An Improved Synthesis of 1,4-Bis(3,4-dimethyl-5-formyl-2-pyrryl)butadiyne and 1,2-Bis(3,4-dimethyl-5-formyl-2-pyrryl)ethyne

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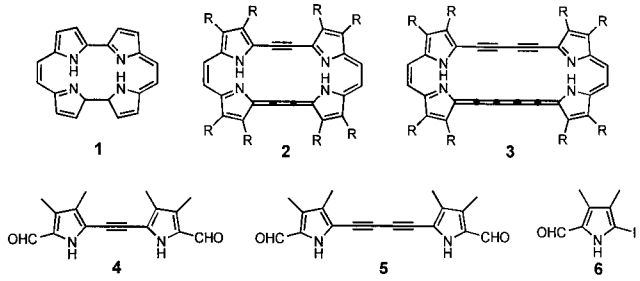
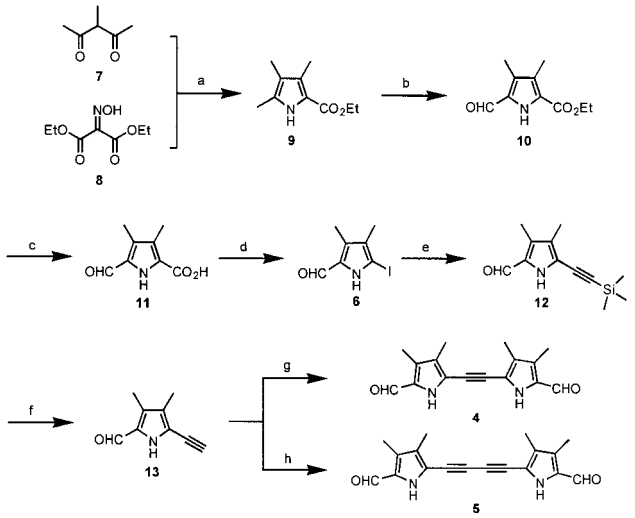
In recent years, the chemistry of pyrrole-containing macrocycles[1] has received increasing attention. Since the porphycene **1**, an isomer of porphyrin, was synthesized,[2] there has been numerous synthetic efforts to devise expanded porphycenes. Vogel and co-workers elegantly synthesized novel porphyrinoids **2** (R = ethyl) and **3** (R = ethyl) with acetylene−cumulene units.[3] As the building blocks of **2** and **3**, the acetylenic and diacetylenic dipyrrole dialdehydes such as compounds **4** and **5** were employed. We are interested in the compounds **4** and **5** due to their synthetic utility as the conjugated pyrrole containing dipole precursors in the quadruple cycloadditive macrocyclization.[4] We report here an efficient, improved synthetic route for **4** and **5** through the common key intermediate **6**.

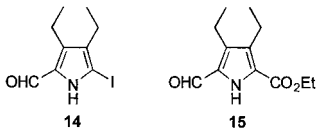


The overall synthetic strategy is shown in Scheme 1. The pyrrole starting material **9** was synthesized by the method of Kleinspehn,[5] a dissolving zinc reduction of diethyl oximinomalonate (**8**) in the presence of 3-methyl-2,4-pentanedione (**7**) in acetic acid. For the direct and efficient synthesis of the key intermediate, 3,4-dimethyl-2-formyl-5-iodopyrrole (**6**),[6] we carried out a three-step sequence from compound **9**: (1) regioselective monooxidation of α-methyl group by using ceric ammonium nitrate,[7] (2) effective hydrolysis of the ethyl ester **10** with $LiOH·H_2O$ in aqueous THF, (3) final iodination of the resulting carboxylic acid **11**. The yield of each step is excellent, and the overall yield for the three-step sequence is 68%. Previous syntheses[3a,8] of 3,4-diethyl-2-formyl-5-iodopyrrole (**14**) required the additional transesterification from ethyl to benzyl ester and cyanovinyl aldehyde protection and deprotection steps. For the synthesis of the ethyl homologue **14** of 2-formyl-5-iodopyrrole, it took six steps in 31% overall yield from compound **15**. Thus,

Scheme 1[a]



[a] Key: (a) zinc, acetic acid, rt, 1 h, 73%; (b) $(NH_4)_2Ce(NO_3)_6$, acetic acid, THF, H_2O, rt, 2 h, 90%; (c) $LiOH·H_2O$, THF, H_2O, 70 °C, 4 h, 93%; (d) ICl, NaOAc, acetic acid, 80 °C, 3 h, 81%; (e) $Pd(PPh_3)_2Cl_2$, CuI, (trimethylsilyl)acetylene, diethylamine, 50 °C, 95%; (f) Bu_4NF, THF, rt, 1 h, 99%; (g) **6** (0.85 equiv), $Pd(PPh_3)_2Cl_2$, CuI, diethylamine, 50 °C, 3 h, 65%; (h) $(PPh_3)_4Pd$, CuI, triethylamine, chloroacetone, benzene, rt, 16 h, 92%.



