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ORIGINAL PAPER

Water-soluble xanthobilirubinic acids?

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Abstract Xanthobilirubinic acid, a model dipyrrinone for one-half of the bilirubin molecule in photochemical and metabolism studies, is more polar than bilirubin and insoluble in water and in chloroform. Replacing the β-alkyl substituents on the lactam ring of xanthobilirubinic acid with methyl-capped ethylene glycol, diethylene glycol, and triethylene glycol (PEG) groups steadily increased the water solubility of the pigment so that the last is completely soluble in both water and chloroform. Synthesized by base-catalyzed condensation of the corresponding methyl-capped 3,4-diPEG-pyrrolin-2-one with 3,5-dimethyl-4(2-ethoxycarbonylethyl)-2-formyl-1*H*-pyrrole, these new PEGylated analogs of xanthobilirubinic acid are yellow-colored dipyrrinones that form intermolecular hydrogen-bonded dimers in chloroform solution but are monomeric in methanol and water, as revealed by ^{1}H NMR spectroscopy and vapor pressure osmometry. Methyl xanthobilirubinate has served as a synthetic precursor to bilirubinoids; its amphiphilic PEGylated analogs suggest a route to water-soluble bilirubinoids and biliverdinoids.

Keywords Dipyrrinone · Pyrroles · Synthesis · NMR · Vapor pressure osmometry

Introduction

Bilirubin (Fig. 1a) is the yellow pigment of jaundice and the end product of heme metabolism [1]. It is insoluble in water at physiologic pH, with K_{sp} at pH ~7 and 37 °C estimated to be $\sim 4 \times 10^{-15}$ M [2]. Its poor aqueous solubility appears to be associated with its energetically most stable conformation, that is shaped like a ridge-tile [2–5] with its propionic acids tucked inward and firmly hydrogen bonded to the opposing dipyrrinones (Fig. 1b). Xanthobilirubinic acid (**5**, Fig. 1c) [6–8], a dipyrrolic yellow pigment, corresponds to one-half of bilirubin and has been used to model bilirubin photochemistry [9–11] and metabolism [12]. (Although xanthobilirubinic acid cannot engage in intramolecular hydrogen bonding, it is still insoluble in water.) Nature increases the aqueous solubility of bilirubin by converting it to β-glucuronide esters, thereby facilitating its hepatic elimination. Recent studies involving attachment of an average molecular weight 2,200 poly(ethylene glycol) (PEG) group to the rubin's *exo*-vinyl group also produced a water-soluble bilirubin that retained intramolecular hydrogen bonding, but in water this derivative was significantly aggregated [13], presumably with bilirubin molecules collected inside a polyether micelle. To overcome the insolubility of xanthobilirubinic acid in water, as a model for improving the aqueous solubility of bilirubin while avoiding aggregation, we prepared its 2,3-dimethoxy analog (**4**, Fig. 1d) [14] and found it to be an order of magnitude more soluble than **5**. Guided by the success of Sessler et al. [15, 16] in improving the aqueous solubility of porphyrins by attaching short polyether chains to the tetrapyrrole perimeter, we synthesized three new PEGylated xanthobilirubinic analogs (**1**–**3**, Fig. 1d) with methyl-capped ethylene glycol (**3**), diethylene glycol (**2**) and triethylene glycol (**1**) groups on the lactam ring. We report their syntheses and characterization herein and compare their properties to those of **4** and **5**.

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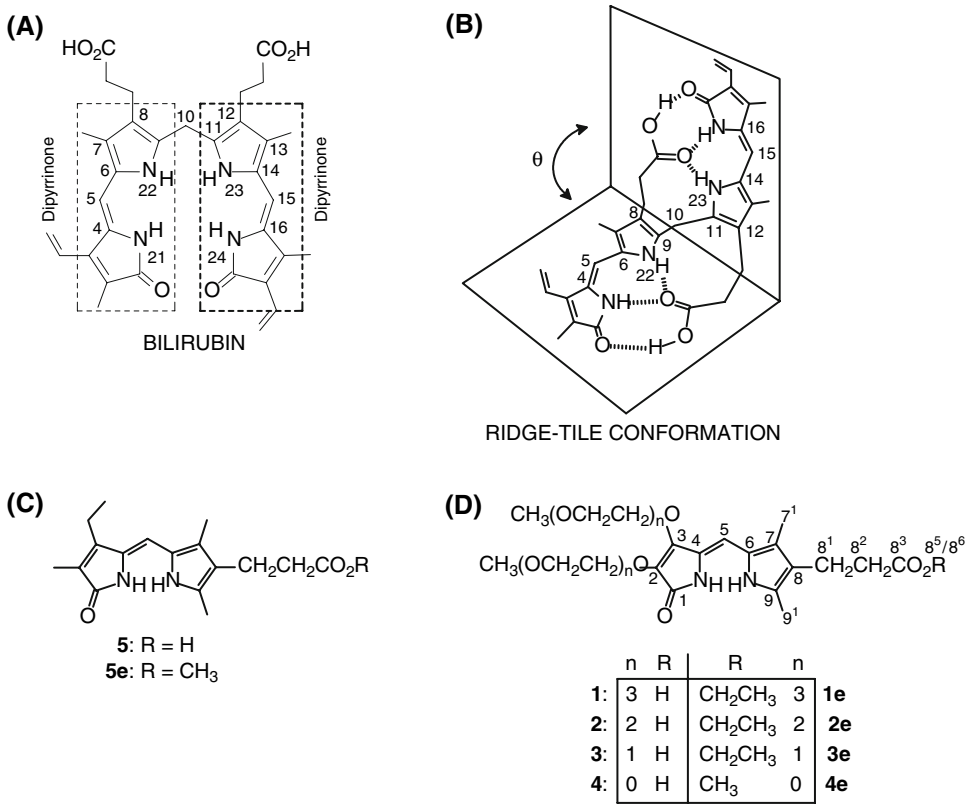


	n	R	R	n	
1:	3	H	CH_2CH_3	3	**1e**
2:	2	H	CH_2CH_3	2	**2e**
3:	1	H	CH_2CH_3	1	**3e**
4:	0	H	CH_3	0	**4e**

Fig. 1 **a** Bilirubin, composed of two dipyrrinones, shown in a porphyrin-like shape and, **b** folded into a ridge-tile structure with six intramolecular hydrogen bonds. **c** The target methyl-capped PEGylated derivatives of xanthobilirubinic acid **1**–**4** and their methyl esters (**1e**–**4e**). **d** Xanthobilirubinic acid (**5**) and its methyl ester (**5e**)

