Registry No. 1, 98858-78-7; 2, 98858-79-8; 3, 89182-81-0; 4, 3696-36-4; 6, 79680-97-0; 8, 98858-80-1; 9, 60419-73-0; 10, 51688-22-3; 11, 19481-82-4; 12, 98858-81-2; 13, 2134-48-7; 2-methylmalonodiamide, 1113-63-9; diethyl methylmalonate, 609-08-5; formamidine acetate, 3473-63-0; 2-bromopropionamide, 5875-25-2; ethyl 2-bromopropionate, 535-11-5.

C-Hydroxy- and *C*-Methylchlorins. A Convenient Route to Heme *d* and Bonellin Model Compounds

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Received May 15, 1985

Although the majority of heme-containing proteins found in nature possesses iron porphyrins as the prosthetic group, a significant number of organisms have now been shown to contain pyrrolic macrocycles based on C-substituted chlorins and isobacteriochlorins. Examples include bonellin (1) isolated from the green echurian worm *Bonellia viridis*,[1] Faktor I from the B_{12}-producing *Clostridium tetanomorphum*,[2] heme *d* (which has just been determined[3] to have a structure derived from **2**) of *Escherichia coli*, heme d_1 from *Pseudomonas aeruginosa*,[4] and sirohydrochlorin of nitrite and sulfite reductases as well as a B_{12} intermediate.[5] The principal difference between these macrocycles and the unsubstituted hydroporphyrins is that the C-substituted compounds can resist dehydrogenation (back to porphyrin) and, therefore, are better suited for undertaking the redox processes with which they may be associated in vivo. As the structures of these unique molecules are being elucidated, it has become timely to investigate the chemistry and to identify their functional roles in their respective host systems. To realize such goals, however, requires workable quantities of materials which are often difficult to obtain from natural sources.

Several rational approaches toward the synthesis of *C*-alkylchlorins have been described very recently.[6-8] Unfortunately these lengthy and demanding syntheses do not seem to lend themselves easily as a serviceable route at providing the compound. Short and reliable syntheses thus far have not been available at producing functionalized C-substituted chlorins for general reactivity and biomimetic studies. This paper presents a very simple solution to this problem and, in addition, reports for the first time, several purified and well-characterized vicinal dihydroxychlorin containing the core structure of heme *d*.

Dihydroxychlorin was first discussed by Fischer who reacted porphyrin with hydrogen peroxide in concentrated sulfuric acid and obtained what he thought at first was the dihydroxy adduct.[9] This product was later determined to contain only one oxygen.[10] It was not until 1960s that the keto-*gem*-dialkylporphyrin (oxochlorin) structure was characterized.[11-13] The acidic hydrogen peroxide oxidation, which yields not only oxochlorins but diketo- (dioxoisobacteriochlorins and dioxobacteriochlorins) and triketoporphyrins arising from pinacolic rearrangements, has prevented the isolation of the expected dihydroxy intermediate. Fischer, however, demonstrated that hydroxylation of type IX porphyrins can be achieved with osmium tetraoxide although the resultant isomeric dihydroxychlorins were not individually identified.[10,14]

In an effort to synthesize **2**, we added 1.2 equiv of OsO_4 to 2,4-dimethyldeuteroporphyrin IX dimethyl ester[15] in CH_2Cl_2. The reaction was quenched after 20 h to yield the two dihydroxychlorins **3a** (37%) and **4a** (8%), plus the unreacted porphyrin (30%). Increasing the amount of OsO_4 and lengthening the reaction time invariably led to the formation of tetrahydroxybacteriochlorin at the expense of the dihydroxy product. A similar reaction was tested on dimethyl 5,8-dimethyl-1,2,3,4-tetraethylporphinedipropionate.[16] With this porphyrin apparently for steric reasons, the dihydroxylation occurred favorably at the "southern" pyrroles affording nearly 1:1 ratio of **3b** and **4b**. Treating the dihydroxychlorin **3b** in CH_2Cl_2 with 70% $HClO_4$ cleanly produced the rearranged ketones **5b** and **6b** in equal amount. The two isomers were separated by chromatography and their structures were determined by nuclear Overhauser enhancements (NOE) on the proton resonances. Selective irradiation of the methyl substituents resulted in NOEs (>5%) at the adjacent positions; by determining the nearest meso protons, it is possible to assign the structures unambiguously. Similar reaction and characterization were applied successfully for the tetramethyl homologues **5a** and **6a**. It is interesting to note that the NH protons of **5b** and **5a** should appear as two peaks while they remain as singlet in **6a** and **6b**. It is not evident whether an alteration of the tautomeric patterns or structural distortions is a possible cause for the splitting of the NH resonance.

