Hexaalkyl Terpyrrole: A New Building Block for the Preparation of Expanded Porphyrins

Jonathan L. Sessler,* Steven J. Weghorn, Yoshio Hiseada, and Vincent Lynch

Abstract: A new, general synthesis of the first β-substituted tetra- and hexaalkyl terpyrroles is described. Also described are two new classes of expanded porphyrins derived from the hexaalkyl terpyrrole. The key step in the terpyrrole formation is the copper(II)-mediated oxidative coupling of the LDA-derived enolates of α-keto pyrroles. The first new expanded porphyrin reported here, the so-called "orangarin", contains five pyrrolic subunits and two bridging carbon atoms, and is formally a 20π-electron nonaromatic macrocycle. The second new class of expanded porphyrins, the "amethyrins", are 24π-electron nonaromatic macrocycles containing six pyrrole units. Both of these new macrocycles, as well as one of the new terpyrrolic precursors have been structurally characterized by single crystal X-ray diffraction analysis.

Keywords
amethyrin · orangarin · porphyrinoids · terpyrroles

Introduction

Pyrroles and 2,2′-bipyrroles are the building blocks for numerous naturally occuring compounds and their derivatives such as heme, chlorophyll, and corrole. Therefore, tremendous effort has been put into the synthesis of these heterocyclic units as part of efforts to prepare these and other pyrrole-containing natural products.[1, 2]

In addition to the synthesis of pyrroles and 2,2′-bipyrroles for the study of naturally occurring macrocycles, recent efforts in the Vogel and Sessler groups have produced the novel bipyrrole-derived porphyrin isomers porphycene **1**[3] and corrphycene **2** (Fig. 1).[4] There has also been a considerable body of research devoted toward the preparation of expanded porphyrins based on bipyrroles. Indeed, the first reported expanded porphyrin, sapphyrin (e.g., **3**, Fig. 2),[5] contains the bipyrrole subunit within a pentapyrrolic aromatic framework. Other examples of bipyrrole-derived expanded porphyrins are smaragdyrin (e.g., **4**),[5b, 6] rosarin (e.g., **5**),[7] and rubyrin (e.g., **6**).[8]

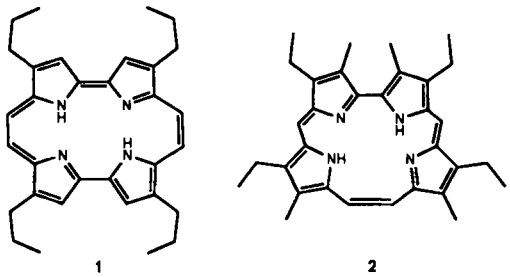

Fig. 1. Porphycene (**1**) and corrphycene (**2**).

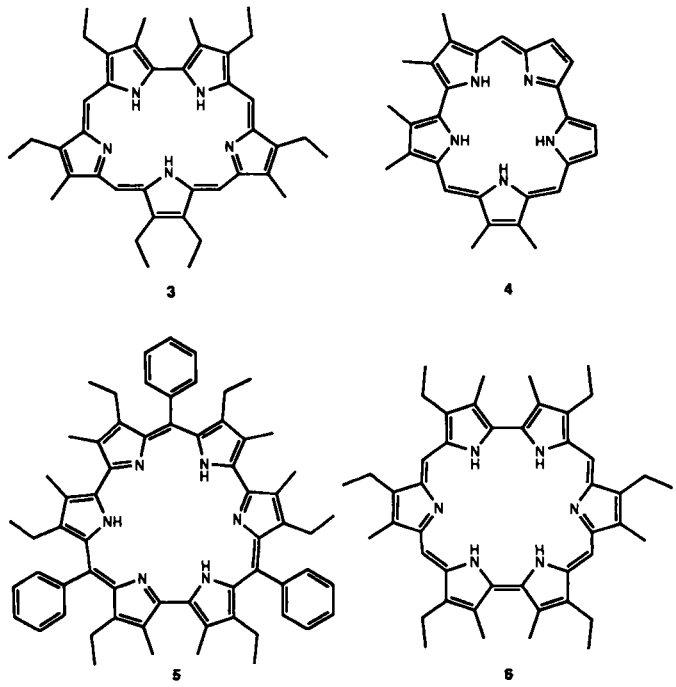

Fig. 2. Sapphyrin (**3**), smaragdyrin (**4**), rosarin (**5**), and rubyrin (**6**).

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While the number of reported 2,2′-bipyrrole-containing porphyrin isomers and expanded porphyrins is now substantial,[9] macrocycles derived from larger, directly linked pyrrolic subunits remain extremely rare. One such example is the so-called turcasarin **7** (Fig. 3).[10] Turcasarin, to the best of our knowledge is, in fact, the only terpyrrole-containing macrocycle reported to date. Other expanded porphyrins containing terpyrrole-like subunits have been described in which the central pyrrole subunit has been replaced by thiophene or furan. Two such examples are the ozaphyrins (e.g., **8**)[11] and bronzaphyrins (e.g., **9**)[12] prepared recently as the result of independent efforts by Ibers, Johnson et al. and Cava et al.[13]

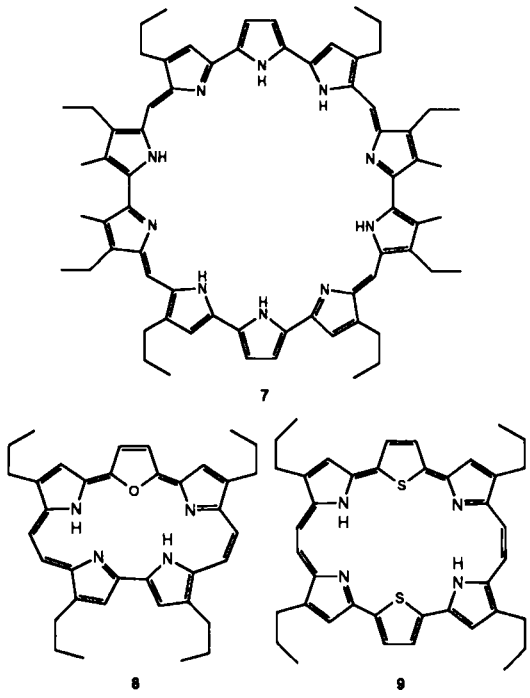


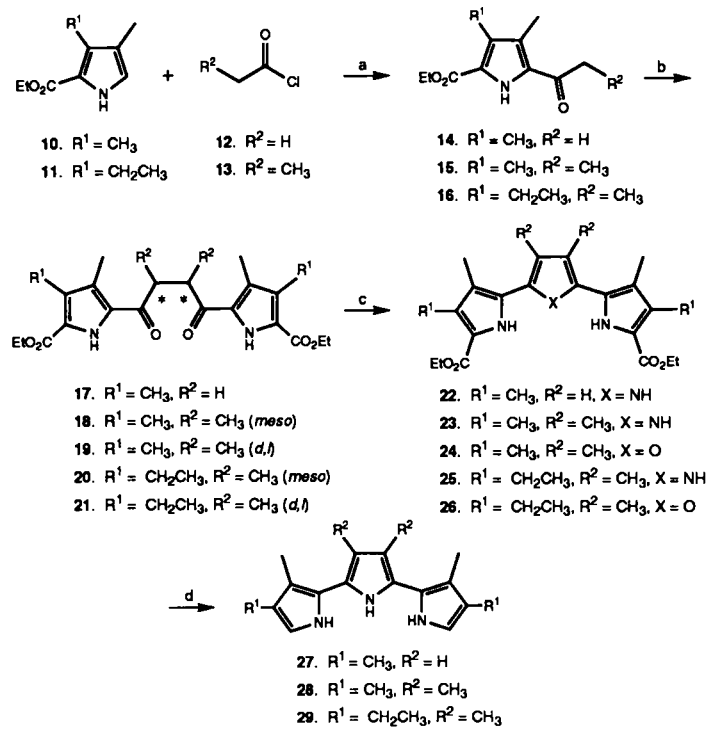
Fig. 3. Turcasarin (**7**), ozaphyrin (**8**), and bronzaphyrin (**9**).

