runs by circulating water from a Haake Model FE constant-temperature circulating bath.

Registry No. **2a**, 4359-34-6; **2b**, 77130-21-3; **2c**, 77130-22-4; **2d**, 81194-61-8; **2e**, 81194-62-9; **2f**, 81194-63-0; **2g**, 101858-70-2; **3a**, 2235-01-0; **3b**, 101858-71-3; **3c**, 81194-70-9; **3d**, 81194-71-0.

On the Hydrogen Peroxide/Sulfuric Acid Oxidation of Mesoporphyrin. Synthesis of Mesoporphyrindiones[1]

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Hans Fischer and his students reported in 1930 a novel method to obtain green-colored chlorins from porphyrins.[2] They reacted mesoporphyrin IX in concentrated sulfuric acid with hydrogen peroxide and yielded a product which was designated as "dioxymesoporphyrin" even though the elementary analysis results were ambivalent in showing whether one or two oxygen atoms had been added to mesoporphyrin. Indeed, they later concluded that the green product resulted from this acid medium contains only one extra oxygen atom and called it "anhydrochlorin".[3] The structure that they proposed, formulated as an epoxide ring across a pyrrole double bond, was again incorrect. Johnson[4,5] and Inhoffen,[6,7] about 20 years ago, independently reinvestigated such oxidation reaction using symmetrical etioporphyrin and octaethylporphryin (OEP) and established that the true identity of the major product from this hydrogen peroxide/sulfuric acid oxidation is a keto chlorin formed by a pinacol rearrangement of the intermediate diol or epoxide. By inference, Fischer's "dioxymesoporphyrin" must also be some sort of keto chlorins but the exact product(s) in mesoporphyrin oxidation is far from clear. For being an unsymmetrically substituted porphyrin, mesoporphyrin could produce up to eight isomeric ketones. Furthermore, as reported originally by Inhoffen and Nolte[6,7] and more recently by Chang[8] using OEP, the oxidation reaction does not stop at the monoketone level; diketones and even triketones arise almost simultaneously under the reaction condition optimized for the monoketone. With OEP, there are five diketones and four triketones identified; with mesoporphyrin, there could be 14 diketone regioisomers alone without counting the diastereomers! The sheer number of anticipated isomeric products from mesoporphyrin must have dissuaded attempts to reexamine this reaction for after more than a half century, Fischer's pioneering yet unsolved work stands unsettled.

We have recently become interested in the dioxoisobacteriochlorins (porphinediones[1]) because we discovered that the green heme prosthetic group in the *cd*-type cytochrome prevailing in microbial denitrifiers may in fact possesses such a macrocyclic core structure.[9] In an effort to understand the intrinsic properties of the 2,4-porphinedione and particularly the difference between d_1 heme and protoheme, we need to obtain a copious supply of similarly structured model compounds. The H_2O_2/H_2SO_4 oxidation of mesoporphyrin therefore offered an attractive choice if the 2,4-mesoporphyrindione can be isolated.

Synthetically, a keto chlorin (porphinone[1]) sometimes can be produced in a stepwise manner: treating porphyrins with osmium tetraoxide[10] to generate a *vic*-dihydroxychlorin, which then undergoes pinacol rearrangement in acid. While this two-step reaction may offer some control over the unwanted monoketone isomers, it is not useful for producing the isobacteriochlorin derivatives. In the presence of excess amounts of osmium tetraoxide, only tetrahydroxybacteriochlorin was observed. Even deuteroporphyrin, which has built-in steric advantages, was found to react with an excess of OsO_4 to yield only the tetrahydroxybacteriochlorin without any trace of the isobacteriochlorin. This reaction pattern may be due to the preferred diagonal π-electron delocalization pathway present in all porphyrins, which prompts the saturation of the two isolated, diagonal pyrrole β,β'-double bonds with minimum loss of π-energy. Similar argument has been advanced to account for the exclusive diagonal reduction of tetraphenylporphyrin by diimide to yield bacteriochlorin.[11] In a medium of concentrated sulfuric acid, however, porphyrin would become doubly protonated, the influence of valence tautomerism would become insignificant, and isobacteriochlorin may be formed. Indeed, in the reaction of OEP with H_2O_2/H_2SO_4, the combined yield of the three dioxoisobacteriochlorins is better than that of the two dioxobacteriochlorins.[8] There is another element buttressing our optimism that the oxidation with mesoporphyrin may be simpler than it appears to be. The pinacolic rearrangement of the diols is dictated by very specific migratory aptitudes:[12] we have recently demonstrated that both ethyl and propionate side chains in a *vic*-dihydroxychlorin have a higher migratory aptitude as compared with the methyl group.[13] Furthermore, the epoxide or diol formation is highly sensitive to the size of the side chain. On the basis of these considerations, one would predict that the desired 2,4-mesoporphyrindione **3** is the favored product.