our improved synthetic route reduced the reaction steps to the half of the previous ethyl homologue syntheses[3a,8] and accordingly increased the overall yield more than twice. The key for the successful improvement rests on the finding of efficient hydrolysis of ethyl ester group and no need of aldehyde protection. Sonogashira coupling[9] of the iodoaldehyde **6** with (trimethylsilyl)acetylene followed by desilylation provided the terminal acetylene **13** in 94% overall yield. The final coupling between compound **13** and **6** afforded 1,2-bis(3,4-dimethyl-5-formyl-2-pyrryl)-ethyne (**4**) in 65% yield. We also tried direct formation of compound **4** by using a double coupling reaction between the iodoaldehyde **6** and acetylene but the yield was very low (ca. 9%) as reported.[3a] Therefore, we adapted to another three-step sequence (coupling−desilylation−coupling) by using (trimethylsilyl)acetylene as the source of acetylenic bridge for the final product **4**. For the synthesis of 1,4-bis(3,4-dimethyl-5-formyl-2-

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pyrryl)butadiyne (**5**), we utilized the known oxidative coupling[3b,10] of the terminal acetylene **13** with tetrakis(triphenylphosphine)palladium(0)/copper(I) iodide catalyst and prepared the product in 92% yield.

In summary, we have successfully explored a very efficient synthetic route for 3,4-dimethyl-2-formyl-5-iodopyrrole (**6**). With this improved process in use, we have synthesized the acetylenic and diacetylenic dipyrrole dialdehydes **4** and **5** in six steps from the pyrrole starting material **9** in 41% and 59% overall yields, respectively. This synthetic route represents one of the most efficient routes for the preparation of the versatile compounds **4** and **5** in multigram quantity and should be in widespread use for the synthesis of dipyrrole dialdehydes and their derivatives in the future.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. The chemical shifts are expressed in ppm (δ) relative to tetramethylsilane or residual nondeuterated solvent. IR spectra were recorded in the FT mode. Mass spectra were recorded at an ionizing voltage of 70 eV by EI. All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise described. Tetrahydrofuran (THF) and benzene were dried and distilled from sodium benzophenone prior to use. Merck silica gel (230−400 mesh) was used for flash chromatography.

2-Ethoxycarbonyl-3,4,5-trimethylpyrrole (9). In a 1-L three-necked round-bottom flask, equipped with an additional funnel, were placed **7** (21.41 g, 0.19 mol) and glacial acetic acid (25 mL). Compound **8** (26.71 g, 0.14 mol) was added dropwise, and zinc dust (18.2 g, 0.56 mol) was added in portions so as to maintain the temperature close to reflux. Halfway through the addition, additional **7** (10.71 g) and acetic acid (25 mL) were added. When the addition was complete, the reaction was essentially over, and before the temperature fell below 100 °C the solution was decanted from the residual zinc, which was washed with acetic acid. The combined supernatant and washings were diluted to four times their volume with water. The product was then crystallized. The product was collected by filtration and thoroughly washed with water. The solid was dissolved in dichloromethane and dried over sodium sulfate. After evaporation of the solvent in vacuo, the white solid **9** (18.72 g, 73%) was obtained by recrystallization from dichloromethane/hexanes (1:1): mp 125−126 °C (lit.[11] mp 124.5−125.5 °C); IR (neat) 3294, 2992, 2922, 1679, 1441, 1278 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, t, J = 7.1 Hz), 1.91 (3H, s), 2.18 (3H, s), 2.25 (3H, s) 4.28 (2H, q, J = 7.1 Hz), 8.55 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 11.0, 11.8, 15.0, 59.9, 117.0, 117.5, 127.8, 129.7, 162.1; MS (EI) *m/e* (relative intensity) 181.1 (M^+, 100), 152.1 (24.4), 135.2 (95.0), 106.1 (66.9), 79.6 (34.4). Anal. Calcd for $C_{10}H_{15}ON$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.37; H, 8.29; N, 7.66.