Interestingly, in each of the above examples, the terpyrrole (or terpyrrole-like) subunits are always found to have alkyl substituents in only two of the six possible β-positions. This finding reflects, presumably, the lack of general terpyrrole syntheses that could give β-substituted tetra- and/or hexaalkyl terpyrroles. While Chierici and Serventi reported in 1960 the synthesis of a hexaalkylterpyrrole,[14] this species was also not fully β-substituted. Further, it was blocked in the α-positions by methyl groups, rendering it useless for macrocycle synthesis. On the other hand, were they available, terpyrroles in which all six β-positions were blocked with alkyls and the α-positions open (or at worst "protected" as carboxylates) would be extremely useful for the construction of expanded porphyrins. Such an arrangement would provide sufficient electron density at the α-positions and facilitate electrophilic attack at these sites. Further, the existence of a terpyrrole in which all six β-positions were alkyl-substituted might facilitate macrocycle synthesis by allowing for a "helical effect" during the condensation.[15] This latter effect, which could arise from steric interactions between the β-substituents, could serve to preorganize the linear oligopyrroles such that the rates of macrocyclization become competitive with those associated with polymerization.

In this paper, we present the first synthesis of a completely β-alkyl-substituted terpyrrole and demonstrate its utility in the synthesis of certain expanded porphyrins. Specifically, we report here the synthesis of the hexa-β-alkyl terpyrrole **29** and two new expanded porphyrins **31** and **37** that are derived from **29**. Also reported here is the synthesis of the tetra-β-alkyl terpyrrole **27**, obtained by the same basic terpyrrole forming synthesis.

Results and Discussion

The synthesis of the terpyrrole **29** is shown in Scheme 1. It is derived from the α-propionylpyrrole **16**. This latter precursor is easily prepared by an $SnCl_4$-activated coupling[16] between an α-free pyrrole (e.g., **11**[17]) and an appropriate acid chloride, such as propionyl chloride **13**. Oxidative coupling of the LDA-derived enolate of this α-propionylpyrrole with $Cu(OTf)_2$ then



Scheme 1. Syntheses of tetra- and hexaalkyl terpyrroles. a: $SnCl_4$, CH_2Cl_2, r.t., 15 min. b: 1) LDA, THF; 2) $Cu(OTf)_2$, DMF, 1 h; 3) 1N HCl. c: $(NH_4)_2CO_3$, HOAc, 120 °C. d: NaOH, ethylene glycol, 180 °C, 30 min.

affords the corresponding γ-diketone as a mixture of diastereomers (**20**/**21**).[18] Both of these compounds may be converted to the corresponding terpyrrole **25** using modified Paal–Knorr conditions.[19] Saponification and decarboxylation of the ethyl esters in ethylene glycol at 180 °C in the presence of NaOH[10] affords the bis-α-free terpyrrole **29** in high yield.

An interesting point to be noted about the above sequence concerns the oxidative coupling of the propionyl pyrrole **16** to afford the mixture of diastereomers **20** and **21**. The assignment of stereochemistry to these two readily separated compounds (*d,l* vs. *meso*) was made based on the fact that the faster reaction rate is known to prevail in all cases that involve the condensation between an amine with the *d,l* mixture of 3,4-dimethyl-2,5-hexanedione isomers.[20] In the present instance, reaction of the putative *d,l* mixture of isomers **21** with ammonium carbonate proceeds to completion nearly ten times faster than does the analogous condensation using what is presumed to be the corresponding *meso* isomer **20**.[21]

The structure of the β-alkyl terpyrrolic species **25** was confirmed by a single crystal X-ray diffraction analysis (see Fig. 4 and Table 1).[23] Interestingly, the molecule adopts a helical twist in the solid state. This helical conformation is in direct contrast to the alternating planar-antiperiplanar–antiperiplanar conformation observed for the simple unsubstituted 2,2′,2″-terpyrrole.[28] This twisting of the molecule, compared to the conformation of 2,2′,2″-terpyrrole, may be considered direct evidence in support of the "helical effect" alluded to above.

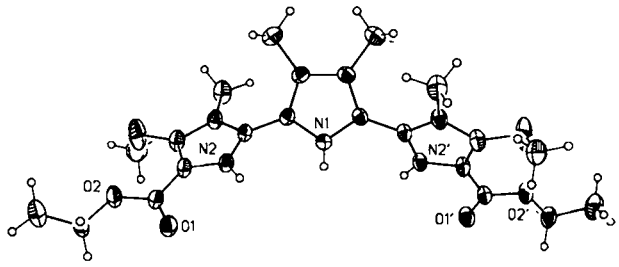
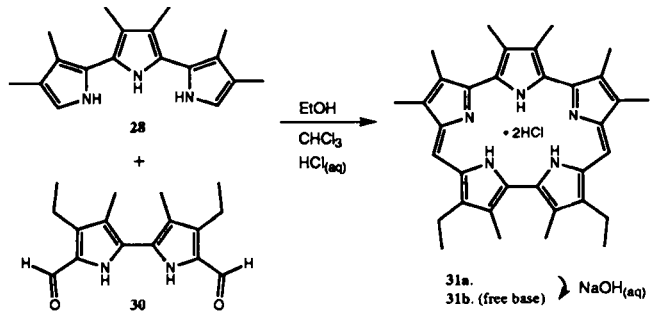


Fig. 4. View of **25** ($C_{26}H_{35}N_3O_4$) showing a partial atom labeling scheme. The molecule lies on a crystallographic twofold rotation axis at 1/4, y, 0 passing through N1 and bisecting the central pyrrole. The dihedral angle between the central pyrrole and the terminal pyrrole is 48.6°. Atoms marked by ′ are related by $1/2-x, y, -z$.

The sequence of reactions used to prepare terpyrrole **29** has also been applied to the synthesis of terpyrroles **27** and **28**. This chemistry, which is straightforward, is detailed further in the Experimental Procedure.

Orangarin: With the desired hexaalkyl terpyrroles **28** and **29** in hand, it became possible to contemplate making new expanded porphyrins. Two such macrocycles have in fact been prepared and are reported here. The synthesis of the first of these is shown in Scheme 2. It involves the acid-catalyzed reaction between hexamethylterpyrrole **28** and diformyl bipyrrole **30**.[5c] After purification, one obtains a pentapyrrolic macrocycle that formulates as **31**, in surprisingly high yield (59%).



Scheme 2. Synthesis of orangarin **31**.

Macrocycle **31** represents the smallest possible macrocycle out of the condensation between terpyrrole and diformyl bipyrrole. It is a pentapyrrolic macrocycle with only two bridging carbon atoms. When comparing the pentapyrrolic macrocycles smaragdyrin,[6] sapphyrin,[5] and pentaphyrin,[29] one should notice the monotonic progression in the number of available *meso*-like carbons. It runs from *two* in the case of **31** to *three* for smaragdyrin, to *four* for sapphyrin, and finally to *five* in the case of pentaphyrin.

The reaction conditions used to form the pentapyrrolic macrocycle **31** are identical to those used to prepare the decapyrrolic system, turcasarin **7**.[10] In the latter instance, reaction of dipropylterpyrrole with diformylbipyrrole **30** affords the "2 + 2" system **7**; no trace of a "1 + 1" adduct is observed as a by-product. In the present case, in addition to the expected turcasarin, a "1 + 1" adduct **31** is also formed. The formation of this material, which is in fact the dominant product, may be rationalized in terms of the wrap-around helical effect mentioned previously. In the present instance, such an effect favors the formation of the smaller "1 + 1" macrocyclic product.

Like turcasarin **7**, macrocycle **31** is fully conjugated upon condensation and requires no further oxidation to become stable. However, like **7**, molecule **31** also does not fit the 4n + 2 Hückel rule for annulene-like aromaticity (it contains a 20π-electron conjugation pathway). In organic solution, this molecule is highly colored; the dihydrochloride salt **31a** is bright orange. Based upon this color, we have assigned the trivial name "orangarin" to this new class of compounds.[30]

The UV/Vis spectrum of **31a** displays three absorption bands in the visible region. It has a "Soret-like" absorbance band at 462.8 nm that is unusually broad, with an extinction coefficient nearly an order of magnitude less than that of turcasarin **7** (for **31a**, $\log\varepsilon = 4.52$). This is presumably the result of unfavorable methyl–methyl steric interactions at the periphery of the macrocycle that partially disrupt the conjugation pathway.