Thus, mesoporphyrin dimethyl ester dissolved in concentrated H_2SO_4 was reacted with H_2O_2, and after about 30 min the solution was neutralized by sodium acetate. The solid product, collected by filtration, contained most of the ketone products with intact propionic esters. Chromatography of this material on silica gel went surprisingly well, and nine different compounds, excluding the unreacted mesoporphyrin, were obtained (Scheme I); the total yield was about 30% (reproducible in three separate runs).[14] Structure identification in most cases was straightforward, aided by absorption and ^1H NMR spectra. The differentiation of the monoketones **1** and **2** and also

(1) The nomenclature of the ketone derivatives of porphyrins has not been standardized. Inhoffen called them geminiporphine-monoketone and -diketone[6,7] and Johnson used the name "oxochlorin".[4,5] The prefix "oxo-", however, could be confused with "oxyporphyrin" or "oxophlorin" which has an oxygen attached to the porphyrin meso position. Furthermore, we have discovered that these "oxo" derivatives have very little chemical properties in common with those of the parent chlorin, isobacteriochlorin, or bacteriochlorin.[21] We prefer to regard these ketones as "quinones" of porphyrin. The use of the suffix -one or -dione is both convenient and specific in that it allows the retention of the trivial name of the porphyrin precursor, as demonstrated by examples given in this paper.

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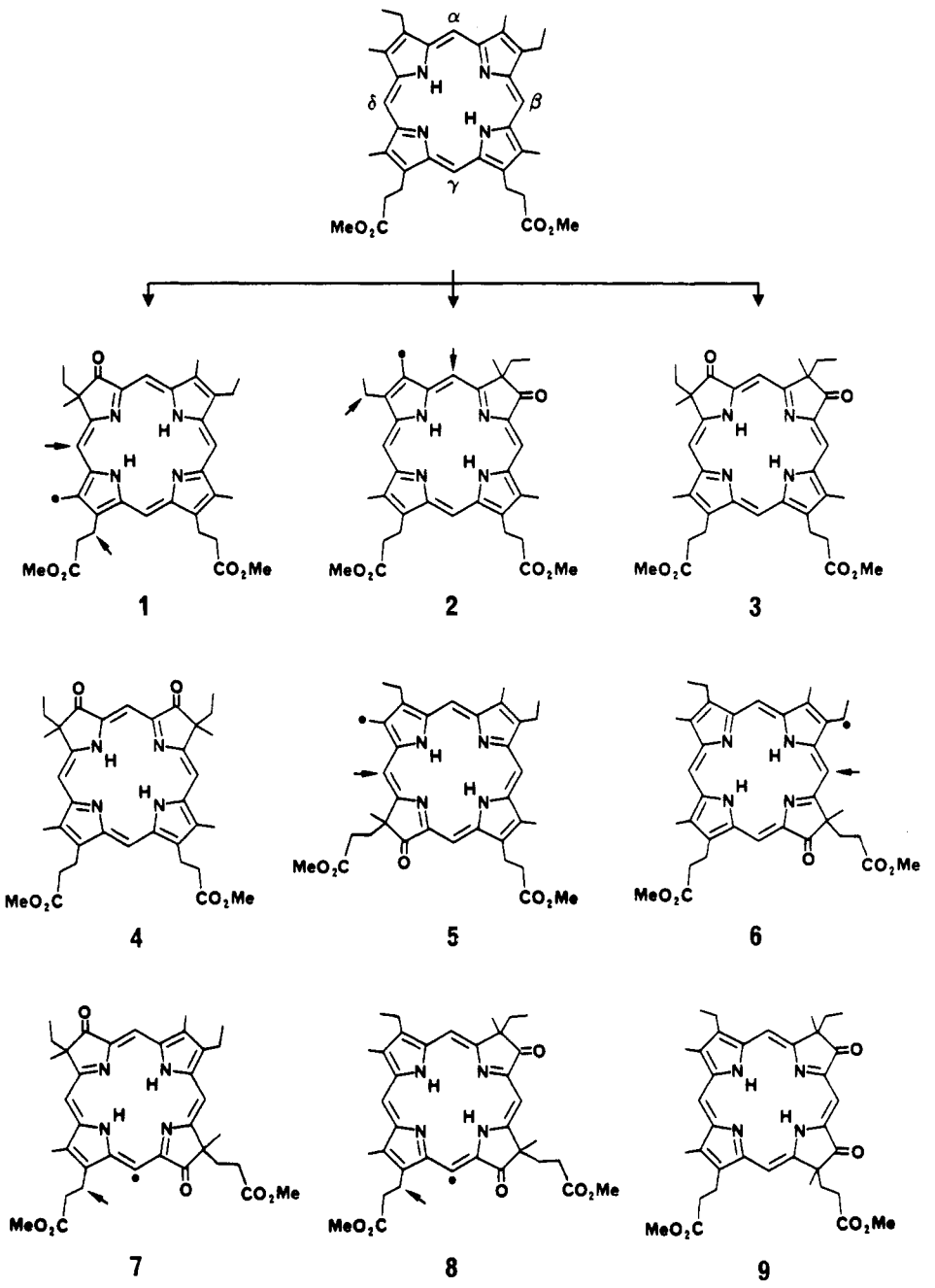
(14) Lower yields were obtained when scaled-up.

