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A NEW METHODOLOGY FOR THE PREPARATION OF 2-CYANOPYRROLES AND SYNTHESIS OF PORPHOBILINOGEN

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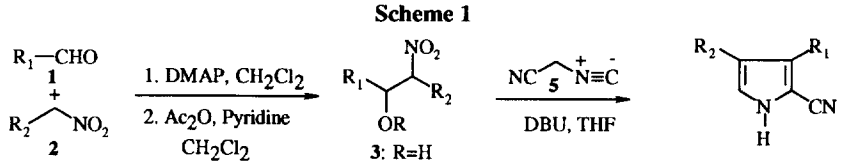
Summary: *Condensation of α-acetoxynitro compounds **4a-f** with isocyanoacetonitrile (**5**) using DBU in THF afforded 2-cyano-3,4-substituted pyrroles **6a-f**, in good yield. Porphobilinogen (PBG, **12**), the key building block for the preparation of tetrapyrrolic natural products, was synthesized from 2-cyano-3,4-substituted pyrrole **6f**, in four steps.* Copyright © 1996 Elsevier Science Ltd

In recent years, considerable interest has been generated in the synthesis of pyrroles and their derivatives. This five-membered heterocyclic unit is present in many natural products which possess important biological properties and constitute the building block for a number of tetrapyrrolic compounds such as porphyrins, chlorophylls, corrins and bile pigments.[1] Recently, a number of tetrapyrrolic compounds have been used as therapeutic agents in photodynamic therapy (PDT) for the treatment of cancer.[2] In addition, the pyrrole derivatives were shown to be useful as organic conductors[3] and for the synthesis of macrocycles.[4] In view of the significant importance of pyrrole for various applications, great efforts have been put into the preparation of this heterocyclic unit.[5] Generally, pyrrole derivatives with different substituents and/or functionalities have been prepared by condensation of α-aminocarbonyl compounds with 1,3-dicarbonyl moieties (Paal-Knorr synthesis),[6] β-aminoenones,[7] β-chlorovinyl ketones,[8] 3-alkoxyacroleins[9] and more recently by reaction of nitro compounds with isocyano acetates.[10] However, there are few syntheses reported for the preparation of 2-cyanopyrroles. Cohnen *et al.*[7a] have prepared 2-cyanopyrroles from 2-amino-1-alkenyl ketones in 37-94% while Verhe *et al.*[11] heated α-chloroaldimines with potassium cyanide to give 2-amino-5-cyanopyrroles in 43-71% yields. Later, Walizei and Breitmaier[9] prepared the 2-cyanopyrroles from aminoacetonitrile and Alberola *et al.*[7b] used 3-alkoxyacroleins or β-enones. Both procedures gave poor to moderate yields of 2-cyanopyrroles. The reported methods involved two steps for the preparation of 2-cyanopyrroles and required harsh conditions.[12] In this paper, we describe the details of a general and efficient method for the preparation of 2-cyano-3,4-substituted pyrroles **6a-f** via the condensation of α-acetoxynitro compounds **4a-f** with isocyanoacetonitrile (**5**),[13] and its application to the synthesis of porphobilinogen (**12**),[14] the key building block in the biosynthesis of "pigments of life".

Scheme 1



R_1= Me, Et, Ph, CH_2CH_2OTHP; R_2= Et, $CH_2CH_2CO_2Me$

The key feature in our methodology for the preparation of 2-cyano-3,4-substituted pyrroles is the utilization of the isocyanoacetonitrile (**5**)[15] as a synthon for the heterocyclic ring formation with the incorporation of cyano functionality at the 2-position. Although, the activating effect of the cyano group on neighboring C-H bonds has been known for nearly a century, it was only in 1968 that Schollkopf and Gerhart[16] discovered that the isocyano group also make the α-hydrogen acidic. The methylene group in isocyanoacetonitrile (**5**) is activated by both cyano and isocyano groups, which should make it suitable for anionization. Thus, the use of **5** in the synthesis, depends partly on the activating effect of isocyano group on the neighboring C-H bond but critically on the ability of the "bivalent" isocyanide carbon to participate in the subsequent heterocyclization process.[17] Isocyanoacetonitrile (**5**) was first prepared by Schollkopf *et al.*[15b] and was used in the preparation of 2-oxazoline-4-carbonitriles. Later, Hartman and Weinstock[15c] used **5** for the synthesis of 1,3-thiazoles. However, the synthetic utility of this important key synthon **5** was barely explored.

Synthesis of α-acetoxynitro compounds 4: The α-acetoxynitro compounds were prepared in two steps by condensation of aldehydes **1a-d** (Henry reaction)[30] with nitrocompounds **2a-b** in presence of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 to afford the α-hydroxynitro compounds. Acetylation of **3a-f** using acetic anhydride and pyridine in CH_2Cl_2 followed by silica gel chromatography afforded the desired α-acetoxynitro compounds **4a-f**.