Structural information for orangarin was obtained from NMR spectroscopy. Both the ^{1}H and ^{13}C NMR spectra of the dihydrochloride salt **31a** are consistent with the presence of a C_2 symmetry element within the molecule. Further, the ^{1}H NMR reveals that the internal NH protons resonate at a remarkably high field location ($\delta \approx -0.2$ to $+0.2$). This unusual location (given the fact that **31** is formally nonaromatic) might suggest the presence of some type of diamagnetic ring current. However, the *meso*-like protons are not shifted *downfield*, as would be expected in the presence of a diamagnetic ring current, but rather appear upfield relative to normal alkene protons. Thus, the shift positions apparently reflect some kind of localized anisotropy effects.[31]

Further confirmation of the structural and oxidation-state assignments made for orangarin came from a single crystal X-ray diffraction analysis of the free-base form **31b** (Fig. 5 and Table 1).[23] In particular, the fact that three hydrogen atoms were found localized on three of the five central pyrrole rings served to confirm the assignment of this macrocycle as being one with a 20π-electron periphery.

From further inspection of Figure 5, one can see that this molecule adopts a nearly planar conformation in the solid state (the mean deviation from planarity of the ring atoms is 0.1366 Å). The primary contribution to the slight distortion from perfect planarity derives from methyl–methyl steric interactions in the bipyrrole unit. Surprisingly, the terpyrrole subunit is almost perfectly planar, with a mean deviation from planarity in this unit of 0.0357 Å (the corresponding value in the bipyrrole unit is 0.1914 Å). Further, the dihedral angle for the bipyrrolic pyrrole units is 30.4°. This latter twisting, which would act to decrease p-orbital overlap between the pyrroles, may account for the broad and relatively weak Soret-like absorbance band observed for the dihydrochloride salt of orangarin (**31a**). Consistent with this supposition is the observation that the double bonds in this molecule appear to be highly localized, as reflected in the disparate bond lengths observed in the X-ray structure. The localized nature of the bonds also supports the claim that this molecule is not aromatic.

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Table 1. Crystallographic data for all new structurally characterized compounds. Data were collected at room temperature on a Enraf-Nonius CAD4 diffractometer using graphite monochromatized $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Lattice parameters were obtained from the least-squares refinement of 25 reflections with $18.8 < 2\theta < 23.2°$. Data were collected using the $\theta-2\theta$ scan technique with a scan range of $1° + 0.35\tan\theta$; backgrounds were offset by 25% of the scan range from the ends of the scan.

	25	**31b**	**37c**	**38c**	**41**	**42**
a/Å	12.671(1)	9.431(1)	12.690(3)	12.144(3)	9.870(4)	10.176(1)
b/Å	14.683(1)	10.701(1)	13.400(3)	12.314(2)	16.476(4)	16.856(2)
c/Å	13.520(2)	14.568(2)	16.864(4)	13.329(3)	12.047(7)	11.860(1)
α/°	90.0	106.62(1)	69.70(2)	104.73(2)	90.0	90.0
β/°	98.170(7)	96.07(1)	81.98(2)	104.08(2)	109.04(4)	107.09(1)
γ/°	90.0	90.13(1)	83.74(2)	113.13(2)	90.0	90.0
V/Å^3	2489.8(4)	1400.1(3)	2657.6(11)	1635.5(8)	1851.9(14)	1944.5(7)
Z	4	2	2	1	2	2
crystal system	monoclinic	triclinic	triclinic	triclinic	monoclinic	monoclinic
space group	$I2/a$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/c$
T/°C	25	−80	−100	−100	−100	25
2θ range/°	4–55	4–55	4–50	4–50	4–50	4–50
ρ_{calcd}/g cc^{-1}	1.21	1.23	1.34	1.47	1.46	1.31
reflections measured	5911	6617	9800	7993	3607	3914
unique reflections	2848	5451	9340	7583	3267	3410
μ/cm^{-1}	0.765	0.684	6.143	6.439	14.27	6.144
crystal size/mm	0.18 × 0.32 × 0.34	0.17 × 0.39 × 0.92	0.09 × 0.49 × 0.52	0.27 × 0.29 × 0.34	0.13 × 0.34 × 0.34	0.14 × 0.19 × 0.30
$R_w(F^2)$ [a]	0.159	0.194	0.0699	0.138	0.162	0.210
$R(F)$ [b]	0.0753	0.0786	0.0783	0.0822	0.074	0.0825
parameters	159	364	592	397	239	235
min,max peaks/e$^-$ Å^{-3}	−0.26, 0.44	−0.36, 0.51	−0.62, 0.74	−0.61, 0.92	−0.92, 0.77	−0.34, 0.38

[a] $R_w = \{\sum w(|F_o|^2 - |F_c|^2)^2 / \sum w(|F_o|)^4\}^{1/2}$ and where the weight, w, is defined as $w = 1/\{\sigma^2(|F_o|^2) + (0.02P)^2\}$; $P = [1/3(\text{Maximum of } 0 \text{ or } |F_o|^2) + 2/3|F_c|^2]$. [b] The conventional R index based on F where the observed relections (1735 reflections) have $F_o > 4(\sigma(F_o))$.

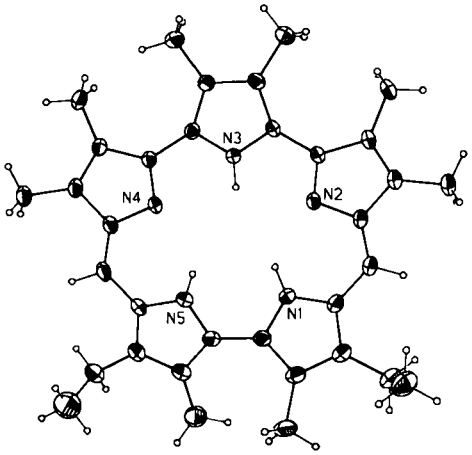


Fig. 5. View of **31b** ($C_{34}H_{39}N_5$) approximately perpendicular to the plane through the macrocycle. The terpyrrole moiety is nearly planar; the mean atomic deviation from planarity is 0.041 Å. The bipyrrole moiety is severely twisted with a dihedral angle of 30.4° between the pyrrolic planes. The C – N bond lengths for the protonated nitrogens are similar and average 1.368(2) Å. The nonprotonated nitrogens have one long and one short C – N bond with average bond lengths of 1.396(4) and 1.322(4) Å, respectively.

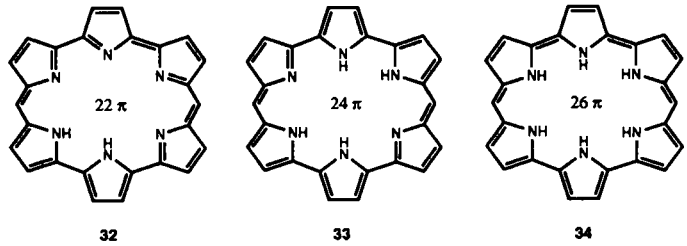
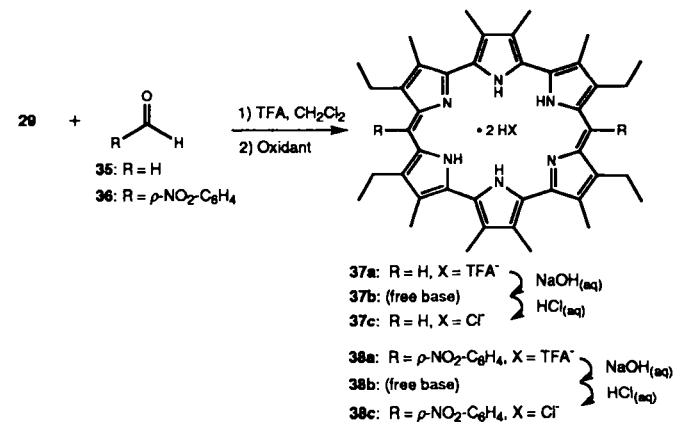


Fig. 6. Generalized structures of the three possible oxidation states of amethyrin: 22π-electron (**32**), 24π-electron (**33**), and 26π-electron (**34**).

Amethyrin: One of the easiest, most straightforward syntheses of porphyrin involves the condensation of pyrrole with an aldehyde under acidic, oxidative conditions.[32] The porphyrin product of this reaction is the smallest possible "4 + 4" macrocycle. When pyrrole is replaced with bipyrrole in the above reaction, the smallest possible "3 + 3" macrocycle, rosarin **5**, is obtained.[7] Such findings then raise the question of what would happen with hexaalkyl terpyrroles.[33] Would a "2 + 2" system form? Assuming that it would, the further question arises as to what oxidation state(s) such a macrocycle may possess. In other words, would one obtain an aromatic structure such as **32** or **34**? Or, would one obtain the nonaromatic species **33** (Fig. 6)?

