potassium amide, as evidenced by the discharge of the blue solution to gray, the appropriate amine was added and the ammonia was evaporated by heating with a steam bath and under a gentle flow of dry nitrogen. Compound **1** or **2** was added then and the reaction mixture stirred for either 2 h for **1** with primary amines or **2** with primary and secondary amines or 4 h for **1** and secondary amines; the reaction of **1** with diisopropylamine required 6 h of stirring at 60 °C. The amine products were obtained by passing the reaction mixture through a column packed with silica G, concentrating the appropriate fraction (rotary evaporator), and then distilling the residue under vacuum.

General Reaction of 1 with Nitriles. Potassium amide (0.2 mol) was prepared in the same manner described above. The appropriate nitrile (0.1 mol) was added over a period of 5 min and the solution stirred for 10 min at which time **1** (0.05 mol) was added dropwise and the resulting solution stirred for 1 h. Then the ammonia was evaporated by heating with a steam bath, and the residue was dissolved in ether and extracted with two 100-mL portions of 6 N HCl. The ether was dried (Na_2SO_4) and evaporated and the residue distilled to yield the amine product.

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Registry No. **1**, 553-94-6; **2**, 2859-78-1; **7** (R = H; R^1 = Pr), 87282-05-1; **7** (R = H; R^1 = Bu), 87282-06-2; **7** (R = H; R^1 = *i*-Bu), 87282-07-3; **7** (R = H; R^1 = *sec*-Bu), 60388-37-6; **7** (R = H; R^1 = *t*-Bu), 87282-08-4; **7** (R,R^1 = Et), 3995-37-7; **7** (R,R^1 = Pr), 87282-09-5; **7** (R,R^1 = *i*-Pr), 87282-10-8; **7** (R,R_1 = Bu), 87282-11-9; **7** (R = Me; R^1 = Bu), 87282-12-0; **7** (R = Et; R_1 = Bu), 87282-13-1; **8** (R = H; R^1 = Bu), 87282-14-2; **8** (R = H; R^1 = *t*-Bu), 87282-15-3; **8** (R,R^1 = *i*-Pr), 87282-16-4; **8** (R = Me;R^1 = Bu), 87282-17-5; **8** (R = Et; R^1 = Bu), 87282-18-6; **9** (R = H), 16213-85-7; **9** (R = Me), 16213-86-8; **9** (R = Et), 16213-87-9; **9** (R = Pr), 16213-88-0; propylamine, 107-10-8; butylamine, 109-73-9; isobutylamine, 78-81-9; *sec*-butylamine, 13952-84-6; *tert*-butylamine, 75-64-9; diethylamine, 109-89-7; dipropylamine, 142-84-7; diisopropylamine, 108-18-9; dibutylamine, 111-92-2; *N*-methylbutylamine, 110-68-9; *N*-ethylbutylamine, 13360-63-9; acetonitrile, 75-05-8; propionitrile, 107-12-0; butyronitrile, 109-74-0; valeronitrile, 110-59-8.

Synthesis of Porphyrinoctakis(dialkylcarboxamides)

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Certain water-soluble porphyrins have been reported as attractive alternatives to currently employed sensitizers in the photochemical reduction of water to hydrogen.[1] They have also been found to accumulate in tumors,[2] and their use as diagnostic[3] and thereapeutic agents has been examined.[4] All of these porphyrins owe their water solubility to the presence of readily ionized substituents (carboxylate,[4] sulfonate,[5] or quaternary ammonium[6] salts). We report here the synthesis of porphyrinoctakis(diethylcarboxamide) **7a** and porphyrinoctakis(dimethylcarboxamide) **7b**, two neutral, meso, unsubstituted porphyrins, which display considerable solubility in water as well as in organic solvents ranging in polarity from toluene to ethanol.