0022-3263/86/1951-2134$01.50/0

Scheme I



5 and 6 was accomplished by nuclear Overhauser enhancements (NOE),[10,13] which was also of great value in confirming the assignment of 7. (The determinant NOE couplings are indicated by arrows and dots, see Experimental Section.) The overall product distribution shows that indeed our anticipated reactivity and migratory aptitudes hold remarkably well with only two exceptions, the "2,3-diketone" 4 and 9, but even in these two, one of the keto groups is in the "correct" place. We suspect that 4 and 9 may arise from the respective precursors 1 and 2; the subsequent pinacol rearrangement went to the "wrong" direction because the formation of the adjacent "2,3-diketone" is energetically favorable, which offsets the regular migratory trend. In all diketones, the presence of diastereomers can be detected by NMR (bifurcation of the pyrroline substituent signals), but attempts to separate them have not been successful.

These keto derivatives are less basic than their parent macrocyclic ligands. The monoketone 1, for example, has a pK_3 value of 3.3 (measured in 2.5% sodium dodecyl sulfate anionic detergent), less than that of mesochlorin (4.2), while the diketone 3 has an astonishingly low pK_3 value of 1.8. The difference in the basicity of the nitrogen can be utilized for separation of these compounds. In the original Fischer's report,[2] they relied on acid extractions to obtain the 3% yield green product, most likely a mixture of 1 and 2.

The clarification of this old literature problem has ample rewards. First, the demonstration that the oxidation of mesoporphyrin behaves in a predictable and reproducible manner and that the separation and identification of individual regioisomers can be accomplished by using routine laboratory facilities and techniques immediately provides access to a rich source of interesting oxochlorin (porphinone), dioxoisobacteriochlorin (2,4- and 2,3-porphinedione), and dioxobacteriochlorin (2,6-porphinedione) derivatives. This is a class of compounds hitherto has received little attention, but their importance and biological relevance are now being recognized. Secondly, the availability of these compounds suggests expeditious synthetic

strategies for reduced porphyrin macrocycles.[10,13] The monoketones and diketones are convenient precursors to alkylated chlorins and isobacteriochlorins such as bonellin[15] and sirohydrochlorin.[16] Further reaction of the diketone with osmium tetraoxide–acid has been shown to yield triketones,[7] which can lead to the parent hexahydroporphyrin,[17] an example of which is a prosthetic group called Factor 430 identified in methanogenic bacteria.[18] Finally and most gratifying to us is that we obtained the desired **3**, which has helped firmly establish the structure of the d_1 pigment after **3** was converted to an acrylic-containing chromophore showing the identical spectral features as d_1.[9b]

Experimental Section

NMR spectra ($CDCl_3$, Me_4Si internal standard) were obtained with a Bruker WM-250 instrument. Mass spectra were obtained with a Varian-MAT CH5 double-focusing instrument equipped with an Ion Tech fast atom bombardment gun. A matrix of thioglycerol–dithioerythreitol–dithiothreitol (2:1:1) containing 0.1% trifluoroacetic acid previously developed for porphyrin FAB-MASS analyses was used.[19] This acidic matrix always produces the monoprotonated porphyrin $(M + H)^+$ ions as the most abundant species in the spectra. Visible absorption spectra (in CH_2Cl_2) were measured with a Cary 219 spectrophotometer. Preparative TLC plates were from Analtech (silica gel G, 1500 μm).

