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Thermal Cycloaddition of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate with Electron-Rich Olefins: 1,2-Diazine and Pyrrole Introduction. Preparation of Octamethylporphin (OMP)

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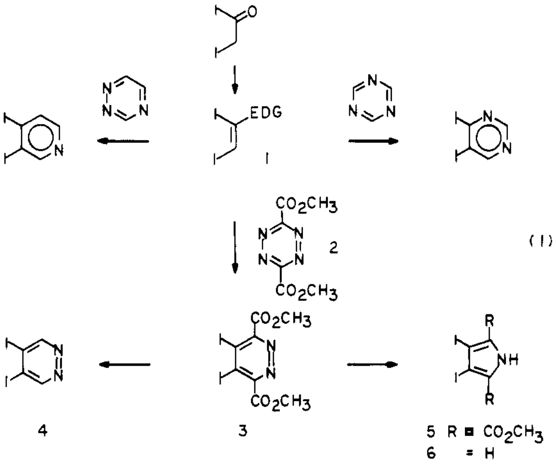
An investigation of the inverse electron demand Diels–Alder reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with electron-rich olefins for the introduction of 1,2-diazines and pyrroles is described. A short synthesis of 2,3,7,8,12,13,17,18-octamethylporphin (OMP) is detailed.

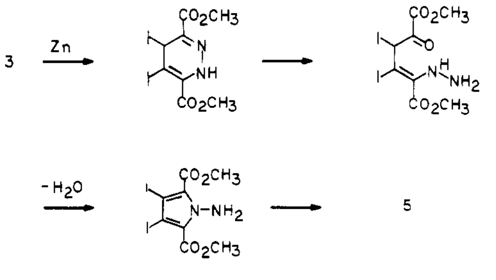
3,4-Substituted-pyrroles with selected functionality at the 2 and/or 5 position serve as precursors for the preparation of the di-, tri-, and tetrapyrroles including the porphyrins.[2] The classical Knorr reaction and its more recent variants have served as the most utilized approach to preparation of such monopyrroles.[2,3] Consequently, the ability to introduce functionality, directly, at the 2,5 positions while controlling the substitution at the 3,4 positions remains a persistent problem in the preparation of many of the monopyrroles commonly used in the synthesis of linear polypyrroles and the porphyrins.

Extensive accounts of the Diels–Alder reactions of 1,2,4,5-tetrazines with electron-rich, unactivated, as well as electron-deficient dienophiles have been reported,[4] and recently Kornfeld and co-workers have described the utilization of one such Diels–Alder adduct, a 4,5-disubstituted-3,6-dicarbomethoxy-1,2-diazine, as a useful intermediate in the preparation of a 3,4-disubstituted-2,5-dicarbomethoxypyrrole.[5] As a preliminary study on the synthesis of monopyrroles to be utilized in the synthesis of polypyrroles including the porphyrins and in conjunction with synthetic efforts on CC-1065,[6] we have investigated and herein report a study of the scope and generality of this process for the introduction of 1,2-diazines *or* pyrroles, eq 1. The results of this study are detailed in Table I and are complementary to the related processes for pyridine[7a] and pyrimidine[7b] introduction which are based on the inverse electron demand Diels–Alder reactions of 1,2,4-triazine and 1,3,5-triazine, respectively, eq 1.

The inverse electron demand Diels–Alder reaction of the electron-deficient azadiene dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[8] (**2**) with electron-rich olefins is often exothermic and is accompanied by the immediate evolution of nitrogen. Final aromatization of the resulting dihydro-1,2-diazine by loss of morpholine (entries 3, 7, and 12, Table I), loss of pyrrolidine (entries 4, 5, and 7, Table I), or loss of alcohol or silylol (entries 1, 6, and 9–11, Table I) is the slow step of the process and consequently accounts for the reaction times detailed in Table I. In addition, the low yields recorded for entries 4 and 8 (Table I) are due to a slow or poor aromatization step and are not representative of the initial inverse electron demand Diels–Alder reaction. In the one instance examined, entry 12, *p*-toluenesulfonic acid catalysis was successful in promoting a slow, final aromatization step. Hydrolysis and decarboxylation of the adducts **3b–d** did provide the parent 1,2-diazines **4b–d**.



Reduction of the 3,6-dicarbomethoxy-1,2-diazines **3a–h** with zinc in acetic acid, 25 °C, 9–24 h, according to the procedure detailed in the example reported by Kornfeld and co-workers,[5] provided the 2,5-dicarbomethoxypyrroles **5a–h** in good yield, 50–70%. The reaction, which presumably proceeds through a sequence such as that outlined in eq 2, is surprisingly tolerant of additional functionality, e.g., entries 8–11. 3-Carbomethoxy-1,2-diazine as well as 1,2-diazine itself failed to provide the corresponding pyrroles in good yield upon similar treatment.[9] Hydrolysis



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[2] "The Porphyrins, Structure and Synthesis" Part A; Dolphin, D., Ed.; Academic Press: New York, 1978.