3,4-Dimethyl-2-ethoxycarbonyl-5-formylpyrrole (10). In a solvent mixture of THF (400 mL), acetic acid (100 mL), and water (400 mL) was dissolved compound **9** (7.29 g, 40 mmol); then ceric ammonium nitrate (89.6 g, 164 mmol) was added in one portion while the mixture was stirred at room temperature for 2 h. The reaction was quenched by pouring into water (1200 mL) and extracted with dichloromethane (3 × 800 mL). After being washed with saturated aqueous sodium bicarbonate solution, the combined dichloromethane layers were dried over anhydrous sodium sulfate and then evaporated. The residue was purified by flash chromatography on silica gel eluting with dichloromethane/methanol (100:1) to give **10** (7.02 g, 90%). An analytical sample was obtained by recrystallization from dichloromethane/hexanes (1:1) as a slightly yellow crystal: mp 106−108 °C (lit.[12] mp 109.5 °C); IR (neat) 3295, 2921, 1686, 1654, 1467, 1264, 858 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.1 Hz), 2.25 (3H, s), 2.27 (3H, s), 4.44 (2H, q, J = 7.1 Hz), 9.48 (1H, br), 9.76 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.9, 10.1, 14.7, 61.3, 124.9, 127.4, 130.4, 130.5 161.4, 179.6; MS (EI) *m/e* (relative intensity) 195.1 (M^+, 47.5), 148.0 (43.8), 121.0 (100), 105.9 (3.7), 91.9 (18.7), 76.2 (5.6). Anal. Calcd for $C_{10}H_{13}O_3N$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.67; H, 6.74; N, 7.05.

2-Carboxy-3,4-dimethyl-5-formylpyrrole (11). To a solution of **10** (460 mg, 2.4 mmol) in THF/H_2O (5:1, 25 mL) was added $LiOH\cdot H_2O$ (201 mg, 4.8 mmol). The mixture was stirred at 70 °C for 4 h. The homogeneous mixture was washed with ether. To the aqueous layer was added a saturated aqueous $KHSO_4$ solution until the pH of a solution was about 3, and then the solution was extracted by dichloromethane. The extracts were dried over $MgSO_4$ and then evaporated. The residue was purified by flash chromatography on silica gel eluting with dichloromethane/methanol (50:1) to give **11** (367 mg, 93%): mp 195 °C dec; IR (KBr) 3163, 2928, 1650, 1553, 1496, 1268 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (3H, s), 2.21 (3H, s), 9.76 (1H, s), 12.23(1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.0, 10.3, 125.4, 126.7, 127.4, 131.2 163.0, 182.6; MS (EI) *m/e* (relative intensity) 167.0 (M^+, 13.2), 120.9 (32.1), 97.0 (41.5), 84.0 (52.2), 72.9 (60.4), 69.0 (100). Anal. Calcd for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.53; H, 5.53; N, 8.36.

2-Formyl-5-iodo-3,4-dimethylpyrrole (6). A suspension of **11** (1.832 g, 11 mmol) and sodium acetate (1.721 g, 21 mmol) in glacial acetic acid (26 mL) was stirred at 80 °C and treated, over 20 min, with a steady stream of a 1.0 M ICl solution (13 mL, 13 mmol) in dichloromethane. After 3 h, the purple I_2 color was discharged by the dropwise addition of minimal 10% aqueous $NaHSO_3$ solution, and then water was added until the product began to crystallize. After 10 min, additional water was added to dilute the mixture to 60 mL. The pale yellow solid were filtered off, washed with water, and dried to give **6** (2.201 g, 81%). An analytical sample was obtained by recrystallization from dichloromethane/hexanes (1:2) as a white needle: mp 179−180 °C (lit.[6] mp 178−180 °C); IR (neat) 3219, 2911, 2851, 1627, 1455, 1366, 1309, 1224, 825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (3H, s), 2.28 (3H, s), 9.16 (1H, s), 9.40 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 11.9, 126.3, 127.2, 131.0, 134.1, 176.4; MS (EI) *m/e* (relative intensity) 249.1 (M^+, 70), 220.0 (14.4), 122.1 (12.3), 93.2 (26.2). Anal. Calcd for C_7H_8ONI: C, 33.76; H, 3.24; N, 5.62. Found: C, 33.67; H, 3.32; N, 5.58.

3,4-Dimethyl-2-formyl-5-[(trimethylsilyl)ethynyl]pyrrole (12). To a solution of **6** (200 mg, 0.80 mmol) in diethylamine (8 mL) were added under argon (trimethylsilyl)acetylene (0.12 g, 1.2 mmol), dichlorobis(triphenylphosphine)palladium(II) (10 mg, 0.014 mmol), and copper(I) iodide (5.2 mg, 0.028 mmol). The homogeneous mixture was stirred at 50 °C for 1 h. After evaporation of the solvent in vacuo, the residue was subjected to chromatography on short silica gel column with *n*-hexane/dichloromethane/ethyl acetate (5:1:1) as eluent to give **12** (158 mg, 95%): mp 128−130 °C; IR (neat) 3248, 2959, 2156, 1637, 1442, 1380, 1250, 887, 843 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (9H, s), 2.04 (3H, s), 2.23 (3H, s), 8.95 (1H, br), 9.57 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2, 9.2, 9.7, 95.4, 102.8, 119.1, 127.1, 129.5, 130.4, 177.4; MS (EI) *m/e* (relative intensity) 219.1 (M^+, 62.5), 204.1 (100), 146.0 (7.5), 116.7 (8.1). Anal. Calcd for $C_{12}H_{17}ONSi$: C, 65.71; H, 7.81; N, 6.39. Found: C, 65.60; H, 7.99; N, 6.12.

