Synthesis of Covalently Linked Dimeric Derivatives of Chlorophyll *a*, Pyrochlorophyll *a*, Chlorophyll *b*, and Bacteriochlorophyll *a*

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Bis(chlorophyllide) ethylene glycol diesters were prepared for each of the title compounds. Pheophytins *a* and *b* isolated from alfalfa and bacteriochlorophyll *a* isolated from *R. sphaeroides* were treated with 80% aqueous trifluoroacetic acid to yield the corresponding pheophorbides. Pyropheophorbide was prepared by a literature procedure. Carbonic anhydride and benzotriazole-1-methanesulfonate activation methods were used in the esterification of the pheophorbides with ethylene glycol at ambient temperature. Each method yielded 75%+ of the pheophorbide ethylene glycol monoester. These monoesters were treated with equimolar amounts of the corresponding pheophorbide by using benzotriazole-1-methanesulfonate/4-(dimethylamino)pyridine in CH_2Cl_2 or dicyclohexylcarbodiimide/4-(dimethylamino)pyridine in CH_2Cl_2 at ambient temperature. Yields of bis(pheophorbide) ethylene glycol diesters averaged about 50% for the former method and 70% for the latter method. Insertion of the magnesium atoms into the *a* series macrocycles was accomplished with iodomagnesium 2,6-di-*tert*-butyl-4-methylphenolate, IMgBHT, in CH_2Cl_2, while the metalation of the *b* and bacterial series macrocycles was carried out with a mixture of IMgBHT and lithium 2,2,6,6-tetramethylpiperidide in thiophene, all at ambient temperature. Both mono- and dimetalated derivatives were isolated and characterized in each case.

Current evidence concerning the nature of P700, the primary photochemical electron donor in photosystem I of green plants, and P865, the analogous species in purple photosynthetic bacteria, identifies these species with special pairs of chlorophyll *a* (**1a**) and bacteriochlorophyll *a* (**4a**), respectively.[1] These special pairs serve as low-energy traps for the electronic excitation produced by illumination of antenna chlorophyll which absorbs light near 680 nm in green plants and near 800 nm in photosynthetic bacteria.

The chlorophyll molecules that comprise the special pair do not differ structurally from their corresponding antenna chlorophylls.[2] In the photoreaction centers of each organism the chlorophyll molecules of the special pairs assume an orientation relative to one another that results in lowering the oxidation potential of the pairs relative to the antenna chlorophyll. Presumably this specific orientation is enforced by the surrounding protein structure.

Several models have been proposed to account for the orientational dependence of both the oxidation potential and the optical spectra of the special pairs.[3-5] Most of these models utilize the wide variety of self-aggregation phenomena associated with the coordinatively unsaturated magnesium atom and the nucleophilic carbonyl groups of the chlorophylls.[1] In these models the magnesium atom of one chlorophyll molecule is coordinated to the heteroatom of a hydrogen-bonding nucleophile, e.g., the oxygen atom of ROH, the proton of which in turn is hydrogen bonded to one of the carbonyl oxygen atoms of a second chlorophyll molecule. Since the strength of both the hydrogen bonds and the coordination bonds maintaining these structures depends strongly on an unfavorable entropy term contributing to the free energy of aggregation of the two chlorophylls, experiments designed to produce such structures have generally been carried out at low temperatures.[3,4] More recently, several special pair models have appeared in the literature which overcome the entropy problem by chemically linking two chlorophyll macrocycles.[5-8] These model special pairs exhibit unique biomimetic properties at room temperature and are the source of many continuing studies.[9-12] The papers dealing with these models to date have given only short outlines of the synthetic methods used to prepare these compounds. In this paper we detail the chemistry used to prepare these compounds and make some observations regarding esterification of the propionic acid side chain of chlorophylls and their derivatives.

Results and Discussion

The original work of Willstätter,[13] later amplified by Fischer,[14] disclosed that the phytyl ester of chlorophylls can be selectively hydrolyzed by the enzyme chlorophyllase with retention of the central magnesium atom or by strong mineral acids to yield the carboxylic acid chlorophyllides and pheophorbides, respectively. Similarly, in the presence of an excess of simple alcohols, e.g., methanol, the same reactions yield the corresponding transesterified alkyl chlorophyllides[14] and alkyl pheophorbides.[15]

In our studies pheophorbide *a* (**1c**) and pheophorbide *b* (**3c**) were prepared by a more selective ester cleavage method than that employed by Fischer. In Fischer's method, treatment of an ethereal solution of pheophytin *a* (**1b**) or pheophytin *b* (**3b**) with concentrated HCl under nitrogen at 25 °C cleaves the phytyl ester in about 90% yield. However, the proton NMR spectrum of the product shows that the acid hydrolysis is only about 80% selective

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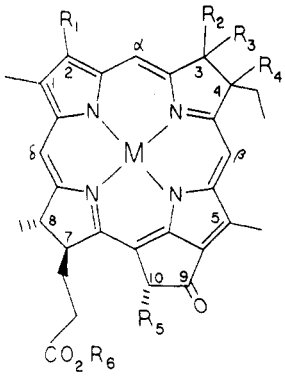
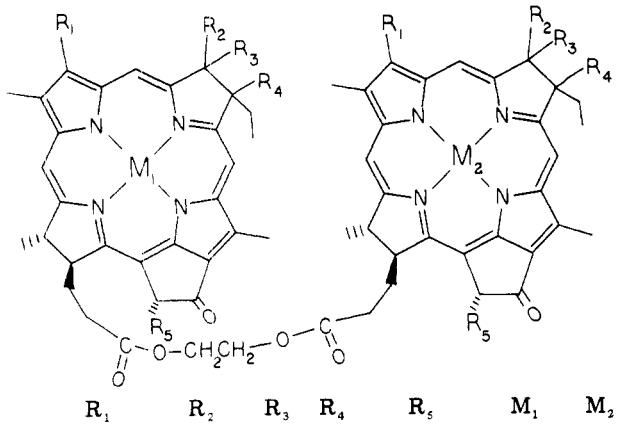