The oxochlorin **6a** reacted sluggishly with methylenetriphenylphosphorane. The excess Wittig reagent present in the reaction invariably converted the ester group into the β-keto methylphosphonium salt.[17] Thus the methyl ester **6a** was first hydrolyzed in aqueous KOH, and the carboxyl groups were protected as the carboxylate ion during the Wittig reaction.[18] The resultant methylenechlorin was esterified and then hydrogenated quantitatively to the methylchlorin **8** with PtO_2 in formic acid.

The dihydroxychlorin isomers **3a**/**4a** and **3b**/**4b** have almost identical visible absorption spectra whose overall features are indistinguishable from that of the common dihydroporphyrins or the methylchlorin **8**. The di-

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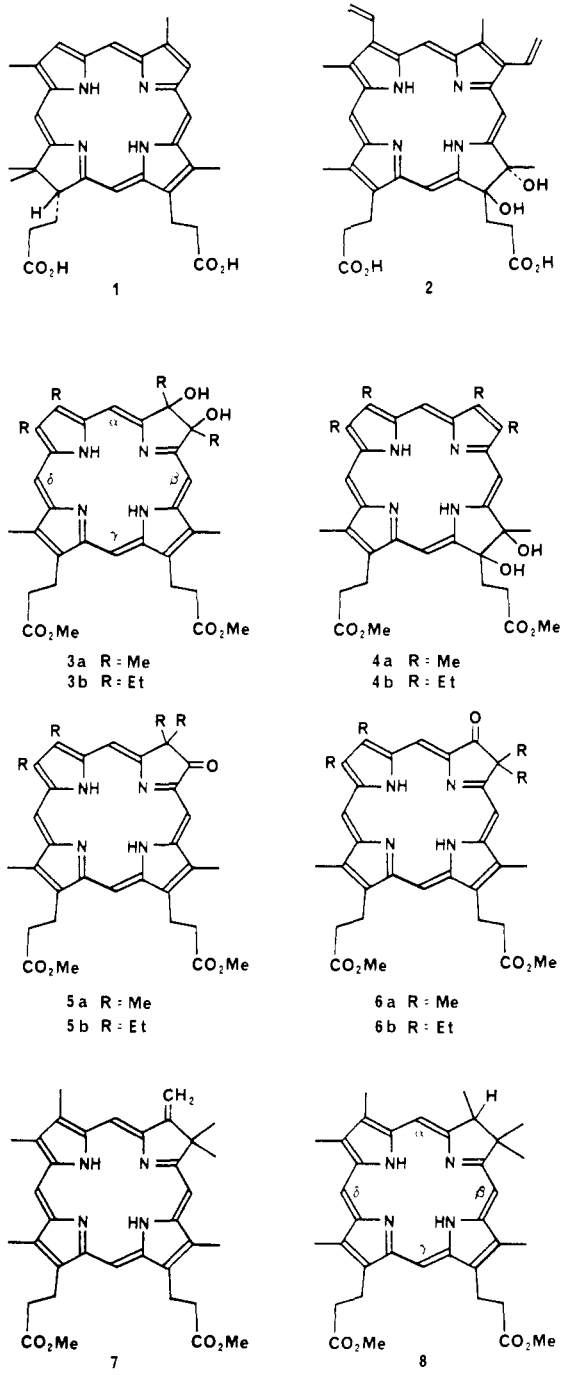
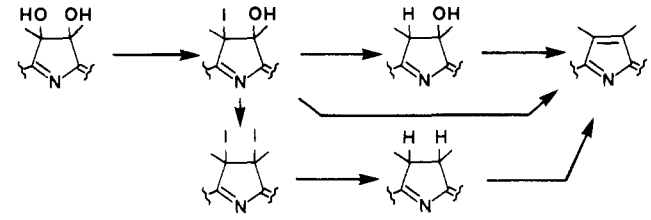