5-Ethynyl-3,4-dimethyl-2-formylpyrrole (13). To a solution of **12** (154 mg, 0.72 mmol) in THF (5.0 mL) was added Bu_4NF (1.0M THF solution, 0.7 mL). After being stirred for 1 h, the resulting mixture was concentrated under reduced pressure. The crude residue was subjected to chromatography on a short silica gel column with dichloromethane as eluent to give white solid **13** (102 mg, 99%): mp 154−155 °C; IR (neat) 3229, 2915, 2853, 1617, 1441, 1379, 1244, 867 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (3H, s), 2.25 (3H, s), 3.44 (1H, s), 9.18 (1H, s), 9.60 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 9.6, 74.9, 84.5, 118.1, 127.4, 129.7, 130.4, 177.6; MS (EI) *m/e* (relative intensity) 147.1 (M^+, 100), 118.0 (36.2), 90.9 (43.8), 64.9 (38.0). Anal. Calcd for C_9H_9ON: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.43; H, 6.07; N, 9.49.

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1,2-Bis(3,4-dimethyl-5-formyl-2-pyrryl)ethyne (4). To a solution of **6** (117 mg, 0.47 mg) and **13** (70 mg, 0.48 mmol) in diethylamine (4.8 mL) were added dichlorobis(triphenylphosphine)palladium(II) (5.9 mg, 0.008 mmol) and copper(I) iodide (3.0 mg, 0.016 mmol). The homogeneous mixture was stirred at 50 °C for 3 h. After evaporation of the solvent in vacuo, the residue was subjected to chromatography on short silica gel column with *n*-hexane/dichloromethane/ethyl acetate (5:1:1) as eluent to give **4** (82 mg, 65%): mp 235 °C dec; IR (neat) 3218, 1627, 1415, 1366, 1225, 825 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.07 (6H, s), 2.24 (6H, s), 9.61 (2H, s), 11.97 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.7, 10.0, 87.4, 118.3, 126.5, 129.5, 130.7, 179.0; MS (EI) *m/e* (relative intensity) 268.2 (M^+, 100), 211.1 (17.6), 196.1 (16.0), 145.9 (18.2), 133.8 (23.3); UV−vis (CH_2Cl_2) λ_{max} [nm] (ϵ) = 228 (2700), 314 (16 700). Anal. Calcd for $C_{16}H_{16}O_2N_2 \cdot 0.5H_2O$: C, 69.30; H, 6.18; N, 10.10. Found: C, 69.30; H, 6.44; N, 10.47.

1,4-Bis(3,4-dimethyl-5-formyl-2-pyrryl)butadiyne (5). A mixture of **13** (115 mg,0.78 mmol) and chloroacetone (0.06 mL, 0.078 mmol) in dry benzene (5 mL) was added to a solution of tetrakis(triphenylphosphine)palladium(0) (18.0 mg, 0.016 mmol), copper(I) iodide(10.7 mg, 0.059 mmol), and triethylamine (0.21 mL, 1.56 mmol) in dry benzene (10 mL). After the reaction mixture was stirred at room temperature for 16 h, the solvent was removed in vacuo, and the residue, dissolved in hot ethyl acetate, was passed through a short silica gel column. Compound **5** (109.2 mg, 92%) was obtained by recrystallization from ethyl acetate/methanol (1:1): mp 206 °C dec; IR (KBr) 3180, 2927, 2139, 1690, 1645, 1624, 1460, 1380, 1253 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 2.02 (6H, s), 2.21 (6H, s), 9.61 (2H, s), 12.31 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) 9.4, 10.0, 76.7, 80.0, 116.6, 129.1, 129.2, 131.3, 179.3; MS (EI) *m/e* (relative intensity) 292.2 (M^+, 100), 263.1 (3.6), 235.1 (7.5), 220.1 (13.1), 206.1 (6.9), 145.8 (29.4) 117.3 (21.9); UV−vis (CH_2Cl_2) λ_{max} [nm] (ϵ) = 268 (2000), 298 (2100), 354 (4300), 374 (4500), 402 (3900). Anal. Calcd for $C_{18}H_{16}O_2N_2 \cdot 1H_2O$: C, 69.66; H, 5.85; N, 9.03. Found: C, 70.01; H, 5.53; N, 8.70.

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