	R_1	R_2	R_3	R_4	R_5	R_6	M
1a	$CHCH_2$	CH_3			CO_2CH_3	$C_{20}H_{39}$	Mg
1b	$CHCH_2$	CH_3			CO_2CH_3	$C_{20}H_{39}$	2 H
1c	$CHCH_2$	CH_3			CO_2CH_3	H	2 H
1d	$CHCH_2$	CH_3			CO_2CH_3	CH_2CH_2OH	2 H
2a	$CHCH_2$	CH_3			H	$C_{20}H_{39}$	Mg
2b	$CHCH_2$	CH_3			H	$C_{20}H_{39}$	2 H
2c	$CHCH_2$	CH_3			H	H	2 H
2d	$CHCH_2$	CH_3			H	CH_2CH_2OH	2 H
3a	$CHCH_2$	CHO			CO_2CH_3	$C_{20}H_{39}$	Mg
3b	$CHCH_2$	CHO			CO_2CH_3	$C_{20}H_{39}$	2 H
3c	$CHCH_2$	CHO			CO_2CH_3	H	2 H
3d	$CHCH_2$	CHO			CO_2CH_3	CH_2CH_2OH	2 H
4a	$COCH_3$	CH_3	H	H	CO_2CH_3	$C_{20}H_{39}$	Mg
4b	$COCH_3$	CH_3	H	H	CO_2CH_3	$C_{20}H_{39}$	2 H
4c	$COCH_3$	CH_3	H	H	CO_2CH_3	H	2 H
4d	$COCH_3$	CH_3	H	H	CO_2CH_3	CH_2CH_2OH	2 H

Figure 1.



	R_1	R_2	R_3	R_4	R_5	M_1	M_2
1e	$CHCH_2$	CH_3			CO_2CH_3	2 H	2 H
1f	$CHCH_2$	CH_3			CO_2CH_3	Mg	2 H
1g	$CHCH_2$	CH_3			CO_2CH_3	Mg	Mg
2e	$CHCH_2$	CH_3			H	2 H	2 H
2f	$CHCH_2$	CH_3			H	Mg	2 H
2g	$CHCH_2$	CH_3			H	Mg	Mg
3e	$CHCH_2$	CHO			CO_2CH_3	2 H	2 H
3f	$CHCH_2$	CHO			CO_2CH_3	Mg	2 H
3g	$CHCH_2$	CHO			CO_2CH_3	Mg	Mg
4e	$COCH_3$	CH_3	H	H	CO_2CH_3	2 H	2 H
4f	$COCH_3$	CH_3	H	H	CO_2CH_3	Mg	2 H
4g	$COCH_3$	CH_3	H	H	CO_2CH_3	Mg	Mg

Figure 2.

for the phytyl ester. The remaining 20% of product is pyropheophorbide *a* (**2c**) in which the carbomethoxy group at position 10 has been hydrolyzed with resultant decarboxylation in addition to hydrolysis of the phytyl ester. Cooling the reaction mixture to 0 °C does not improve the selectivity of the hydrolysis and leads only to diminished total yields of products.

We have found that dissolution of **1b** or **3b** in oxygen-free 80% trifluoroacetic acid at 0 °C results in a homogeneous reaction mixture that gives 90%+ yields of ester hydrolysis products in 45 min with better than 95% selectivity toward phytyl cleavage alone. The remaining 5% of pyropheophorbide is easily removed by column chromatography. The preparation of **2c** from **2b** does not pose a problem, as the Fischer method is adequate for the pyro compound.

The hydrolysis of the phytyl ester of bacteriopheophytin *a* (**4b**) by aqueous HCl has been reported to yield substantial quantities of 2-acetyl-2-devinylpheophorbide *a*.[16] This result suggests that oxidation of the 2 and 3 positions of bacteriochlorins by oxygen is rapid in strongly acidic solutions. The same reaction was carried out with careful exclusion of oxygen from the reaction mixture. Workup of the reaction mixture after 1 h of stirring at room temperature yielded unchanged **4b**. It was noted, however, that the reaction mixture was highly heterogeneous, with **4b** only slightly soluble in the aqueous HCl.

Fischer obtained the first authentic sample of **4c** by the action of chlorophyllase on **4a**.[16] He obtained a mixture of **4b** and **4c** in about 25% yield. In order to prepare synthetically useful quantities of **4c** we treated **4a** with oxygen-free 80% aqueous trifluoroacetic acid in the dark for 2 h at ambient temperature. This method produced a 90% yield of **4c**. The proton NMR spectrum of **4c** was consistent with better than 99% selectivity in the hydrolysis of the phytyl ester.

The synthesis of alkyl pheophorbides is complicated by the intrinsic reactivity of the pheophorbide macrocycle. The macrocycle is degraded by a variety of reaction conditions usually employed for esterifications. Transesterifications of pheophytins or acid-catalyzed esterification of pheophorbides requires large excesses of alcohol and is limited by concomitant replacement of the methyl ester at position 10 with the alcohol desired at the propionic acid side chain. On the other hand, strong bases and nucleophiles react with the ketone at C-9, leading to cleavage of ring V.[17,18] Oxidation at C-10 is also rapid under basic conditions.[19] In addition, the 2 and 3 positions of bacteriochlorins are susceptible to oxidation as noted above. Finally, heating pheophorbides in basic organic solvents results in decarboxylation at C-10, yielding the corresponding pyro compounds.[20] Thus, the chemistry of the β-keto ester in ring V dominates the reactivity of the macrocycle. Although removal of the carbomethoxy group alleviates many of these problems, various structural models of special pair chlorophyll utilize the keto group of the carbomethoxy function for hydrogen bonding,[4] thus making the preparation of models that retain this group of particular interest.

There are numerous mild esterification methods in the literature.[21] The majority of these methods are adaptations of peptide linkage procedures and involve the preparation of an activated ester of the carboxylic acid with subsequent alcoholysis to form the desired ester. However, most of these procedures require reaction conditions that are incompatible with the preservation of ring V of the pheophorbides. For example, the well-known acyl imidazolide coupling method normally requires temperatures

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at which pheophytins are degraded to pyropheophytins in the basic reaction medium. Although by no means exhaustive, the methods presented in this work were found to be very effective in esterifying the propionic acid side chains selectively in high yield.