Results and discussion

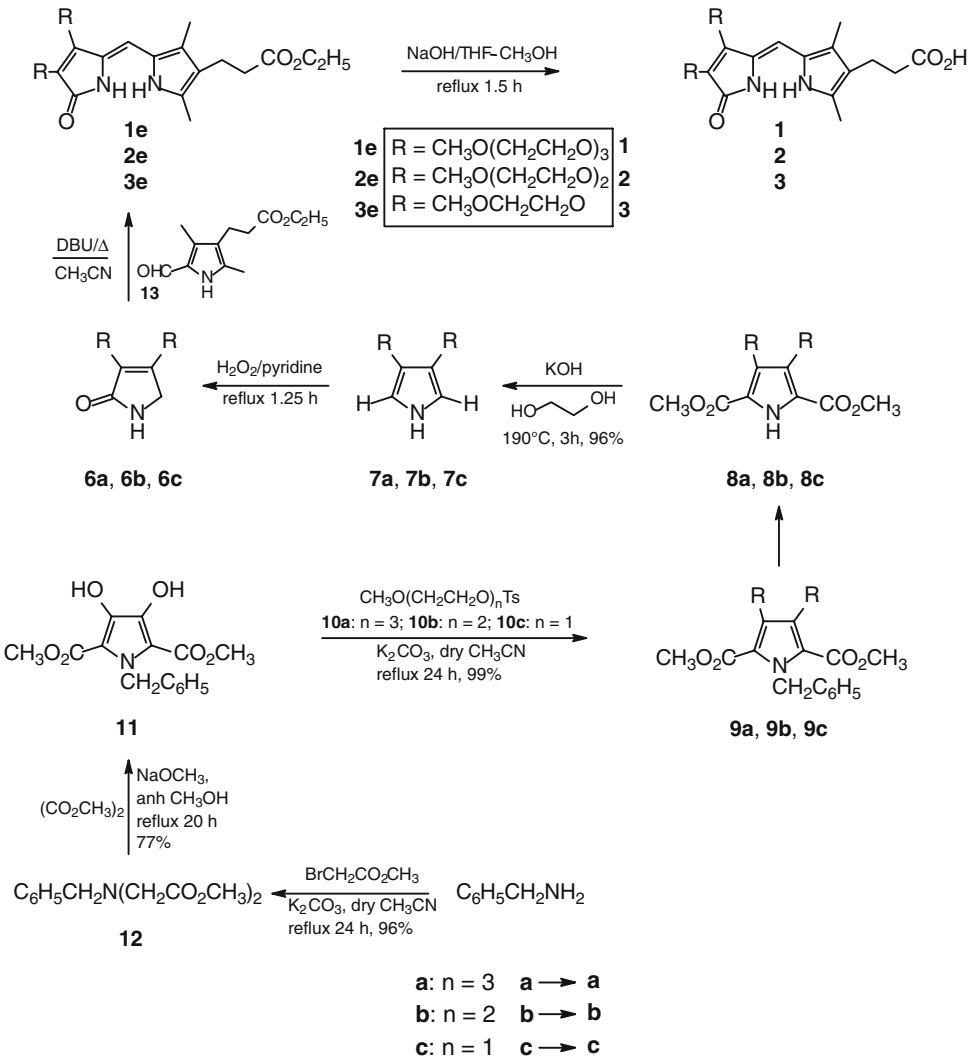
Synthesis aspects

Our approach to the syntheses of **1**–**3** was similar to an earlier convention [14] in which we synthesized **4** by condensing pyrrole α-aldehyde (**13**) (Scheme 1) and 3,4-dimethoxy-3-pyrrolin-2-one. The pyrrole aldehyde was known from previous studies: 3,5-dimethyl-4-(2-ethoxycarbonylethyl)-2-formyl-(1*H*)-pyrrole (**13**) [17] from treatment of its 2-carbo-*tert*-butoxy precursor [18] with trifluoroacetic acid and triethyl orthoformate. PEGylated pyrrolinone components (**6**), synthesized from PEGylated pyrroles **7a**, **b**, and **c**, were substituted for 3,4-dimethoxy-3-pyrrolin-2-one [14] in the condensation reaction to produce **1e**–**3e**. Saponification of the last produced **1**–**3**. The synthesis of **7a** was indicated by Tvermoes and Sessler [16], a procedure that was modified and adapted to our syntheses of **7a**–**7c**. The key intermediate monopyrrole (**11**) [19] has hydroxyl (enol?) groups at the pyrrole *β* positions, and when its NH was protected by a removable benzyl group, we were able to attach (via an ether linkage) the desired methyl-capped polyether chains in K_2CO_3-promoted S_N2 reactions between **11** and the previously reported [20, 21] $CH_3O(CH_2CH_2O)_nTs$, where $n = 1$, 2, and 3 for **10a**, **10b**, and **10c**, respectively. The *N*-benzyl protecting group of products **9a**, **9b**, and **9c** was removed in good yield by brief treatment with hot CF_3CO_2H–H_2SO_4 in the presence of anisole. The resulting pyrroles (**8a**, **8b**, and **8c**) were smoothly saponified, then decarboxylated, to afford the parent α-free pyrroles (**7a**, **7b**, and **7c**) in excellent yields. Subsequent reaction with 30% hydrogen peroxide in hot pyridine produced the target pyrrolinones (**6a**, **6b**, and **6c**). Unlike the synthesis of **4** [14], where 3,4-dimethoxy-3-pyrrolin-2-one was a reactant, reaction of **6a**–**6c** with excess **13** in hot methanolic potassium hydroxide did not lead to the formation of the expected yellow dipyrrinones but to elimination of the polyether chains. However, after considerable experimentation with various non-nucleophilic bases and solvents, our best product yields were achieved with diazabicycloundecene (DBU) in CH_3CN by heating (sealed tube) at 120 °C for 7 days. This led to dipyrrinone esters **1e**–**3e** in acceptable yields. The target free acids (**1**–**3**) were obtained from the corresponding esters in excellent yield by saponification with NaOH.

Structures and NMR spectroscopy

The constitutional structures of **1**–**3** and their ethyl esters (**1e**–**3e**) follow from the method of synthesis and comparison of their ^{13}C NMR spectral data with those of the known analog **4** (Table 1). The methoxy carbons appear in the expected range, as do the $-CH_2-O$ carbons, and, as expected, differences in chemical shifts at ring carbons C(1) and C(3) are not profound in the series **1**–**4**. As observed earlier with **4**, the lactam carbonyls of **1**–**3** are shifted 5–6 ppm upfield,

Scheme 1



and C(4) is shifted 8–9 ppm upfield, both relative to xanthobilirubinic acid (**15**). Other carbon chemical shifts of **1**–**3** are similar to those of **4**, and the presence of OCH_3 groups on the lactam rings of **1**–**4** was fully evident from the CH_3 chemical shifts near 60 ppm.

The structure assignments are also consistent with the ^{1}H NMR spectra, from which one learns, in addition, that the favored pigment conformation is *syn-Z* (Fig. 2), as deduced from nuclear *Overhauser* spectroscopic (N*O*E) measurements. Thus in **1**–**3** (and **1e**–**3e**) in $CDCl_3$ and $(CD_3)_2SO$ solvents one sees N*O*Es between the pyrrole lactam and NH hydrogens, and between the C(5)–H and the flanking groups at C(3) and C(7)—as seen previously in **4** [14] and **5** [22].