Table: Synthesis of 2-Cyano-3,4-substituted Pyrroles **6a-f** from α-Acetoxynitro compounds **4a-f**.

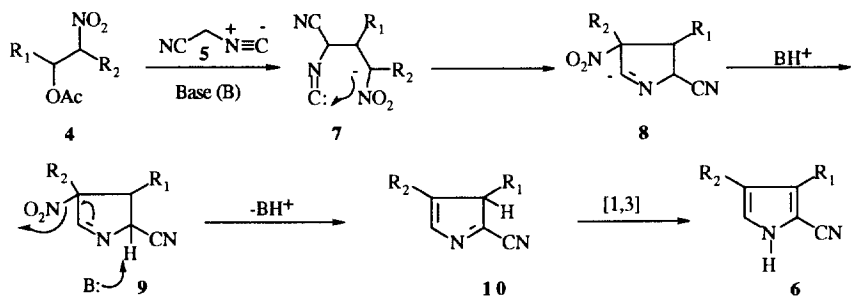
Entry	α-Acetoxynitro compound **4**	R_1	R_2	Base[a,b]/Solvent/ Temp(°C)/ Time (h)	2-Cyanopyrrole **6**	%Yield[c,d]	mp °C[e]
1	**4a**	Me	Et	DBU/THF/0-rt/2.0	**6a**	90	63-4
2	**4a**	Me	Et	DBU/Ether/0-rt/2.5	**6a**	78	
3	**4a**	Me	Et	TMG/THF/0-rt/2.0	**6a**	89	
4	**4b**	Et	Et	DBU/THF/0-rt/2.5	**6b**	77	72-3
5	**4c**	Ph	Et	DBU/THF/0-rt/2.0	**6c**	87	oil
6	**4d**	Me	$CH_2CH_2CO_2Me$	DBU/THF/0-rt/2.0	**6d**	60	56-8
7	**4d**	Me	$CH_2CH_2CO_2Me$	TMG/THF/0-rt/2.0	**6d**	83	
8	**4e**	Et	$CH_2CH_2CO_2Me$	DBU/THF/0-rt/2.5	**6e**	70	oil
9	**4f**	CH_2CH_2OTHP	$CH_2CH_2CO_2Me$	DBU/THF/0-rt/1.5	**6f**	81	oil

a) 3.0 Equiv. of freshly prepared isocyanoacetonitrile were used. b) 3.2 Equiv. of 1,8-diazabicyclo[5.4.0]undec 7-ene (DBU) or 1,1,3,3-Tetramethyl guanidine (TMG) were used. c) Isolated yield. d) Reactions were carried on 1.0 mmol scale except for **6f** (see experimental). e) Melting points were determined on the compounds purified by silica gel column chromatography.

Reaction of α-acetoxynitro compounds (4) with isocyanoacetonitrile (5): Typically, the freshly prepared isocyanoacetonitrile (**5**) in THF was treated with α-acetoxynitro compound **4a-f** at 0 °C followed by addition of base (3.2 equiv.). After 15 min, the mixture was allowed to warm to room temperature and stirred for 1.5-2.5 h and quenched with water. The 2-cyanopyrroles **4a-f** were purified by silica gel column chromatography (20-25% EtOAc in *n*-hexane). The method (table) generally afforded good to excellent yields of 2-cyanopyrroles (60-90%) with THF as solvent and using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a non-nucleophilic base. The synthesis was quite efficient when 1,1,3,3-tetramethylguanidine (TMG) was used to promote the reaction (see entries 1 and 3 or 6 and 7) which afforded comparable yields of the 2-cyanopyrrole product. Use of ether as solvent (entry 2) afforded pyrroles in somewhat lower yield [see entry 2 (78%) vs entry 1 (90%)] presumably due to the poor solubility of the reactants during the reaction.

Based on the mechanism reported by Van Leusen *et al.*[18] for the condensation of toluenesulfonylmethyl isocyanide with electron deficient olefins and by Barton *et al.*[11b] for the preparation of 2-carboxypyrroles, we believe that the reaction leading to 2-cyanopyrroles **6** proceeds as shown in Scheme 2. Michael addition of isocyanoacetonitrile (**5**) conjugate base to the nitroalkene which is generated *in situ* from α-acetoxynitro compound **4** in the presence of a base, gives the adduct **7**. Intramolecular cyclization of **7** initiated by the attack of the anion on the carbon of the isocyano group then affords the cyclic intermediate **8**. The intermediate **8** upon proton exchange, elimination of nitrite ion and subsequent aromatization via a [1,3] sigmatropic shift of hydrogen in **10** then gives 2-cyanopyrroles **6**.