Fischer and Schmidt successfully reesterified **1c** with several natural-product alcohols by using phosgene in pyridine as the coupling reagent.[22] We have employed the more convenient phosgene derivative isobutyl chloroformate. Wieland successfully used chloroformates in the presence of excess tertiary amine to produce activated esters which were rapidly cleaved by nucleophiles, such as amines and alcohols.[23] We found that free acids **1c–4c** all react readily with isobutyl chloroformate in the presence of triethylamine or pyridine in THF to produce an activated ester which is quickly cleaved by primary alcohols to yield the corresponding esters. The preparation using ethylene glycol is detailed in the Experimental Section, but other alcohols such as methyl, phytyl, and benzyl alcohol all react under identical conditions to give esters in similar yield.

The scope of the carbonic anhydride method is limited somewhat in that the activated carboxylic acid is extremely sensitive toward hydolysis by trace amounts of water in the reaction medium. Since the molarity of the pheophorbide solutions is always very low due to sample and solubility considerations, residual water competes effectively with the alcohol for the activated carboxylic acid. This can be overcome by utilizing large excesses of the esterifying alcohol, but this is clearly not desirable in most cases, the goal being the final coupling of a pheophorbide ethylene glycol monoester with another mole of pheophorbide to yield the desired special pair model.

While exploring the properties of acidic *N*-hydroxy compounds, Itoh found that sulfonate esters of these compounds such as benzotriazole-1-methanesulfonate are very effective in activating carboxylic acids toward ester formation.[24] More importantly, the alcoholysis of these activated species proceeds rapidly at room temperature in the presence of excess tertiary amine. These conditions are compatible with preserving the integrity of ring V. This procedure was applied to the esterification of **1c–4c** with ethylene glycol. The yields of isolated product were consistently above 75% in all cases. Successful esterifications may be easily accomplished with a 1:1 molar ratio of pheophorbide to alcohol, although in cases for which the alcohol is readily available the rate of the reaction is accelerated by the addition of excess alcohol. The benzotriazole active ester does not display the sensitivity to water that the carbonic anhydrides do.

As mentioned above, we found that the chloroformate coupling reagent was much too sensitive to traces of water in the reaction mixture to compete effectively with pheophorbide ethylene glycol monoesters to make the dimeric diesters. On the basis of this finding, we examined the applicability of the Itoh method to this problem. In this case, using equimolar quantities of **1c** and **1d** in THF with 1 equiv of benzotriazole-1-methanesulfonate and 2 equiv of triethylamine produced only a few percent of diester **1e**. Increasing the amount of coupling reagent to a fourfold molar excess did not improve the yield of product. Changing the solvent to CH_2Cl_2 once again did not increase the yield substantially, but when the hypernucleophilic catalyst 4-(dimethylamino)pyridine was added to the CH_2Cl_2 solvent instead of triethylamine, the rate of the reaction increased and boosted the yield to about 50%. This method gave consistent results with comparable yields of each bis(pheophorbide) in series **1–4**.

In the literature there have been two reports that 4-(dimethylamino)pyridine may be used to catalyze the esterification of carboxylic acids when dicyclohexylcarbodiimide is used as a coupling reagent.[26,27] The reaction is carried out in CH_2Cl_2 or DMF and gives good-to-excellent yields of esters for a wide variety of acids and alcohols. We tested this method for the preparation of bis(pheophorbides) and found the method to work very well. The procedure detailed for the synthesis of **2e** was applied to each diester synthesis. Good yields were obtained in each case and, in general, averaged about 20% higher than those obtained with the Itoh reagent. In terms of ease of application and overall yield the carbodiimide/4-(dimethylamino)pyridine method is the method of choice in preparing these dimeric diesters.

The introduction of magnesium into pheophytins and their derivatives remains a problem of continuing interest. Once again the sensitivity of the functionality in ring V of the pheophytin macrocycle presents several problems. Pyropheophytins may be magnesiated by refluxing the compound in pyridine containing a very large excess of $Mg(ClO_4)_2$.[28] The sluggishness of this reaction and the vigorous, prolonged reflux necessary to achieve insertion of the metal often result in greatly diminished yields of product.

The $Mg(ClO_4)_2$/pyridine method is clearly not applicable to pheophytins with a carbomethoxy group at C-10 because the reaction conditions result in removal of this group. This problem has been examined in great detail by Eschenmoser's group.[29] They found that the metalation reaction requires two conditions that are seemingly incompatible at first glance. The magnesium salt that performs the metalation must possess ligands that coordinate only weakly to the magnesium. At the same time a fairly strong base must serve to deprotonate the central NH groups of the macrocycle while preserving the integrity of ring V. These conditions are fulfilled quite well with iodomagnesium 2,6-di-*tert*-butyl-4-methylphenolate (I-MgBHT) in chlorinated hydrocarbon solvents. The phenolate base is sufficiently basic to deprotonate the NH groups yet remains highly nonnucleophilic due to the steric shielding of the phenolate oxygen atom by the *tert*-butyl groups. The steric crowding around the oxygen atom also reduces significantly its ability to ligate the magnesium atom. This latter property is illustrated nicely by the fact that the presence of a variety of organic solvents possessing nucleophilic sites, e.g., acetone, THF, and pyridine, that coordinate strongly with the magnesium stop the metalation reaction. The Eschenmoser procedure works extremely well for the *a* series pheophytin derivatives but proves to be sluggish for the *b* series and bacteriochlorin series. Yields of metalated product are greatly diminished by the side reactions that predominate when IMgBHT is used in refluxing thiophene in order to metalate the *b* and bacterial series pheophytins.[29] The NH protons of these macrocycles are apparently sufficiently less acidic than

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those of the *a* series to require a somewhat stronger base to remove them.

Recently we reported the use of the strong proton-selective base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in the presence of the Eschenmoser reagent to effect the metalation of bacteriopheophytin *a* at room temperature.[30] The reaction proceeds rapidly and without formation of large quantities of side products. We have employed this procedure to metalate both **3e** and **4e** in moderate yield. The principal reaction products other than the desired metalated diester are both the monometalated diester and the unreacted diester.

Experimental Section

Pheophytins *a* (**1b**) and *b* (**3b**) were obtained by the large-scale extraction of partially dehydrated alfalfa (Western Alfalfa, Shawnee Mission, KS) with refluxing acetone. Acidification of the extract, neutralization of the excess acid, and chromatography on silica gel (Merck 60–200 mesh, elution with 5% acetone in toluene) yielded pure **1b** and **3b**. Pyropheophytin *a* (**2b**) was prepared by refluxing **1b** in pyridine according to existing procedures.[31] Bacteriochlorophyll *a* (**4a**) was obtained from the large-scale (20 L) culture of *Rhodopseudomonas sphaeroides*.[32]

Thiophene (Aldrich Gold Label) was purified by refluxing over potassium metal for 4 h, followed by distillation and storage over Linde 3A molecular sieves. 2,2,6,6-Tetramethylpiperidine was purified by refluxing over potassium hydroxide for 1 h, followed by distillation and storage over Linde 3A molecular sieves under nitrogen. All other required dry solvents were dried over Linde 3A sieves before use.