Nuclear Overhauser enhancements were measured by difference between a spectrum with preirradiation on a target peak (indicated by an arrow) minus a spectrum with equivalent preirradiation at a dummy position. The magnitudes of NOEs were calculated as the area of the enhanced resonance in difference spectra divided by the area in the control spectrum with no enhancement. The neighboring protons which exhibited NOEs in the range of 2–6% are indicated by a dot in the structure drawings (only the determinant ones are shown). The unique NOE coupling relationship elicited from compounds that were already categorized by absorption spectra thus ruled out other structure possibilities.

Mesoporphyrin IX dimethyl ester[20] (350 mg) was dissolved in concentrated sulfuric acid (30 mL, *d* 1.84) in an ice bath. To this solution under stirring was added 6% H_2O_2 (2 mL) dropwise such that the reaction mixture was kept below 10 °C. After the addition was complete (15 min), the dark red solution was stirred an additional 10 min in the ice bath and then at room temperature for 25 min or until the solution became dark green. The reaction was quenched by pouring the mixture into a large beaker containing sodium acetate (20 g) and crushed ice (120 g). After standing at room temperature for 2 h, the solids were collected by filtration, washed with water, and dried (ca. 200 mg). The filtrate was concentrated in vacuo and then mixed with methanol (200 mL) and chloroform (100 mL) to effect esterification. This mixture, after washing with water, afforded about 150 mg of solid material containing small amounts of unreacted mesoporphyrin dimethyl ester, together with other intractable oxidation products. Therefore, in later reaction runs, the acid filtrate was discarded.

The solid oxidation product was chromatographed on a 2 × 10 in. silica gel column eluted with methylene chloride/methanol (98:2). A fairly pure compound 1 was obtained from the first 20–30 mL eluent, and the rest of pigments were collected into three fractions. Each fraction was concentrated and chromatographed again on preparative TLC plates (CH_2Cl_2 with 1% MeOH) to give eight additional compounds. Alternatively, as a group, the diketones can be cleanly separated from the monoketones on a silica gel column by using methylene chloride containing 5% formic acid as eluent. Subsequent separations within each group can be carried out on preparative TLC plates. The nine keto products tabulated roughly according to their R_f values are given below.

2-Mesoporphyrinone dimethyl ester or dimethyl 7,13-diethyl-3,7,12,17-tetramethyl-8-porphinone-2,18-dipropionate (1): 29.5 mg (8.2%); NMR δ 0.41 (3 H, t, Et saturated), 1.82 (3H, t, Et), 2.07 (3H, s, Me saturated), 2.77 (2H, q, Et saturated), 3.26 (4 H, m, CH_2CH_2COO), 3.48, 3.55, 3.58 (3 H each, s, ring Me), 3.68 (6 H, s, CO_2Me), 4.02 (2 H, q, Et), 4.25, 4.40 (2 H each, t, CH_2CH_2COO), 9.14 (1 H, s, meso δ), 9.86 (1 H, s, meso α), 9.88 (1 H, s, meso γ), 9.90 (1 H, s, meso β), −2.96 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (34 600), 585 (5800), 547 (12 400), 508 (8800), 407 (165 200); MS, found *m/e* 611.3242 for $(M + H)^+$, $C_{36}H_{43}N_4O_5$ requires *m/e* 611.3236.