Dipyrrinones are typically monomeric in $(CD_3)_2SO$, with NH hydrogen bonding to solvent [4] and lactam and pyrrole NH chemical shifts near 9.6 and 10.3 ppm, respectively, in the ^{1}H NMR spectra [23, 24]. This is seen again in the very similar sets of lactam and pyrrole NH chemical shifts of **1**–**4** and **1e**–**4e**, and the near coincidence with those from **5** and **5e** (Table 2). In contrast, intermolecularly hydrogen-bonded dimers are favored in $CDCl_3$, as typically indicated by greater deshielding of the lactam NH resonance to ~11 ppm and relatively smaller changes in the pyrrole NH chemical shift [22–24]. The NH chemical shifts of **1**–**3** in $CDCl_3$ are very similar (Table 2) and suggest intermolecularly hydrogen-bonded dimers. Likewise, those of **1e**–**4e**, and they trend in the right direction for hydrogen-bonded dimers. Two different types of hydrogen-bonded dimer were discerned earlier—a planar dimer held together by hydrogen bonds of the dipyrrinone to dipyrrinone type and a stacked dimer involving acid to dipyrrinone hydrogen bonds [23, 24]. The latter is found with dipyrrinone acids of the xanthobilirubinic acid (**5**) type; the former with esters like methylxanthobilirubinate (**5e**) and dipyrrinones devoid of CO_2H appendages [23, 24]. At high dilution, however, solutions of **5** tend toward monomers, which exhibit extrapolated lactam and pyrrole NH shifts of 7.00 and 7.75 ppm, respectively [22]. Consequently, allowing for alterations in NH chemical shifts because of the electronegative β substituents, it appears that

Table 1 Comparison of the ^{13}C NMR chemical shifts (δ/ppm) of methyl-capped PEGylated analogs **1–3** and their esters **1e–3e**, 4-desethyl-3-desmethyl-3,4-dimethoxyxanthobilirubinic acid (**4**), and xanthobilirubinic acid (**5**) in $CDCl_3$ solvent

	Carbon[a]	**1**	**1e**	**2**	**2e**	**3**[b]	**3e**	**4**[b]	**5**[c]
1	C=O	168.7	168.5	168.8	168.5	168.7	168.4	165.9	171.5
2	–C=	124.9	125.1	125.0	125.1	125.1	125.3	125.9	122.6
3	–C=	147.9	148.4	148.0	148.4	148.0	148.4	146.4	147.2
4	–C=	119.8	119.4	119.8	119.5	119.7	119.33	119.6	127.3
5	–CH=	101.1	101.2	101.1	101.2	101.3	101.4	96.6	97.6
6	–C=	124.9	124.8	124.9	124.8	124.9	125.0	121.2	121.7
7	–C=	122.5	122.3	122.4	122.4	122.5	122.3	122.0	122.3
8	–C=	119.2	119.3	119.1	119.3	119.1	119.31	118.6	118.7
9	–C=	131.5	131.9	131.5	131.8	131.6	132.0	129.4	129.4
2^1	CH_3	–[d]	–[d]	–[e]	–[e]	–[f]	–[f]	–	8.1
2^2	CH_3	–	–	–	–	–		60.2	–
3^1	CH_2	–[d]	–[d]	–e	–[e]	–[f]	–[f]	–	17.2
3^2	CH_3	–	–	–	–	–	–	59.0	14.8
7^1	CH_3	9.8	9.8	9.7	9.8	9.7	9.8	9.1	9.2
8^1	CH_2	20.3	20.1	20.3	20.1	20.3	20.1	19.4	19.5
8^2	CH_2	35.7	35.5	35.6	35.5	35.7	35.4	35.0	35.0
8^3	CO_2H/R	177.9	173.5	178.2	173.5	178.7	173.6	174.0	174.0
9	CH_3	11.8	11.6	11.8	11.6	11.7	11.6	11.0	11.0

[a] For carbon numbering system, see Fig. 1

[b] Dey and Lightner [14]

[c] Boiadjiev et al. [12]

[d] $CH_3O(CH_2CH_2O)_3$

[e] $CH_3O(CH_2CH_2O)_2$

[f] $CH_3OCH_2CH_2O$

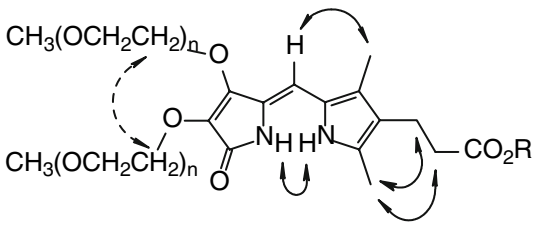
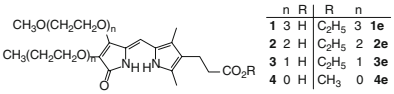


Fig. 2 Nuclear *Overhauser* effects observed and shown by *curved arrows* that confirm a *syn-Z* conformation in **1**, **2**, **3**, and **4** (R = H, n = 3, 2, 1, 0, respectively) and **1e**, **2e**, **3e**, and **4e** ($R = CH_2CH_3$, n = 3, 2, 1, 0, respectively) in $CDCl_3$

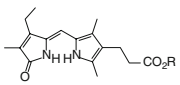
1–4 are dimers of the stacked type, like **5** [23, 24]; whereas, **1e–4e** are planar dimers, like **5e** [23, 24].

Vapor pressure osmometry (VPO) molecular weight measurements [25] of **1–4** and **1e–4e** in $CHCl_3$ (Table 3) confirmed that the dipyrrinones are dimers within the concentration range 1–8 $\times$ 10^{-3} M. However, molecular weight measurements in CH_3OH revealed that these dipyrrinones are monomers. Apparently, the more polar CH_3OH solvent and the potential for hydrogen bonding to it disrupts the dimers. All but **1** were insufficiently soluble for VPO measurements in H_2O. However, in this solvent, as in CH_3OH, the pigment is monomeric.

Table 2 Comparison of the ^1H NMR N–H chemical shifts of dipyrrinones **1–5** and their esters in $CDCl_3$ and $(CD_3)_2SO$



n	R	R	n	
1	3	H	C_2H_5	3 **1e**
2	2	H	C_2H_5	2 **2e**
3	1	H	C_2H_5	1 **3e**
4	0	H	CH_3	0 **4e**



5: R = H
5e: R = CH_3

Compound	$CDCl_3$		$(CD_3)_2SO$	
	Lactam NH	Pyrrole NH	Lactam NH	Pyrrole NH
1	10.26	9.30	9.56	10.18
2	10.27	9.26	9.55	10.17
3	10.28	9.20	9.57	10.18
4	Insol.	Insol.	9.54	10.19
5	9.90[a]	8.84[a]	9.67	10.18
1e	10.65	9.85	9.56	10.20
2e	10.51	9.82	9.57	10.19
3e	10.62	9.86	9.58	10.21
4e	10.61	9.90	9.60	10.21
5e	10.92	10.13	9.72	10.26

Chemical shifts in δ/ppm downfield from $(CH_3)_4Si$ at 22 °C for 10^{-3} M concentrations

[a] Concentration $<10^{-6}$ M due to insolubility; values from [23, 24]

Table 3 Molecular weights (MWs) of dipyrrinones **1–4** and **1e–4e** determined by vapor pressure osmometry at 45 °C in $CHCl_3$, 45 °C in CH_3OH, and 60 °C in H_2O

Compound	Formula weight (FW) (g mol^{-1})	Measured weight (MW) (g mol^{-1})		
		$CHCl_3$	CH_3OH	H_2O
1	584	1,152 ± 30	547 ± 45	642 ± 55
2	496	966 ± 23	453 ± 40	Insuff. sol.
3	408	803 ± 47	364 ± 21	Insuff. sol.
4	320	Insol.	295 ± 20	Insuff. sol.
1e	612	1,203 ± 44	564 ± 51	Insol.
2e	524	992 ± 34	504 ± 30	Insol.
3e	436	815 ± 65	416 ± 20	Insol.
4e	334	670 ± 59	302 ± 22	Insol.