Melting points were determined with a Thomas-Hoover melting point apparatus. Electronic spectra were recorded with a Cary 14 spectrophotometer. Mass spectral data were obtained with a time-of-flight mass spectrometer equipped with a heated-filament source. Proton NMR spectra were obtained at 220 MHz on a Varian HR220 instrument operating in the pulse–Fourier transform mode. All NMR data are referenced to Me_4Si. Microanalyses were performed by Micro-Tech Laboratories. The magnesium-containing derivatives were demetalated prior to microanalysis. The resulting ligands yielded analyses in excellent agreement with those obtained for the same ligands prior to magnesium insertion.

Pheophorbide *a* (1c). **1b** (1.03 g, 1.18 mmol) was dissolved in cold (0 °C) 80% aqueous trifluoroacetic acid (150 mL) which had been bubbled with nitrogen for 10 min. The resulting green solution was protected from light and stirred under a nitrogen blanket at 0 °C for 45 min. The reaction mixture was poured into water (1 L) and extracted with $CHCl_3$. The extract was washed five times with water and twice with 10% $NaHCO_3$, and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a brown residue which was chromatographed on powdered confectioner's sugar (3–8 cm × 30 cm columns, elution with 10% acetone in CCl_4). Following elution of a small amount of unreacted **1b**, the large product band was collected. The CCl_4–acetone solution of the product was evaporated and the residue taken up in $CHCl_3$. The $CHCl_3$ solution was washed three times with water and dried over anhydrous $NaSO_4$. Evaporation of the solvent followed by precipitation of the product from CH_2Cl_2–petroleum ether yielded pure **1c**: 642 mg; 92%; mp 190–195 °C (lit. mp 190–200 °C[17]); ^1H NMR ($CDCl_3$) δ 1.62 (t, J = 7.5 Hz, 4b-H), 1.74 (d, J = 7.5 Hz, 8a-H), 2.27 (m, 7a-H), 2.54 (m, 7b-H), 3.16 (s, 3-CH_3), 3.35 (s, 1-CH_3), 3.60 (q, J = 7.5 Hz, 4a-H), 3.64 (s, 5-CH_3), 3.81 (s, 10b-CH_3), 4.16 (m, 7- or 8-H), 4.43 (m, 7- or 8-H), 6.17 (s, 10-H), 6.26 (m, 2b-H), 7.98 (m, 2a-H), 8.54 (s, δ-H), 9.35 (s, α-H), 9.49 (s, β-H); electronic spectrum (in acetone), λ_{max} (ϵ) 667 (55 200), 610 (7970), 535 (9470), 507 (12 100), 409 (119 200) nm.

Pheophorbide *b* (3c). **3b** (0.300 g, 0.339 mmol) was treated by the same method outlined for the preparation of **1c** to yield **3c**: 191 mg; 93%; mp 220–223 °C (lit. mp 215–225 °C[33]); ^1H NMR ($CDCl_3$) δ 1.49 (t, J = 7.5 Hz, 4b-H), 1.74 (d, J = 7.5 Hz, 8a-H), 2.23 (m, 7a-H), 2.59 (m, 7b-H), 3.27 (s, 1-CH_3), 3.46 (q, J = 7.5 Hz, 4a-H), 3.51 (s, 5-CH_3), 3.73 (s, 10b-CH_3), 4.14 (m, 7- or 8-H), 6.16 (s, 10-H), 6.20 (m, 2b-H), 7.86 (m, 2a-H), 8.49 (s, δ-H), 9.32 (s, β-H), 10.10 (s, α-H), 10.89 (s, 3a-H); electronic spectrum (in acetone), λ_{max} (ϵ) 653 (39 800), 602 (9270), 553 (9320), 530 (12 300), 439 (154 000) nm.

Pyropheophorbide *a* (2c). **2b** (800 mg, 0.99 mmol) was hydrolyzed with concentrated HCl (200 mL). Workup was the same as in the preparation of **1c**: yield of **2c** 475 mg; 90%; mp 210–220 °C (lit. mp 210–220 °C[33]); ^1H NMR ($CDCl_3$) δ 1.59 (t, J = 7.5 Hz, 4b-H), 1.73 (d, J = 7.5 Hz, 8a-H), 2.27 (m, 7a-H), 2.62 (m, 7b-H), 3.15 (s, 3-CH_3), 3.36 (s, 1-CH_3), 3.59 (q, J = 7.5 Hz, 4a-H), 3.59 (s, 5-CH_3), 4.27 (m, 7- or 8-H), 4.43 (m, 7- or 8-H), 5.16 (m, 10-H), 6.19 (m, 2b-H), 7.93 (m, 2a-H), 8.51 (s, δ-H), 9.32 (s, α-H), 9.43 (s, β-H); electronic spectrum (in acetone), λ_{max} (ϵ) 667 (55 100), 610 (7960), 535 (9470), 507 (12 000), 409 (119 200) nm.

Bacteriopheophorbide *a* (4c). **4a** (990 mg, 1.09 mmol) was treated with 80% aqueous trifluoroacetic acid at ambient temperature for 2 h by the methods described for the preparation of **1c**: yield 598 mg; 90%; mp 260 °C dec (lit. mp 257 °C dec[16]); ^1H NMR (pyridine-d_5) δ 0.96 (t, J = 7 Hz, 3a- and 8a-CH_3), 1.66 (d, J = 7 Hz, 3a- and 8a-CH_3), 2.10 (m, 4a-H), 2.62 (m, 7a-H), 2.92 (m, 7b-H), 3.11 (s, 2b-CH_3), 3.38 (s, 5-CH_3), 3.42 (s, 1-CH_3), 3.81 (10b-CH_3), 4.12 (m, 3,4-H or 7,8-H), 4.30 (m, 3,4-H or 7,8-H), 6.70 (s, 10-H), 8.62 (s, δ-H), 8.66 (s, β-H), 9.38 (s, α-H); electronic spectrum (in acetone), λ_{max} (ϵ) 750 (49 100), 677 (6950), 524 (19 300), 490 sh (3890), 384 (44 800), 357 (80 500) nm.