[3] For recent work, see: (a) Cheng, D. O.; LeGoff, E. *Tetrahedron Lett.* **1977**, *1469*. Chamberlin, K. S.; LeGoff, E. *Heterocycles* **1979**, *12*, 1567. Kaesler, R. W.; LeGoff, E. *J. Org. Chem.* **1982**, *47*, 5243; **1983**, *48*, 4399. (b) Paine, J. B., III; Kirshner, W. B.; Moskowitz, D. W.; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 3857.

[4] Boger, D. L. *Tetrahedron* **1983**, *39*, 2869 and references cited therein.

[5] Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschall, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481.

[6] Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240.

[7] (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179. Boger, D. L.; Panek, J. S.; Meier, M. M. *Ibid.* **1982**, *47*, 895. (b) Boger, D. L.; Schumacher, J.; Mullican, M. D.; Patel, M.; Panek, J. S. *Ibid.* **1982**, *47*, 2673 and references cited therein.

[8] (a) Spencer, G.H., Jr.; Cross, P. C.; Wiberg, K. B. *J. Chem. Phys.* **1961**, *35*, 1939. (b) Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Chem. Ber.* **1965**, *98*, 1435. We have reproducibly executed this preparation of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate on scales providing 20–40 g of pure **2**.

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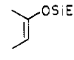
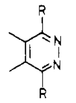
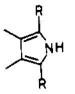
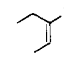
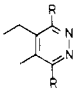
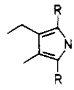
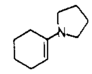
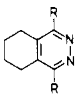
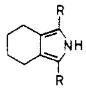
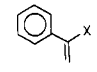
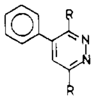
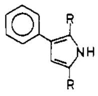
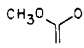
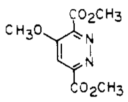
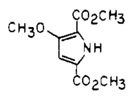
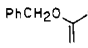
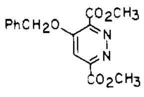
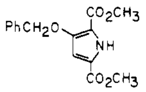
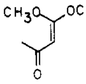
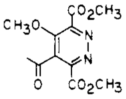
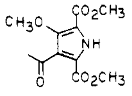
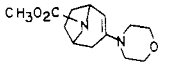
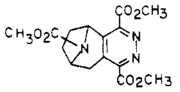
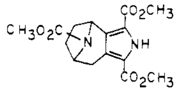
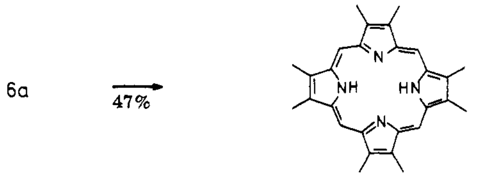
Table I. Diels–Alder Reactions of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate: 1,2-Diazine and Pyrrole Introduction

		conditions[a]			conditions[d]		
entry	dienophile 1	equiv of 1, temp, °C (time, h)	1,2-diazine[b]	% yield[c]	temp, °C (time, h)	pyrrole[b]	% yield[c]
1[f]		1.5, 25 (12)	 3a, R = CO_2CH_3	87	25 (24)	 [e] 5a, R = CO_2CH_3 6a, R = H	63 49
2	2-butyne	2-6, 25 (12)	3a	trace			
3[g] 4[h]	 X = morpholino X = pyrrolidino	2, 25 (48) 2, 25 (48)	 [e] 3b, R = CO_2CH_3 4b, R = H	70 trace 47	25 (24)	 [e] 5b, R = CO_2CH_3 6b, R = H	70 47
5		1.5, 25 (12)	 [e] 3c, R = CO_2CH_3 4c, R = H	85 42	25 (22)	 5c, R = CO_2CH_3	52
6[i] 7[g] 8[h]	 X = $OSiMe_3$ X = morpholino X = pyrrolidino	1, 25 (5) 1.2, 25 (1.5) 1.5, 25 (12)	 [e] 3d, R = CO_2CH_3 4d, R = H	92 87 trace 57	25 (9)	 [e] 5d, R = CO_2CH_3 6d, R = H	65 49
9[j]		1.5, 25 (0.5)	 3e	65	25 (24)	 5e	67
10[k]	 R = $Si(Me)_2$-*t*-Bu	1.5, 5-25 (0.5)	 3f	33	25 (24)	 5f	62
	(benzyloxy)acetylene	2-3, 25 (6)	3f	82			
11[l]		1.5, 101 (3)	 3g	71	25 (24)	 5g	56
12[m]		1, 25 (5)[n]	 3h	69	25 (36) 25 (14)	 5h	48 37