hydroxychlorins are inert toward quinone oxidation; at room temperature they are relatively stable in most acids (including concentrated HCl) and undergo the pinacolic rearrangement only with >60% sulfuric acid or perchloric acid.[19] When left in concentrated HI/HOAc, the dihydroxychlorin slowly changes into porphyrin presumably via one of the sequences in Scheme I. This conversion is probably responsible for Barrett[20] to propose that porphyrin *d* from *Aerobacter aerogenes* is a dihydroporphyrin. Reductive removal of the OH group by HI was also used previously by us to prepare symmetric alkylated chlorins and isobacteriochlorins.[21] The present series of *C*-methyl- and *C*-hydroxychlorindipropionic acids is particularly useful for hemoprotein reconstitution studies. Results of

Scheme I



chlorin reconstituted myoglobins will be reported elsewhere.

Experimental Section

^{1}H NMR spectra ($CDCl_3$, Me_4Si internal standard) were obtained with a Bruker WM-250 instrument. Nuclear Overhauser enhancements were measured by difference between a spectrum with preirradiation on a target peak minus a spectrum with equivalent preirradiation at a dummy position. 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. Mass spectra (direct insertion probe, 70 eV, 200–300 °C) were measured with a Finnigan 4021 or a Varian MAT CH-5 mass spectrometer. Elementary analyses were performed by MicAnal. Visible absorption spectra (in CH_2Cl_2) were measured with a Cary 219 spectrophotometer. Preparative TLC plates were supplied by Analtech (1500 μm, silica gel).

3,4-Dihydroxy-2,4-dimethyldeuterochlorin Dimethyl Ester (3a). Osmium tetraoxide (300 mg, 1.2 mmol) in anhydrous ether (3 mL) was added to a methylene chloride (200 mL) solution of 2,4-dimethyldeuteroporphyrin dimethyl ester (566 mg, 1 mmol). Dry pyridine (0.2 mL) was added subsequently, and the mixture was allowed to stir at room temperature, under nitrogen, in the dark for 20 h. The solvents were then evaporated, and the residue was dissolved in a mixture of MeOH (100 mL) and CH_2Cl_2 (30 mL). Hydrogen sulfide was passed through the solution for 15 min in order to decompose the osmium ester. The precipitated osmium sulfide was removed by filtration, and the crude product in the filtrate was chromatographed on a silica gel column. Unreacted porphyrin was eluted first with CH_2Cl_2/1% MeOH while the two green dihydroxychlorins were partially differentiated by CH_2Cl_2/3% MeOH. The slower moving major isomer which turned out to be **3a** was crystallized from CH_2Cl_2–hexane. The mother liquor combined with the faster moving component was chromatographed once again by preparative TLC (CH_2Cl_2/2% MeOH) to give pure **4a**. Yields: unreacted porphyrin, 164 mg, 30%; **3a**, 220 mg, 37%; **4a**, 50 mg, 8%. **3a**: NMR δ 2.10 (3 H, s, Me), 2.12 (3 H, s, Me), 3.11, 3.13 (2 H each, t, $CH_2CH_2CO_2$), 3.40 (6 H, s, 2 Me), 3.43 (3 H, s, Me), 3.45 (3 H, s, Me), 3.63, 3.66 (3 H each, s, CO_2Me), 4.15, 4.22 (2 H each, t, $CH_2CH_2CO_2$), 9.07, 9.09 (1 H each, s, methine α,β), 9.68 (2 H, s, methine γ, δ), −2.78 (2 H, br s, NH); mass spectrum, *m/e* 600.2936 (calcd for $C_{34}H_{40}N_4O_6$ 600.2950); UV–vis λ_{max} (ϵ_M) 642 nm (44 700), 614 (3800), 588 (4700), 522 (3400), 495 (13 300), 490 (13 300), 392 (179 000).

5,6-Dihydroxy-2,4-dimethyldeuterochlorin dimethyl ester (4a): NMR δ 1.80 (3 H, s, 5-Me), 3.05, 3.23 (2 H each, t, $CH_2CH_2CO_2$), 3.30 (6 H, s, 2 Me), 3.34 (3 H, s, Me), 3.40 (3 H, s, Me), 3.43, 3.48 (3 H each, s, CO_2Me), 3.70 (2 H, m, 6-$CH_2CH_2CO_2$), 3.87 (br, OH), 4.17 (2 H, m, 7-$CH_2CH_2CO_2$), 9.02, 9.08 (1 H each, s, methine α,β) 9.59, 9.71 (1 H each, s, methine γ, δ), −2.65 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 643 nm (43 400), 614 (3400), 589 (3900), 521 (2500), 495 (13 400), 490 (13 400), 392 (188 000).