Esterification Method A. Pheophorbide *a* Ethylene Glycol Monoester (1d). All operations were performed in a nitrogen-filled glovebox. **1c** (250 mg, 0.42 mmol) was dissolved in freshly distilled, dry THF (20 mL). Dry pyridine (1 mL) was added to the solution with stirring. Isobutyl chloroformate (0.5 mL, 6.8 mmol) was added dropwise with stirring over 5 min. A dry 1:1 (v/v) mixture of ethylene glycol and THF (5 mL) was added all at once to the reaction mixture. The resulting solution was stirred 10 min longer, poured into water, and extracted with ether. The ether extract was washed three times with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a dark brown residue which was chromatographed on silica gel (60–200 mesh, 8 cm × 30 cm column, elution with 25% acetone in CCl_4) to give pure ester **1d**: 195 mg; 72%; mp 120–124 °C; ^1H NMR ($CDCl_3$) δ 1.61 (t, J = 7.5 Hz, 4b-H), 1.74 (d, J = 7.5 Hz, 8a-H), 2.30 (m, 7a-H), 2.51 (m, 7b-H), 3.18 (s, 3-CH_3), 3.35 (s, 1-CH_3), 3.59 (q, J = 7.5 Hz, 4a-H), 3.62 (s, 5-CH_3), 3.81 (s, 10b-CH_3), 4.01 (m, glycol H), 4.16 (m, 7- or 8-H), 4.39 (m, 7- or 8-H), 6.19 (m, 2b-H), 6.22 (s, 10-H), 7.91 (m, 2a-H), 8.51 (s, δ-H), 9.30 (s, α-H), 9.49 (s, β-H); electronic spectrum (in acetone), λ_{max} (ϵ) 667 (55 300), 611 (7890), 535 (9490), 507 (12 100), 409 (119 400) nm; MS m/e 636 (M^+). Anal. Calcd for $C_{37}H_{40}N_4O_6$: C, 69.79; H, 6.33. Found: C, 69.68; H, 6.40.

Esterification Method B. Bacteriopheophorbide *a* Ethylene Glycol Monoester (4d). **4c** (425 mg, 0.64 mmol) was dissolved in dry THF (50 mL). Benzotriazole-1-methanesulfonate (1.36 g, 6.4 mmol) was added to the solution along with triethylamine (2 mL). The reaction mixture was protected from light and stirred 10 min. Ethylene glycol (2 mL) was added, and the resulting mixture was stirred at ambient temperature for 2 h. The resulting solution was poured into water and extracted with ethyl acetate. The extract was washed with water (5×) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a purple residue which was chromatographed on silica gel (60–200 mesh, 8 cm × 30 cm column, elution with 25% acetone in CCl_4) to yield **4d**: 308 mg; 73%; mp 155–157 °C; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 8 Hz, 4b-CH_3), 1.62 (d, J = 7 Hz, 3a- or 8a-CH_3), 1.72 (d, J = 7 Hz, 3a- or 8a-CH_3), 2.0–2.6 (m, 4a,7a,7b-H), 3.14 (s, 2b-CH_3), 3.42 (s, 5-CH_3), 4.00 (m, 3,4-H or 7,8-H), 4.09 (m, glycol H), 4.24 (m, 3,4-H or 7,8-H), 6.08 (s, 10-H), 8.43 (s, δ-H), 8.49 (s, β-H), 9.01 (s, α-H); electronic spectrum (in acetone), λ_{max} (ϵ) 750 (49 200), 676 (6970), 522 (19 400), 492 sh (3900), 384 (45 000), 357 (80 600) nm; MS m/e 654.8 (M^+). Anal. Calcd for $C_{37}H_{42}N_4O_7$: C, 67.87; H, 6.47. Found: C, 67.80; H, 6.52.

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Pyropheophorbide *a* Ethylene Glycol Monoester (2d). 2c (302 mg, 0.57 mmol) was esterified (method B) with ethylene glycol to yield ester **2d**: 282 mg; 86%; mp 117–121 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (t, J = 7.5 Hz, 4b-H), 1.75 (d, J = 7.5 Hz, 8a-H), 2.26 (m, 7a-H), 2.60 (m, 7b-H), 3.22 (s, 3-CH_3), 3.37 (s, 1-CH_3), 3.60 (s, 5-CH_3), 3.61 (q, J = 7.5 Hz, 4a-H), 4.01 (m, glycol H), 4.30 (m, 7- or 8-H), 4.41 (m, 7- or 8-H), 5.16 (m, 10-H), 6.19 (m, 2b-H), 7.99 (m, 2a-H), 8.51 (s, δ-H), 9.32 (s, α-H), 9.45 (s, β-H); electronic spectrum (in acetone), λ_{max} (ϵ) 667 (55 100), 609 (7950), 535 (9470), 507 (12 100), 409 (119 200) nm; MS m/e 578.7 (M^+). Anal. Calcd for $C_{35}H_{38}N_4O_4$: C, 72.64; H, 6.62. Found: C, 72.58; H, 6.70.

Pheophorbide *b* Ethylene Glycol Monoester (3d). 3c (150 mg, 0.25 mmol) was esterified (method B) with ethylene glycol to yield ester **3d**: 114 mg; 71%; mp 150–154 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (t, J = 7.5 Hz, 4b-H), 1.63 (d, J = 7.5 Hz, 8a-CH_3), 2.29 (m, 7a-H), 2.53 (m, 7b-H), 3.28 (s, 1-CH_3), 3.40 (s, 3-CH_3), 3.77 (q, J = 7.5 Hz, 4a-H), 3.79 (s, 10b-CH_3), 4.10 (m, glycol H), 4.25 (m, 7- or 8-H), 4.39 (m, 7- or 8-H), 6.10 (s, 10-H), 6.31 (m, 2b-H), 7.94 (m, 2a-H), 8.46 (s, δ-H), 9.28 (s, β-H), 10.28 (s, α-H), 11.12 (s, 3a-H); electronic spectrum (in acetone), λ_{max} (ϵ) 654 (39 800), 603 (9270), 553 (9320), 530 (12 300), 439 (154 000) nm; MS m/e 650.7 (M^+). Anal. Calcd for $C_{37}H_{38}N_4O_7$: C, 68.29; H, 5.89. Found: C, 68.25; H, 5.95.