The macrocycle forming reaction used here (Scheme 3) consists of reacting 2,5-bis(4-ethyl-3-methyl-2-pyrryl)-3,4-dimethylpyrrole **29** with formaldehyde in CH_2Cl_2 using TFA as the acid catalyst. Perhaps not surprisingly, this reaction does proceed in high yield to afford a "2 + 2" adduct. Further, upon treatment with *p*-chloranil, the fully conjugated 24π-electron species **37a** (corresponding to generalized structure **33**) is obtained. Isolation of this macrocycle was achieved by chromatography on basic silica gel (i.e., pre-treated with NH_3) with CH_2Cl_2 as the eluent. Subsequent protonation with HCl and crystallization from $CHCl_3$ layered with *n*-hexane provided the

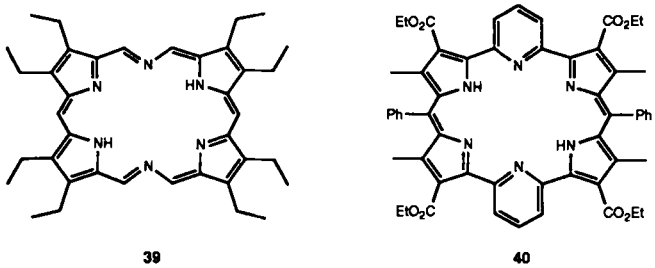


Scheme 3. Syntheses of amethyrins **37** and **38**.

24 π-electron hexapyrrolic macrocycle **37c** in the form of green crystals with a metallic luster (64% yield). Based on the dull purple color of the protonated form of this macrocycle in organic solution, we have assigned the trivial name "amethyrin" (from Greek *amethus*) to this expanded porphyrin.[34]

To date, no homologues higher than the "2 + 2" product represented by **37** have been detected under the reaction conditions used. Nor, interestingly, were any of the possible 26 π- or 22 π-electron (i.e., aromatic) macrocycles, corresponding to parent structures **32** and **34**, observed under these oxidative conditions. In fact, all attempts to prepare these latter species using a variety of oxidants failed (only the 24 π-electron species or decomposition products were obtained). Thus, this reaction bears closer analogy to that used to obtain rosarin[7] than it does to the Rothemund-like reactions used to generate porphyrins.[35]

This new macrocycle resembles structurally two recently reported expanded porphyrins, specifically **39** and **40**.[36, 37] On the one hand, it has the same number of inward-pointing nitrogen atoms and the same overall macrocyclic structure as Dolphin's porphocyanine (e.g., **39**, Fig. 7).[36] On the other hand, compound **37** is not aromatic. Thus, it resembles electronically the structurally similar expanded porphyrin **40** recently prepared by Corriu et al.[37]



39 **40**

Fig. 7. Porphocyanine (**39**), and Corriu's 24 π-electron macrocycle (**40**).

When protonated in organic solution (e.g., CH_2Cl_2), amethyrin appears bright red at higher concentration or when observed in longer pathlengths. Interestingly, it appears dull gray-purple at lower concentrations. In more quantitative terms, the UV/Vis absorption spectrum of the dihydrochloric acid salt **37c** displays three absorbance bands, with one rather strong Soret-like absorbance at 492.8 nm ($\log\varepsilon = 5.04$), one weaker, but still strong Q-like absorbance band at 597.0 nm ($\log\varepsilon = 4.75$), and one weak N-type absorption at 384.0 nm ($\log\varepsilon = 4.46$). The UV/Vis absorption spectrum of the free base of amethyrin (**37b**) has only one rather broad absorbance band (λ_{max} [nm] ($\log\varepsilon$): 467.8 (4.66), CH_2Cl_2), that is considerably less intense than its protonated counterpart. This free base form may be prepared by washing an organic solution of the protonated macrocycle with a 10% aqueous NaOH solution. In its free base form, amethyrin is bright orange in organic solution and is apparently quite stable. This finding has made it possible to explore the metal-binding chemistry of this new system, as will be described later.

Structural information for this macrocycle was gleaned from the ^1H and ^{13}C NMR spectra. The symmetry observed in the ^1H NMR spectrum as well as the number of observed peaks in the carbon spectrum support the structural assignment given for amethyrin **37**. Additionally, there is a remarkable downfield shift of the internal NH proton peaks to around $\delta = 24$, and an upfield shift of the *meso*-proton signal to $\delta = 3.4$. These shifts support the contention that this macrocycle is not aromatic. However, as discussed above in the case of orangarin, the origin of these unusual chemical shifts is currently not fully understood.[38]

Additional confirmation of the oxidation state and structure of the macrocycle was obtained from a single crystal X-ray structural analysis of the dihydrochloride salt of amethyrin (**37c**) (Fig. 8 and Table 1).[23] Here, the diprotonated macrocycle was shown to exist in a nearly planar conformation in the solid state, with the two chloride counteranions bound by hydrogen bonds to the ligating internal pyrrole NH groups. Deviation from planarity appears, as expected, to be the result of unfavorable methyl–methyl interactions between the central pyrrole ring and the two terminal pyrroles of each terpyrrole unit. These interactions serve to push the NH groups of the central pyrroles in opposite directions (i.e., above and below the mean plane of the macrocycle), and thus account for the observed solid state geometry.

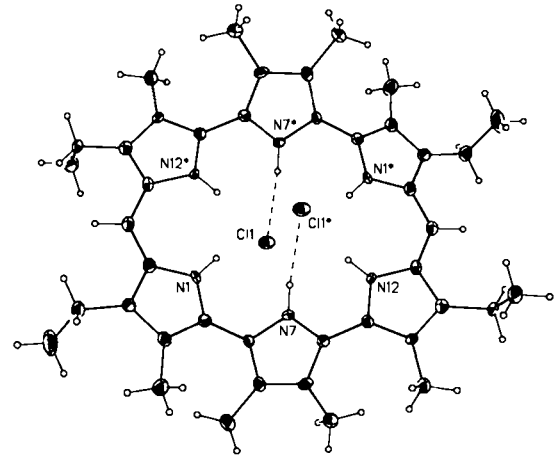


Fig. 8. View of molecule **37c** ($((C_{42}H_{52}N_6)^{+2}2Cl^-)$) showing a partial atom labeling scheme. The complex lies around an inversion center at 1/2, 1/2, 1/2. The central pyrrole of one terpyrrole moiety and the two terminal pyrroles of the second terpyrrole point towards one chloride ion. The Cl^- ion is within H-bonding distance of one hydrogen as indicated by the dashed lines. The relevant parameters are: N7–H7···Cl1 (related by $1-x$, $1-y$, $1-z$), N···Cl 3.214(6) Å, H···Cl 2.320(6) Å, N–H···Cl 172.1(6)°. The Cl ion is also close to the two remaining N–H protons: Cl···H1 2.509(6) Å and Cl···H12 2.779(6) Å, where Cl1, H1 and H12 are related by $1-x$, $1-y$, $1-z$.

Amethyrin Metalation Chemistry: The size of the internal core for amethyrin **37**, and its apparent stability under strongly basic conditions led us to suggest that this macrocycle could display a rich metal complexation chemistry. Since the fully deprotonated form of the macrocycle would be tetraanionic, one could envision that this system would potentially function as receptor for two M^{2+} centers. This promise has in fact been realized in the case of several first-row transition metals. For example, the bis-zinc adduct **41** was prepared by the reaction of the amethyrin **37c** with $ZnCl_2$ in methanol using triethylamine as the base (Scheme 4). After chromatographic separation, one obtains a rather acid-sensitive metal complex that formulates as $[H_2Zn_2(X)_2$(amethyrin)] (**41**), where X is a ca. 60:40 mixture of hydroxide and chloride (based on a single crystal X-ray diffraction analysis; see below). It is presumed that the chloride anion exchanges with hydroxide during the course of purification on basic silica.