4-Mesoporphyrinone dimethyl ester or dimethyl 8,12-diethyl-3,7,12,17-tetramethyl-13-porphinone-2,18-dipropionate (2): 35.6 mg (9.9%); NMR δ 0.41 (3 H, t, Et saturated), 1.80 (3 H, t, Et), 2.06 (3 H, s, Me saturated), 2.75 (2 H, q, Et saturated), 3.21 (4 H, m, CH_2CH_2COO), 3.45, 3.56, 3.59 (3 H each, ring Me), 3.62, 3.65 (3 H each, s, CO_2Me), 4.01 (2 H, q, Et), 4.22, 4.38 (2 H each, t, CH_2CH_2COO), 9.10 (1 H, s, meso α), 9.80 (1 H, s, meso β), 9.82 (1 H, s, meso δ), 9.92 (1H, s, meso γ), −2.97, −2.81 (1 H each, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (33 300), 585 (6000), 547 (12 000), 508 (10 000), 407 (175 000); MS (direct probe, 70 eB), *m/e* 610 (M^+).

2,4-Mesoporphyrindione dimethyl ester or dimethyl 7,12-diethyl-3,7,12,17-tetramethyl-8,13-porphinedione-2,18-dipropionate (3): 16.8 mg (4.5%); NMR δ 0.50, 0.70 (3 H, each, t, Et saturated), 1.88, 1.91 (3 H each, s, Me saturated), 2.62 (4 H, m, Et), 3.11 (4 H, m, CH_2CH_2COO), 3.27, 3.32 (3 H each, s, ring Me), 3.60, 3.63 (3 H each, s, CO_2Me), 4.16 (4 H, m, CH_2CH_2COO), 8.42 (1 H, s, meso δ), 8.63 (1 H, s, meso α), 9.28 (1 H, s, meso β), 9.51 (1 H, s, meso γ), −0.04 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 638 nm (16 800), 592 (15 300), 584 (15 700), 544 (9600), 438 (97 000), 417 (94 000), 402 (74 800); MS, found *m/e* 627.3178 for $(M + H)^+$, $C_{36}H_{43}N_4O_6$ requires *m/e* 627.3185.

2,3-Mesoporphyrindione dimethyl ester or dimethyl 7,13-diethyl-3,7,13,17-tetramethyl-8,12-porphinedione-2,18-dipropionate (4): 7.5 mg (2.0%); NMR δ 0.55 (6 H, t, Et saturated), 1.95, 1.97 (3 H each, s, Me saturated), 2.68 (4 H, q, Et), 3.22 (4H, t, CH_2CH_2COO), 3.46 (6 H, s, ring Me), 3.62 (6 H, s, CO_2Me), 4.37 (4 H, t, CH_2CH_2COO), 8.90 (2 H, s, meso β,δ), 9.74 (1 H, s, meso α), 9.90 (1 H, s, meso γ), −1.63 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 622 nm (18 000), 592 (9400), 435 (102 000), 417 (133 000); MS, found *m/e* 627.3194 for $(M + H)^+$, $C_{36}H_{43}N_4O_6$ requires *m/e* 627.3185.

7-Mesoporphyrinone dimethyl ester or dimethyl 8,13-diethyl-3,7,12,17-tetramethyl-2-porphinone-3,18-dipropionate (5): 4.5 mg (1.2%); NMR δ 1.53 (2 H, m, CH_2CH_2COO saturated), 1.79, 1.80 (3 H each, t, Et), 2.10 (3 H, s, Me saturated), 3.09 (2 H, t, CH_2CH_2COO saturated), 3.22 (2 H, t, CH_2CH_2COO), 3.24, 3.44, 3.60 (3 H each, s, ring Me), 3.62, 3.64 (3 H each, s CO_2Me), 3.90, 4.04 (2 h each, q, Et), 4.34 (2 H, t, CH_2CH_2COO), 9.17 (1 H, s, meso δ), 9.82 (1 H, s, meso γ), 9.86, 9.90 (1 H each, s, meso α,β), −2.99, −2.92 (1 H each, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (33 300), 585 (6000), 547 (12 000), 508 (10 000), 407 (175 000); MS, found *m/e* 611.3245 for $(M + H)^+$, $C_{36}H_{43}N_4O_5$ requires *m/e* 611.3236.