Scheme I

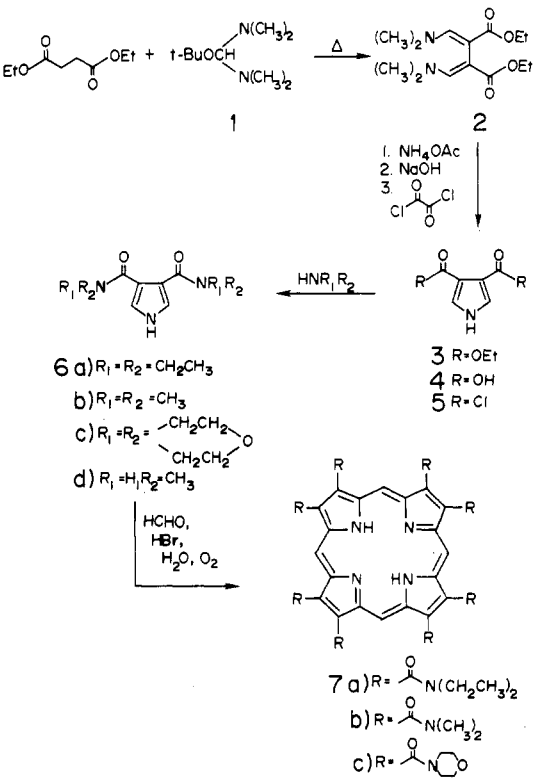

Table I. Maximum Solubilities of Porphyrins 7a and 7b in Selected Solvents

	solubility, g/L (mol/L at 25 °C)	
solvent	7a	7b
H_2O[a]	0.013 (1.2×10^{-5})	2.4 (2.7×10^{-3})
EtOH	3.5 (3.2×10^{-2})	1.6 (1.8×10^{-3})
EtOAc	2.2 (2.0×10^{-3})	0.097 (1.1×10^{-4})
CH_2Cl_2	96 (8.7×10^{-2})	65 (7.4×10^{-2})
Et_2O	0.051 (4.6×10^{-5})	0.004 (4.3×10^{-6})
toluene	7.9 (7.2×10^{-3})	0.05 (5.7×10^{-5})

[a] Plots of the absorbance of the Soret band vs. the concentration of **7a** (1.2×10^{-5} to 1.0×10^{-7} M) and **7b** (7.4×10^{-5} to 2.6×10^{-6} M) obey Beer's law, implying a lack of self-aggregation at these low concentrations. Higher concentrations of **7b** were not tested.

Recently, we described the acid-catalyzed condensations of formaldehyde and various 3,4-disubstituted pyrroles in ethanol as a convenient route to octasubstituted porphyrins.[7] Pyrroles bearing two strongly deactivating benzoyl, carbethoxy,[8] or trifluoromethyl[9] groups fail to undergo this reaction. The condensation of slightly less deactivated pyrroledicarboxamides with formaldehyde, however, had not been explored.[10] Scheme I summarizes the syntheses of a series of pyrrole-3,4-dicarboxamides **6a–d** and their conversion to porphyrins **7a–c**.

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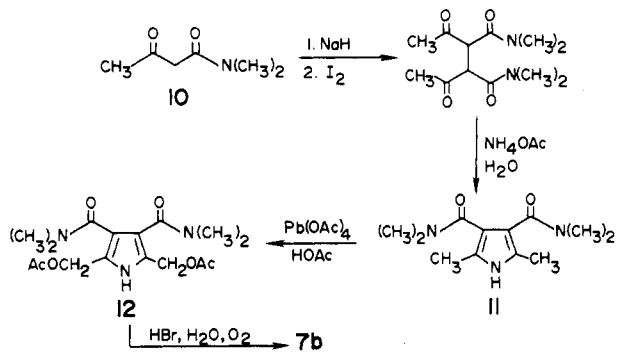
0022-3263/83/1948-4399$01.50/0

Scheme II

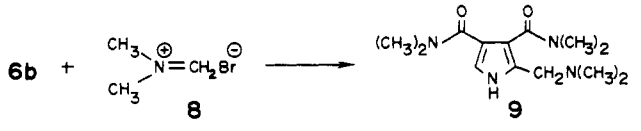


The 3,4-dicarbethoxypyrrole (**3**) is prepared in nearly quantitative yield by refluxing bis(enamine) **2**, obtained from diethyl succinate and **1**[11] in an ethanolic solution of ammonium acetate.[12] Hydrolysis of **3** to 3.4-dicarboxypyrrole (**4**) followed by treatment with oxalyl chloride gives pyrrole **5**,[12a] which on addition to an excess of a primary or secondary amine provides the pyrroledicarboxamides **6a–d** in good overall yields.[13]