Calibrated with benzil (FW = 210 g mol^{-1}, found MW = 210 ± 15 g mol^{-1}) and d-10-camphorsulfonic acid (FW = 232.30 g mol^{-1}, found MW = 230 ± 20 g mol^{-1}); molecular wt in g mol^{-1}; conc. range, 1.1–7.0 × 10^{-3} mol kg^{-1}

Solubility

The characterization of PEGylated-dipyrrinones **1–3** indicates the great similarity in solution and crystal structure and hydrogen bonding to the methoxylated parent (**4**) and to xanthobilirubinic acid (**5**). As found earlier, while the dimethoxy analog clearly behaves like **5**, it did exhibit different solubility properties in water from **5** (which is very insoluble). In order to investigate this aspect of behavior, we examined their aqueous solubility and their solubility in CH_3OH as a control. UV–visible spectroscopy was used to determine the concentrations relative to standard ~1 × 10^{-5} M solutions. The CH_3OH control experiment shows that the solubility of the pigment at 1–3 × 10^{-5} M in pure CH_3OH is almost exactly the same as that in CH_3OH–2% $CHCl_3$ (vol/vol) in which the pigment is freely soluble. All of the pigments are also freely soluble in a reference standard: H_2O–2% $(CH_3)_2SO$ (vol/vol). Comparing pure H_2O with this reference (Table 4), one finds that of **1–3** are approximately 3–4 times more soluble in water than **4**, which is ten times more soluble than **5**. At saturation, the aqueous solubilities of **1** and **1e** are ~4.8 and 0.68 mg/cm^3 H_2O; **2** and **2e** are 0.039 and 0.030 mg/cm^3; **3** and **3e** are 0.027 and 0.017 mg/cm^3; **4** and **4e** [14] are 0.003 and 0.001 mg/cm^3.

UV–visible spectroscopy

As might be expected, compounds **1**, **2**, **3** and their esters (**1e**, **2e**, **3e**) show only small variations in the intense long-wavelength band, either in position or intensity (Table 5). Most noticeable is the low value for ε of **1e**, **2e**, and **3e** in water, where, unlike the corresponding acids, it appears likely that the esters are "solubilized" as aggregates.

Table 4 Comparison of the solubility of dipyrrinones (**1–4**) in methanol and water

Dipyrrinone	Methanol[a] [pigment]f/[pigment]	Water[b] [pigment]f/[pigment]
1	(0.79/0.79) 1:1	(0.71/0.72) 0.99:1
1e	(1.2/1.2) 1:1	(0.62/0.63) 0.98:1
2	(0.79/0.78) 1.01:1	(0.62/0.69) 0.9:1
3	(0.89/0.89) 1:1	(0.61/0.79) 0.77:1
4	(0.681/0.723) 0.99:1	(0.215/0.793) 0.27:1
4e	(0.631/0.636) 1:1	(0.0893/0.292) 0.31:1
5	(0.448/0.443) 1:1	(0.0250/0.419) 0.06:1
5e	(0.768/0.972) 1:1	(0.00883/0.388) 0.023:1

[a] Ratio of pigment concentration in methanol solvent versus standard solution (2% $CHCl_3$ in CH_3OH) as compared by UV–visible spectroscopy

[b] Ratio of pigment concentration (in H_2O) versus standard solution (2% DMSO in H_2O), compared by UV–visible spectroscopy. Solubility of **1** in H_2O: 4.81 mg/cm^3; solubility of **1e** in H_2O: 0.68 mg/cm^3. The standard solutions are prepared and ultrasonicated, the UV–visible absorbance at λ_{max} is recorded. The solution is evaporated to dryness and then the pure solvent (CH_3OH or H_2O) is added, the solution/mixture is ultrasonicated, and the absorbance is re-measured. In all cases it is less than that of the standard solutions. The ratio of absolute pigment concentrations is found in parentheses, the relative pigment concentrations are outside the parentheses. The methodology is given in the text

Concluding comments

The presence of two short-chain PEG groups on the dipyrrinone lactam rings renders the pigment more soluble than the corresponding pigment with alkyl groups by a factor of approximately 500 times over the dimethoxydipyrrinone at saturation. Although the amphiphilicity was improved by the presence of methoxyl groups, complete aqueous solubility arose with the triethylene glycol monomethyl ether PEGylated analog, while partial water solubility was encountered when shorter chains were present—2-methoxyethoxyl and 2-(2-methoxyethoxy)ethoxyl groups. Work is in progress underway to prepare such bilirubinoids with these β substituents.

Experimental

All nuclear magnetic resonance (NMR) spectra were obtained on a Varian 500 MHz (^1H) and 125 MHz (^{13}C) instrument, in deuteriochloroform unless otherwise indicated. Chemical shifts were reported in ppm referenced to the residual chloroform proton signal at 7.26 ppm and ^{13}C signal at 77.23 ppm, unless otherwise noted. Melting points

Table 5 Solvent dependence of the ultraviolet–visible spectral data of **1–3** and **1e–3e**

	Benzene	Chloroform	Acetone	Acetonitrile	DMSO	MeOH	Water
1	402 (28,000)	399 (28,100)	393 (32,000)	392 (31,000)	401 (32,000)	405 (35,000)	405 (29,500)
1e	399 (34,000)	397 (30,000)	392 (33,700)	391 (34,000)	400 (34,600)	400 (36,000)	404 (19,300)
2	403 (30,000)	399 (30,000)	395 (33,000)	392 (32,000)	400 (33,000)	405 (36,000)	405 (28,700)
2e	399 (29,000)	397 (29,100)	390 (31,500)	390 (30,000)	396 (30,000)	398 (32,000)	400 (15,000)
3	405 (29,000)	400 (28,500)	395 (33,500)	391 (32,600)	400 (34,000)	402 (36,000)	404 (25,000)
3e	401 (33,600)	399 (30,300)	393 (33,000)	395 (34,000)	401 (34,500)	402 (35,300)	402 (12,500)

λ nm (ε/dm^3 mol^{-1} cm^{-1})

were taken on a Mel-Temp capillary apparatus and are corrected. Combustion analyses were performed by Desert Analytics, Tucson, AZ, USA, and gave results within ±0.4% of theoretical values. For some compounds FAB HRMS mass determinations of the molecular ion were obtained from the Nebraska Center for Mass Spectrometry. Infrared spectra were recorded on a Perkin–Elmer FT-IR infrared spectrophotometer, model Spectrum 2000. All ultraviolet–visible spectra were recorded on a Perkin–Elmer λ-12 spectrophotometer. VPO measurements were performed on an Osmomat 070-SA instrument (Gonotech, Germany) in HPLC grade $CHCl_3$ (Fisher) at 45 °C. Analytical thin-layer chromatography (TLC) was carried out on J.T. Baker silica gel IB-F plates (125 μm layer). For final purification, radial chromatography was carried out on Merck silica gel PF_{254} with calcium sulfate binder, preparative layer grade. All solvents were reagent-grade from Fisher–Acros, as were the poly(ethylene glycol) methyl ethers.