[a] The Diels–Alder reactions were carried out in dioxane (0.25 M in **2**) under nitrogen as described in the experimental section. [b] All products exhibited the expected or previously reported ^1H NMR, IR, and MS characteristics, consistent with the assigned structure. All new compounds gave satisfactory C, H, N analysis or HRMS information. [c] All yields are based on pure material isolated by chromatography (SiO_2 or Al_2O_3). [d] All zinc (9–20 weight equiv) reductions were carried out in acetic acid (0.09 M in substrate) under nitrogen as described in the Experimental Section. [e] Ester hydrolyses (NaOH, tetrahydrofuran, reflux) and the subsequent decarboxylation (200 °C, 1,3,5-triisopropylbenzene; or 10 equiv of copper powder, quinoline, 200 °C) were carried out as described in the Experimental Section. [f] 2-[(Triethylsilyl)-oxy]-2-butene was prepared by reductive silylation of methyl vinyl ketone: see ref 13. [g] The morpholino enamines were prepared with the aid of $TiCl_4$: White, W. A.; Weingarten, H. J. *J. Org. Chem.* **1967**, *32*, 213. [h] The pyrrolidine enamines were prepared with the aid of activated 4- Å molecular sieves: Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570 (entries 4 and 7) or in the presence of anhydrous magnesium sulfate: Zoretic, P. A.; Barcelos, F.; Branchard, B. *Org. Prep. Proc. Int.* **1976**, *8*, 211 (entry 5). [i] Available from Aldrich Chemical Company. [j] Available from Wiley Organics. [k] 1-[(*tert*-Butyldimethylsilyl)oxy]-1-(benzyloxy)ethylene was prepared by the procedure described: Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67. (Benzyloxy)acetylene was prepared as described and used without purification: Wunderli, A.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Chimia* **1972**, *26*, 643. [l] 4,4-Dimethoxy-3-buten-2-one was prepared as described: Banville, J.; Brasard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852. [m] *N*-(Methoxycarbonyl)nortropinone was prepared from tropinone (available from Aldrich Chemical Company) with the aid of methyl chloroformate: Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325. The morpholino enamine was prepared with the aid of *p*-toluenesulfonic acid in benzene with azeotropic removal of water: Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovic, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207. [n] The crude product of the Diels–Alder reaction, primarily the 3-morpholino-3,4-dihydro-1,2-diazine, was treated with catalytic *p*-toluenesulfonic acid (benzene, 70 °C, 14 h) to effect aromatization.

of **5a,b,d** and decarboxylation of the 2,5-pyrroledicarboxylates provided the parent 3,4-disubstituted-pyrroles **6a,b,d**.

Condensation of 3,4-dimethylpyrrole (**6a**) with formaldehyde in the presence of hydrogen chloride in ethanol under conditions conducive to air oxidation as described by LeGoff[3a] provided 2,3,7,8,12,13,17,18-octamethylporphin (OMP), eq 3.



(3)

7

Experimental Section

Proton nuclear magnetic resonance spectra (^1H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian FT-80A spectrometer, and chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (δ 0.00). Infrared spectra (IR) were recorded on an IBM FTIR 32 spectrometer as KBr pellets (for solids) or thin films (liquids). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron impact mass spectra (EIMS) and high resolution mass spectra (HRMS) were recorded on a Varian CH-5 or Ribermag R10-10 spectrometer by Charles Judson and Robert Drake. Microanalyses were performed by Tho I. Ngyuen on a Hewlett-Packard Model 185 CHN analyzer at the University of Kansas. Medium pressure liquid chromatography (MPLC) was performed on Merck silica gel 60 (230–400 mesh).[10] Preparative centrifugal thin-layer chromatography (PCTLC)[11] was performed on a Harrison Model 7924 Chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel 60 PF_{254} containing $CaSO_4 \cdot {}^1/_2H_2O$ binder. All extraction and chromatographic solvents, ethyl acetate (EtOAc), ether (Et_2O), hexane, methylene chloride (CH_2Cl_2), pentane and chloroform ($CHCl_3$), were distilled before use. Quinoline was distilled from Zn dust and dioxane from calcium hydride before use. All other solvents and reagents were used as received from commercial sources.

General Procedure for the Preparation of 3,6-Dicarbomethoxy-4,5-disubstituted-1,2-diazines. 3,6-Dicarbomethoxy-4,5-dimethyl-1,2-diazine (3a).[12] 2-[(Triethylsilyl)oxy]-2-butene[13] (0.7 g, 3.75 mmol, 1.5 equiv) was added to a slurry of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[8] (0.5 g, 2.52 mmol) in 10 mL of dioxane, and the resulting mixture was stirred under N_2 at 25 °C for 12 h. Removal of the solvent in vacuo and chromatography (MPLC, 15 × 500 mm SiO_2, 80% ether–hexane) afforded 489 mg of **3a** (565 mg theoretical, 87%) contaminated with a small amount of the isomeric 3,6-dicarbomethoxy-4-ethyldiazine. Recrystallization (methanol) afforded pure **3a**: mp 101–101.5 °C (lit.[12] mp 101–102 °C); ^1H NMR ($CDCl_3$) δ 4.04 (s, 6 H, OCH_3), 2.47 (s, 6 H, Ar CH_3); IR (KBr) ν_{max} 2961, 1740, 1441, 1266, 1204, 1169, 1076 cm^{-1}; EIMS, *m/e* (relative intensity) 224 (M^+, 9), 209 (2), 193 (12), 166 (80), 107 (base).