6-Mesoporphyrinone dimethyl ester or dimethyl 8,13-diethyl-3,7,12,17-tetramethyl-18-porphinone-2,17-dipropionate (6): 4.5 mg (1.2%); NMR δ 1.50 (2 H, m, CH_2CH_2COO saturated), 1.78, 1.80 (3 H each, t, Et), 2.10 (3 H, s, Me saturated), 3.08 (2 H, t, CH_2CH_2COO saturated), 3.23 (2 H, t, CH_2CH_2COO), 3.25, 3.43, 3.59 (3 H each, s, ring Me), 3.60, 3.70 (3 H each, s, CO_2Me), 3.87, 4.02 (2 H each, q, Et), 4.34 (2 H, t, CH_2CH_2COO), 9.12 (1 H, s, meso β), 9.78 (1 H, s, meso γ), 9.80, 9.90 (1 H each, s, meso α,δ), −2.95, −2.84 (1 H each, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (33 000), 585 (5900), 547 (12 000), 508 (9900), 407 (176 000); MS (direct probe, 70 eV), *m/e* 610 (M^+).

2,6-Mesoporphyrindione dimethyl ester or dimethyl 7,17-diethyl-3,7,12,17-tetramethyl-8,18-porphinedione-2,17-dipropionate (7): 9.5 mg (2.6%); NMR δ 0.44 (3 H, t, Et satu-

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rated), 1.56 (2 H, m, CH_2CH_2COO saturated), 1.75 (3 H, t, Et), 1.99, 2.02 (3 H each, s, Me saturated), 2.71 (2 H, q, Et saturated), 3.02 (2 H, t, CH_2CH_2COO saturated), 3.29 (2 H, t, CH_2CH_2COO), 3.49, 3.50 (3 H each, s, ring Me), 3.51, 3.75 (3 H, s, CO_2Me), 3.93 (2 H, q, Et), 4.29 (2 H, t, CH_2CH_2COO), 9.05, 9.06 (1 H each, s, meso β,δ), 98.66 (1 H, s, meso γ), 9.74 (1 H, s, meso α), -2.78, -2.74 (1 H each, br s, NH); UV-vis λ_{max} (ϵ_M) 685 nm (95 000), 652 (7300), 622 (6800), 556 (10 700), 514 (8100), 486 (5700), 411 (187 000), 401 (164 000); MS, found m/e 627.3198 for $(M + H)^+$, $C_{36}H_{43}N_4O_6$ requires m/e 627.3185.

4,6-Mesoporphyrindione dimethyl ester or dimethyl 8,12-diethyl-3,7,12,17-tetramethyl-13,18-porphinedione-2,17-dipropionate (8): 7.0 mg (1.9%); NMR δ 0.61 (3 H, t, Et saturated), 1.70 (3 H, t, Et), 1.76 (2 H, t, CH_2CH_2COO saturated), 1.95, 1.96 (3 H each, s, Me saturated), 2.63 (2 H, q, Et), 2.94 (2 H, t, CH_2CH_2COO saturated), 3.13 (2 H, t, CH_2CH_2COO), 3.43, 3.44 (3 H each, s, ring Me), 3.46, 3.72 (3 H each, s, CO_2Me), 3.75 (2 H, q, Et), 4.14 (2 H, t, CH_2CH_2COO), 8.57, (1 H, s, meso α), 8.78 (1 H, s, meso β), 9.32 (1 H, s, meso γ), 9.52 (1 H, s, meso δ), -0.61 (2 H, br s, NH); UV-vis λ_{max} (ϵ_M) 637 nm (15 800), 592 (14 400), 583 (15 000) 544 (9100), 437 (92 000), 417 (90 000), 402 (72 000); MS (direct probe, 70 eV), m/e 626 (M^+).

4,5-Mesoporphyrindione dimethyl ester or dimethyl 8,12-diethyl-3,7,12,18-tetramethyl-13,17-porphinedione-2,18-dipropionate (9): 2.0 mg (0.5%); NMR δ 0.52 (3 H, m, Et saturated), 1.77 (3 H, m, Et), 1.82 (2 H, m, CH_2CH_2COO saturated), 1.98, 2.01 (3 H each, s, Me saturated), 2.68 (2 H, q, Et saturated), 3.00 (2 H, t, CH_2CH_2COO saturated), 3.17 (2 H, t, CH_2CH_2COO), 3.34, 3.37 (3 H each, s, ring Me), 3.57, 3.65 (3 H each, s, CO_2Me), 3.91 (2 H, q, Et), 4.25 (2 H, t, CH_2CH_2COO), 8.93 (1 H, s, meso α), 8.97 (1 H, s, meso γ), 9.66 (1 H, s, meso β), 9.80 (1 H, s, meso δ), -1.82 (2 H, br s, NH); UV-vis λ_{max} (ϵ_M) 623 nm (19 000), 592 (9500), 436 (100 000), 417 (135 000); MS, found m/e 627.3190 for $(M + H)^+$, $C_{36}H_{43}N_4O_6$ requires m/e 627.3185.

