Supplementary Material (ESI) for Chemical Communications

Supporting Information

b-Bilene to a,c-biladiene transformation during syntheses of isoporphyrins and porphyrins

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Experimental Procedures

Di-*t*-butyl 2,3,7,8,12,13,17,18-Octamethyl-b-bilene-1,19-dicarboxylate Hydrochloride (5a)

50.0 mg (0.14 mmol) of dipyrromethane monocarboxylic acid **(6)** and 1-formyldipyrromethane **(7)** (40 mg, 0.12 mmol) were dissolved in 10 ml of dry dichloromethane and stirred under argon. *p*-Toluenesulfonic acid hydrate (53.0 mg, 2 equiv.) was added in two portions to the solution and stirring was continued for 2 h after which TLC showed no starting material and the UV/Visible spectrum showed a strong absorption at 502 nm. The dark red solution was washed with 5% sodium carbonate solution and water and dried over magnesium sulfate. Evaporation of solvent under reduced pressure afforded the tetrapyrrolic intermediate **5a** (b-bilene). The dark residue was then dissolved in 5 ml dichloromethane and hydrogen chloride gas was bubbled through the yellowish-orange solution for 10 seconds and the color changed to dark red, forming the hydrochloride salt. Immediately, the solvent was evaporated and the residue taken up twice in dry toluene and evaporated in order to remove any traces of water and HCl. The residue was recrystallized from dichloromethane/hexane and left in the freezer overnight. Filtration of solvent yielded orange-red prisms of the title compound (54 mg, 70%). UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm (ε x 10^5, $M^{-1}.cm^{-1}$): 502 (1.11); ^1H NMR ($CDCl_3$, 250 MHz) δ 13.8 (br, NH^+, 2H), 10.4 (br, NH, 2H), 7.08 (1H), 4.2 (CH_2, 4H), 2.23, 2.18, 2.04, 2.02, (each CH_3, 6H), 1.55 (*t*-butyl, 18H).

General procedure for cyclization of b-bilene (5a) with dicarbonyl compounds to obtain zinc(II) isoporphyrin (13).

Cold TFA (0.2 ml) was added to 50 mg (0.08 mmol) of b-bilene hydrochloride (**5a**) in a 50 ml RBF and left to stir under argon for 10 min. The mixture was diluted with dry dichloromethane (20 ml) followed by addition of α-ketoester/ α-diketone (1 equiv. of methyl, ethyl pyruvate and 1,2-diketone, and excess of phenyl and *i*-butyl pyruvates). The reaction mixture was left to stir under argon for 1 h after which the UV/Visible spectrum showed no starting material but a new product absorbing at 450 and 520 nm. Excess TFA was removed by washing with aqueous Na_2CO_3, changing the product color from reddish to green. The UV/Visible absorption maxima for the green product was 430 and 790 nm. $Zn(OAc)_2$ (20 mg) dissolved in 1 ml of dry methanol was added to the green product in dry dichloromethane and stirred under argon. The reaction mixture immediately changed color to reddish, and after stirring for 5 min the UV/Visible spectrum indicated a new absorption at around 470 and 540 nm.

50 mg (0.22 mmol) of DDQ dissolved in dry dichloromethane (0.3 ml) was added to oxidize the product. After 15 min, the UV-Visible spectrum of the mixture absorbed at 430 and 840 nm confirming formation of a zinc isoporphyrin. The mixture was washed with water, then brine, and then dried over Na_2SO_4.

Purification on an alumina column (grade III) eluting with dichloromethane separated the main fraction which absorbed at 430 and 830 nm, characteristic of a zinc isoporphyrin. Further purification was done on silica using dichloromethane/ethyl acetate 7:3 to yield a pure product which was further recrystallized using dichloromethane /petroleum ether.

Zinc(II) 2,3,5,7,8,12,13,17,18-Nonamethyl-5-methoxycarbonylisoporphyrin Chloride (13):

25 mg, 55% yield. UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm (ε x 10^4, $M^{-1}.cm^{-1}$): 430 (3.37), 830 (2.63) ; ^{1}H NMR ($CDCl_3$, 300MHz) δ, ppm 7.69 (s, *meso*-H, 1H), 7.62 (s, *meso*-H, 2H), 3.73 (s, 5-OCH_3, 3H), 2.58, 2.47, 2.45, 2.42 (s, β-CH_3, 24H), 2.01 (s, 5-CH_3, 3H); HR ESI calcd. for $C_{31}H_{33}N_4O_2Zn$ 557.1889, found *m/z* 557.1895 (M^+); MS MALDI-TOF calc. 559.01, found *m/z* 559.80 (M^+) (dithranol).

Zinc(II) 5-Ethoxycarbonyl-2,3,5,7,8,12,13,17,18-nonamethylisoporphyrin Chloride (16a):

25 mg, 54% yield. UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm (ε x 10^4, $M^{-1}.cm^{-1}$): 429 (3.58), 826 (2.89) ; ^{1}H NMR ($CDCl_3$, 400MHz) δ, ppm 7.68 (s, *meso*-H, 1H), 7.61 (s, *meso*-H, 2H), 4.10-4.15 (q, OCH_2CH_3, 2H), 2.45, 2.43, 2.40, 2.31 (s, β-CH_3, 24H), 1.96 (s, 5-CH_3, 3H), 1.07-1.04 (t, OCH_2CH_3, 3H); HR ESI calcd. for $C_{32}H_{35}N_4O_2Zn$ 571.2051, found *m/z* 571.2041 (M^+); MS MALDI-TOF calc. 573.04, found *m/z* 573.70 (M^+) (dithranol).

