1H, 15-H), 10.07 (s, 1H, 10-H), 9.93 (s, 1H, 20-H), 9.75 (s, 1H, 5-H), 8.18 (d, *J* = 16.2 Hz, 1H, 3a-H), 7.31 (dt, *J* = 16.2, 6.2 Hz, 1H, 3b-H), 4.41 (m, 3H, 12-CO₂Me), 4.39 (t, 2H, 17a-CH₂), 3.89 (q, *J* = 7.8 Hz, 2H, 8a-CH₂), 3.85 (s, 3H, 11-Me), 3.61 (s, 3H, CO₂Me), 3.69 (s, 3H, CO₂Me), 3.16 (s, 3H, 12-Me), 3.58 (s, 3H, 18-Me), 3.39 (t, 2H, 17b-CH₂), 1.89 (t, *J* = 7.6 Hz, 8-Me), -4.48 (br s, 2H, NH); chlorin, 9.75 (s, 1H, 10'-H), 9.67 (s, 1H, 5'-H), 8.51 (s, 1H, 20'-H), 5.43 (dd, *J* = 6.3 Hz, 17'-H), 5.04 (d, *J* = 6.2, 2H, 7'-CH₂), 4.46 (m, 3H, N-CH₂ + 18'-H), 3.89 (q, *J* = 7.8 Hz, 2H, 8'a-CH₂), 3.87 (s, 3H, 12'-Me), 3.76 (q, *J* = 7.8 Hz, 2H, 3'a-CH₂), 3.59 (s, 3H, CO₂Me), 3.18 (s, 6H, 2-Me, 2'-Me), 2.82 (s, 3H, 7-Me), 2.71 (m, 1H, 17'a-H), 2.43 (m, 2H, 17'-a',b), 2.02 (m, 3H, 17'-b', hexyl-b'-CH₂), 1.89 (t, *J* = 7.6 Hz, 8'-Me), 1.83 (m, 2H, hexyl-c'-CH₂), 1.83 (t, *J* = 7.6 Hz, 8'-Me), 1.78 (d, *J* = 6.2, 3H, 18'-Me), 1.63 (t, *J* = 7.5 Hz, 3'-Me), 1.56 (m, 8H, hexyl-d',e'-CH₂), 0.98 (m, 6H, hexyl-f'-Me), 0.12 (br s, 1H, NH), -0.04 (br s, 1H, NH); HRMS, calcd 1225.6353, C₇₄H₈₃N₉O₈ requires 1225.6364.

Scheme 2. A Proposed Mechanism for the Formation of a Carbon–Carbon Dimer



Scheme 3

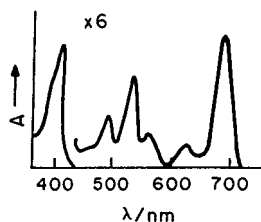
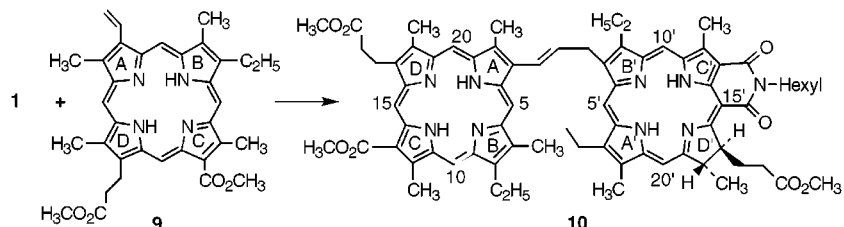


Figure 3. Electronic absorption spectrum of heterodimer **10**.

and if an aromatic compound containing a vinyl substituent is added in large excess, it might be able to “trap” this intermediate to produce a heterodimeric structure. To prove this hypothesis, we reacted a 3-fold excess of rhododoporphyrin IX dimethyl ester **9** with 7,8-*vic*-dihydroxypurpurin imide **1** [*cis*-hydroxy groups up or down relative to ring D (*trans*-reduced)] under the conditions discussed for the preparation of the symmetrical dimer **4**. As predicted, along with the 8-keto derivative **2** (10%) and 8-vinyl purpurin *N*-hexylimide **3** (42%), the novel porphyrin–chlorin heterodimer **10** (Scheme 3) was isolated in 31% yield ($m/z = 1225.6$), without formation of the homodimer **4**. The UV/vis spectrum of heterodimer **10** exhibited distinctive structural features for both porphyrin and chlorin subunits (Figure 3). In a manner similar to that of the symmetrical dimer **4**, in the NMR spectrum of **10** the 5-*meso*-hydrogen and the resonances for

the 7-methyl protons of the vinyl-porphyrin showed upfield shifts ($\Delta\delta = -0.28$ and -0.7 ppm, respectively). These data indicate that in this heterodimer **10** the porphyrin unit is orientated in a tilted fashion above the chlorin plane, as observed in dimer **4**.

In summary, we have developed a simple method to convert the *vic*-dihydroxybacteriochlorins into the corresponding new carbon–carbon linked homodimers. We have also shown the utility of this approach in constructing heterodimeric structures as models for “twisted intermolecular charge-transfer” systems.⁴ In these model systems, the connecting bridges have slight flexibility to allow minimum overlap between the chromophore π -systems.⁴ The photo-physical studies of these novel dimers are currently in progress and will be reported elsewhere.

Acknowledgment. The authors thank Mallinckrodt Medical Inc., St. Louis, LA, the National Institutes of Health (CA 55791), and the Roswell Park Alliance Foundation for financial support. Partial support of the NMR facility by NIH Grant CA 16056 is also acknowledged.

Supporting Information Available: Experimental procedures and full characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL990150I