3,6-Dicarbomethoxy-4-ethyl-5-methyl-1,2-diazine (3b): yield 70% (see Table I); mp 50–52 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 4.03 (s, 6 H, OCH_3), 2.84 (q, 2 H, J = 8 Hz, CH_2CH_3), 2.48 (s, 3 H, Ar CH_3), 1.23 (t, 3 H, J = 8 Hz, CH_2CH_3); IR (KBr) ν_{max} 2955, 1738, 1441, 1271, 1165, 1088 cm^{-1}; EIMS, *m/e* (relative intensity) 238 (M^+, 12), 223 (6), 207 (22), 180 (86), 165 (21), 148 (23), 121 (base).

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.60; H, 5.96; N, 11.90.

1,4-Dicarbomethoxy-5,6,7,8-tetrahydrophthalazine (3c):[14] yield 85% (see Table I); mp 131–132 °C (methanol); ^1H NMR ($CDCl_3$) δ 4.01 (s, 6 H, OCH_3), 2.91 (m, 4 H, C5-2H, C8-2H), 1.83 (m, 4 H, C6-2H, C7-2H); IR ($CHCl_3$) ν_{max} 3038, 2975, 1740, 1444, 1278, 1220, 1165, 1030 cm^{-1}; EIMS, *m/e* (relative intensity) 250 (M^+, 7), 219 (10), 192 (42), 177 (7), 160 (5), 133 (base).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.22; H, 5.63; N, 11.23.

3,6-Dicarbomethoxy-4-phenyl-1,2-diazine (3d):[8b] yield 87–92% (see Table I); mp 92–93 °C (methanol; lit.[8b] mp 94–95.5 °C); ^1H NMR ($CDCl_3$) δ 8.21 (s, 1 H, C5-H), 7.46 (s, 5 H, Ph), 4.09 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3); IR (KBr) ν_{max} 3040, 2955, 1742, 1584, 1447, 1399, 1287, 1244, 1142, 766 cm^{-1}; EIMS, *m/e* (relative intensity) 272 (M^+, 9), 242 (7), 241 (6), 214 (34), 182 (10), 155 (base).

Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 62.01; H, 4.50; N, 10.19.

3,6-Dicarbomethoxy-4-methoxy-1,2-diazine (3e): yield 65% (see Table I); mp 104–105 °C (methanol); ^1H NMR ($CDCl_3$) δ 7.74 (s, 1 H, C5-H), 4.08 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3); IR (KBr) ν_{max} 2955, 1748, 1728, 1568, 1447, 1306, 1242, 1136, 1021 cm^{-1}; EIMS, *m/e* (relative intensity) 226 (M^+, 6), 195 (16), 168 (54), 138 (13), 109 (base); HRMS, *m/e* 226.0600 ($C_9H_{10}N_2O_5$ requires 226.0589).

4-(Benzyloxy)-3,6-dicarbomethoxy-1,2-diazine (3f): yield 82% (see Table I); mp 126–127 °C (methanol); ^1H NMR ($CDCl_3$) δ 7.73 (s, 1 H, C5-H), 7.37 (s, 5 H, Ph), 5.28 (s, 2 H, $PhCH_2$), 4.05 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3); IR (KBr) ν_{max} 3073, 2959, 1740, 1572, 1443, 1375, 1254, 1136, 1015 cm^{-1}; EIMS, *m/e* (relative intensity) 302 (M^+, 1), 271 (1), 243 (2), 211 (1), 138 (1), 121 (2), 91 (base); HRMS, *m/e* 302.0905 ($C_{15}H_{14}N_2O_5$ requires 302.0902).

5-Acetyl-3,6-dicarbomethoxy-4-methoxy-1,2-diazine (3g): yield 71% (see Table I); mp 76–77.5 °C (methanol); ^1H NMR ($CDCl_3$) δ 4.09 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 2.60 (s, 3 H, CH_3CO); IR (KBr) ν_{max} 2960, 1743, 1729, 1715, 1538, 1447, 1394, 1305, 1277, 1221, 1066 cm^{-1}; EIMS, *m/e* (relative intensity) 268 (M^+, 7), 253 (2), 238 (19), 210 (17), 195 (14), 181 (5),167 (9), 151 (12), 109 (22), 43 (base); HRMS, *m/e* 268.0693 ($C_{11}H_{12}N_2O_6$ requires 268.0694).

3,6-Dicarbomethoxy-*N*-carbomethoxynortropinono[3,4-*d*]-1,2-diazine (3h): yield 69% (see Table I); mp 119–121 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 5.60–6.52 (m, 1 H, CH), 4.75–4.42 (m, 1 H, CH), 4.07 (s, 3 H, CO_2CH_3), 4.01 (s, 3 H, CO_2CH_3), 3.64 (s, 3 H, NCO_2CH_3), 3.51–3.33 (m, 1 H, CH), 2.93 (dd, 1 H, J = 1, 18 Hz, CH), 2.53–1.54 (m, 4 H, CH_2CH_2); IR (KBr) ν_{max} 2957, 1749, 1737, 1701, 1460, 1450, 1439, 1399, 1390, 1329, 1270, 1241, 1211, 1203, 1178, 1145, 1109, 1004, 820, 761, 757 cm^{-1}; EIMS, *m/e* (relative intensity) 335 (M^+, 12), 308 (7), 307 (35), 306 (16), 304 (10), 277 (32), 276 (7), 249 (9), 248 (45), 218 (9), 216 (8), 188 (30), 145 (9), 144 (30), 131 (9), 130 (12), 78 (6), 77 (14), 59 (base); HRMS, *m/e* 335.1120 ($C_{15}H_{17}N_3O_6$ requires 335.1116).