Zinc(II) 5-Ethoxycarbonyl-2,3,7,8,12,13,17,18-octamethyl-5-phenylisoporphyrin Chloride (16b):

18 mg, 35% yield. UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm (ε x 10^4, $M^{-1}.cm^{-1}$): 439 (4.84), 842 (4.27) ; ^{1}H NMR ($CDCl_3$, 300MHz) δ, ppm 8.35, 7.70 (m, 5H, Ph), 7.77 (s, *meso*-H, 1H), 7.66 (s, *meso*-H, 2H), 4.27-4.24 (q, OCH_2CH_3, 2H,), 2.50, 2.44, 2.34, 1.94 (s, β-CH_3, 24H), 1.14 (t, OCH_2CH_3, 3H); HR ESI calcd. for $C_{37}H_{37}N_4O_2Zn$ 633.2207, found *m/z* 633.2202 (M^+); MS MALDI-TOF calc. 635.10, found *m/z* 635.61 (M^+) (dithranol).

Zinc(II) 13,17-Diethyl-5-ethoxycarbonyl-5-isobutyl-2,3,7,8,12,18-hexamethylisoporphyrin Chloride (16c):

16 mg, 33% yield. UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm (ε x 10^4, $M^{-1}.cm^{-1}$): 431 (2.75), 822 (2.28) ; ^{1}H NMR ($CDCl_3$, 400MHz) δ, ppm 7.89 (s, *meso*-H, 1H), 7.80 (s, *meso*-H, 2H), 4.01-3.89 (q, OCH_2CH_3, 2H), 3.04-2.96 (q, -CH_2CH_3, 4H), 2.55, 2.51, 2.43 (s, β-CH_3, 18H), 1.96 (s, 5-CH_3, 3H), 1.32-1.20 (m, -CH_2-CH-, 3H), 1.01-0.96 (t, OCH_2CH_3, 3H), 0.94-0.86 (t, -CH_2CH_3, 6H), 0.44 (d, -CH $(CH_3)_2$, 6H); HR ESI calcd. for $C_{37}H_{45}N_4O_2Zn$ 641.2833, found *m/z* 641.2832 (M^+); MS MALDI-TOF calc. 643.17, found *m/z* 643.56 (M^+) (dithranol).

Zinc(II) 5-Acetyl-2,3,5,7,8,12,13,17,18-nonamethylisoporphyrin Chloride (16d):

24 mg, 54% yield. UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm (ε x 10^4, $M^{-1}.cm^{-1}$): 430 (4.23), 812 (3.87) ; ^{1}H NMR ($CDCl_3$, 400MHz) δ, ppm 8.10 (s, *meso*-H, 1H), 8.07 (s, *meso*-H, 2H), 2.60, 2.57(s, β-CH_3, 24H), 2.30 (s, COMe, 3H), 1.91 (s, 5-CH_3, 3H); HR ESI calcd. for

$C_{31}H_{33}N_4OZn$ 541.1940, found *m/z* 541.1943 (M^+); MS MALDI-TOF calc. 543.01, found *m/z* 542.80 (M^+) (dithranol).

Intermediate (8) – Reaction Mixture (Orange-red)

Excess TFA and dichloromethane from the reaction mixture were evaporated off and dried under vacuum before measuring the ^1H NMR spectra of the intermediates.

UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm: 454, 524 ; ^1H NMR ($CDCl_3$, 300MHz) δ, ppm 12.74, 12.64, 12.39, 12.04 (s, NH, 4H) 7.61 (d, 1-H, 1H), 7.33 (s, 5-H, 1H), 7.27 (s, 15-H, 1H), 4.36 (s, 10-H, 2H), 4.27-4.24 (q, CH_3-C*H*-CO_2CH_3, 1H), 3.70(s, OCH_3, 3H), 2.31-.2.28, 2.08-1.97 (s, CH_3, 24H), 1.64 (d, -CH_3-CH-, 3H); MS MALDI-TOF calc. 500.67, found *m/z* 500.47 (M^+).

Intermediate (11) – After washing fraction (8) with sodium bicarbonate, or separation on an alumina (grade III) column (Green)

UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm: 431, 789 ; ^1H NMR ($CDCl_3$, 300MHz) δ, ppm 11.95 (s, NH, 2H), 11.34, 11.15 (s, NH, 2H) 7.00 (s, 1-H, 1H), 6.43 (s, 5-H, 1H), 6.41 (s, 15-H, 1H), 5.44 (s, 10-H, 1H), 4.33 (q, CH_3-C*H*-CO_2CH_3, 1H), 3.69 (s, OCH_3, 3H), 2.18-2.15, 2.08-1.95 (s, CH_3, 24H), 1.62 (d, -CH_3-CH-, 3H)

Intermediate (12) – After addition of zinc acetate to the green fraction (11) (Reddish)

MS MALDI-TOF calc. 560.04, found *m/z* 560.07 (M^+).