The single crystal X-ray structure of this mixed-ligand bis-zinc complex is shown in Figure 9 (see Table 1).[23] When

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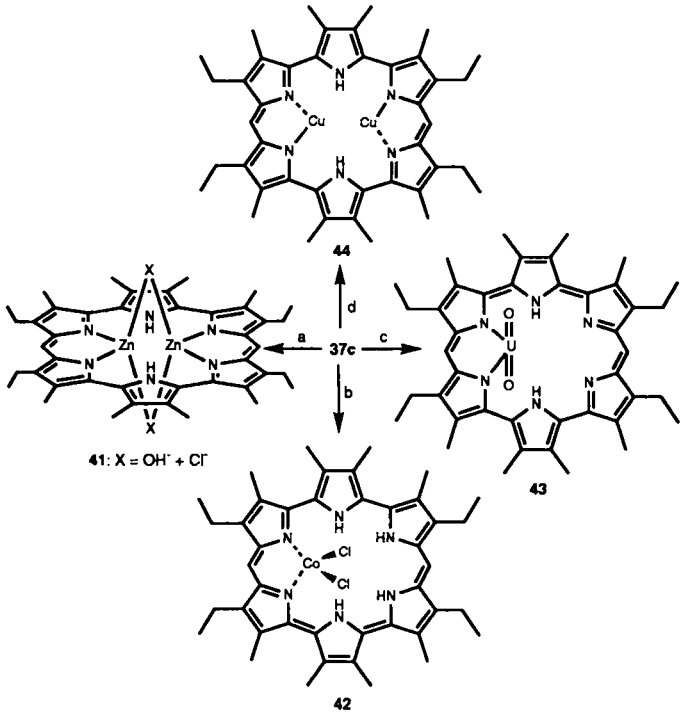


Scheme 4. Amethyrin metalation reactions. a: $ZnCl_2$, MeOH, Et_3N. b: $CoCl_2$, MeOH, Et_3N. c: UO_2Cl_2, MeOH, Et_3N. d: CuCl, MeOH, Et_3N.

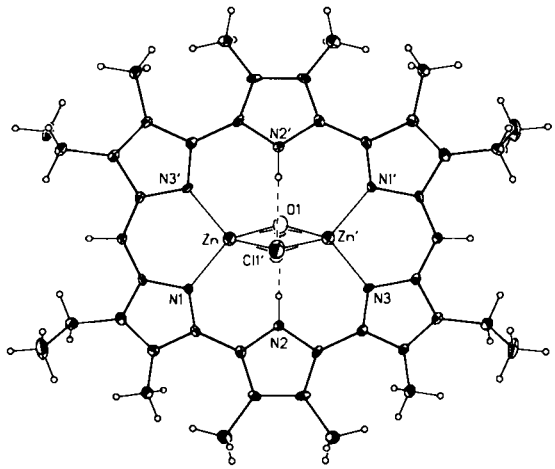


Fig. 9. View of **41** ($(C_{42}H_{48}N_6)Zn_2(OH)_{1.2}Cl_{0.8}$), showing a partial atom labeling scheme, approximately perpendicular to the hexaaza plane. The macrocycle lies around a crystallographic inversion center at 0, 0, 1/2. Atoms marked by ′ are related by $-x, -y, 1-z$. The bridging anion site is partially occupied by Cl^- and OH^- ions. The Zn···Zn distance is 2.824(2) Å. The central pyrrole ring has an average dihedral angle of 36.8° with respect to the terminal pyrroles.

looked upon from an end-on perspective, it is apparent that the two zinc atoms lie directly within the pocket of the macrocycle. Like the bis HCl salt, however, this species is not entirely planar. The central pyrroles of each terpyrrole unit within the macrocycle appear not to participate in metal binding. Instead, they apparently still possess their respective protons. Thus they point above or below the mean macrocyclic plane, and appear to form hydrogen bonds to the bridging anion. Nevertheless, when considered from the standpoint of the four "corner" pyrroles, one sees that this structure, at least as far as concerns the two zinc atoms and the four corner pyrrole nitrogens, is very nearly planar.

While it is clear from the X-ray structure that there is a nearly even mixture of chloride and hydroxide bridging anions, the fact that there is any hydroxy bridging at all is rather remarkable. Only very few examples of structurally characterized mono- or bis-hydroxide-bridged zinc complexes have appeared in the literature.[39] Why this is so is not exactly clear. One contributing factor may, however, be the ability of the H atom of the OH^- bridge to insert itself into other zinc–ligand bonds, leaving behind simple metal–oxygen species.[39] In the particular case of **41**, the hydrogen-bonding interactions could provide the stability needed to allow for formation of the isolated hydroxide-bridged product.

The isolation of the bis-zinc complex **41** is indeed a significant accomplishment. Not only does it represent the first structurally characterized in-plane bis-metalated expanded porphyrin, it also leads us to suggest that expanded porphyrins could have a role to play in bioinorganic modeling chemistry. For instance, while a majority of zinc-containing enzymes appear to contain only one zinc(II) ion in their active sites,[40] two recent structures of enzymes containing two zinc atoms in close proximity have been reported.[41]

In addition to zinc, amethyrin appears, as judged from UV/Vis and FAB mass spectrometric analyses, to form complexes with other divalent first row transition metals such as nickel, copper, and cobalt. Interestingly, however, in the case of cobalt(II), single crystal X-ray diffraction analysis (cf., Fig. 10 and Table 1)[23] of a complex prepared in a fashion analogous to that used to obtain bis-zinc amethyrin complex **41** (Scheme 4) revealed that only a single metal center is bound (e.g., **42**). In this case, it appears that the amethyrin ligand is only serving to fill the coordination sphere of the starting cobalt(II) chloride. This interesting result demonstrates, at the very least, that amethyrin is a versatile ligand capable of stabilizing both mono- and bis-metal complexes.

In any event, in the cobalt complex **42**, as in the bis-Zn complex, the cobalt is held within the mean plane of the macrocycle. Also, in analogy to complex **41**, in the cobalt structure, there appears to be a strong hydrogen-bonding interaction between the chloride atoms and the appropriate pyrrolic protons and again, it is presumed that this hydrogen bonding serves to stabilize the complex significantly.

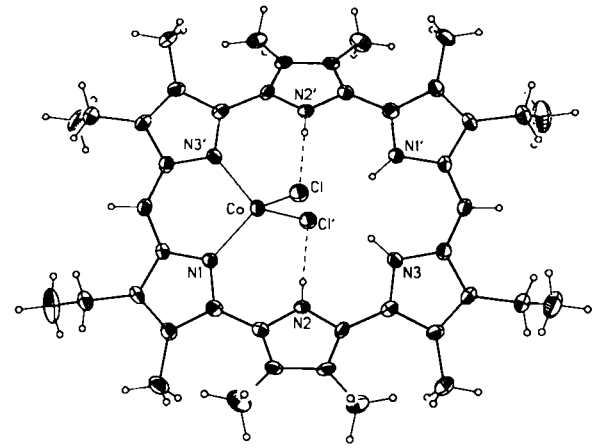
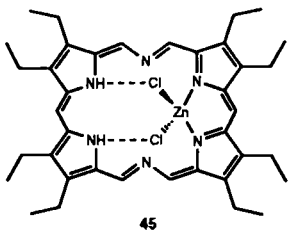


Fig. 10. View of **42** ($C_{42}H_{50}N_6CoCl_2$) with a partial atom labeling scheme. The macrocycle lies around a crystallographic inversion center at 0, 0, 0. This requires the Co^{2+} ion to be disordered about two equivalent positions in the macrocycle. By symmetry, the Co^{2+} ion is evenly divided about the two sites. The central pyrrole N–H group is directed toward the coordinated Cl^- ion. The geometry of this interaction is: N2–H2···Cl1, N···Cl 3.195(6) Å, H···Cl 2.295(6) Å, N–H···Cl 177.4(6)°.

The cobalt binding mode described above for amethyrin bears important analogy to some of the metalation chemistry seen in the case of the structurally similar porphocyanine **39**. For instance, reaction of $ZnCl_2$ with porphocyanine gives the monometalated species **45**[36a] (rather than a bis-Zn^{II} complex analogous to **41**). Complex **45** resembles the monocobalt–amethyrin adduct **42** in that the porphocyanine ligand serves only to fill the tetrahedral coordination sites of the $ZnCl_2$. As in the case of the $CoCl_2$–amethyrin complex **42**, the double bonds in the porphocyanine are set up such that two of the "end" pyrroles bear protons on the pyrrolic nitrogens, and the other end pyrroles are pyridine-like and can coordinate easily to the metal. Interestingly, as in the present instance, the crystal structure of $ZnCl_2$–porphocyanine complex **45** (Fig. 11), reveals hydrogen bonds involving the pyrrolic NH groups that serve, presumably, to stabilize the complex. However, in the porphocyanine case, the hydrogen bonds involve the "end" pyrroles and do not radiate out from central pyrrolic NH groups.