General Procedure for the Preparation of 4,5-Disubstituted-1,2-Diazines. 4-Phenyl-1,2-diazine (4d). A solution of **3d** (660 mg, 2.42 mmol) in 50 mL of THF and 7 mL of 2.5 N NaOH (17.5 mmol) was warmed to reflux for 12 h. The solvents were removed in vacuo, the residue was dissolved in H_2O, and the solution was made acidic to pH 2 with 10% HCl and extracted with EtOAc (5 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford 440 mg (591 mg theoretical, 74% crude yield) of the dicarboxylic acid. A slurry of this acid (55 mg, 0.225 mmol) in 2.0 mL of 1,3,5-triisopropylbenzene was warmed with stirring to 200 °C under N_2 for 15 min and cooled. Chromatography (1.5 × 10 cm SiO_2, hexane, then EtOAc eluant) afforded 27.3 mg (35 mg theoretical, 78% from the diacid, 57% from the diester **3d**) of **4d**: mp 84.5–85.5 °C (hexane; lit.[15] mp 83.5–84 °C); ^1H NMR ($CDCl_3$) δ 9.46 (dd,

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(9) Dimethyl 1,2-diazine-3,6-dicarboxylates appear to be particularly prone to ring reduction. For instance, sodium borohydride reduction of 1,2-diazine **3g**, 25 °C, with excess reagent lead to ketone and 1,2-diazine reduction. Aluminum amalgam reduction of 1,2-diazine **3c** in moist ether failed to produce the corresponding pyrrole **5c** in good yield.

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1 H, J = 1, 2.5 Hz, C3-H), 9.22 (dd, 1 H, J = 1, 5 Hz, C6-H), 7.4–7.7 (m, 6 H, C5-H and Ph); EIMS, *m/e* (relative intensity) 156 (M^+, base), 128 (26), 102 (91), 76 (27).

4-Ethyl-5-methyl-1,2-diazine (4b):[16] yield 47% (see Table I); ^1H NMR ($CDCl_3$) δ 8.90 (s, 2 H, C3-H and C6-H), 2.67 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 2.31 (s, 3 H, CH_3), 1.26 (t, 3 H, J = 7.5 Hz, CH_2CH_3); EIMS, *m/e* (relative intensity) 122 (M^+, base), 91 (13), 79 (58), 77 (71).

5,6,7,8-Tetrahydrophthalazine (4c):[17] yield 42% (see Table I); ^1H NMR ($CDCl_3$) δ 8.80 (s, 2 H, C1-H and C4-H), 2.5–2.8 (m, 4 H, C5-2H and C8-2H), 1.6–1.9 (m, 4 H, C6-2H and C7-2H).

General Procedure for the Preparation of 2,5-Dicarbomethoxy-3,4-disubstituted-pyrroles.[5] **2,5-Dicarbomethoxy-3,4-dimethylpyrrole (5a).** Zinc dust (340 mg, 5.2 mmol) was added to a solution of diazine **3a** (129 mg, 0.575 mmol) in 6.8 mL of glacial acetic acid and the reaction was stirred at 25 °C for 5 h when a second portion of zinc dust (340 mg) was added. After being stirred for 24 h, the reaction was filtered through Celite, and the filtrate was made basic with NH_4OH and extracted with 1:1 $CHCl_3$:*i*-PrOH (4 × 50 mL). The combined extracts were washed with saturated NaCl (50 mL) and dried (Na_2SO_4), and the solvents were removed in vacuo to afford a light brown solid. Chromatography (PCTLC, 1 mm SiO_2, ether eluant) gave 77 mg (121 mg theoretical, 63%) of **5a** as a white, crystalline solid: mp 155–156.5 °C (methanol); ^1H NMR ($CDCl_3$) δ 9.3 (br, 1 H, NH), 3.88 (s, 6 H, OCH_3), 2.26 (s, 6 H, CH_3); IR (KBr) ν_{max} 3310, 2957, 1705, 1562, 1468, 1437, 1275, 1210, 1138 cm^{-1}; EIMS, *m/e* (relative intensity) 211 (M^+, base), 196 (27), 180 (25), 164 (41), 150 (71), 148 (75), 119 (29); HRMS, *m/e* 211.0830 ($C_{10}H_{13}NO_4$ requires 211.0844).

2,5-Dicarbomethoxy-3-ethyl-4-methylpyrrole (5b): yield 70% (see Table I); mp 93–94 °C (ethanol); ^1H NMR ($CDCl_3$) δ 3.88 (s, 6 H, OCH_3), 2.75 (q, 2 H, J = 7 Hz, CH_2CH_3), 2.27 (s, 3 H, CH_3), 1.10 (t, 3 H, J = 7 Hz, CH_2CH_3); IR (KBr) ν_{max} 3305, 2953, 1715, 1563, 1468, 1439, 1273, 1208, 1144 cm^{-1}; EIMS, *m/e* (relative intensity) 225 (M^+, 64), 210 (78), 178 (base), 160 (52).