13,17-Bis[2-(methoxycarbonyl)ethyl]-2,3-dihydroxy-12,18-dimethyl-2,3,7,8-tetraethylchlorin (3b). Osmium tetraoxide (90 mg, 0.35 mmol) in ether (1 mL) was added to dimethyl 5,8-dimethyl-1,2,3,4-tetraethylporphine-6,7-dipropionate[16] (170 mg, 0.27 mmol) in CH_2Cl_2 (50 mL), followed by dry pyridine (0.1 mL). The reaction was allowed to proceed in the dark for 20 h and worked up in the same manner as described above. The products isolated according to their elution pattern from the silica gel column were the unreacted porphyrin (20 mg, 11.8%), isomer **3b** (50 mg, 28%), and isomer **4b** (47 mg, 28%). (Notice that the isomer **3b** is the faster moving chlorin in this case.) **3b**: NMR δ 0.90, 0.98 (3 H each, t, CH_3CH_2 of pyrroline ring), 1.74, 1.76 (3

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H each, t, CH_3CH_2), 2.50, 2.58 (2 H each, q, CH_3CH_2 of pyrroline ring), 2.93, 3.06 (2 H each, t, $CH_2CH_2CO_2$), 3.27, 3.37 (3 H each, s Me), 3.59, 3.66 (3 H each, s, CO_2Me), 3.85 (4 H, q, Et), 3.94, 4.06 (2 H each, t, $CH_2CH_2CO_2$), 8.92, 9.00 (1 H each, s, methine α,β), 9.46, 9.67 (1 H each, s, methine γ, δ), −2.62 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 643 nm (46 900), 614 (4000), 590 (4200), 522 (2900), 494 (14 200), 490 (14 200), 392 (198 000).

13,17-Bis[2-(methoxycarbonyl)ethyl]-12,13-dihydroxy-12,18-dimethyl-2,3,7,8-tetraethylchlorin (4b): NMR δ 1.80 (12 H, m, Et), 2.14 (3 H, s, 12-Me), 2.50 (2 H, t, 13-$CH_2CH_2CO_2$), 3.15, 3.32 (2 H each, t, $CH_2CH_2CO_2$), 3.37 (3 H, s, Me), 3.51, 3.66 (3 H each, s, CO_2Me), 3.85 (8 H, m, Et), 4.08 (2 H, t, 17-$CH_2CH_2CO_2$), 8.98, 9.04 (1 H each, s, methine α,β), 9.62, 9.69 (1 H each, s, methine γ, δ), −2.60 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 643 nm (44 000), 615 (3600), 590 (3900), 521 (2600), 494 (13 700), 490 (13 700), 392 (19 300).

13,17-Bis[2-(methoxycarbonyl)ethyl]-3,3,7,8,12,18-hexamethyl-2-oxochlorin (5a) and 13,17-Bis[2-(methoxycarbonyl)ethyl]-2,2,7,8,12,18-hexamethyl-3-oxochlorin (6a). Perchloric acid (70%, 1 mL) was added to a methylene chloride solution (60 mL) of **3a** (150 mg, 0.25 mmol). The mixture was allowed to stir at room temperature for $^1/_2$ h before being extracted with water (3×, 60 mL each). The CH_2Cl_2 layer contained the mixture of **5a** and **6a**, which were separated on preparative TLC plates (silica gel, CH_2Cl_2/1% MeOH), yielding 60 mg (42%) each of the oxochlorins. The structure assignment for the slower moving **5a** and the faster moving **6a** was achieved via NOE measurements.