Dimer Preparation Method A. Bis(pheophorbide *a*) Ethylene Glycol Diester (1e). 1c (800 mg, 1.35 mmol) was dissolved in dry CH_2Cl_2 (50 mL) contained in a 100-mL round-bottomed flask equipped with a nitrogen inlet. Benzotriazole-1-methanesulfonate (1.63 g, 7.65 mmol) and 4-(dimethylamino)pyridine (0.93 g, 7.62 mmol) were added with stirring to the solution of **1c**. The reaction mixture was stirred an additional 10 min. **1d** (728 mg, 1.14 mmol) was added to the reaction mixture. Stirring was continued for 2 h more, and the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed five times with water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the products were chromatographed on silica gel (60–200 mesh, two 8 cm × 30 cm columns, elution with 20% ethyl acetate in CH_2Cl_2). After elution of a minor component the main product band eluted. The solvent was evaporated and the solid reprecipitated from CH_2Cl_2–hexane to yield diester **1e**: 643 mg; 47%; mp 126–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.59 (t, J = 7.5 Hz, 4b-H), 1.66 (d, J = 7.5 Hz, 8a-H), 2.14 (m, 7a-H), 2.46 (m, 7b-H), 3.14 (s, 3-CH_3), 3.30 (s, 1-CH_3), 3.57 (s, 5-CH_3), 3.60 (q, J = 7.5 Hz, 4a-H), 3.77 (s, 10b-CH_3), 4.04 (s, glycol H), 4.06 (m, 7- or 8-H), 4.34 (m, 7- or 8-H), 6.14 (s, 10-H), 6.19 (m, 2b-H), 7.89 (m, 2a-H), 8.47 (s, δ-H), 9.27 (s, α-H), 9.38 (s, β-H); electronic spectrum (in acetone), λ_{max} (ϵ) 668 (55 200), 610 (7970), 533 (9470), 505 (12 000), 409 (119 200) nm; MS m/e 1211 (M^+). Anal. Calcd for $C_{72}H_{74}N_8O_{10}$: C, 71.39; H, 6.16. Found: C, 71.32; H, 6.21.

Dimer Preparation Method B. Bis(pyropheophorbide *a*) Ethylene Glycol Diester (2e). 2c (240 mg, 0.45 mmol), **2d** (231 mg, 0.40 mmol), and dicyclohexylcarbodiimide (463 mg, 2.25 mmol) were dissolved in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred and 4-(dimethylamino)pyridine (25 mg, 0.2 mmol) was added to catalyze the esterification. The reaction mixture was protected from moisture and stirred 30 min, and the solvent was evaporated. The products were chromatographed on silica gel (60–200 mesh, 8 cm × 30 cm column, elution with 15% acetone in CCl_4) to yield diester **2e**: 327 mg; 81%; mp 128–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (t, J = 7.5 Hz, 4b-H), 1.59 (d, J = 7.5 Hz, 8a-H), 2.11 (m, 7a-H), 2.46 (7b-H), 3.08 (s, 3-CH_3), 3.22 (s, 1-CH_3), 3.47 (s, 5-CH_3), 3.52 (q, J = 7.5 Hz, 4a-H), 4.04 (m, 7- or 8-H), 4.07 (s, glycol H), 4.27 (m, 7- or 8-H), 4.95 (m, 10-H), 6.08 (m, 2b-H), 7.80 (m, 2a-H), 8.33 (s, δ-H), 9.15 (s, α-H), 9.23 (s, β-H); electronic spectrum (in acetone), λ_{max} (ϵ) 667 (55 400), 611 (7890), 534 (9460), 505 (12 100), 409 (119 300) nm; MS m/e 1095 (M^+). Anal. Calcd for $C_{68}H_{70}N_8O_6$: C, 67.42; H, 5.82. Found: C, 67.32; H, 5.88.

Bis(pheophorbide *b*) Ethylene Glycol Diester (3e). 3c (150 mg, 0.25 mmol) was esterified (method B) with **3d** (130 mg, 0.20 mmol) to yield diester **3e**: 103 mg; 42%; mp 148–154 °C; ^{1}H NMR ($CDCl_3$) δ 1.58 (t, J = 7.5 Hz, 4b-H), 1.62 (d, J = 7.5 Hz, 8a-H), 2.20 (m, 7a-H), 2.51 (m, 7b-H), 3.26 (s, 1-CH_3), 3.37 (s, 5-CH_3), 3.77 (s, 10b-CH_3), 3.79 (q, J = 7.5 Hz, 4a-H), 4.20 (m, 7- or 8-H), 4.26 (s, glycol H), 4.38 (m, 7- or 8-H), 6.10 (s, 10-H), 6.26 (m, 2b-H), 7.97 (m, 2a-H), 8.44 (s, δ-H), 9.24 (s, β-H), 10.25 (s, α-H), 11.06 (s, 3a-H); electronic spectrum (in acetone), λ_{max} (ϵ) 654 (39 700), 602 (9270), 551 (9300), 530 (12 200), 439 (154 000) nm; MS m/e 1239 (M^+). Anal. Calcd for $C_{72}H_{70}N_8O_{12}$: C, 69.78; H, 5.69. Found: C, 69.69; H, 5.76.

Bis(bacteriopheophorbide *a*) Ethylene Glycol Diester (4e). 4c (236 mg, 0.39 mmol) was esterified with **4d** (255 mg, 0.39 mmol) by utilizing dimer preparation method A to yield **4e**: 202 mg; 42%; mp 148–153 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J = 8 Hz, 4b-CH_3), 1.62 (d, J = 7 Hz, 3a- or 8a-CH_3), 1.71 (d, J = 7 Hz, 3a- or 8a-CH_3), 2.0–2.6 (m, 4a,7a,7b-H), 3.14 (s, 2b-CH_3), 3.42 (s, 5-CH_3), 3.45 (s, 1-CH_3), 3.79 (s, 10b-CH_3), 4.00 (m, 3,4-H or 7,8-H), 4.08 (s, glycol H), 4.23 (m, 3,4-H or 7,8-H), 6.08 (s, 10-H), 8.41 (s, δ-H), 8.47 (s, β-H), 9.00 (s, α-H); electronic spectrum (in acetone), λ_{max} (ϵ) 750 (49 300), 675 (6970), 522 (19 400), 494 sh (3900), 384 (45 100), 355 (80 500) nm; MS m/e 1247 (M^+). Anal. Calcd for $C_{72}H_{78}N_8O_{12}$: C, 69.32; H, 6.30. Found: C, 69.22; H, 6.39.