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.50; H, 6.65; N, 6.22.

2,5-Dicarbomethoxy-3,4-tetramethylenepyrrole (5c): yield 52% (see Table I); mp 204–205 °C (ethanol); ^1H NMR ($CDCl_3$) δ 3.87 (s, 6 H, OCH_3), 2.77 (br m, 4 H, $ArCH_2$), 1.73 (br m, 4 H, $ArCH_2CH_2$); IR (KBr) ν_{max} 3330, 2960, 1715, 1560, 1440, 1270, 1135 cm^{-1}; EIMS, *m/e* (relative intensity) 237 (M^+, 82), 222 (base) 204 (41), 190 (40), 172 (50), 146 (38).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.32; N, 5.90. Found: C, 60.39; H, 6.58; N, 5.80.

2,5-Dicarbomethoxy-3-phenylpyrrole (5d): yield 65% (see Table I); mp 122–123 °C (methanol); ^1H NMR ($CDCl_3$) δ 7.5–7.1 (br m, 5 H, Ph), 6.9 (d, 1 H, J = 3 Hz, C4-H), 3.9 (s, 3 H, OCH_3), 3.8 (s, 3 H, OCH_3); IR (KBr) ν_{max} 3305, 3029, 2950, 1728, 1458, 1437, 1279, 1009, 762, 698 cm^{-1}; EIMS, *m/e* (relative intensity) 259 (M^+, base), 227 (52), 196 (54), 169 (86), 140 (67).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.10; H, 4.99; N, 5.48.

2,5-Dicarbomethoxy-3-methoxypyrrole (5e): yield 67% (see Table I); mp 149.5–150.5 °C (methanol); ^1H NMR ($CDCl_3$) δ 9.3 (br, 1 H, NH), 6.51 (d, 1 H, J = 3 Hz, C4-H), 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3); IR (KBr) ν_{max} 3289, 3006, 2957, 1721, 1680, 1570, 1514, 1437, 1283, 1229 cm^{-1}; EIMS, *m/e* (relative intensity) 213 (M^+, 98), 198 (6), 180 (26), 166 (13), 153 (77), 150 (99), 138 (19), 123 (72); HRMS, *m/e* 213.0634 ($C_9H_{11}NO_5$ requires 213.0636).

3-(Benzyloxy)-2,5-dicarbomethoxypyrrole (5f): yield 62% (see Table I); mp 161.5–162.5 °C (methanol); ^1H NMR ($CDCl_3$) δ 9.2 (br, 1 H, NH), 7.38 (m, 5 H, Ph), 6.48 (d, 1 H, J = 3 Hz, C4-H), 5.12 (s, 2 H, $PhCH_2$), 3.89 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3); IR (KBr) ν_{max} 3304, 3029, 2953, 1734, 1566, 1507, 1437, 1283, 1227 cm^{-1}; EIMS, *m/e* (relative intensity) 289 (M^+, 6), 258 (1), 230 (1), 198 (1), 166 (2), 138 (2), 91 (base); HRMS, *m/e* 289.0957 ($C_{15}H_{15}NO_5$ requires 289.0949).

3-Acetyl-2,5-dicarbomethoxy-4-methoxypyrrole (5g): yield 56% (see Table I); mp 70–72 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 9.4 (br, 1 H, NH), 3.92 (s, 6 H, OCH_3), 3.89 (s, 3 H, OCH_3), 2.56 (s, 3 H, $COCH_3$); IR (KBr) ν_{max} 3274, 2957, 1725, 1696, 1557, 1495, 1439, 1293, 1246 cm^{-1}; EIMS, *m/e* (relative intensity) 255 (M^+, 18), 240 (18), 208 (base), 192 (18); HRMS, *m/e* 255.0729 ($C_{11}H_{13}NO_6$ requires 255.0742).

2,5-Dicarbomethoxy-*N*-carbomethoxynortropinono[3,4-*c*]pyrrole (5h): yield 48% (see Table I); mp 172–174 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 9.23 (br, 1 H, NH), 5.43 (m, 1 H, CH), 4.58 (m, 2 H, CH_2), 3.82 (s, 3 H, CO_2CH_3), 3.77 (s, 3 H, CO_2CH_3), 3.58 (s, 3 H, NCO_2CH_3), 3.30 (dd, 1 H, J = 1, 18 Hz, CH), 2.68 (dd, 1 H, J = 1, 18 Hz, CH), 2.42–1.52 (m, 3 H, $CHCH_2$); IR (KBr) ν_{max} 3184, 2955, 1728, 1705, 1686, 1449, 1383, 1306, 1283, 1190, 1165, 1119, 999, 777 cm^{-1}; EIMS, *m/e* (relative intensity) 322 (M^+, 50), 295 (10), 294 (58), 293 (66), 279 (44), 263 (7), 262 (23), 261 (base), 248 (10), 247 (32), 232 (13), 231 (18), 203 (13), 199 (10), 184 (12), 91 (16), 78 (11), 77 (22); HRMS, *m/e* 322.1166 ($C_{18}H_{18}N_2O_6$ requires 322.1163).