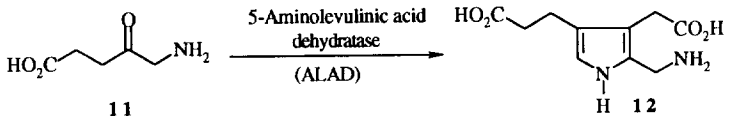
Scheme 2



Synthesis of Porphobilinogen (12): Porphobilinogen (PBG, **12**) was isolated by Westall in 1952 from the urine of a patient with acute porphyria.[19] Later, the structure of PBG (**12**) was determined by Cookson and Rimington.[20] PBG (**12**) is the key building block in the biosynthesis of tetrapyrrolic natural products, such as heme, porphyrins, chlorophylls, corrins and vitamin B_{12}.[1] The biosynthetic pathway to all these "pigments of life" initially follows the same track starting from 5-aminolevulinic acid (ALA **11**, scheme 3). Two molecules of ALA (**11**) are condensed in *vivo*, with the elimination of two molecules of water in a Knorr reaction, catalyzed by the enzyme, aminolevulinic acid dehydratase (ALAD) to give a molecule of PBG (**12**).[1] This enzymatic dimerization process of ALA (**11**) is inhibited by heavy metals such as lead (Pb). The toxicity of lead is well known and even a trace amount can alter the cellular heme synthesis thereby causes adverse effects in the development of brain and nervous system. It is generally recognized that lead poisoning occurs mainly in

the pediatric population from the contamination of environmental sources such as water, dust and soil. In children with blood lead concentration at 70 μg/dl (3.38 mmol/L) anemia, lethargy, or peripheral neuropathy are commonly evident.[21] Thus, rapid determination of even very low levels of lead in the biological and environmental samples is increasingly important to public health. Since lead inhibits ALAD's ability to catalyze the dimerization process of ALA (**11**), quantification of the condensation products (PBG, **12**) has been shown to be a useful marker for the measurement of lead.[22]

Scheme 3

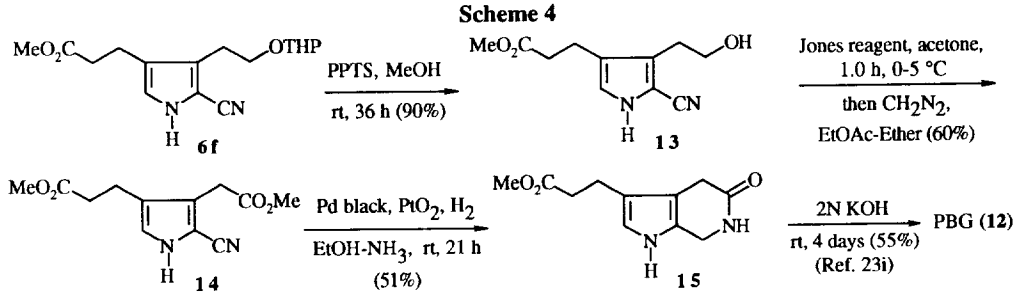


11 **12**

In view of the importance of PBG (**12**), a number of methods have been reported for its synthesis utilizing classical approaches proceeding through 2-methylpyrrole-5-caboxylates[23], azaindole[24] or from pyrrole.[25] Also, the nonenzymatic condensation of ALA (**11**) has been studied and reported to give PBG (**12**) in alkaline solutions[26] and using resin[27] in low (≤10%) yields. However, recent work by Butler and George[28] have shown that no PBG (**12**) was formed from ALA (**11**) in acidic or basic conditions.

Our strategy for the synthesis of PBG (**12**) involves the construction of the suitably functionalized 2-cyano-3,4-substituted pyrrole **6f** (table, entry 9) as shown in scheme 4. Thus, the tetrahydropyranyl ether in **6f** was cleaved by using pyridinium *p*-tolunesulfonate (PPTS) in anhydrous methanol at room temperature for 36 h and the crude compound was purified by silica gel column chromatography to afford the alcohol **13** in excellent yield (90%). The alcohol **13** was then converted to methyl ester **14**,[23d] first by oxidation with Jones reagent (1.6 equiv.) then by esterification of the resulting crude acid with diazomethane in ether-ethyl acetate solvent at 0 °C, in 60% yield after purification by silica gel column chromatography.

Scheme 4



The only remaining transformation in the synthesis of PBG (**12**) was the conversion of cyano group to the aminomethyl functionality. This transformation was achieved via hydrogenation of **14** using Pd black-PtO_2 in ammonia saturated ethanol for 21 h at 14 PSI pressure, which afforded the PBG lactam methyl ester **15** in 51% yield. Finally, **15** was hydrolyzed by following the procedure developed by Kenner *et al.*[23i] using 2N KOH followed by HPLC purification, to afford porphobilinogen (**12**) in 55% yield.