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Registry No. 1, 101954-76-1; 2, 101954-77-2; 3, 101954-78-3; 4, 101954-79-4; 5, 101954-80-7; 6, 101954-81-8; 7, 101954-82-9; 8, 101954-83-0; 9, 101954-84-1; mesoporphyrin IX dimethyl ester, 1263-63-4.

Preparation of Diaryl Ethers from Tyrosine or 4-Hydroxyphenylglycine Using Organomanganese Chemistry

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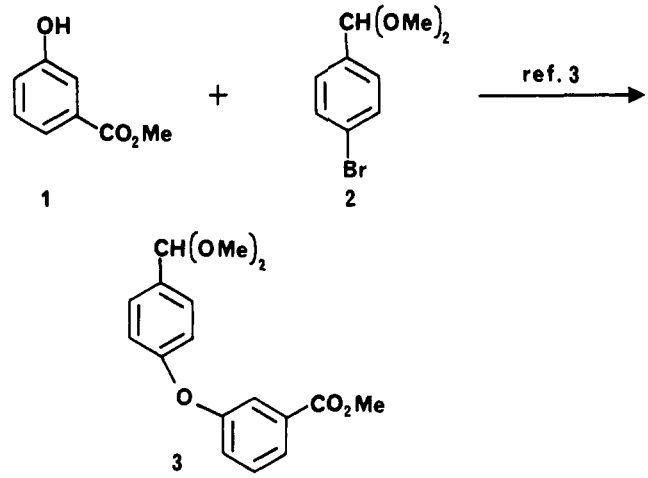
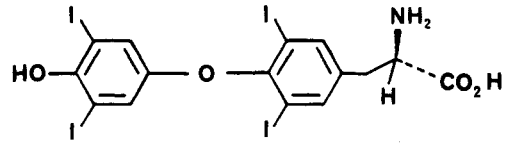
Diaryl and polyaryl ethers are important subunits in a wide variety of natural products,[1] but the commonly used method for constructing the ether linkage, i.e., Ullman coupling,[2] proceeds only under quite harsh conditions. One example, taken from the recent litearature,[3] is the coupling of phenolic compound 1 with haloaromatic 2 to give diaryl



ether 3. Although this reaction proceeds in good yield, the prolonged treatment required in basic solvent (pyridine) at elevated temperature (reflux, 24 h) is expected to lead to problems during similar coupling of molecules having base- and heat-sensitive side chains.

Several important natural products have polyaryl ether structures to which are attached, e.g., amino acid or peptide units. Examples are given by thyroxine (4) and the more



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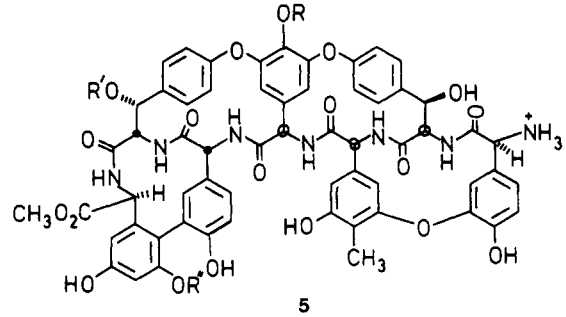
complex glycopeptide antibiotics related to ristocetin A (5),[4] and any projected synthesis of such compounds, in



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optically active, diastereomerically pure form, requires the development of milder procedures for diaryl ether formation. With respect to the ristocetin problem, it may be noted that phenylglycine derivatives are racemized quite readily under basic conditions.[5]

Several years ago, Pauson described the reaction of phenoxide anion with (chlorobenzene)$Mn(CO)_3$ cation (6) under mild conditions to give the complex 7. Decomplexation of this to give diphenyl ether was accomplished by heating in acetonitrile.[6] Since these conditions appear

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(5) Bodanszky, M.; Bodanszky, A. *Chem. Commun.* **1967**, 591. We have examined the racemization of *N*-acetyl-4-hydroxyphenylglycine methyl ester in hot pyridine. After 24 h at reflux, typical conditions for Ullmann coupling (see ref 3), complete racemization occurred.

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