The acid-catalyzed condensation of **6a** with formaldehyde affords a 25% yield of prophyrin **7a**. The reaction can be carried out in alcoholic solvents, water, or preferably a mixture of both, which allows direct crystallization of **7a** after air oxidation. Surprisingly, the condensation of **6b** is solvent dependent, providing a 14% yield of **7b** when carried out in water, but affording no prophyrin in alcoholic solvents.

Porphyrin **7a** shows high solubility in a number of organic solvents as well as appreciable solubility in water (Table I). The solubility of **7b** in water is increased significantly due to the less aliphatic nature of its amide substituents. Attempts to prepare a porphyrin from the even less aliphatic pyrrole-3,4-bis(methylcarboxamide) (**6d**) under a variety of conditions and solvents failed. The synthesis of porphyrinoctakis(morpholinocarboxamide) (**7c**), possessing an additional heteroatom capable of hydrogen bonding with water, proves impractical, affording only spectroscopic amounts of the desired porphyrin.

The 2-[(dimethylamino)methyl]-[14] and 2,5-bis(acetoxymethyl)pyrroles[15] are potential precursors to octasubstituted porphyrins. We have explored the use of similar derivatives in search of a more efficient synthesis of **7b**. The C-alkylated pyrrole **9** is prepared by refluxing pyrrole



6b with 1 equiv of the Mannich reagent **8**[16] in 1,2-dichloroethane. At lower temperatures predominatly the N-alkylated product is formed. The acid-catalyzed self-condensation of **9**, studied under a variety of conditions, gave trace amounts of the desired porphyrin.

Scheme II summarizes the preparation of the 2,5-bis(acetoxymethyl)pyrrole **12** and its conversion to **7b**. Dimerization of *N,N*-dimethylacetylacetamide (**10**) followed by heating with ammonium acetate provides the 2,5-dimethylpyrrole **11** in an overall yield of 40% (65% based on consumption of **10**) without the need for isolation of intermediates. Subsequent oxidation with $Pb(OAc)_4$[15] affords the desired porphyrin precursor **12**, which on self-condensation in acidified water provides a 10% yield of **7b**. The overall yield of **7b** is lower in the second syntheses; however, the latter procedure is shorter and considerably more convenient.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (Nujol mull) were obtained on a Perkin-Elmer 237 grating spectrophotometer. Electronic absorption spectra were measured on a Cary 219 spectrophotometer. Mass spectra were obtained on a Finnigan 4000 instrument at 70 eV. NMR spectra (in $CDCl_3$, Me_4Si as an internal standard) were recorded on a Varian T-60 or a Bruker WM-250 (^1H NMR at 250 MHz and ^{13}C NMR, ^1H coupled and decoupled, at 62.9 MHz) instrument. Elemental analyses were performed by Galbraith Laboratories. Finely divided NaH (Ventron) was used as a 50% mineral oil dispersion.[17] $Pb(OAc)_4$[18] and *N,N*-dimethylacetylacetamide[19] were prepared as previously described.

Diethyl Bis[(dimethylamino)methylene]succinate (2). According to the method of Bredereck,[11] a solution of diethyl succinate (2.00 g, 11.5 mmol) and *tert*-butoxybis(dimethylamino)methane[20] (**1**; 6.00 g, 34.5 mmol) was heated under a nitrogen atmosphere for 5 h at 160 °C in a magnetically stirred flask, equipped with a distilling head and condenser. The flask was cooled to 50 °C, evacuated to 0.3 mm pressure, and heated at 110 °C for another 45 min. During the course of this procedure a clear liquid distilled from the reaction mixture. The remaining dark oil was cooled at −10 °C overnight, and the resulting crystals were triturated with ether (4 mL) and cooled at −10 °C for 5 h. The ether was decanted and the process repeated. Recrystallization from hexane gave 2.05 g (63%) of **2** as yellow needles: mp 73.5–74.5 °C (lit.[11] mp 70.5 °C); ^1H NMR (60 MHz) δ 1.16 (6 H, t, J = 7 Hz), 2.90 (12 H, s), 4.02 (4 H, q, J = 7 Hz), 7.25 (2 H, s).