The spectral data were obtained in spectral grade solvents (Aldrich or Fisher). The other starting compounds: 3,5-dimethyl-4-(2-ethoxycarbonylethyl)-2-formylpyrrole (**13**) [17], 3,4-dimethoxyxanthobilirubinic acid (**4**) [14], xanthobilirubinic acid (**5**), its methyl ester (**5e**) [7, 8], and 2-[2-(-methoxyethoxy)ethoxy]ethyl-*p*-toluenesulfonate (**10a**), 2-[(2-methoxyethoxy)ethyl]-*p*-toluenesulfonate (**10b**) [21], and 2-methoxyethyl-*p*-toluenesulfonate (**10c**) [20] were synthesized according to literature methods.

Solubility in H_2O and CH_3OH

In order to compare the aqueous solubility of **1–4** and **1e–4e**, stock solutions of each were prepared in $CHCl_3$ and in $(CH_3)_2SO$ solvents. Measured aliquots were withdrawn and diluted in 5.00 cm^3 volumetric flasks with CH_3OH or H_2O to create $\sim$1–3 $\times$ 10^{-5} M pigment solutions in CH_3OH–2% $CHCl_3$ and in H_2O–2% $(CH_3)_2SO$. The UV–visible absorbances of each were determined ($\sim$30,000), and the solvent was removed to dryness. Then pure CH_3OH was added to the residue from evaporation of CH_3OH–2% $CHCl_3$ solutions, and pure H_2O (pH 7) was added to the residue from evaporation of the 10^{-5} M $CHCl_3$ solutions. After digestion by ultrasonication and centrifugation, the absorbances of the reconstituted CH_3OH and H_2O solutions were determined and compared with those of the original $\sim$1–3 $\times$ 10^{-5} M solutions in order to determine the pigment concentrations.

*2-Desmethyl-3-desethyl-2,3-bis-(triethylene glycol methyl ether) xanthobilirubinic acid (**1**; $C_{28}H_{46}N_2O_{11}$) and ethyl ester* (**1e**; $C_{30}H_{50}N_2O_{11}$)

Pyrrolinone **6a** (2.5 g, 6.2 mmol) and 0.50 g (2.2 mmol) pyrrole aldehyde **13** were dissolved in 10 cm^3 acetonitrile and placed in a pressure tube. 1,5-Diazabicyclo undecene (1.7 cm^3, 10 mmol) was added and the pressure tube was heated under argon at 120 °C for 7 days during which time the reaction course was monitored by checking (TLC) samples. When a substantial amount of yellow product was detected, the reaction mixture was cooled, diluted with 200 cm^3 CH_2Cl_2 and washed with 100 cm^3 5% aqueous HCl to remove the DBU. The organic layer was removed, dried over Na_2SO_4 (anhyd) and evaporated (rotovap) to yield the crude dipyrrinone, which was purified first by radial chromatography on silica gel using 5% (vol/vol) CH_3OH in CH_2Cl_2 as eluent, then by a second radial chromatography using ethyl acetate–hexane (1:1 vol/vol) as eluent. The purified fractions were collected, and the solvent was evaporated (rotovap) under vacuum. Hexane was then added to the residue and the solution cooled to 5 °C to crystallize the desired products. Pure ester **1e** is a yellow–brown gel. Yield: 280 mg (29%); oil; ^{1}H NMR: δ = 1.25 (3H, t, J = 7.2 Hz), 2.10 (3H, s),2.38 (3H, s), 2.4 (2H, t, J = 7.4 Hz), 2.7 (2H, t, J = 7.4 Hz), 3.35 (3H, s), 3.39 (3H, s), 3.58–3.8 (20H, m), 4.1 (4H, q, J = 7.2 Hz), 4.25 (2H, m), 4.62 (2H, m), 6.35 (1H, s), 9.85 (1H, s), 10.65 (1H, s) ppm; ^{13}C NMR: δ = 9.8, 11.6, 14.5, 20.1, 35.5, 59.2, 60.5, 70.1, 70.3, 70.79, 70.86, 79.90, 71.0, 71.5, 72.16, 72.19, 10.2, 119.32, 119.36, 122.3, 124.8, 125.1, 131.9, 148.4, 168.5, 173.5 ppm.

Dipyrrinone ester **1e** (380 mg, 0.62 mmol) was dissolved in $\sim$20 cm^3 dry THF and 2 cm^3 CH_3OH. Solid NaOH ($\sim$0.1 g) was added, and the mixture was heated at reflux for 1.5 h under N_2. The reaction was quenched by pouring into 200 cm^3 of ice–water, acidified carefully to

pH = 4.0 using dilute HCl and extracted into CH_2Cl_2 (3 × 100 cm^3). The organic phases were combined, dried over anhyd. Na_2SO_4 and evaporated in vacuo (rotovap). The crude product was purified by radial chromatography using 5% (vol/vol) CH_3OH in CH_2Cl_2. The pure fractions were collected and evaporated to obtain pure **1**. Yield: 337 mg (93%); mp 42–44 °C; ^{1}H NMR: δ = 2.1 (3H, s), 2.31 (3H, s), 2.46 (2H, t, J = 7.5 Hz), 2.7 (2H, t, J = 7.5 Hz), 3.36 (3H, s), 3.37 (3H, s), 3.5–3.8 (20H, m), 4.26 (2H, m), 4.59 (2H, m), 6.26 (1H, s), 9.29 (1H, brs), 10.26 (1H, brs), 11.6 (1H, brs) ppm; ^{13}C NMR: δ = 9.8, 11.8, 20.3, 35.6, 59.22, 59.23, 70.2, 70.3, 70.70, 70.73, 70.76, 70.85, 70.87, 71.0, 71.4, 72.05, 72.12, 72.14, 101.1, 119.2, 119.8, 122.5, 124.9, 131.5, 147.9, 168.8, 177.9 ppm.