45

Fig. 11. $ZnCl_2$–porphocyanine complex.

In addition to the above, amethyrin was also found to form a complex with uranyl cation (e.g., **43**, Scheme 4). This complex, however, is very labile. Demetalation occurs rapidly even in weakly acidic conditions. Nonetheless, suitable low and high resolution mass spectral evidence for this material could be obtained.

Amethyrin **37c** has also been shown to form a remarkably stable bimetallic complex with Cu^{I} of presumed structure **44** (Scheme 4). In this case, as in the cases of the divalent first-row metal cations, high-resolution mass spectrometry confirmed the formation of a bimetallic complex. However, based upon mass spectral evidence, the existence of a parent species containing three or even four copper atoms can not as yet be ruled out. This interesting complex is, therefore, currently being studied further in our laboratories.

Bis(*p*-nitrophenyl)amethyrin: As is true for the porphyrins and rosarins, formation of amethyrin by the reaction of hexaalkylterpyrroles with aldehydes appears to be quite general. For example, terpyrrole **29** reacts with *p*-nitrobenzaldehyde to form, after oxidation, the 24 π-electron macrocycle **38a** (Scheme 3). It is interesting to note that in this case a stronger oxidant (DDQ) was required to effect the oxidation of the intermediate sp^3 condensation product. This is presumably the result of ethyl–phenyl steric interactions that raise the activation barrier for oxidation. This augmentation in presumed barrier height is thus reminiscent of the chemistry of the highly strained tetraphenyloctaalkylporphyrins[42] and trisphenylrosarins[7] where again DDQ was required in order to effect the preparations.

Confirmation of the chemical constitution and oxidation state of the bis(*p*-nitrophenyl)amethyrin derivative **38** was achieved by means of NMR analyses and a single crystal X-ray diffraction study. Here, for instance, analysis of the ^1H and ^{13}C NMR spectra of **38c** served to confirm the expected symmetry of the macrocycle, with one important exception. The methylene protons of the ethyl groups do not appear as one simple quartet, which is the expected multiplicity based on the high symmetry apparent in the rest of the spectrum. Rather, the methylene signal is split into two poorly resolved quartets of equal intensity. Further, these resonances appear at a higher field than is normally observed for such protons. Based on the location and observed multiplicity of these peaks, it is assumed that there is an interaction between the ethyl groups and the *meso*-phenyl rings. If this is the case, the proximity of the methylene protons to the aromatic π-cloud of the phenyl ring could account for the upfield shift of these protons. Further, this ethyl–phenyl proximity may serve both to slow free rotation in the ethyl group as well as to distort the macrocycle such that two (or more) low energy conformations may be available to the macrocycle. If interconversion between these conformations is slow on the NMR time scale, then, as in turcasarin, the possibility exists that the methylene protons would become diastereotopic and split, as is observed by experiment.

The single crystal X-ray diffraction structure of **38c** revealed the presence of two chloride counter anions and thus confirmed that the oxidation state of the macrocycle was indeed that of a 24 π-electron annulene (Fig. 12 and Table 1).[23] This same analysis served to reveal that the basic structure of the macrocycle is

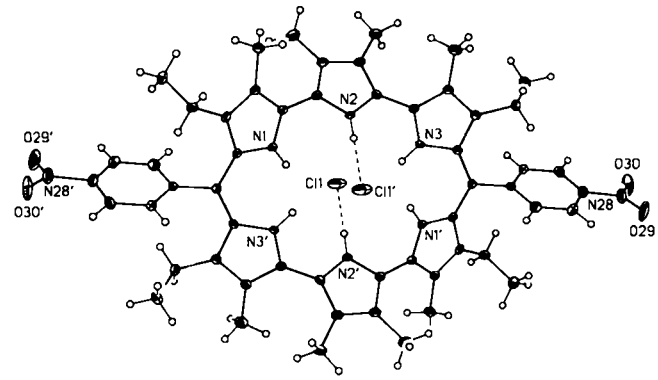


Fig. 12. View of **38c** ($(C_{54}H_{58}N_8O_4)^{2+}2Cl^-$) with a partial atom labeling scheme. The macrocycle lies around a crystallographic inversion center at 1/2, 1/2, 1/2. Atoms marked by ' are related by $1-x, 1-y, 1-z$. The central pyrrolic N–H group is within H-bonding distance of the Cl– ions with relevant geometry: N2–H2···Cl1', N···Cl 3.172(3) Å, H···Cl 2.300(3) Å, N–H···Cl 163.2(4)°. The plane through the central pyrrole has an average dihedral angle of 39.6° with planes through the terminal pyrroles.

relatively unaffected by *meso* substitution. This conclusion becomes apparent when the structures of amethyrins **37c** and **38c** are superimposed.[43] However, when viewed from the side, the X-ray structure of **38c** reveals a slight twisting in the macrocycle that results in the phenyl rings being pushed slightly in opposite directions above and below the mean plane of the macrocycle. Provided that interconversion between the resulting two apparent conformations is slow, the origin of the observed diastereotopicity in the methylene protons can easily be understood.

Conclusions

In this paper we have reported the first ever synthesis of hexa-β-alkyl, α-free terpyrroles. We have also shown this synthetic procedure to be useful in the preparation of tetra-β-alkyl terpyrroles. Further, we have demonstrated that these new hexaalkyl terpyrroles are useful in the preparation of novel expanded porphyrins. It is thus likely that these terpyrrolic precursors will allow for a further development of expanded porphyrin chemistry, just as their smaller bipyrrolic "cousins" are continuing to do.

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Experimental Procedure

General: Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 25 °C on a GE QE-300 spectrometer at 300 and 75.5 MHz, respectively. UV/Vis spectra were recorded on a Beckman DU-650 spectrophotometer. Elemental analyses were performed by Atlantic Microlabs. Low resolution FAB and CI mass spectra were obtained on a Finnigan MAT TSQ 70 mass spectrometer. High resolution FAB and CI mass spectra were obtained on a VG ZAB2-E mass spectrometer. FAB spectra were obtained using a nitrobenzyl alcohol (NBA) matrix.

Dichloromethane was dried by distillation under nitrogen from calcium hydride. Tetrahydrofuran (THF) was dried by distillation under nitrogen from sodium benzophenone ketyl. Toluene was distilled under nitrogen from sodium. All other solvents, acids, and bases were obtained commercially and used as received. Propionyl chloride, tin tetrachloride, copper(II) triflate, *p*-chloranil, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), $CoCl_2$, CuI, and trifluoroacetic acid (TFA) were purchased from Aldrich Chemical Company and used as received. $ZnCl_2$ was purchased from Fisher Scientific and used as received. UO_2Cl_2 was purchased from Strem Chemicals and used as received. Acetic anhydride, ammonium carbonate and aqueous formaldehyde were purchased from J. T. Baker Inc. and used as received.

14 (Ethyl 5-acetyl-3,4-dimethylpyrrole-2-carboxylate): In a 500 mL round-bottomed flask equipped with a magnetic stirrer, an argon inlet, and a rubber septum, ethyl-3,4-dimethylpyrrole-2-carboxylate (**10**) [44] (7.16 g, 42.9 mmol) was dissolved in 200 mL of dry CH_2Cl_2. Acetyl chloride (3.66 mL, 51.4 mmol) was then added and the reaction mixture cooled in an ice water bath to 0 to 5 °C. $SnCl_4$ (4.0 mL, 34.3 mmol) was added over five minutes with a syringe. After the addition of $SnCl_4$ was complete, the deep red reaction mixture was stirred at room temperature for 15 min. Water was added to quench the reaction (50 mL) and the mixture stirred until the red color disappeared. The CH_2Cl_2 layer was separated off using a separatory funnel and then washed with 1 N HCl (2 × 50 mL), 10% aqueous NaOH (1 × 50 mL), and water (1 × 50 mL). The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo on a rotary evaporator to afford a light yellow solid. *n*-Hexane (25 mL) was added to the solid and the flask was placed in the freezer overnight. Filtration and washing with cold *n*-hexane afforded a white to off-white solid. A second crop of clean product was obtained by concentrating the mother liquor and placing it in the freezer. Yield: 7.90 g (88%). M.p.: 96–98.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.32 (q, J = 7.1 Hz, 2H, CH_2CH_3), 9.54 (br, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.9, 11.1, 14.3, 28.6, 60.6, 122.3, 125.5, 127.2, 130.5, 161.0, 188.6; LRMS (CI +) *m/e*: 164 (19.2), 209 (42.6), 210 (100.0), 211 (11.2); HRMS (CI +) *m/e* calc'd. for $C_{11}H_{16}NO_3$ $(M+1)^+$: 210.1130, found: 210.1142.