In summary, a convenient method for the preparation of 2-cyano-3,4-substituted pyrroles (**6**) was developed, which consisted of base promoted condensation of α-acetoxynitro compounds **4a-f** with isocyanoacetonitrile (**5**) in 60-90% yield. Our method allowed the incorporation of 2-cyano group into the pyrrole ring easily and afforded convergence and flexibility for the introduction of various substituents at 3 and 4-positions of the pyrrole system. The methodology was applied for the synthesis of porphobilinogen (**12**), the key building block in the biosynthesis of "pigments of life", in seven steps and 6.3% overall yield from commercially available methyl 4-nitrobutyrate (**2b**).

Experimental

General Procedure: IR spectra were recorded on Perkin-Elmer 1600 spectrometer using sodium chloride plates for liquids and potassium bromide disks for solids. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer. Mass spectra were obtained on a Nermang 3010 MS-50 or JEOL SX102-A mass spectrometers or Perkin-Elmer Siex API III electrospray mass spectrometer. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). Ozone Generator, mode T-816 was purched from Polymetrics, Inc., San Jose, CA. Thin layer chromatography was performed on pre-coated Whatman MK6F silica gel 60 Å plates (layer thickness:250um) and were visualized with UV light and/or using $KMnO_4$ solution ($KMnO_4$ (1.0 g), NaOH (8.0 g) in water (200 mL) unless otherwise noted. THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone. CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen. All reagents were purchased from Aldrich Chemical Co., Milwaukee, WI or Sigma Chemical Co., St. Louis, MO and were used without further purification, except where noted. All solvents employed were of HPLC grade, purchased from EM Science, Gibbstown, NJ and were used as received. Analytical HPLC was performed on Waters RCM, μBondapak C18, 10μ (8 x 100 mm) reversed phase column and preparative HPLC Waters RCM, μBondapak C18, 10μ (40 x 100 mm) reversed phase column using MeCN:0.1% HCO_2H in water at 225 nm. Melting points were recorded in open capillary tubes on a Electrothermal Melting Point Apparatus and are uncorrected.

The α-acetoxy nitocompounds (**4a-f**) were prepared in two steps. The aldehyde **1** was treated with nitro compound **2** (Henry reaction)[30] using 4-dimethylaminopyridine in CH_2Cl_2 at room temperature for 48 h to afford the α-hydroxynitro compounds (**3a-f**) in 63-84% yield, followed by acetylation using Ac_2O in pyridine and CH_2Cl_2, 0 °C to room temperature for 12 h in 44-74% yield. The α-acetoxy nitocompounds, 2-acetoxy-3-nitropentane (**4a**)[10b] from acetaldehyde (**1a**) and 1-nitropropane (**2a**) , 4-acetoxy-3-nitrohexane (**4b**)[10b] from propionaldehyde (**1b**) and 1-nitropropane (**2a**), 1-acetoxy-2-nitro-1-phenylbutane (**4c**)[31] from benzaldehyde (**1c**) and 1-nitropropane (**2a**) were prepared. The methyl-5-acetoxy-4-nitrohexanoate (**4d**)[10b] from acetaldehyde (**1a**) and methyl-4-nitrobutyrate (**2b**) and methyl-5-acetoxy-4-nitroheptanoate (**4e**)[32] from propionaldehyde (**1b**) and methyl-4-nitrobutyrate (**2b**), were prepared. Isocyanoacetonitrile (**5**) was freshly prepared according to the literature procedure[15d] from N-formylamino acetonitrile[15] prior to the condensation reactions and used without purification.

3-[(Tetrahydro-2H-pyran-2-yl)oxy]-propanal (1d): 3-Buten-1-ol (10.8 g, 150.0 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C and added 3,4-dihydro-2H-pyran (16.4 mL, 180.0 mmol, 1.2 equiv.) followed by

PTS acid (150 mg). After stirring the mixture for 5 h, solid $NaHCO_3$ (2.0 g) was added and stirred for 0.5 h. The mixture was washed with water (2 x 30 mL), brine (20 mL), dried ($MgSO_4$) and the solvent was removed on rotary evaporator. The crude compound was purified by silica gel column chromatography (10% ethyl acetate in *n*-hexane) to afford 19.8 g of 1-[(tetrahydro-2H-pyran-2-yl) oxy]-3-buten in 84% yield as a colorless liquid.[29a] ^1H NMR ($CDCl_3$): δ 1.45-1.90 (m, 6H), 2.32-2.40 (m, 2H), 3.42-3.54 (m, 2H), 3.75-3.91 (m, 2H), 4.59-4.61 (m, 1H), 5.02-5.13 (m, 2H), 5.78-5.89).