3,4-Bis-(triethylene glycol methyl ether)-3-pyrrolin-2-one (**6a**; $C_{18}H_{35}NO_9$)

Pyrrole **7a** (200 mg, 0.500 mmol) was taken up into 2–3 cm^3 pyridine under an N_2 atmosphere. To the solution 0.1 cm^3 30% H_2O_2 was added, and the solution was heated at reflux for 55 min. Pyridine was removed (rotovap) by azeotroping with toluene. The residue was purified by column chromatography followed by radial chromatography using 5% (vol/vol) CH_3OH–CH_2Cl_2 to obtain **6a** as a brown oil. Yield: 60 mg (29%); oil; ^{1}H NMR: δ = 3.34 (6H, s), 3.5–3.72 (20H, m), 3.75 (2H, s), 4.21 (2H, m), 4.49 (2H, m), 6.41 (brs, NH) ppm; ^{13}C NMR: δ = 59.1, 63.9, 70.0, 70.6, 70.8, 71.1, 72.1, 101.7, 136.9 ppm.

3,4-Bis-(triethylene glycol methyl ether)-1H-pyrrole (**7a**; $C_{18}H_{35}NO_8$)

Following the procedure in [16], pyrrole ester **8a** (0.81 g, 1.60 mmol) was placed in a 100-cm^3 round-bottomed flask and dissolved in 50 cm^3 ethylene glycol. The solution was degassed on a high-vacuum pump for 2 h. Then KOH (0.36 g, 6.42 mmol) was added, and the mixture was placed in a preheated oil bath at 190 °C and stirred for 3 h under argon. After 3 h the reaction was cooled to 50 °C before adding 100 cm^3 H_2O. The reaction mixture was then extracted with CH_2Cl_2 (4 × 100 cm^3). The combined organic phases were washed with brine, dried, and evaporated (rotovap) to give **6c** as a brown oil. Yield: 0.6 g (96%); oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.37 (6H, s), 3.56 (4H, m), 3.60 (4H, m), 3.65 (4H, m) 3.70 (4H, m), 3.78 (4H, m), 4.04 (4H, m), 6.24 (2H, d, J = 3.0 Hz), 7.21 (1H, brs), 6.23 (brm, NH); ^{13}C NMR: δ = 59.2, 70.4, 70.8, 70.9, 72.2, 74.0, 101.6, 137.3 ppm.

Dimethyl 3,4-bis-(triethylene glycol methyl ether)-1H-pyrrole-2,5-dicarboyxlate (**8a**; $C_{22}H_{37}NO_{12}$)

According to a reported procedure [26] for debenzylation of a different pyrrole, a mixture of 3 g (5.0 mmol) **9a**, 8 cm^3 TFA, 1 cm^3 anisole, and 0.2 cm^3 conc. H_2SO_4 was heated in a preheated oil bath at 90 °C for 30 min. TFA was then recovered by distillation, and the residue was dissolved in ~100 cm^3 CH_2Cl_2, with cooling in ice bath, and carefully neutralized with saturated aqueous $NaHCO_3$. The neutralized solution was then extracted with CH_2Cl_2 (5 × 100 cm^3), dried, evaporated under vacuum to crude product **8a**, which was then purified by radial chromatography using ethyl acetate–*n*-hexane (1:1 vol/vol) as eluent. Yield: 6.7 g (79%); oil; ^{1}H NMR: δ = 3.35 (6H, s), 3.53 (4H, m), 3.63 (8H, m), 3.64 (4H, m), 3.68 (4H, m), 3.88 (6H, s), 4.29 (4H, m), 8.93 (1H, brs) ppm; ^{13}C NMR: δ = 52.1, 59.2, 70.4, 70.75, 70.83, 70.88, 72.2, 74.0, 113.4, 141.5, 160.3 ppm.

Dimethyl 3,4-bis-(triethylene glycol methyl ether)-1-benzylpyrrole-2,5-dicarboxylate (**9a**; $C_{29}H_{43}NO_{12}$)

Following the procedure of [16], dihydroxypyrrole **11** (0.97 g, 3.18 mmol), K_2CO_3 (1.05 g, 7.5 mmol), and triethylene glycol monomethyl ether-*p*-toluene sulfonate (2.22 g, 2.2 equiv.) were dissolved in 30 cm^3 dry acetonitrile, and the mixture was heated at reflux for 15 h, making the entire solution turn yellow. The solution was cooled to room temperature and the solids were removed by filtration and washed with acetonitrile. The filtrate was evaporated under vacuum to obtain the crude product, which was purified using radial chromatography using ethyl acetate–*n*-hexane as eluent. Yield: 1.88 g (96%); oil; ^{1}H NMR: δ = 3.3 (6H, s), 3.5–3.7 (16H, m), 3.75 (4H, m), 3.8 (6H, s), 4.20 (4H, m), 5.96 (2H, s), 6.87–6.90 (2H, m), 7.14–7.21 (3H, m) ppm; ^{13}C NMR: δ = 49.0, 51.8, 59.2, 70.5, 70.7, 70.8, 70.9, 72.2, 74.0, 116.6, 126.1, 127.1, 128.6, 139.1, 142.4, 160.9 ppm.

*2-Desmethyl-3-desethyl-2,3-bis-(diethylene glycol methyl ether) xanthobilirubinic acid (**2**; $C_{24}H_{38}N_2O_9$) and ethyl ester* (**2e**; $C_{26}H_{42}N_2O_9$)

Dipyrrinone **2** and its ester **2e** were prepared according to the procedure for synthesizing **1** and **1e**. Pure acid **2** is a yellow solid. Yield: 248 mg (94%); mp 114–116 °C; ^{1}H NMR: δ = 2.08 (3H, s), 2.25 (3H, s), 2.45 (2H, t, J = 7.2 Hz), 2.78 (2H, t, J = 7.2 Hz), 3.35 (3H, s), 3.39 (3H, s), 3.58–3.9 (12H, m), 4.25 (2H, m), 4.6 (2H, m), 6.26 (1H, s), 9.2 (1H, s), 10.26 (1H, s) ppm; ^{13}C NMR: δ = 9.8, 11.6, 20.1, 35.5, 59.2, 59.3, 60.5, 62.0, 70.1, 70.4, 70.6, 70.9, 71.5, 72.0, 72.16, 72.22, 101.2, 119.3, 119.5, 122.4, 124.8, 125.0, 131.8, 148.0, 168.8, 173.5 ppm.

Pure ester **2e** is a yellow solid. Yield: 0.3 g (35%); mp 64–68 °C; ^{1}H NMR: δ = 1.24 (3H, t, J = 7.2 Hz), 2.1 (3H, s), 2.33 (3H, s), 2.41 (2H, t, J = 7.5 Hz), 2.70 (2H, t, J = 7.5 Hz), 3.35 (3H, s), 3.39 (3H, s), 3.58–3.9 (12H, m), 4.11 (2H, q, J = 7.2 Hz), 4.27 (2H, m), 4.63 (2H, m), 6.32 (1H, s), 9.82 (1H, brs), 10.51 (1H, brs) ppm; ^{13}C NMR: δ = 9.8, 11.6, 14.5, 20.1, 35.5, 59.24, 59.27, 62.0, 70.0, 70.4, 70.5, 70.7, 70.9, 71.5, 72.16, 72.22, 72.7, 101.2, 119.3, 119.5, 122.4, 124.9, 125.1, 131.8, 148.4, 168.5, 173.5 ppm.