3,4-Dicarbethoxypyrrole (3). A solution of bis(enamine) **2** (2.00 g, 7.11 mmol) and ammonium acetate (2.74 g, 35.5 mmol) in 95% ethanol (40 mL) was heated under reflux for 24 h. The solution was cooled, poured into water (250 mL) and extracted with CH_2Cl_2. The combined organic fractions were washed with saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. Evaporation of the solvent and recrystallization from THF gave 1.45 g (97%) of **3** as colorless crystals: mp 150–151 °C (lit.[12a] mp 151–152 °C); ^1H NMR (250 MHz) δ 1.33 (6 H, t, J = 7 Hz), 4.29 (4 H, q, J = 7 Hz), 7.42 (2 H, d, J = 3 Hz), 10.50 (1 H, br s); ^{13}C NMR δ 14.35, 60.24, 115.04, 126.43, 164.41; mass spectrum, m/e (relative intensity) 211 (12, M^+), 166 (34), 138 (100), 94 (16), 66 (20).

3,4-Dicarboxypyrrole (4). According to the procedure of Groves,[12a] a solution of diester **3** (1.50 g, 7.10 mmol) and NaOH (1.40 g) in 50% EtOH (15 mL) was heated under reflux for 2 h. The solution was diluted with water (50 mL), warmed on a steam bath, and slowly acidified with 10% HCl. Suction filtration and thorough washing with water gave 1.05 g (95%) of 4 as an insoluble white powder: mp 300 °C dec (lit.[12a] mp 300 °C dec); IR 3160 (NH), 2000–3000 (OH), 1590 (C=O) cm^{-1}; mass spectrum, m/e (relative intensity) 155 (100, M^+).

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Pyrrole-3,4-bis(diethylcarboxamide) (6a). A suspension of diacid **4** (0.960 g, 6.19 mmol) and oxalyl chloride (8.0 mL) in dry toluene (100 mL) was magnetically stirred under an inert atmosphere in a flask equipped with an efficient condenser. Four drops of DMF were added, and the suspension was heated to 85 °C. After 50 min the yellow, homogeneous solution was cooled to 40 °C and evacuated for 30 min (0.5 mm pressure), keeping the temperature at 40–50 °C. (This efficiently removed excess oxalyl chloride without destruction of the diacid chloride). The warm toluene solution of **5** (approximately 60 mL) was added slowly via cannula to a flask, equipped with a drying tube and containing a cooled (ice bath) solution of diethylamine (40 mL) and toluene (40 mL). This was stirred overnight, allowing the temperature to rise to 25 °C. The mixture was concentrated on a rotary evaporator, dissolved in water (250 mL), and extracted thoroughly first with ether and then with $CHCl_3$. The combined $CHCl_3$ fractions were dried over anhydrous Na_2SO_4 and concentrated. The resulting yellow oil was treated with ether (10 mL) and cooled at −10 °C overnight. The solid was suction filtered and washed with ether. Recrystallization from toluene gave 1.46 g (89%) of **6a** as colorless crystals: mp 123–124 °C; ^1H NMR (60 MHz) δ 1.12 (12 H, t, J = 7 Hz), 3.42 (8 H, q, J = 7 Hz), 6.66 (2 H, d, J = 2.5 Hz), 10.96 (1 H, br s); ^{13}C NMR δ 13.50, 41.06, 117.94, 118.24, 167.42; mass spectrum, m/e (relative intensity) 265 (12, M^+), 193 (67), 192 (62), 122 (41), 72 (100); IR 3170 (NH), 1620 (C=O cm^{-1}. Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.40, H, 8.68. Found: C, 63.44; H, 8.94.