17 (1,4-Bis(3,4-dimethyl-5-ethoxycarbonyl-2-pyrryl)-1,4-butanedione): In a three neck 500 mL round-bottomed flask equipped with an argon inlet and a dropping funnel, *n*-butyl lithium (45 mL, 71.9 mmol; 1.6 M in *n*-hexane) was mixed with 60 mL of dry THF and cooled to 0 °C in an ice water bath. Diisopropylamine (10.1 mL, 71.9 mmol) was added dropwise *via* an addition funnel (addition time about 10 min) and the mixture stirred at 0 °C for 15 min. A solution of **14** (7.16 g, 34.2 mmol) in 40 mL of dry THF was added dropwise over 10 min. The resulting yellow suspension was allowed to stir at room temperature for 45 min before being cooled to 0 °C. Copper(II)triflate (13.6 g, 37.7 mmol) was dissolved in 60 mL of dry DMF and added rapidly *via* an addition funnel (addition time ca. 1 min.). The dark green solution was stirred at 0 °C for 15 min and then at room temperature for 45 min. HCl was added (0.5 N, 100 mL) to quench the reaction. The resulting two phase mixture was then stirred for 10 min. The flask contents were transferred to a separatory funnel and extracted with chloroform (5 × 50 mL). The combined organic layers were then washed with 1 N HCl (1 × 100 mL) and brine (1 × 100 mL) and dried over Na_2SO_4. The solvent was then removed in vacuo on a rotary evaporator to give a brown oil in which some precipitate began to form. Ethanol (10 mL) and *n*-hexane (10 mL) were added to the crude mixture resulting in large quantities of precipitate. Still, the flask was placed in the freezer overnight to induce yet further precipitation. The total quantity of yellow solid that was finally obtained in this way was filtered off. It was washed with cold 50:50 ethanol in *n*-hexane, followed by cold *n*-hexane, and dried in vacuo. Yield of bright yellow solid diketone (**17**): 3.23 g (45%). M.p.: 163–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1, 6H, OCH_2CH_3), 2.26 (s, 6H, CH_3), 2.32 (s, 6H, CH_3), 3.23 (s, 4H, $C(O)CH_2$), 4.32 (q, J = 7.1, 4H, OCH_2CH_3), 9.63 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.9, 11.1, 14.3, 28.6, 60.6, 122.3, 125.5, 127.2, 130.5, 161.0, 188.6; LRMS (CI +) *m/e*: 415 (35.5), 416 (63.0), 417 (100.0), 418 (29.8); HRMS (CI +) *m/e* calcd for $C_{22}H_{29}N_2O_6$ $(M+1)^+$: 417.2025, found: 417.2021.

22 (2,5-Bis(3,4-dimethyl-5-ethoxycarbonyl-2-pyrryl)pyrrole): In a 100 mL round-bottomed flask, **17** (2.00 g, 4.81 mmol) was suspended in 50 mL of glacial acetic acid under an argon blanket. Ammonium carbonate was added (4.62 g, 48.1 mmol) at a rate such that excessive effervescence was avoided. The mixture was then heated to 120–130 °C for 25 min. The greenish solution was allowed to cool to 80 °C as a light green solid began to precipitate out. This suspension was poured over 100 mL of ice water with stirring. After 30 min stirring, the light green solid was collected by filtration and washed with water. The solid was dissolved in 25 mL of CH_2Cl_2 by adding small amounts of methanol as necessary to effect full dissolution (ca. 5 mL). This solution was washed with 50% sat. $NaHCO_3$ (1 × 50 mL). The organic phase was separated off and dried over Na_2SO_4. The solvent was removed in vacuo to afford a green solid. Methanol was added (10 mL) and the suspension stirred vigorously for 30 min. The product was filtered off as a light green solid that was dried in vacuo. Yield: 1.59 g (83%). M.p.: 243–245 °C (decomp.); ^{1}H NMR (300 MHz, $[D_6]$DMSO): δ = 1.30 (t, J = 7.1 Hz, 6H, CH_2CH_3), 2.08 (s, 6H, CH_3), 2.24 (s, 6H, CH_3), 4.25 (q, J = 7.1 Hz, 4H, CH_2CH_3), 6.39 (d, J = 1.3 Hz, 2H, CH), 11.07 (s, 2H, NH), 11.13 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $[D_6]$DMSO): δ = 10.0, 10.4, 14.5, 59.1, 108.7, 116.0, 117.0, 124.1, 126.6, 126.9, 161.0; LRMS (CI +) *m/e*: 415 (35.5), 416 (63.0), 417 (100.0), 418 (29.8); HRMS (CI +) *m/e* calcd for $C_{22}H_{27}N_3O_4$ $(M)^+$: 397.2002, found: 397.2011.

27 (2,5-Bis(3,4-dimethyl-2-pyrryl)pyrrole): In a 100 mL round-bottomed flask equipped with a reflux condenser and an argon inlet, **22** (274 mg, 0.69 mmol) and excess NaOH (1 g) were suspended in 5 mL ethylene glycol. While under an argon sweep, the flask was immersed in a silicon oil bath held at 180 °C for 30 min. The light green solution was allowed to cool to 100–120 °C before 30 mL of degassed water was added. The resulting precipitate was collected by vacuum filtration under an argon sweep and dried in vacuo to afford a light gray powder that darkens rapidly on exposure to air. Yield: 140 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 6H, CH_3), 2.18 (s, 6H, CH_3), 6.14 (s, 2H, CH), 6.48 (s, 2H, CH), 7.58 (br, 2H, NH), 8.09 (br, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.8, 10.2, 105.8, 114.1, 114.9, 119.4, 122.1, 125.7; LRMS (CI +) *m/e*: 205 (25.8), 220 (24.7), 253 (4.0); HRMS (CI +) *m/e* calcd for $C_{16}H_{19}N_3$ (M^+): 253.1579, found: 253.1594.

15 (Ethyl 3,4-dimethyl-5-propionylpyrrole-2-carboxylate): In a 500 mL round-bottomed flask equipped with a magnetic stirrer, an argon inlet, and a rubber septum, ethyl 3,4-dimethylpyrrole-2-carboxylate (**10**) [44] (16.85 g, 101 mmol) was dissolved in 200 mL of dry CH_2Cl_2. Propionyl chloride (10.52 mL, 120 mmol) was then added, and the reaction mixture was cooled in an ice water bath to 0–5 °C. $SnCl_4$ (6.5 mL, 55.6 mmol) was added over 5 min with a syringe. After the addition of $SnCl_4$ was complete, the deep red reaction mixture was stirred at room temperature for 15 min. Water was added to quench the reaction (100 mL) and the mixture stirred until the red color disappeared. The CH_2Cl_2 layer was separated off in a separatory funnel and then washed with 1 N HCl (2 × 100 mL), 10% NaOH (1 × 100 mL), and water (1 × 100 mL). The organic layer was dried over Na_2SO_4, and the solvent removed in vacuo on a rotary evaporator to afford a light yellow oil. This oil was dissolved in *n*-hexane (50 mL) and placed in the freezer overnight to allow for crystallization. Filtration and washing with cold *n*-hexane afforded the product as a white to off-white solid. Second and third crops of clean product were obtained by concentrating the mother liquor and placing it in the freezer. Yield: 20.5 g (91%). M.p.: 74.0–75.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.33 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.22 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.77 (q, J = 2 Hz, 7.3H, CH_2CH_3), 4.29 (q, J = 2 Hz, 7.1H, CH_2CH_3), 9.54 (br, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 7.7, 9.9, 11.1, 14.2, 33.8, 60.4, 122.0, 124.7, 127.1, 130.2, 161.0, 191.8; LRMS (CI +) *m/e*: 225 (27), 224 (100), 223 (64), 194 (21), 178 (38), 148 (26); HRMS (CI +) *m/e* calcd for $C_{12}H_{17}NO_3$ $(M+1)^+$: 223.1208, found: 223.1212.