5a: NMR δ 2.09 (6 H, s, Me), 3.12, 3.15 (2 H each, t, $CH_2CH_2CO_2$), 3.37, 3.43, 3.46, 3.49 (3 H each, s, Me), 3.57, 3.59 (3 H each, s, CO_2Me), 4.15, 4.30 (2 H each, t, $CH_2CH_2CO_2$), 9.02 (1 H, s, methine α), 9.70 (1 H, s, methine β), 9.75 (1 H, s, methine γ), 9.84 (1 H, s, methine δ), −3.06, −2.86 (1 H, each, br s, NH); mass spectrum, m/e 582.2838 (calcd for $C_{34}H_{38}N_4O_5$ 582.2844); mp 265–266 °C; UV–vis λ_{max} (ϵ_M) 642 nm (32 400), 585 (6000), 546 (12 000), 508 (9500), 490 (6200), 404 (169 000).

6a: NMR δ 2.00 (6 H, s, Me), 3.13, 3.18 (2 H each, t, $CH_2CH_2CO_2$), 3.39, 3.44, 3.46, 3.50 (3 H each, s, Me), 3.59 (6 H, s, CO_2Me), 4.16, 4.32 (2 H each, t, $CH_2CH_2CO_2$), 9.07 (1 H, s, methine β), 9.74 (1 H, s, methine α), 9.79 (1 H, s, methine γ), 9.80 (1 H, s, methine δ), −3.12 (2 H, br s, NH); mass spectrum, m/e 582 (M^+); mp 266–268 °C; UV–vis λ_{max} (ϵ_M) 642 nm (32 300), 585 (5500), 546 (11 300), 508 (8500), 490 (5600), 404 (151 000). Anal. Calcd: C, 70.07; H, 6.58; N, 9.62. Found: C, 70.18; H, 6.66; N, 9.57.

13,17-Bis[2-(methoxycarbonyl)ethyl]-12,18-dimethyl-3,3,7,8-tetraethyl-2-oxochlorin (5b) and 13,17-Bis[2-(methoxycarbonyl)ethyl]-12,18-dimethyl-2,2,7,8-tetraethyl-3-oxochlorin (6b). The dihydroxychlorin **3b** (50 mg, 0.076 mmol) in CH_2Cl_2 was treated with perchloric acid (70%, 1 mL), and the reaction was worked up in the same manner as described above to afford 19 mg of each (40%) of the isomeric oxochlorins.

5b (slower component on TLC): NMR δ 0.38 (6 H, t, Et), 1.86 (4 H, q, Et), 2.75 (4 H, q, Et), 3.20, 3.24 (3 H each, t, $CH_2CH_2CO_2$), 3.48, 3.59 (3 H each, s, Me), 3.65, 3.66 (3 H each, CO_2Me), 4.00, 4.06 (3 H each, q, Et), 4.25, 4.40 (2 H each, t, $CH_2CH_2CO_2$), 9.13 (1 H, s, methine α), 9.84 (1 H, s, methine β), 9.85 (1 H, s, methine δ), 9.95 (1 H, s, methine δ, −2.91, −2.78 (1 H each, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (34 700), 586 (5900), 546 (11 800), 508 (9600), 490 (6300), 406 (173 000).

6b (first band on TLC): NMR δ 0.38 (6 H, t, Et), 1.85 (6 H, t, Et), 2.76 (4 H, q, Et), 3.21, 3.28 (3 H each, t, $CH_2CH_2CO_2$), 3.48, 3.58 (3 H, s, Me), 3.67, 3.68 (3 H each, s, CO_2Me), 4.06 (4 H, q, Et), 4.25, 4.41 (2 H each, t, $CH_2CH_2CO_2$), 9.13 (1 H, s, methine β), 9.84 (1 H, s, methine α), 9.88 (1 H, s, methine γ), 9.93 (1 H, s, methine δ), −2.90 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (35 000), 586 (5700), 546 (11 800), 508 (9000), 490 (6000), 406 (162 000).

13,17-Bis[2-(methoxycarbonyl)ethyl]-2,2,7,8,12,18-hexamethyl-3-methylenechlorin (7). The methyl ester groups of oxochlorin **6a** (100 mg, 0.18 mmol) were hydrolyzed in a mixture of equal volume of THF and 2 N aqueous KOH. The mixture was stirred for 12 h before the THF solvent was removed in a rotorvap. The remainder of the aqueous solution was acidifed with HCl, and the precipitated oxochlorin diacid was collected by filtration, washed with water, and dried.