In a dry two-necked round bottom flask equipped with magnetic stir bar and nitrogen balloon was placed 1-[(tetrahydro-2H-pyran-2-yl) oxy]-3-buten (3.05 g, 19.5 mmol) in methanol (75 mL) and CH_2Cl_2 (75 mL), and were added pyridine (6 drops) followed by Sudan III indicator (3 drops). The resulting pale pink color mixture was cooled to -78 °C in a dry ice-acetone bath and ozone was passed (oxygen flow: 8.0; Volts: 90V; ozone flow: 1.0) through the inlet untill the color of the solution turned blue (for about 1.0 h). The ozone flow was stopped and methyl sulfide (6.0 mL) was added at -78 °C with stirring and the mixture was allowed to warm to room temperature. After 2.0 h the solvent was removed on a rotary evaporator and the mixture was diluted with water (30 mL) and CH_2Cl_2 (75 mL). The aqueous layer was re-extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (20% ethyl acetate in *n*-hexane) to afford 3-[(tetrahydro-2H-pyran-2-yl)oxy] propanal (**1d**) 1.61 g in 52% yield as a colorless liquid.[29] ^1H NMR ($CDCl_3$): δ 1.48-1.80 (m, 6H), 2.68 (t, 2H, J=6.0 Hz), 3.50-3.54 (m, 1H), 3.71-3.87 (m, 2H), 4.05-4.12 (m, 2H), 4.61 (bs, 1H), 9.80 (t, 1H, J=1.8 Hz); ESMS: 159 $(M+H)^+$.

Methyl-4-nitro-5-acetoxy-7-[(tetrahydro-2H-pyran-2-yl)oxy]-heptanoate (4f): In a dry single-necked round bottom flask were placed methyl 4-nitrobutyrate (**2b**) (2.2 g, 15.0 mmol, 1.5 equiv.) and 3-[(tetrahydro-2H-pyran-2-yl)oxy] propanal (**1d**) (1.58 g, 10.0 mmol) in dry CH_2Cl_2 (25 mL) under nitrogen. To this mixture 4-dimethyl aminopyridine (DMAP) (1.22 g, 10.0 mmol, 1.0 equiv.) was added at room temperature and stirred for 48 h. The solvent was removed using a rotary evaporator and the crude mixture was purified by silica gel column chromatography (20-50% ethyl acetate in *n*-hexane) to afford 1.75 g of **3f** in 58% yield as a colorless thick oil. ^1H NMR ($CDCl_3$): δ 1.45-1.65 (m, 4H), 1.65-1.97 (m, 4H), 2.10-2.50 (m, 4H), 3.42-3.64 (m, 2H), 3.65 (s, 3H), 3.76-4.00 (m, 2H), 4.10-4.20 (m, 1H), 4.4.56-4.60 (m, 2H); ESMS: 306 $(M+H)^+$, 323 $(M+NH_4)^+$; FAB HRMS: calcd for $C_{13}H_{24}NO_7$, 306.1553 $(M+H)^+$; found, 306.1555.

In a dry two-necked round bottom flask α-hydroxy nitro compound **3f** (1.63 g, 5.35 mmol) was dissolved in dry CH_2Cl_2 (35 mL) and to this, anhydrous pyridine (0.65 mL, 8.0 mmol, 1.5 equiv.) was added. After the mixture was cooled to 0-5 °C, acetic anhydride (2.01 mL, 21.37 mmol, 4.0 equiv.) was added dropwise. After 2.0 h, the mixture was allowed to warm to room temperature and stirred for 4 h. It was then poured into aq. 10% $NaHCO_3$ solution (50 mL), the organic layer was separated and the aqueous layer re-exctracted with CH_2Cl_2 (2 x 50 mL). The combined exctracts were washed with 5% HCl (20 mL), water (30 mL), brine (15 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude compound was purified by silica gel column chromatography (25% ethyl acetate in *n*-hexane) to afford 1.615 g of α-acetoxynitro compound **4f** in 87% yield as a colorless thick oil. IR (neat): 2950, 1740, 1555, 1440, 1374, 1225, 1035, 870, 815 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46-2.04 (m, 8H), 2.04 and 2.07 (two s, 3H), 2.20-2.42 (m, 4H),

3.42-3.51 (m, 2H), 3.68 (s, 3H), 3.78-3.86 (m, 2H), 4.51 and 4.57 (br s, 1H), 4.83-4.90 (m, 1H), 5.30-5.40 (m, 1H); ESMS: 365 $(M+NH_4)^+$; FAB HRMS: calcd for $C_{15}H_{26}NO_8$, 348.1658 $(M+H)^+$; found, 348.1651.