General Procedure for the Preparation of 3,4-Disubstituted-Pyrroles. 3,4-Dimethylpyrrole (6a).[18] A solution of **5a** (318 mg, 1.5 mmol) in 27 mL of tetrahydrofuran (THF) and 4.8 mL of 2.5 N NaOH (12 mmol, 4 equiv) was warmed to reflux under N_2 for 18 h. The solvents were removed in vacuo, and the residue was dissolved in 10 mL of H_2O, the solution was made acidic with 10% HCl, and the precipitate was filtered and dried in vacuo to afford 211 mg (273 mg theoretical, 77% crude yield) of the pyrrole dicarboxylic acid. A mixture of this acid (100 mg, 0.549 mmol) and copper powder (350 mg) in 1.8 mL quinoline was warmed to 200 °C under N_2 for 20 min.[19] The reaction was cooled, diluted with 25 mL of Et_2O, and filtered through Celite. The filtrate was washed with 5% HCl (2 × 30 mL), the combined acid phase was extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (1.5 × 15 cm SiO_2, 10% Et_2O–pentane eluant) afforded 33 mg (52 mg theoretical, 63% from the diacid, 49% from the diester **5a**) of **6a** identical with an authentic[18] sample: ^1H NMR ($CDCl_3$) δ 7.6 (br, 1 H, NH), 6.49 (d, 2 H, J = 2.5 Hz, C2-H and C5-H), 2.02 (s, 6 H, CH_3).

3-Ethyl-4-methylpyrrole (6b):[20] yield 47% (see Table I); ^1H NMR ($CDCl_3$) δ 7.6 (br, 1 H, NH), 6.50 (d, 2 H, J = 2.5 Hz, C2-H and C5-H), 2.45 (q, 2 H, J = 7 Hz, CH_2CH_3), 2.04 (s, 3 H, $ArCH_3$), 1.18 (t, 3 H, J = 7 Hz, CH_2CH_3); EIMS, *m/e* (relative intensity) 109 (M^+, 63), 94 (base), 80 (7), 67 (22).

3-Phenylpyrrole (6d):[21] yield 49% (see Table I); ^1H NMR ($CDCl_3$) δ 8.0 (br, 1 H, NH), 6.8–7.5 (m, 6 H), 6.77 (m, 1 H), 6.52 (m, 1 H); EIMS, *m/e* (relative intensity) 143 (M^+, 80), 115 (base), 89 (29), 63 (44).

2,3,7,8,12,13,17,18-Octamethylporphin (7).[3a] A solution of **6a** (275 mg, 2.9 mmol) in 30 mL of 95% ethanol was added to a solution of 3 mL of 40% aqueous formaldehyde and 2 mL of 1 N HCl in 30 mL of 95% ethanol at 60 °C. The mixture was stirred at 60 °C for 1 h and then allowed to stand at 25 °C for 3 days exposed to air. Filtration afforded 35 mg of **7**. The filtrate was diluted with H_2O, neutralized with 10% $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 30 mL). Concentration of the organic extracts in vacuo followed by trituration with cold methanol afforded an additional 160 mg of **7**. Crystallization (80 mg) from boiling nitrobenzene followed by trituration with hexane:benzene (1:1) afforded pure **7** (56 mg, 47% overall yield); ^1H NMR ($CDCl_3$–trace CF_3CO_2D) δ 10.48 (s, 4 H, meso-H), 3.59 (s, 24 H, CH_3); ^{13}C NMR ($CDCl_3$–CF_3CO_2H)[22] δ 142.2 (α-pyrrole), 138.2 (β-pyrrole), 98.5 (meso), 11.9 (CH_3); HRMS, *m/e* 422.2471 ($C_{28}H_{30}N_4$ requires 422.2469).

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[22] OMP was dissolved in a minimal amount of trifluoroacetic acid (TFA); TFA was then removed in vacuo and 25 mg of sample was dissolved in 1.5 mL of $CDCl_3$.