Bis(chlorophyllide *a*) Ethylene Glycol Diester (1g). The preparation was performed in a glovebox filled with dry nitrogen. A Grignard reagent was prepared from Mg (25.7 mg, 1.06 mmol), CH_3I (65 μL, 1.04 mmol), and ether (5 mL). A solution of 2,6-di-*tert*-butyl-4-methylphenol (265.3 mg, 1.21 mmol) in dry CH_2Cl_2 (30 mL) was deoxygenated by bubbling 99.999% argon through the solution. The solution of the phenol was stirred vigorously and protected from light. The entire Grignard reagent solution was pipetted all at once into the phenol solution. The resulting solution was stirred for 15 min. **1e** (260 mg, 0.215 mmol) was dissolved in CH_2Cl_2 (20 mL). The solution of **1e** was deoxygenated by bubbling with argon and was then pipetted slowly over 3 min into the phenolate reagent solution. The reaction was allowed to proceed under an argon blanket and protected from light for 15 min at ambient temperature. The resultant dark green solution was poured into pH 4.5 phosphate buffer (250 mL) which had been previously bubbled with nitrogen. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with additional buffer three times and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a green product that was chromatographed on powdered confectioner's sugar (2–8 cm × 30 cm columns, elution with 5% acetone in CCl_4). The small fast-moving gray band of unreacted starting material was followed by a gray-green band and finally a large green band. Some green side products remained at the top of the column. Following elution from the column, the gray-green and green fractions were washed with water to remove dissolved sugar and dried over anhydrous Na_2SO_4. Evaporation of the solvents and precipitation from CH_2Cl_2–hexane yielded green diester **1g** (107 mg; 40%; mp 151–154 °C) and gray-green chlorophyllide *a*–pheophorbide *a* ethylene glycol diester (**1f**) (53 mg; 20%; mp 141–143 °C).

Data for **1g**: ^{1}H NMR (benzene-d_6/5% pyridine-d_5) δ 1.47 (d, J = 8 Hz, 8a-CH_3), 1.60 (t, J = 8 Hz, 4b-CH_3), 1.8–2.4 (m, 7a-H and 7b-H), 3.21 (s, 3a-CH_3), 3.27 (s, 1-CH_3), 3.55 (s, 5-CH_3), 3.60 (s, 10b-CH_3), 3.65 (q, J = 7.5 Hz, 4a-H), 4.10 (s, glycol H), 4.34 (m, 7- and 8-H), 6.10 (m, 2b-H), 6.50 (s, 10-H), 8.05 (m, 2a-H), 8.43 (s, δ-H), 9.62 (s, α-H), 9.82 (s, β-H); electronic spectrum (in benzene/5% pyridine), λ_{max} (ϵ) 663 (87 800), 612 (15 700), 435 (118 000) nm.

Data for **1f**: the ^{1}H NMR (benzene-d_6/5% pyridine-d_5) spectrum is a superposition of those reported for **1e** and **1g**, except that the singlet at δ 4.07 due to the protons of the glycol link is broadened; electronic spectrum (in benzene/5% pyridine), λ_{max} (ϵ) 667 (58 900), 610 (9350), 534 (7230), 505 (8230), 438 sh (51 100), 413 (87 600) nm.

Bis(pyrochlorophyllide *a*) Ethylene Glycol Diester (2g). 2e (650 mg, 0.59 mmol) was treated with 5 mmol of iodomagnesium 2,6-di-*tert*-butyl-4-methylphenolate as in the preparation of **1g**, except that dry $CHCl_3$ (EtOH free) was used as the reaction solvent. The reaction mixture was refluxed for 15 min and worked up as outlined for **1g** to yield **2g**: 515 mg; 77%; mp 157–160 °C; ^{1}H NMR (benzene-d_6/5% pyridine-d_5) δ 1.63 (t, J = 7.5 Hz, 4b-H), 1.65 (d, J = 7.5 Hz, 8a-H), 1.8–2.4 (m, 7a,7b-H), 3.16 (s, 3-CH_3), 3.34 (s, 1-CH_3), 3.56 (s, 5-CH_3), 3.60 (q, J = 7.5 Hz, 4a-H), 4.01 (m, 7- or 8-H), 4.10 (m, 7- or 8-H), 4.15 (s, glycol H), 5.20 (m, 10-H), 6.07 (m, 2b-H), 8.11 (m, 2a-H), 8.47 (s, δ-H), 9.66 (s, α-H), 9.83 (s, β-H); electronic spectrum (in benzene/5% pyridine), λ_{max} (ϵ) 663 (87 800), 612 (15 700), 435 (118 000) nm.

Pyrochlorophyllide *a*–Pyropheophorbide *a* Ethylene Glycol Diester (2f). 2e (300 mg, 0.27 mmol) was treated with

5 mmol of IMgBHT in CH_2Cl_2 as in the preparation of **1g**. The methylene chloride solution was refluxed for 30 min and worked up as outlined for **1g** to yield **2f**, (163 mg, 54%), **2g** (35 mg) and unreacted **2e** (48 mg). Data for **2f**: mp 142-145 °C; the ^1H NMR (benzene-d_6/5% pyridine-d_5) spectrum is a superposition of those reported for **2e** and **2g**, except that the singlet at δ 4.10 due to the protons of the glycol link is broadened; electronic spectrum, λ_{max} (ε) 667 (58900), 610 (9350), 534 (7230), 505 (8230), 438 sh (51100), 413 (87600) nm.