Synthesis of (13) using the MacDonald '2 + 2' route

Dibenzyl 5-(Methoxycarbonyl)-2,3,5,7,8-pentamethyldipyrromethane-1,9-dicarboxylate (20)

600 mg (0.0025 mol) of α-free pyrrole (**19**) were dissolved in 30 ml dry dichloromethane, followed by excess TFA (100 equiv.), and 0.125 g (0.0012 mol) of methyl pyruvate. The reaction mixture was left to stir under argon at room temperature for 12 h after which time TLC confirmed completion of reaction. The mixture was washed with water, then aqueous Na_2CO_3, then water again, before being purified on a silica gel column using dichloromethane as eluant. A yellow fraction was collected first, followed by a slow moving fraction (product). Evaporation of the solvent yielded a yellowish liquid product, which was dried under vacuum to give 70% (1.0 g) of **20**. ^{1}H NMR ($CDCl_3$, 300MHz) δ, ppm 9.3 (s, NH, 2H), 7.48-7.34 (m, Ph-H, 10H), 5.36 (s, -CH_2-Ph, 4H), 3.77(s, OMe, 3H), 2.30, 1.65 (s, β-Me, 12H), 1.98 (s, 5-Me, 3H)

5-Methoxycarbonyl-2,3,5,7,8-pentamethyldipyrromethane-1,9-dicarboxylic Acid (17)

Dibenzyl dipyrromethane (**20**, 500 mg, 0.88 mmol) was dissolved in approximately 50 ml of freshly distilled THF and degassed with argon for approximately 15 minutes. 10% Pd/C (0.10 g) was added to the solution and the flask evacuated of air, sealed and filled with hydrogen gas. (Hydrogen gas was replenished from a balloon connected to the reaction flask.) The reaction mixture was left to stir for 16 h after which TLC showed reaction was complete. The reaction mixture was then filtered through a bed of Celite cto remove the catalyst, which was washed with THF. The collected filtrate was evaporated to yield an off-white solid after recrystalization from THF/petroleum ether in 84% (254 mg) yield.

^{1}H NMR (DMSO-d_6, 250MHz) δ, ppm 10.33 (s, NH, 2H), 3.64(s, OMe, 3H), 2.11, 1.39 (s, β-Me, 12H), 1.89 (s, 5-Me, 3H).

Zinc(II) 13,17-Diethyl-5-methoxycarbonyl-2,3,5,7,8,12,18-heptamethylisoporphyrin Chloride (13)

193 mg (0.53 mmol) of dipyrromethane dicarboxylic acid (**17**) was suspended in 30 ml of dry dichloromethane before addition of p-TsOH hydrate (406 mg) dissolved in 4 ml dry methanol. The suspension cleared and 153 mg (0.53 mmol) of diformyldipyrromethane (**18**) was added to the mixture, followed by zinc(II) acetate (40 mg) in dry methanol (2 ml). The reaction mixture was left to stir under argon overnight, then opened to air for 3 more days. It was then washed with water, aqueous $NaHCO_3$, then brine and dried over Na_2SO_3. Purification was done on a silica gel column using dichloromethane as eluant to separate a fast moving porphyrin fraction (purple), then gradually increasing the solvent polarity (1% MeOH/dichloromethane) to separate a second fraction (yellowish), then a third fraction which appeared red on the column (major product - isoporphyrin) to give **13** in 14% yield (46 mg). UV/Vis (CH_2Cl_2): $\lambda_{max,}$nm (ε x 10^4, $M^{-1}.cm^{-1}$): 433 (3.22), 839 (2.45); ^{1}H NMR ($CDCl_3$, 300MHz) δ, ppm 7.68 (s, *meso*-H, 1H), 7.63 (s, *meso*-H, 2H), 3.67 (s, 5-OCH_3, 3H), 2.92-2.90 (q, -CH_2-CH_3, 4H), 2.49, 2.45, 2.27, 2.23 (s, β-CH_3, 18H), 1.90 (s, 5-CH_3, 3H), 0.92-0.87 (t, -CH_2-CH_3, 6H); MS MALDI-TOF calc. for $C_{33}H_{37}N_4O_2Zn$ 587.06, found *m/z* 587.68 (M^+) (dithranol).

General procedure for synthesis of *meso*-monosubstituted porphyrins (21) from (13)

Zinc(II) isoporphyrin (**13**) (10 mg, 0.018 mmol) was dissolved in dry dichloromethane (10 ml) followed by addition of 1 ml of 5% KOH dissolved in methanol. The reaction mixture was left to stir under argon for 1 h after which the color of the reaction mixture turned purple. The UV/Visible spectrum indicated no starting material. Excess KOH was neutralized by washing with acetic acid (pH=5) and then with water several times. It was dried over Na_2SO_3, and purified on an alumina grade III column using dichloromethane as eluant, to isolate the target compound (**21)** (2.7 mg, 30%).