Typical procedure for the preparation of 2-cyanopyrroles (6), Example: 2-Cyano-3-[2-(tetrahydro-2H-pyran-2-yl)oxy] ethyl-4-(2-methoxycarbonylethyl)pyrrole (6f): In a dry single-necked round bottom flask equipped with magnetic stir bar and nitrogen inlet was placed N-formylamino acetonitrile[15] (2.70 g, 30.0 mmol) in CH_2Cl_2 (40 mL). Triethylamine (7.5 mL, 54.0 mmol, 1.8 equiv.) was added and the reaction mixture was cooled to -25 °C (acetone/limited amount of dry ice and monitored by thermometer). Phosphorous oxychloride (2.8 mL, 30.0 mmol, 1.0 equiv.) was added via syringe slowly over 10 min. The mixture was stirred for additional 10 min. The cooling bath was then removed and reaction was allowed to warm to room temperature. After 10 min, the mixture was diluted with CH_2Cl_2 (30 mL) and poured into aq. 20% Na_2CO_3 (10 mL). The organic layer was separated and washed with aq. 20% Na_2CO_3 (10 mL), water (20 mL) and dried ($MgSO_4$). The solvent was removed via rotary evaporation at low temperature (about 0-5 °C by placing the round bottom flask occasionally in the water bath). The crude dark brown colored isocyanoacetonitrile (2.7 g) was dissolved in THF (10 mL) and the solution was cooled with ice bath under nitrogen. α-Acetoxynitro compound **4f** (3.47 g, 10.0 mmol) in THF (40 mL) was added via double-ended needle followed by DBU (5.37 mL, 36 mmol, 3.2 equiv.) with a syringe. After stirring the mixture for 30 min at 0-5 °C, the cooling bath was removed, the mixture was allowed to warm to room temperature and stirr for 1.5 h. The resulting orange-red colored precipitate was quenched with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (20 mL), brine (15 mL), dried ($MgSO_4$) and the solvent was removed using rotary evaporator. The crude compound was purified by silica gel column chromatography (30% ethyl acetate in *n*-hexane) to afford 2.54 g of **6f** in 81% yield as a colorless thick oil. IR (neat): 3300, 2950, 2210, 1735, 1435, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.49-1.90 (m, 6H), 2.57 (t, 2H, J=7.2 Hz), 2.77 (t, 2H, J=7.2 Hz), 2.87 (t, 2H, 6.9 Hz), 3.43-3.60 (m, 2H), 3.67 (s, 3H), 3.72-3.92 (m, 2H), 4.60 (br s, 1H), 6.68 (d, 1H, J=2.7 Hz), 8.70 (br s, 1H); ESMS: 307 $(M+H)^+$, 324 $(M+NH_4)^+$; FAB HRMS: calcd for $C_{16}H_{23}N_2O_4$, 307.1658; found, 307.1655.

Also 2% of 2-cyano-4-(2-methoxy carbonyl ethyl)pyrrole (0.33 g) was isolated as thick oil: IR (neat): 3265, 2215, 1710, 1445 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.57 (t, 2H, J=7.8 Hz), 2.80 (t, 2H, J=7.5 Hz), 3.68 (s, 3H), 6.69 (d, 1H, J=1.8 Hz), 6.76 (d, 1H, J=1.8 Hz), 9.05 (bs, 1H); DCI MS: 179 $(M+H)^+$, 196 $(M+NH_4)$+; FAB HRMS: calcd for $C_9H_{11}N_2O_2$, 179.0821; found, 179.0816.

2-Cyano-3-ethyl-2-methylpyrrole (6a): Crude product was purified by silica gel column chromatography (20% ethyl acetate in *n*-hexane); yield: 90%; mp: 63-64 °C; IR (KBr): 3314, 2967, 2209, 1397, 1249, 1087, 808 689 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (t, 3H, J=7.5 Hz), 2.17 (s, 3H), 2.41 (q, 2H, J=7.5 Hz), 6.66 (d, 1H, J=3.3 Hz), 8.49 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 9.8, 14.3, 18.2, 99.4, 115.0, 120.6, 126.5, 130.6; DCI MS: 134 (M^+), 152 $(M+NH_4)^+$, 169 $(M+NH_4+NH_3)^+$; EI HRMS: calcd for $C_8H_{10}N_2$, 134.0844; found, 134.0842; Analysis calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.87; found: C, 71.39; H, 7.64; N, 20.68.

2-Cyano-2,3-diethylpyrrole (6b): Crude product was purified by silica gel column chromatography (25% ethyl acetate in *n*-hexane); yield: 77%; mp: 72-73 °C; IR (KBr): 3306, 2967, 2202, 1457, 1399, 1252,

1101, 942, 818, 687, 584 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, J=7.5 Hz), 1.21 (t, 3H, J=7.8 Hz), 2.44 (q, 2H, J=7.5 Hz), 2.60 (q, 3H, J=7.5 Hz), 6.66 (d, 1H, J=2.7 Hz), 8.52 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.6, 15.1, 18.1, 18.3, 98.7, 115.1, 120.8, 125.9, 136.5; DCI MS: 166 $(M+NH_4)^+$, 183 $(M+NH_4+NH_3)^+$; EI HRMS: calcd for $C_9H_{12}N_2$, 148.1000; found, 148.0997. A satisfactory elemental analysis could not be obtained.