Registry No. 2, 2166-14-5; **3a**, 23900-50-7; **3b**, 92144-06-4; **3c**, 71124-72-6; **3d**, 2166-27-0; **3e**, 92144-07-5; **3f**, 92144-08-6; **3g**, 92144-09-7; **3h**, 92144-10-0; **4b**, 92144-11-1; **4c**, 37813-95-9; **4d**, 92184-43-5; **5a**, 78331-70-1; **5b**, 91248-34-9; **5c**, 25473-58-9; **5d**, 92144-12-2; **5e**, 92144-13-3; **5f**, 92144-14-4; **5g**, 92144-15-5; **5h**, 92144-16-6; **6a**, 822-51-5; **6b**, 488-92-6; **6d**, 27649-43-0; **7**, 1257-25-6; $CH_3CH{=}C(OSiEt_3)CH_3$, 53379-23-0; $CH_3C{\equiv}CCH_3$, 503-17-3; $PhC(OSiMe_3){=}CH_2$, 13735-81-4; $(MeO)_2C{=}CH_2$, 922-69-0; $PhCH_2OC({=}CH_2)OSiMe_2$-*t*-Bu, 92144-04-2; $CH_3C(O)CH{=}C(OCH_3)_2$, 50473-61-5; 4-(1-ethyl-1-propenyl)morpholine, 13654-48-3; 1-(1-ethyl-1-propenyl)pyrrolidine, 13750-57-7; 1-(1-phenyl-1-ethenyl)pyrrolidine, 3433-56-5; 8-(methoxycarbonyl)-3-morpholino-8-azabicyclo[3.2.1]oct-2-ene, 92144-05-3; 1-(1-cyclohexenyl)pyrrolidine, 1125-99-1; 4-(1-phenylethenyl)morpholine, 7196-01-2; 3,4-dimethyl-1*H*-pyrrole-2,5-dicarboxylic acid, 92144-17-7; *N*-(methoxycarbonyl)nortropin-3-one, 53416-88-9; 3-morpholino-3,4-dihydro-1,2-diazine, 92184-44-6; 4-phenyl-1,2-diazine-3,6-dicarboxylic acid, 92144-18-8.

Preparation and Reactions of 4-(Trimethylsilyl)indole

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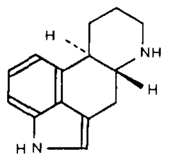
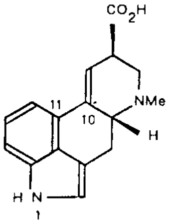
Indole or 1-(trimethylsilyl)indole was reacted sequentially with lithium–chlorotrimethylsilane and with 1,4-benzoquinone to produce 1,4-bis(trimethylsilyl)indole (50% and 55%, respectively). Methanolysis gave 4-(trimethylsilyl)indole which reacted with electrophiles at C-3. However, the derivative 1-acetyl-4-(trimethylsilyl)indole reacted with acetyl, 2-chloropropanoyl, or propenoyl chlorides via clean C-4 ipso substitution. Attempts to extend the reaction to a useful synthesis of derivatives of 5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole, a lysergic acid synthon, were prevented by low yields.

Introduction

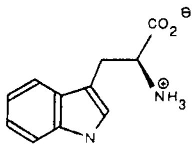
The ergot alkaloids are a group of biologically active metabolites produced by various species of the fungus *Claviceps*. these clinically important compounds are widely applied in the treatment of hypertension, migraine, prolactin dependent disorders, and postpartum hemorrnage.[1] The parent unit present in all the ergot alkaloids is the ergoline ring system **1**. An example is lysergic acid (**2**) which is obtained by the alkaline hydrolysis of the ergot peptide alkaloids. Several synthesis of this pivotal molecule **2** have been recorded.[1-3] In the total synthesis of **2** it is necessary to decide how to establish the single C-10 to C-11 carbon–carbon bond. Clearly in concise syntheses of **2**, indole precursors including L-tryptophan (**3**) are attractive starting materials. There is, however, a major problem in using indole precursors: the C-4 (indole numbering) center is considerably less reactive toward electrophiles than either C-3 or C-2. Thus, when lysergic acid (**2**) has been prepared from indole derivatives, one of two strategies has been adopted. Either the indole is already C-4 functionalized or the indole precursor is masked at the indoline oxidation level. Examples of these two strategies are the elegant synthesis and use of indole-4-carboxaldehyde by Kozikowski[4] and the succinct synthesis of **2** from 2,3-dihydro-L-tryptophan reported by Rebek.[3]



1



2



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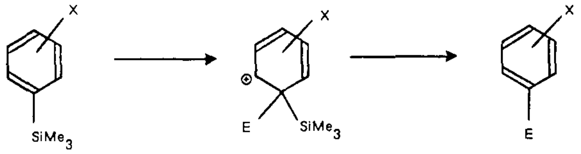
Scheme I



4 **5** **6**

A tenet of organosilicon chemistry is the generalization that "a silicon–carbon bond stabilizes a carbonium ion β to it".[5] For example diverse aryltrimethylsilanes[4] undergo ipso substitution by electrophiles to produce **6** on account of preferential formation of the Wheland intermediate **5** (Scheme I). This ipso attack may overwhelm the effects of other directing substituents. Thus 2-(trimethylsilyl)benzoic acid reacted with bromine to produce 2-bromobenzoic acid, whereas 3-(trimethylsilyl)toluene gave 3-methylbenzophenone on Friedel–Crafts benzoylation. In principle, such a reversal of the aromatic electrophilic substitution pattern mediated by a trimethylsilyl group should be applicable to indole chemistry. Indeed the production of 4-(trimethylsilyl)indole (**7a**) should be of relevance to C-4 electrophilic substitution and ultimately to lysergic acid (**2**) total synthesis.

In 1960 Smith reported[6] that indole (**7b**) was reduced under Birch conditions to produce an inseparable mixture of 4,7-dihydro- and 4,5,6,7-tetrahydroindoles (**8a** and **9**).

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