Porphyrinoctakis(diethylcarboxamide) (7a). A solution of pyrrole-3.4-bis(diethylcarboxamide) (**6a**; 0.70 g, 2.64 mmol), 37% formaldehyde (4.0 mL), and 48% HBr (1.4 mL) in water (85 mL) and EtOH (20 mL) was heated under a nitrogen atmosphere at 80 °C for 36 h and then allowed to stand in a large open beaker for 14 days (slow air oxidation). Filtration of the reaction mixture and recrystallization of the solid from H_2O–MeOH (20:1) gave 0.182 g (25%) of **7a** as purple crystals: mp > 350 °C; ^1H NMR (60 MHz) δ −3.36 (2 H, s), 1.16 (24 H, br t, J = 7 Hz), 1.65 (24 H, br t, J = 7 Hz), 3.61 (16 H, br q, J = 7 Hz), 3.96 (16 H, br q, J = 7 Hz), 10.10 (4 H, s); ^{13}C NMR δ 13.38 (q), 14.32 (q), 39.79 (t), 44.45 (t), 102.85 (d), 136.67 (s), 142.80 (s), 165.74 (s); UV–vis ($CHCl_3$)[21] λ_{max} (ϵ_M) 416 (249 000), 508 (20 000), 540 (7800), 581 (3600), 634 (2900); IR 3350 (NH), 2820 (CH), 1630 (C=O) cm^{-1}. Anal. Calcd for $C_{60}H_{86}N_{12}O_8$: C, 65.34; H, 7.80. Found: C, 65.86; H, 7.53.

Pyrrole-3,4-bis(dimethylcarboxamide) (6b). Diacid chloride **5** was prepared in toluene as described above and added slowly via cannula to a flask equipped with a drying tube, a dry-ice condenser, and a magnetic stirrer and containing anhydrous dimethylamine (approximately 100 mL) at −78 °C. This was stirred overnight, allowing the reaction mixture to warm slowly to 25 °C and the dimethylamine to evaporate. The mixture was heated on a steam bath for 30 min, removing residual dimethylamine, and was then cooled in an ice bath. The white, crystalline solid was suction filtered, washed with cold toluene, and air-dried. This was dissolved in a saturated, aqueous $NaHCO_3$ solution (30 mL) and stirred overnight with an equal volume of CH_2Cl_2. (For a maximum yield of the water-soluble pyrrole this extraction was repeated.) The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated. Recrystallization from THF–CH_2Cl_2 (15:1) gave 1.2. g (93%) of **6b** as colorless needles: mp 206–207 °C; ^1H NMR (250 MHz) δ 3.02 (12 H, s), 6.72 (2 H, d, J = 2.75 Hz), 11.22 (1 H, br s); ^{13}C NMR δ 37.37, 118.02, 119.81, 167.98; mass spectrum, m/e (relative intensity) 209 (29, M^+), 165 (40), 164 (59), 122 (100), 94 (21), 44 (20); IR 3110 (NH), 1630 and 1610 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.42; H, 7.18. Found: C, 57.11, H, 7.35.

Porphyrinoctakis(dimethylcarboxamide) (7b). A solution of pyrrole-3.4-bis(dimethylcarboxamide) (**6b**; 0.70 g, 3.35 mmol), 37% formaldehyde (4.0 mL), and 48% HBr (1.4 mL) in water (105 mL) was refluxed for 36 h and then allowed to stand in a large open beaker for 14 days. This was extracted with CH_2Cl_2, and the combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated. Chromatography of the residue (activity I neutral alumina, elution with $CHCl_3$–3% *sec*-butyl alcohol) and recrystallization from CH_2Cl_2–Et_2O gave 0.10 g (14%) of **7b** as purple needles: mp >350 °C; ^1H NMR (250 MHz) δ −3.26 (2 H, s), 3.27 (24 H, s), 3.59 (24 H, s), 10.21 (4 H, s); ^{13}C NMR δ 35.73 (q), 39.92 (q), 103.68 (d), 137. 10 (s), 142.65 (s), 166.60 (s); UV–vis ($CHCl_3$)[21] λ_{max} (ϵ_M) 418 (241 000), 510 (17 000), 543 (6000), 584 (6000), 636 (2000);[21] IR 3350 (NH), 2860 (CH), 1675 (C=O) cm^{-1}. Anal. Calcd for $C_{44}H_{54}N_{12}O_8 \cdot H_2O$: C, 58.93; H, 6.25. Found: C, 59.11; H, 6.29.