Bis(chlorophyllide *b*) Ethylene Glycol Diester (3g). The preparation was performed in a glovebox filled with dry nitrogen. A Grignard reagent was prepared from Mg (24 mg, 1.0 mmol), CH_3I (62 μL, 1.0 mmol), and dry ether (2 mL). A solution of BHT in dry thiophene (15 mL) was deoxygenated by bubbling with 99.999% argon. The solution of BHT was stirred vigorously and protected from light. The Grignard reagent solution was pipetted all at once into the BHT solution, and the resulting solution was allowed to react for 15 min. A solution of lithium 2,2,6,6-tetramethylpiperidide, prepared by dissolving the corresponding amine (85 μL, 0.5 mmol) in ether (1 mL) followed by careful addition of *n*-BuLi (0.25 mL of a 1.6 M solution in hexane (0.4 mmol)), was syringed into the reaction mixture. After 5 min of stirring, a solution of **3e** (125 mg, 0.101 mmol) in dry thiophene (25 mL) which had been previously deoxygenated with argon was pipetted into the reagent solution. The reaction proceeded for 30 min at ambient temperature. The resulting yellow-green solution was poured in pH 4.5 phosphate buffer (250 mL). Extraction of the mixture with $CHCl_3$, followed by washing of the extract three times with additional buffer, drying over anhydrous Na_2SO_4, and evaporation of the solvent, yielded a green product. This material was chromatographed on an 8 cm × 30 cm column of powdered confectioner's sugar (elution with 10% acetone in CCl_4). The fast-moving brown band of unreacted starting material was followed by a brownish green band and finally a green band. Following elution from the column, the brownish green and green fractions were each washed with water to remove the dissolved sugar and dried over anhydrous Na_2SO_4. Evaporation of the solvents and precipitation from CH_2Cl_2-hexane yielded green diester (**3g**) (74 mg; 58%; mp 173-176 °C) and brownish green chlorophyllide *b*-pheophorbide *b* ethylene glycol diester (**3f**) (22 mg; 17%; mp 160-164 °C).

Data for **3g**: ^1H NMR (benzene-d_6/5% pyridine-d_5) δ 1.49 (t, J = 7.5 Hz, 4b-H), 1.60 (d, J = 7.5 Hz, 8a-H), 2.25 (m, 7a-H), 2.50 (m, 7b-H), 3.20 (s, 1-CH_3), 3.52 (s, 5-CH_3), 3.80 (q, J = 7.5 Hz, 4a-H), 3.95 (s, 10b-CH_3), 4.20 (m, 7- or 8-H), 4.20 (s, glycol H), 4.35 (m, 7- or 8-H), 6.12 (s, 10-H), 6.18 (m, 2b-H), 7.92 (m, 2a-H), 8.50 (s, δ-H), 9.31 (s, β-H), 10.52 (s, α-H), 11.10 (s, 3a-H); electronic spectrum (in benzene/5% pyridine), λ_{max} (ε) 642 (66400), 594 (11000), 434 (194000) nm.

Data for **3f**: the ^1H NMR (benzene-d_6/5% pyridine-d_5) spectrum is a superposition of those reported for **3e** and **3g**, except that the singlet at δ 4.23 is broadened; electronic spectrum (benzene/5% pyridine), λ_{max} (ε) 650 (45400), 600 (10000), 553 (9500), 530 (14200), 436 (168000) nm.

Bis(bacteriochlorophyllide *a*) Ethylene Glycol Diester (4g). The preparation of diester **4g** was carried out by treating diester **4e** (62 mg, 0.05 mmol) with IMgBHT (1 mmol) and LiTMP (0.5 mmol) in dry thiophene (50 mL), utilizing the same procedures employed for the preparation of **3g** (yield of bluish diester **4g**, 28 mg; 44%) and purple-red bacteriochlorophyllide *a*-bacteriopheophorbide *a* ethylene glycol diester (**4f**) (10 mg; 16%).

Data for **4g**: mp 167-172 °C; ^1H NMR (benzene-d_6/5% pyridine-d_5) δ 0.62 (t, J = 8 Hz, 4b-CH_3), 1.28 (d, J = 7 Hz, 8a-CH_3), 1.54 (d, J = 7 Hz, 3a-CH_3), 1.8-2.4 (m, 7a,7b-H), 2.79 (s, 2b-CH_3), 3.16 (s, 1-CH_3), 3.32 (m, 4a-H), 3.40 (s, 5,10b-CH_3), 3.95 (m, 3,4,7,8-H), 4.00 (s, glycol H), 6.30 (s, 10-H), 8.22 (s, δ-H), 8.36 (s, β-H), 9.59 (s, α-H); electronic spectrum (in benzene/5% pyridine), λ_{max} (ε) 774 (94100), 720 sh (12200), 576 (21600), 535 sh (3760), 390 (53600), 359 (79100) nm.

Data for **4f**: mp 155-159 °C; the ^1H NMR (benzene-d_6/5% pyridine-d_5) spectrum is a superposition of those reported for **4e** and **4g**, except that the singlet at δ 4.04 due to the protons of the glycol link is broadened; electronic spectrum (benzene/5% pyridine), λ_{max} (ε) 775 (94100), 747 (49100), 720 (12000), 675 (6900), 576 (12200), 527 (21000), 490 (4000), 390 (54000), 360 (160000) nm.

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Reactions of 1,5-Dichloroanthraquinone with Nucleophiles

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Reactions of 1,5-dichloroanthraquinone (**1**) with various nucleophiles were examined to evaluate possibilities for selective substitution. 1-Amino-5-chloroanthraquinone was obtained from **1** by reaction with (a) sodium azide in dimethyl sulfoxide and (b) ammonia in the presence of potassium fluoride, but **1** with potassamide in ammonia gave 3-chlorobenzoic acid. Conditions were found for preferential substitution in reactions of **1** with (c) 4-toluidine, (d) hexamethylphosphoric triamide, and (e) *N*-methylformamide. Reagent e is preferred for making 1-chloro-5-(methylamino)anthraquinone, though this compound predominates in mixtures produced when d is used. Potassium hydroxide in 2-ethoxyethanol converts **1** to the corresponding mono- and diethers of 1,5-dihydroxyanthraquinone, while sodium hydrosulfide and **1** give bis(5-chloroanthraquinonyl) sulfide.

1,5-Dichloroanthraquinone (**1**) offers a number of possibilities as a starting material for the synthesis of more complex molecules because of the juxtaposition of the chlorine atoms and the carbonyl groups of the central ring. A key to developing such syntheses lies in differential nucleophilic substitution of the chlorine atoms in **1**. We now report the outcome of a number of experiments to this end.

We first examined reactions of **1** with a number of nitrogen nucleophiles. In some instances, differential displacement was readily achieved. For example, **1** reacted readily with sodium azide in boiling dimethyl sulfoxide

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