2-Cyano-3-ethyl-2-phenylpyrrole (6c): Crude product was purified by silica gel column chromatography (25% ethyl acetate in *n*-hexane); yield: 87% (thick oil); IR (neat): 3298, 2965, 2212, 1603, 1517, 1384, 769, 699 cm-1; ^1H NMR ($CDCl_3$): δ 1.16 (t, 3H, J=7.5 Hz), 2.57 (q, 2H, J=7.8 Hz) 6.79 (d, 1H, J=3.0), 7.37-7.50 (m, 5H), 9.35 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.7, 18.6, 98.8, 115.6, 121.7, 125.8, 127.6, 128.7, 128.9, 132.8, 134.6; DCI MS: 214 $(M+NH_4)^+$, 231 $(M+NH_4+NH_3)^+$; EI HRMS: calcd for $C_{13}H_{12}N_2$, 196.1000; found, 196.0997.

2-Cyano-4-(2-methoxycarbonylethyl)-3-methylpyrrole (6d): Crude product was purified by silica gel column chromatography (20-30% ethyl acetate in *n*-hexane); yield: 60%; mp: 56-58 °C; IR (KBr): 3301, 2215, 1709, 1435, 1290, 1212, 982, 712 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H), 2.55 (t, 2H, J=7.8 Hz), 2.73 (t, 2H, J=7.8 Hz), 3.67 (s, 3H), 6.67 (d, 1H, J=2.7 Hz), 9.00 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 9.8, 20.3, 34.5, 51.8, 99.8, 114.7, 121.4, 122.6, 130.2, 173.6; DCI MS: 210 $(M+NH_4)^+$, 227 $(M+NH_4+NH_3)^+$; EI HRMS: calcd for $C_{10}H_{12}N_2O_2$, 192.0899; found, 192.0895; Analysis calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57; found: C, 62.54; H, 6.44; N, 14.51.

2-Cyano-3-ethyl-4-(2-methoxycarbonylethyl)pyrrole (6e): Crude product was purified by silica gel column chromatography (25% ethyl acetate in *n*-hexane); yield: 70% (thick oil); IR (neat): 3321, 2968, 2211, 1736, 1438, 1403, 1197, 1177, 686 cm-1; ^1H NMR ($CDCl_3$): δ 1.21 (t, 3H, J=7.5 Hz), 2.54-2.63 (m, 4H), 2.75 (t, 2H, J=7.8 Hz), 3.68 (s, 3H), 6.68 (d, 1H, J=2.7 Hz), 8.79 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.2, 18.2, 20.2, 34.8, 51.8, 98.9, 114.9, 121.5, 121.9, 136.5, 173.7; DCI MS: 206 $(M)^+$, 224, $(M+NH_4)^+$, 241 $(M+NH_4+NH_3)^+$; EI HRMS: calcd for $C_{11}H_{14}N_2O_2$, 206.1055; found, 206.1055.

2-Cyano-3-(2-hydroxyethyl)-4-(2-methoxycarbonylethyl)pyrrole (13): The THP-ether **6f** (2.50 g, 8.16 mmol) was dissolved in methanol (20 mL). Pyridinium *p*-toluene sulfonate (PPTS, 2.1g, 8.57 mmol, 1.05 equiv.) was added at room temperature. After stirring the mixture for 48 h, the solvent was removed using rotary evaporator and the remaining mixture was diluted with water (30 mL) and ethyl acetate (75 mL). The aqueous layer was separated and re-extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated via rotary evaporation. The crude compound was purified by silica gel column chromatography (50% ethyl acetate in *n*-hexane) to afford 1.66 g of alcohol **13** in 90% yield. The product was crystallized from acetone-*n*-hexane mixture to afford 1.06 g of **13** in 62% (one crop) yield as colorless solid. mp: 130-133 °C; ^1H NMR (acetone-d_6): δ 2.61 (s, 2H, J=8.1 Hz), 2.76-2.92 (m, 4H), 3.65 (s, 3H), 3.73 (q, 2H, J=6.9 Hz), 3.85 (t, 2H, J=6.0 Hz), 6.94 (s, 1H), 10.87 (br s, 1H); ESMS: 223 $(M+H)^+$, 240 $(M+NH_4)^+$; FAB HRMS: calcd for $C_{11}H_{14}N_2O_3$, 222.1004; found, 222.1003; Analysis calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.6; Found: C, 59.41; H, 6.41; N, 12.61.