2,5-Dimethylpyrrole-3,4-bis(dimethylcarboxamide) (11). A 2000-mL flask, equipped with a mechanical stirrer and an efficient condenser, was charged under nitrogen with NaH (10.0 g, 0.208 mol) and anhydrous Et_2O (1200 mL). This was stirred and warmed to a gentle reflux, and *N,N*-dimethylacetylacetamide (**10**; 20.0 g, 0.155 mol) was added dropwise over 30 min. After 24 h, I_2, dissolved in a minimum amount of Et_2O, was added dropwise in portions (20, 10, 5, and 5 g) at 1-h intervals to the vigorously stirred suspension. This was stirred at gentle reflux for another 24 h and cooled to room temperature, and a solution of $NaHSO_3$ (10 g) and NH_4OAc (30 g) in water (300 mL) was added slowly. The ether was removed on a rotary evaporator, and the remaining aqueous solution was stirred at 70 °C for 15 h, cooled to 25 °C, neutralized with $NaHCO_3$, and thoroughly extracted with ether. The aqueous layer was saturated with NaCl and stirred overnight with an equal volume of CH_2Cl_2. (For a maximum yield of the water-soluble pyrrole this extraction was repeated.) The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and concentrated, providing 15.5 g of a dark oil. Recrystallization from a minimum amount of THF gave 8.15 g of crude starting material **10** and 7.35 g (40%) of **11** as colorless crystals: mp 183–184.5 °C; ^1H NMR (250 MHz) δ 2.10 (6 H, s), 2.97 (12 H, s), 9.37 (1 H, br s); ^{13}C NMR δ 11.56, 35.33, 38.65, 114.17, 127.37, 168.82; mass spectrum, m/e (relative intensity) 237 (20, M^+), 192 (30), 150 (100), 122 (24), 121 (30), 42 (34); IR 3200 (NH), 1620 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{19}N_3O_2$: C 60.76; H, 8.02. Found: C, 60.60; H, 8.12.

2,5-Bis(acetoxymethyl)pyrrole-3,4-bis(dimethylcarboxamide) (12). A solution of **11** (4.00 g, 16.9 mmol) and $Pb(OAc)_4$ (18.7 g, 42.1 mmol) in acetic acid (70 mL) and acetic anhydride (1.2 mL) was stirred under nitrogen at 50 °C for 26 h. This was cooled to 25 °C, added to a saturated, aqueous NaCl solution (250 mL), and stirred overnight with an equal volume of $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and concentrated, affording 8.0 g of a yellow oil, consiting of **12** and acetic acid. Due to the high solubility of **12** in water and its sensitivity to base, this mixture was used directly in the preparation of **7b**. An analytical sample was obtained by recrystallization from THF–Et_2O: mp 117–118 °C; ^1H NMR (250 MHz) δ 2.07 (6 H, s), 2.99 (12 H, s), 5.08 (4 H, s), 9.60 (1 H, br s); ^{13}C NMR δ 20.88, 35.17, 39.08, 57.22, 118.18, 126.88, 166.61, 171.96; mass spectrum, m/e (relative intensity) 309 [1, $(M - (CH_3)_2N)^+$], 293 [4, $(M - CH_3CO_2H)^+$], 250 (8), 207 (23), 190 (9), 147 (11), 60 (43), 45 (72), 43 (100); IR 3140 (NH), 1750 (C=O), 1625 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_3O_6$: C, 54.36; H, 6.52. Found: C, 54.52; H, 6.55.

Porphyrinoctakis(dimethylcarboxamide) (7b) Prepared from 12. A solution of crude **12** (8.0 g) in H_2O (750 mL) was purged of oxygen by bubbling a strong stream of nitrogen through the solution at 60 °C for 3 h. To this was added 48% HBr (29 mL), and the mixture was heated under nitrogen at 75 °C for 100 h and then allowed to stand in a large open beaker for 14 days. This was extracted with CH_2Cl_2, and the combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated. Chromatography of the residue (activity I basic alumina, elution with $CHCl_3$–3% *sec*-butyl alcohol) and recrystallization from CH_2Cl_2–Et_2O gave 0.37 g (10%, based on 16.9 mmol of **11**) of **7b**.