To a suspension of Ph_3PCH_3Br (614 mg, 1.72 mmol) in dry THF (20 mL) was added an equivalent amount of *n*-butyllithium (1.6 M solution in hexane) under nitrogen. The resultant orange suspension was allowed to stir at room temperature for 30 min before being added to a solution of the oxochlorin diacid (95 mg, 0.172 mmol) in dry THF (25 mL) at 0 °C. The mixture was allowed to stir at room temperature for 12 h, after which time the reaction was quenched with water. The solvent was evaporated, and the residue was esterified in dry methanol (50 mL), saturated with HCl gas, and left overnight. The solvent was again evaporated, and the residue was taken in CH_2Cl_2, washed with water, and chromatographed on silica gel (CH_2Cl_2). The methylenechlorin **7** (68 mg, 71% yield), migrating in front of the unreacted **6a** (20 mg), was further purified by crystallization from CH_2Cl_2/hexane: NMR δ 2.03 (6 H, s, *gem*-Me), 3.17, 3.20 (2 H each, t, $CH_2CH_2CO_2$), 3.41 (6 H, s, Me), 3.45, 3.49 (3 H each, s, Me), 3.66, 3.67 (3 H each, s, CO_2Me), 4.19, 4.33 (2 H each, t, $CH_2CH_2CO_2$), 5.81, 6.78 (1 H each, s, $=CH_2$), 8.86, 9.38 (1 H each, methine α,β), 9.65, 9.71 (1 H each, s, methine γ, δ), −2.54 (2 H, br s, NH); mass spectrum, m/e 580.3049 (calcd for $C_{35}H_{40}N_4O_4$ 580.3052); UV–vis λ_{max} (ϵ_M) 656 nm (36 000), 600 (4400), 534 (13 000), 506 (9600), 498 (9600), 400 (136 000).

13,17-Bis[2-(methoxycarbonyl)ethyl]-2,2,3,7,8,12,18-heptamethylchlorin or 2,4,4-Trimethyldeuterochlorin Dimethyl Ester (8). The above chlorin **7** (10 mg) was dissolved in formic acid (88%, 8 mL), to which a small amount of Adams catalyst (PtO_2, 5 mg) was added. A gentle stream of hydrogen was passed into the mixture for 5 min. A distinct color change was observed. The hydrogenated product was obtained almost quantitatively by evaporating the formic acid and purified by passing through a short silica gel pad with CH_2Cl_2: NMR δ 1.83, 2.01 (3 H each, s, *gem*-Me), 1.98 (3 H, d, tertiary Me), 3.17, 3.20 (2 H each, t, $CH_2CH_2CO_2$), 3.41, 3.42, 3.47, 3.50 (3 H each, s, ring Me), 3.67 (6 H, s, CO_2Me), 4.20, 4.33 (2 H, t, $CH_2CH_2CO_2$), 4.55 (1 H, q, tertiary H), 8.81, 8.85 (1 H each, s, methine α,β), 9.68, 9.70 (1 H each, s, methine γ, δ), −2.42 (2 H, br s, NH); mass spectrum, m/e 582.3200 (calcd for $C_{35}H_{42}N_4O_4$ 582.3208); UV–vis λ_{max} (ϵ_M) 643 nm (36 900), 614 (3700), 589 (4200), 524 (4000), 497 (9900), 490 (9800), 392 (141 000).

Acknowledgment. We thank Dr. Russell Timkovich for a preprint prior to publication. This work was supported in part by NIH (GM 34468, joint with Oregon Graduate Center). C.K.C. is a recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1981–1985.

Registry No. **3a**, 98821-76-2; **3b**, 98821-78-4; **4a**, 98821-77-3; **4b**, 98821-79-5; **5a**, 98821-80-8; **5b**, 98821-81-9; **6a**, 98838-34-7; **6a** (diacid), 98821-83-1; **6b**, 98821-82-0; **7**, 98821-84-2; **7** (diacid), 98821-86-4; **8**, 98821-85-3; Ph_3PCH_3Br, 1779-49-3; 2,4-dimethyldeuteroporphyrin dimethyl ester, 78986-42-2; dimethyl 5,8-dimethyl-1,2,3,4-tetraethylporphine-6,7-dipropionate, 66145-61-7.

A New Convenient Method for Esterification Using the Ph_3P/CCl_4 System

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Received November 7, 1984

In connection with one of our ongoing projects, well-established esterification methods,[1-3] such as the reaction of metal salts of carboxylic acids with alkyl halides, were not successful due to competing side reactions. Other

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