3,4-Bis-(diethylene glycol methyl ether)-3-pyrrolin-2-one (**6b**; $C_{14}H_{27}NO_7$)

Pyrrolinone **6b** was synthesized from **7b** according to the method described (above) for converting **7a** into **6a**. Thus, 4.0 g (13.2 mmol) **7b** in 20 cm^3 pyridine was reacted with 2.5 cm^3 30% H_2O_2 for 2.5 h at reflux. The pyridine was removed under vacuum by azeotroping with toluene, and the residue was purified by column chromatography to afford **6b** that was sufficiently pure for the condensation step. Yield: 1.8–2.0 g (30–35%); oil; ^{1}H NMR: $\delta = 3.34$ (3H, s), 3.37 (3H, s) 3.50–3.75 (12H, m), 3.78 (2H, s), 4.25 (2H, m), 4.50 (2H, m), 6.0 (1H, s) ppm; ^{13}C NMR: $\delta = 43.0$, 59.2, 59.3, 70.2, 70.3, 70.5, 70.81, 70.83, 71.3, 72.1, 72.2, 125.4, 152.9, 171.8 ppm.

3,4-Bis-(diethylene glycol methyl ether)-1H-pyrrole (**7b**; $C_{14}H_{27}NO_6$)

Pyrrole ester **8b** (20 g, 48 mmol) was placed in a 250 cm^3 round-bottomed flask and dissolved in 150 cm^3 ethylene glycol. The solution was degassed on a high-vacuum pump for 2 h. Then KOH (10.77 g, 190 mmol) was added and the mixture was placed in a preheated oil bath at 190 °C and stirred for 3 h under argon. After 3 h the reaction was cooled to 50 °C before adding 200 cm^3 H_2O. The reaction mixture was then extracted with CH_2Cl_2 (8 × 100 cm^3). The combined organic phases were washed with brine, dried, and evaporated (rotovap) to give **7b**. Yield: 14 g (92%); oil; ^{1}H NMR: $\delta = 3.37$ (6H, s), 3.55 (2H, m), 3.65 (2H, m), 3.78 (4H, m), 4.29 (4H, m), 6.24 (2H, d, $J = 2.5$ Hz), 7.18 (1H, brs) ppm; ^{13}C NMR: $\delta = 59.3$, 70.4, 70.7, 72.2, 74.0, 101.7, 137.4 ppm.

Dimethyl 3,4-bis-(diethylene glycol methyl ether)-1H-pyrrole-2,5-dicarboxylate (**8b**; $C_{18}H_{29}NO_{10}$)

A mixture of 20 g (19.6 mmol) **9b**, 24 cm^3 TFA, 3 cm^3 anisole, and 0.8 cm^3 conc. H_2SO_4 was heated in a preheated oil bath at 90 °C for 30 min. TFA was then recovered under vacuum. The residue was dissolved in ~100 cm^3 CH_2Cl_2, cooled in an ice bath, then carefully neutralized with saturated aqueous $NaHCO_3$. The neutralized solution was then extracted with CH_2Cl_2 (5 × 100 cm^3), dried, and evaporated under vacuum to crude product **8b**, which was then purified by radial chromatography using ethyl acetate–*n*-hexane (1:1 vol/vol) as eluent. Yield: 6.5 g (79%); oil; ^{1}H NMR: $\delta = 3.37$ (6H, s), 3.55 (4H, m), 3.68 (4H, m), 3.78 (4H, m), 3.88 (6H, s), 4.29 (4H, m), 8.93 (1H, brs) ppm; ^{13}C NMR: $\delta = 52.1$, 59.3, 70.4, 70.7, 72.2, 74.0, 113.3, 141.5, 160.3 ppm.

Dimethyl 3,4-bis-(diethylene glycol methyl ether)-1-benzylpyrrole-2,5-dicarboxylate (**9b**; $C_{25}H_{35}NO_{10}$)

Dihydroxypyrrole **11** (5 g, 16 mmol), K_2CO_3 (5.75 g, 41 mmol), and diethylene glycol monomethyl ether-*p*-toluenesulfonate (9.9 g, 36 mmol) were dissolved in 100 cm^3 dry acetonitrile, and the mixture was heated at reflux for 15 h, making the entire solution turn yellow. The solution was cooled to room temperature and the solids were removed by filtration and washed with acetonitrile. The filtrate was evaporated under vacuum to obtain the crude product, which was purified using radial chromatography using ethyl acetate–*n*-hexane as eluent. Yield 8.0 g (95%); oil; ^{1}H NMR: $\delta = 3.36$ (6H, s), 3.53 (4H, m), 3.66 (4H, m), 3.70 (4H, m), 3.78 (6H, s), 4.21 (4H, m), 5.98 (2H, s), 6.90 (2H, d, $J = 7.5$ Hz), 7.20 (3H, m) ppm; ^{13}C NMR: $\delta = 49.0$, 51.9, 59.2, 70.5, 70.8, 72.2, 74.0, 116.6, 126.1, 127.1, 128.6, 139.1, 142.4, 160.9 ppm.

*2-Desmethyl-3-desethyl-2,3-bis-(ethylene glycol methyl ether) xanthobilirubinic acid (**3**; $C_{20}H_{30}N_2O_7$) and ethyl ester* (**3e**; $C_{22}H_{34}N_2O_7$)

3,4-Bis-(2-methoxyethoxy)-3-pyrrolin-2-one **6c** was condensed with aldehyde **13** as indicated for the syntheses of **1** and **1e** above. Pure acid **3** is a yellow solid. Yield: 183 mg (93%); mp 159–160 °C; ^{1}H NMR: $\delta = 2.08$ (3H, s), 2.31 (3H, s), 2.48 (2H, t, $J = 7.5$ Hz), 2.74 (2H, t, $J = 7.5$ Hz), 3.39 (3H, s), 3.44 (3H, s), 3.63 (2H, m), 3.72 (2H, m), 4.27 (2H, m), 4.60 (2H, m), 6.28 (1H, s), 9.20 (1H, brs) ppm; ^{13}C NMR: $\delta = 9.7$, 11.7, 20.3, 35.7, 59.0, 59.4, 71.3, 71.5, 71.6, 71.9, 101.3, 119.0, 119.6, 122.4, 124.9, 125.1, 131.5, 148.0, 168.7, 178.7 ppm.

Pure ester **3e** is a yellow solid. Yield: 380 mg (40%); mp 70–71 °C; ^{1}H NMR: $\delta = 1.25$ (3H, t, $J = 7.2$ Hz), 2.11 (3H, s), 2.35 (3H, s), 2.42 (2H, t, $J = 7.5$ Hz), 2.70 (2H, t, $J = 7.5$ Hz), 3.60 (2H, m), 3.73 (3H, m), 4.12 (2H, q, $J = 7.2$ Hz), 4.26 (2H, m), 4.60 (2H, m), 6.35 (1H, s), 9.86 (1H, s), 10.61 (1H, s) ppm; ^{13}C NMR: $\delta = 9.8$, 11.6, 14.5, 20.1, 35.4, 59.1, 59.4, 60.6, 71.38, 71.42, 71.6, 72.2, 101.4, 119.31, 119.33, 122.3, 125.0, 125.3, 132.0, 168.4, 173.6 ppm.