Acknowledgment. A SOHIO Fellowship and a Dow Fellowship awarded to R.W.K. are gratefully acknowledged.

(21) As previously observed with other symmetrical porphyrins bearing eight deactivating substituents in the β-positions,[15] the visible spectra of **7a,b** in $CHCl_3$ resemble a phyllo-type absorption more so than the expected etiotype.[14] In water under neutral conditions **7b** exhibits a true phyllo-type absorption: λ_{max} (ϵ_M) 416 (264 000), 513 (17 500), 547 (6800), 585 (7400), 636 (2900). Under basic conditions (KOH, H_2O, 25 °C) the Soret band is shifted to longer wavelength with a concurrent change in the visible bands: λ_{max} (ϵ_M) 434 (215 000), 252 (sh, 6700), 567 (14 200), 603 (sh, 6100). This spectrum is attributed to the dianion of **7b** since the visible absorption pattern is very similar to the pattern observed for the corresponding zinc derivative (prepared by heating with $Zn(OAc)_2$ in dioxane).

Registry No. 1, 5815-08-7; 2, 39654-83-6; 3, 41969-71-5; 4, 935-72-8; 5, 41969-73-7; 6a, 86492-07-1; 6b, 86492-08-2; 7a, 86492-10-6; 7b, 87282-76-6; 10, 2044-64-6; 11, 87282-77-7; 12, 87282-78-8; diethyl succinate, 123-25-1.

Novel Synthetic Route to the Key Intermediate for Hirsutic Acid

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Recently we reported the first asymmetric total synthesis of hirsutic acid (1, Chart I), with high stereo- and regiochemical control.[2] In this paper we describe another synthetic route to the key synthetic intermediate **2**, which involves the chelation-controlled methylation from the sterically more crowded face of the molecule.

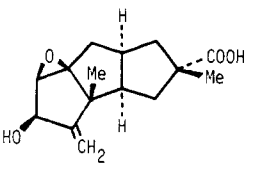
In our previous synthesis,[2] the key intermediate **2** was prepared stereospecifically by using the Simmons–Smith reaction as the key step. Alternatively, we made a search for another stereocontrolled route to **2**. It is generally known that the alkylation of the enolates generated from the compounds such as **3** proceeds predominantly at the convex face of the *cis*-bicyclo[3.3.0]octane skeleton. In fact, the methylation of the lithium enolate derived from **4** afforded a mixture of **8** and **9** in a ratio of 1.7:1 (LDA, THF, MeI), suggesting that it is unlikely to accomplish an alternative and efficient synthesis of **2** by using this methodology. However, it was assumed that, with the ester **5** carrying the MEM ether in the endo configuration, the resulting lithium enolate would preferentially exist in some rigid chelate, fixing the lithium ion on the endo side. Furthermore, we anticipated that the unshared electrons of iodine would coordinate to the lithium cation,[3] allowing an approach of methyl iodide at the concave face.

In order to test our assumption, the ester **5** was prepared as follows. Successive treatment of the MEM ether **10**[4] with (1) NBS in aqueous Me_2SO, (2) tributyltin hydride in benzene containing a catalytic amount of AIBN, and (3) PCC in methylene chloride afforded the ketone (**11**) in 50% overall yield with high regiochemical control.[5] The ketone **11** was reacted with (methoxymethylene)triphenylphosphorane to give the enol ether **12** in 85% yield. Hydrolysis of **12** with AcOH–H_2O–THF (3:1:1) produced the aldehyde **13**, which was then successively treated with Jones reagent and ethereal diazomethane to afford the ester **5** as a mixture of the stereoisomers **5a**/**5b** (ca. 5:1) in 68% overall yield. The stereochemistry of both **5a** and **5b** was tentatively assigned on the basis of the observation that treatment of either **5a** or **5b** with LDA in THF, followed by the kinetic protonation, afforded the ester **5b** as the major product in a ratio of ca. 5:1 **5b**/**5a**.