2-Cyano-3-(1-methoxycarbonylmethyl)-4-(2-methoxycarbonylethyl)pyrrole (14): In a single necked round bottom flask, the alcohol **13** (0.280g, 1.26 mmol) was dissolved in acetone (22 mL), cooled to 0 °C with ice bath and Jones reagent (2.67 M solution, 0.76 mL, 2.02 mmol, 1.6 equiv.) was added in three portions over 1.5 h. The reaction mixture was stirred for additional 1h, quenched with isopropanol (2.6 mL) and stirred for 30 min at room temperature. The mixture was diluted with acetone (22 mL) and filtered through celite powder. The celite powder was washed with acetone (30 mL) and the filtrate was concentrated to dryness using a rotary evaporator. The resulting crude acid was dissolved in ether-ethyl acetate mixture (1:1, 10 mL), cooled to 0 °C and treated with freshly prepared ethereal diazomethane (2.4 mL). After stirring the mixture for 2.0 h, the solvent was carefully removed using a rotary evaporator and the crude compound was purified by silica gel column chromatography (35 % ethyl acetate in *n*-hexane) to afford 0.190 g of **14** in 60% yield as a thick oil. HPLC: MeCN:0.1% HCO_2H-H_2O/30:70; 2.0 mL/min at 225 nm/ R_t: 4.19 min, 99%; ^1H NMR ($CDCl_3$): δ 2.57 (t, 2H, J=6.9 Hz), 2.74 (t, 2H, J=7.2 Hz), 3.63 (s, 2H), 3.67 (s, 3H), 3.73 (s, 3H), 6.73 (s, 1H), 9.05 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.1, 30.4, 34.5, 51.8, 52.4, 100.9, 113.9, 121.8, 123.1, 125.9, 171.2, 173.6; ESMS: 251 $(M+H)^+$, 268 $(M+NH_4)^+$; EI HRMS: calcd for $C_{12}H_{14}N_2O_4$, 250.0954; found, 250.0954.

Methyl ester of porphobilinogen lactam (15): 2-Cyanopyrrole derivative **14** (0.125 g, 0.5 mmol) was placed in a hydrogenation flask and dissolved in ammonia saturated ethanol (20 mL). To this solution, Pd black (0.032 g) and platinum oxide ((0.075g) were added and the mixture was hydrogenated at 14 psi. After 24 h, the pressure was released and the mixture was heated to 50 °C for 10 min and filtered through celite powder. The celite powder was washed with ethanol (20 mL) and the filtrate was concentrated using rotary evaporator. Purification of the crude compound by preparative HPLC [Waters RCM, μBondapak C18, 10μ (40 x 100 mm) reversed phase column (MeCN:0.1% HCO_2H-H_2O/30:70, flow rate: 50 mL/min at 225 nm] followed by lyophilization afforded 0.056 g of **15** in 51% yield as a colorless powder.[23i] mp: 239-242 °C [lit.[33] 240-242 °C, lit.[23i] 245-246 °C]; Analytical HPLC: MeCN:0.1% HCO_2H-H_2O/ 30:70, 2.0 mL/min at 225 nm/ R_t: 2.85 min: 98.6%; ^1H NMR (DMSO-d_6): δ 2.45-2.55 (t, 2H, merged with DMSO-d_6), 3.13 (t, 2H, J=3.0 Hz), 3.33 (s, 2H), 3.57 (s, 3H), 4.24 (d, 2H, J=1.8 Hz), 6.45 (d, 1H, J=2.1 Hz), 10.30 (br s, 1H); ESMS: 223 $(M+H)^+$.

Porphobilinogen (12):[23i] In a dry single-necked round bottom flask was placed the PBG lactam methyl ester **15** (0.011 g, 0.05 mmol) and to this 2M KOH solution (1.5 mL) was added at room temperature under nitrogen atmosphere and stirred for 4 days in darkness . The pH of the solution was adjusted with 40% glacial acetic acid to 6.2 using pH meter. Purification of the crude product by preparative HPLC using Waters RCM, μBondapak C18, 10μ (40 x 100 mm) reversed phase column (MeCN:0.1% HCO_2H-H_2O/10:90, flow rate: 50 mL/min at 225 nm) followed by lyophilization afforded 0.006 g of porphobilinogen (**12**) in 55% yield. mp: 171-175 °C dec., [lit.[24b] 167 °C, lit.[25a] 174-177 °C dec.]; Analytical HPLC: MeCN:0.1% HCO_2H-H_2O/ 10:90, flow rate 2.0 mL/min at 225 nm/ R_t: 2.28 min, 99%; PBG (**12**) purchased from Sigma Chemical Co., HPLC: MeCN:0.1% HCO_2H-H_2O/ 10:90, flow rate 2.0 mL/min at 225 nm/ R_t: 2.28 min; Coinjection of synthetic and authentic PBG (**12**): HPLC: MeCN:0.1% HCO_2H-H_2O/ 10:90, flow rate 2.0 mL/min at 225 nm/ R_t: 2.28 min; ^1H NMR (DMSO-d_6): δ 2.38 (t, 2H, J=8.7 Hz), 2.49-2.56 (t, 2H, merged with DMSO-d_6), 3.09 (s, 2H), 3.82 (s, 2H), 6.41 (s, 1H), 10.46 (br s, 1H); ESMS: 227 $(M+H)^+$.

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