3,4-Bis-(2-methoxyethoxy)-3-pyrrolin-2-one (**6c**; $C_{10}H_{19}NO_5$)

Pyrrolinone **6c** was synthesized from pyrrole **7c** as described above for the synthesis of **6b** from **7b**. Yield: 550 mg (29%); yellow–brown oil; ^{1}H NMR: $\delta = 3.36$ (3H, s), 3.39 (3H, s), 3.60 (2H, m), 3.63 (2H, m), 3.79 (2H, s), 4.21 (2H, m), 4.50 (2H, m), 6.54 (1H, brs) ppm; ^{13}C NMR: $\delta = 43.2$, 59.0, 59.3, 70.6, 71.3, 71.4, 71.6, 125.3, 153.2, 172.2 ppm.

3,4-Bis-(2-methoxyethoxy)-1H-pyrrole (**7c**; $C_{10}H_{19}NO_4$)

Pyrrole ester **8c** (22 g, 67 mmol) was placed in a 250 cm^3 round-bottomed flask and dissolved in 150 cm^3 ethylene glycol. The solution was degassed on a high-vacuum pump for 2 h. Then KOH (14.9 g, 270 mmol) was added and the mixture was placed in a preheated oil bath at 190 °C and stirred for 3 h under argon. After 3 h the reaction was cooled to 50 °C before adding 200 cm^3 H_2O. The reaction

mixture was then extracted with CH_2Cl_2 (8×100 cm^3). The combined organic phases were washed with brine, dried, and evaporated (rotovap) to give **7c**. Yield: 11 g (72%); oil; ^{1}H NMR: $\delta = 3.42$ (6H, s), 3.70 (4H, m), 4.04 (4H, m), 6.25 (2H, d, $J = 3.0$ Hz), 7.16 (1H, brs) ppm; ^{13}C NMR: $\delta = 59.3$, 71.2, 71.5, 101.8, 137.4 ppm.

Dimethyl 3,4-bis-(2-methoxyethoxy)-1H-pyrrole-2,5-dicarboxylate (**8c**; $C_{14}H_{21}NO_8$)
A mixture of 10 g (23.8 mmol) **9c**, 29 cm^3 TFA, 3.4 cm^3 anisole, and 0.9 cm^3 conc. H_2SO_4 was heated in a preheated oil bath at 90 °C for 30 min. TFA was then recovered under vacuum. The residue was dissolved in ~100 cm^3 CH_2Cl_2, cooled in an ice bath, then carefully neutralized with saturated aqueous $NaHCO_3$. The neutralized solution was then extracted with CH_2Cl_2 (5×100 cm^3), dried, and evaporated under vacuum to crude product **8c**, which was then purified by radial chromatography using ethyl acetate–*n*-hexane (1:1 vol/vol) as eluent. Yield: 6.7 g (85%); oil; ^{1}H NMR: $\delta = 3.35$ (6H, s), 3.72 (4H, m), 3.87 (6H, s), 4.14 (4H, m), 8.93 (1H, brs) ppm; $\delta = 52.1$, 59.3, 71.2, 71.5, 113.4, 141.5, 160.3 ppm.

Dimethyl 3,4-bis-(2-methoxyethoxy)-1-benzylpyrrole-2,5-dicarboxylate (**9c**; $C_{21}H_{27}NO_8$)
Dihydroxypyrrole **11** (5 g, 16 mmol), K_2CO_3 (5.75 g, 41 mmol), and ethylene glycol monomethyl ether-*p*-toluenesulfonate (8.3 g, 36 mmol) were dissolved in 100 cm^3 dry acetonitrile, and the mixture was heated at reflux for 15 h, making the entire solution turn yellow. The solution was cooled to room temperature and the solids were removed by filtration and washed with acetonitrile. The filtrate was evaporated under vacuum to obtain the crude product, which was purified using radial chromatography using ethyl acetate–*n*-hexane as eluent. Yield: 9.0 g (90%); oil; ^{1}H NMR: $\delta = 3.41$ (6H, s), 3.68 (4H, m), 3.79 (6H, s), 4.19 (4H, m), 6.90 (2H, d, $J = 7.5$ Hz), 7.20 (3H, m) ppm; ^{13}C NMR: $\delta = 49.0$, 51.9, 59.2, 71.8, 73.9, 116.7, 126.1, 127.1, 128.6, 139.2, 142.5, 160.9 ppm.

Dimethyl N-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate (**11**; $C_{15}H_{15}NO_6$)
According to the procedure in [16], sodium metal (9.6 g, 0.40 g-atoms) was added to 125 cm^3 dry CH_3OH at 0 °C in a three-necked round-bottomed flask with attached mechanical stirrer, reflux condenser with N_2 inlet, and thermometer. After all the Na had dissolved, diethyl oxalate (35 g, 1.25 equiv) and dimethyl *N*-benzyliminodiacetate (48.5 g, 193 mmol) were added, and the solution was heated at reflux overnight (after ~2 h, a yellow colored solid came out of the solution). After 15 h reflux, without allowing cooling acetic acid was added until all the solid dissolved and the pH reached ~5. The reaction mixture was poured into 500 g ice and stirred well to cause the product to crystallize. It was sufficiently pure for the next step. Yield: 45 g (77%); mp 154–156 °C; ^{1}H NMR: $\delta = 3.92$ (6H, s), 5.80 (2H, s), 6.85–7.40 (5H, m), 7.70 (2H, s); ^{13}C NMR: $\delta = 49.5$, 52.1 111.3, 125.9, 127.3, 128.7, 139.2, 139.8, 162.9 ppm.

Dimethyl N-benzyliminodiacetate (**12**; $C_{13}H_{17}NO_4$)
Following a reported procedure [16], but with a change of solvent from acetone to acetonitrile to improve the product yield, benzylamine (5.5 mL, 0.05 mol) and methyl bromoacetate (11.86 cm^3, 0.125 mol) were added to a stirred suspension of K_2CO_3 (55.3 g, 0.40 mol) in 100 cm^3 dry acetonitrile and the solution was heated at reflux for 24 h. The reaction mixture was then cooled and to it 100 cm^3 H_2O was added, which dissolved the solid and separated the organic layer. The aqueous layer was washed with CH_2Cl_2 (3×100 cm^3) and the combined organic layers were dried and evaporated under vacuum to yield a crude oil. This oil was distilled under vacuum and pure product came over at bp 130–134 °C (0.5 mm Hg). Yield: 12.2 g (96%); oil; ^{1}H NMR: $\delta = 3.50$ (4H, s), 3.60 (6H, s), 3.88 (2H, s), 6.85–7.40 (5H, m) ppm; ^{13}C NMR: $\delta = 51.1$, 53.7, 57.6, 127.1, 128.1, 128.7, 138.0, 171.2 ppm.

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