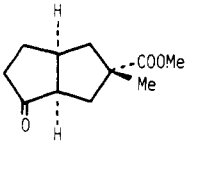
In the first place, the alkylation reaction of **5** was carried out in THF with LDA as a base and methyl iodide as an alkylating agent. As was expected, it was observed that the methyl ester **14** was formed as a major product though in a low stereoselectivity (**14**/**15**, 1.2:1). The product ratio was determined from the ^1H NMR spectrum of a mixture of the products, which displayed two singlets at δ 1.30 (**14**) and 1.20 (**15**). Being encouraged by these results, we examined a variety of reaction conditions in order to improve the stereoselectivity. At first, solvent effects were studied in detail, showing that the alkylation reaction in ether provides **14** with the highest stereoselectivity (**14**/**15**, 2.3:1; 87% yield). The results are summarized in Table I.

Use of other protecting groups of the hydroxy functionality did not improve the stereoselectivity.[6] For ex-

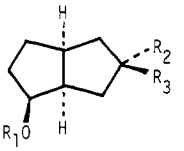
Chart I

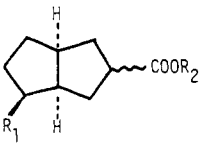


1



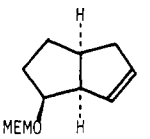
2



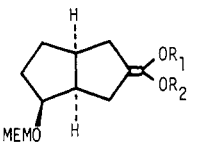


5a: R_1=MEM, R_2=COOMe, R_3=H
5b: R_1=MEM, R_2=H, R_3=COOMe
8: R_1=CH_2Ph, R_2=Me, R_3=COOMe
9: R_1=CH_2Ph, R_2=COOMe, R_3=Me
11: R_1=MEM, R_2-R_3=O
12: R_1=MEM, R_2-R_3=CHOMe
13: R_1=MEM, R_2=CHO, R_3=H
14: R_1=MEM, R_2=COOMe, R_3=Me
15: R_1=MEM, R_2=Me, R_3=COOMe
16: R_1=MOM, R_2=COOMe, R_3=Me
17: R_1=MOM, R_2=Me, R_3=COOMe
20: R_1=MEM, R_2=COO*i*-Pr, R_3=Me
21: R_1=MEM, R_2=Me, R_3=COO*i*-Pr
22: R_1=H, R_2=COOMe, R_3=Me

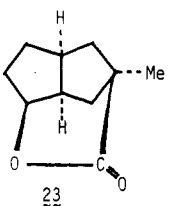
3: R_1=H, R_2=Me
4: R_1=OCH_2Ph, R_2=Me
5: R_1=OMEM, R_2=Me
6: R_1=OMOM, R_2=Me
7: R_1=OH, R_2=Me
19: R_1=OMEM, R_2=*i*-Pr



10



18a: R_1=Me, R_2=Li
18b: R_1=Li, R_2=Me



23

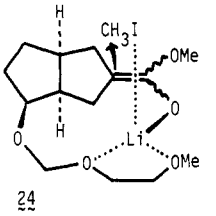


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Table I. Methylation Reaction of the Ester 5 in Various Solvents[a]

solvent	product ratio 14	15
THF	1.2	1.0
ether	2.3	1.0
DME	2.0	1.0
MeOMe	1.4	1.0
$(MeO)_2CH_2$	1.4	1.0

[a] All reactions were carried out by using LDA as a base and me thyl iodide as an alkylating agent.

(1) Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan.
(2) Shibasaki, M.; Yamazaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1982**, 5311.
(3) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
(4) Prepared in large quantities by starting with 1,3-cyclooctadiene in three steps. See: Crandall, J. K.; Chang, L.-H. *J. Org. Chem.* **1967**, *32*, 532.
(5) Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1981**, 1245.
(6) The hydroxy ester **7** was also employed for the methylation reaction in order to examine the effects of the lithium alkoxide moiety on the stereoselectivity of the alkylation reaction. However, in this case the lactone **23** was formed exclusively.

0022-3263/83/1948-4402$01.50/0