18 and **19** (*meso*- and *d,l*-1,4-Bis(3,4-dimethyl-5-ethoxycarbonyl-2-pyrryl)-2,3-dimethyl-1,4-butanedione): In a three-neck, 500 mL round-bottomed flask equipped with an argon inlet and a dropping funnel, *n*-butyllithium (69.0 mL, 110.2 mmol; 1.6 M in *n*-hexane) was mixed with 70 mL of dry THF and cooled to 0 °C with an external ice water bath. Diisopropylamine (15.45 mL, 110.2 mmol) was added dropwise by means of an addition funnel (addition time about 10 min), and the resulting mixture stirred at 0 °C for 15 min. A solution of **15** (12.44 g, 52.5 mmol) in 25 mL of dry THF was added dropwise over 10 min. The yellow reaction mixture was allowed to stir at room temperature for 45 min. The resulting yellow suspension was then cooled to 0 °C. Copper(II) triflate (21.31 g, 57.7 mmol) was dissolved in 60 mL of dry DMF and added rapidly through an addition funnel (addition time ca. 1 min). The resulting dark green solution was stirred at 0 °C for 15 min, and then at room temperature for 45 min. HCl was added (0.5 N, 200 mL) to quench the reaction and the two phase mixture stirred for 10 min. The flask contents were transferred to a separatory funnel and extracted with chloroform (5 × 50 mL). The combined organic layers were then washed with 1 N HCl (1 × 100 mL) and brine (1 × 100 mL) and dried over Na_2SO_4. The solvent was then removed in vacuo on a rotary evaporator to give a brown oil. Ethanol (10 mL) and *n*-hexane (50 mL) were added to the oil and the flask placed in the freezer overnight. The white solid so obtained was filtered off, washed with ethanol and then *n*-hexane, and dried in vacuo to give 2.6 g (26%) of the *meso* compound (**18**). The *d,l* mixture of isomers was isolated by concentrating the mother liquor further before adding EtOH (1 mL) and *n*-hexane (10 mL) and then placing the resulting mixture in the freezer. This afforded 2.7 g (27%) of the *d,l* mixture of isomers (**19**) as an off-white solid. Overall diketone yield: 5.3 g (53%). *meso* material (**18**): M.p.: 215–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, J = 5.5 Hz, 6H, $CHCH_3$), 1.36 (t, J = 7.1 Hz, 6H, OCH_2CH_3), 2.25 (s, 6H, CH_3), 2.27 (s, 6H, CH_3), 2.36 (s, 6H, CH_3), 3.70 (m, 2H, $CHCH_3$), 4.34 (q, J = 7.1 Hz, 4H, OCH_2CH_3), 9.60 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.9, 11.2, 14.3, 16.8, 44.7, 60.0, 60.7, 122.8, 126.3, 127.6, 129.8, 160.9, 194.3; LRMS (CI +) *m/e*: 445 (100), 446 (19); HRMS (CI +) *m/e* calcd for $C_{24}H_{32}N_2O_6$ (M^+): 444.2260, found: 444.2253. *d,l* material (**19**): M.p.: 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, J = 5.9 Hz, 6H, $CHCH_3$), 1.34 (t, J = 7.2 Hz, 6H, CH_2CH_3), 2.27 (s, 6H, CH_3), 2.35 (s, 6H, CH_3), 3.65 (m, 2H, $CHCH_3$), 4.31 (q, J = 7.1 Hz, 4H, CH_2CH_3), 9.51 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.9, 10.9, 14.3, 15.3, 44.8, 60.4, 122.5, 125.6, 127.4, 129.2, 160.8, 195.2; LRMS

(CI +) *m/e*: 278 (83), 445 (79), 446 (100), 447 (71); HRMS (CI +) *m/e* calcd for $C_{24}H_{33}N_2O_6$ (M + 1)$^+$: 445.2339, found: 445.2342.

23 (2,5-Bis(3,4-dimethyl-5-ethoxycarbonyl-2-pyrryl)-3,4-dimethylpyrrole): In a 100 mL round-bottomed flask, **18** and **19** (1.2 g, 2.7 mmol) were suspended in 50 mL of glacial acetic acid under an argon blanket. Acetic anhydride (1 mL) was added, followed by ammonium carbonate (2.6 g, 27 mmol) at a rate such that excessive effervescence was avoided. The mixture was then heated to 120–130 °C for 16 h. The greenish solution was allowed to cool to 80 °C and then poured over 50 mL of ice water with stirring. After 30 min stirring, the light green solid was collected by filtration and washed with water. Recrystallization from $CHCl_3$ layered with *n*-hexane and drying in vacuo afforded a light gray powder. Yield: 1.0 g (90%). M.p.: 215.5–218 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.28 (t, J = 7.1 Hz, 6H, OCH_2CH_3), 1.94 (s, 12H, $2\times CH_3$), 2.23 (s, 6H, CH_3), 4.21 (q, J = 7.0 Hz, 4H, OCH_2CH_3), 10.47 (s, 1H, NH), 10.86 (s, 2H, NH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 10.0, 10.4, 10.6, 14.5, 58.9, 116.8, 117.3, 117.7, 120.4, 126.2, 126.9, 160.9; LRMS (FAB +) *m/e*: 333 (38), 379 (69), 425 (100); HRMS (FAB +) *m/e* calcd for $C_{24}H_{31}N_3O_4$ (M$^+$): 425.2315, found: 425.2322.

24 (2,5-Bis(3,4-dimethyl-5-ethoxycarbonyl-2-pyrryl)-3,4-dimethylfuran): This compound was obtained as a by-product of the reaction used to prepare **23**. It was isolated during the course of the purification of the latter by chromatographic separation (silica gel, $CHCl_3$ as eluent) as the first fraction (glows blue under UV light on silica gel TLC plate). Yield: ca. 5%. M.p.: 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, J = 7.1 Hz, 6H, OCH_2CH_3), 2.09 (s, 6H, CH_3), 2.11 (s, 6H, CH_3), 2.31 (s, 6H, CH_3), 4.32 (q, J = 7.1 Hz, 4H, CH_2CH_3), 8.80 (br, 2H NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.5, 10.2, 10.4, 14.5, 60.0, 119.3, 119.4, 119.5, 123.6, 127.5, 142.0, 161.5; LRMS (FAB +) *m/e*: 380 (50), 426 (100); HRMS (FAB +) *m/e* calcd for $C_{24}H_{30}N_2O_5$ (M$^+$): 426.2155, found: 426.2161.

28 (2,5-Bis(3,4-dimethyl-2-pyrryl)-3,4-dimethylpyrrole): In a 100 mL round-bottomed flask equipped with a reflux condenser and an argon inlet, **23** (860 mg, 2.0 mmol) and excess NaOH (2 g) were suspended in 10 mL of ethylene glycol. While under an argon sweep, the flask was immersed in a silicon oil bath held at 180 °C for 30 min. The resulting light green solution was allowed to cool to 100–120 °C before 25 mL of degassed water was added. The somewhat air-sensitive precipitate that resulted was collected by vacuum filtration under an argon sweep and dried in vacuo to afford a gray to light green powder. The terpyrrolic product may be recrystallized, if desired, from CH_2Cl_2/*n*-hexane on the rotary evaporator in order to remove any trace of furan-containing compound arising from **24**. Yield: 546 mg (96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (s, 6H, CH_3), 2.08 (s, 6H, CH_3), 2.09 (s, 6H, CH_3), 6.58 (s, 2H, α-pyrrolic-*H*), 7.67 (br, 1H, NH), 7.75 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.8, 10.1, 10.4, 115.0, 115.9, 116.6, 119.1, 121.3, 121.7; LRMS (CI +) *m/e*: 281 (39), 282 (100), 283 (29); HRMS (CI +) *m/e* calcd for $C_{18}H_{24}N_3$(M + 1)$^+$: 282.1970, found: 282.1981.

16 (Ethyl 3-ethyl-4-methyl-5-propionylpyrrole-2-carboxylate): In a 500 mL round-bottomed flask equipped with a magnetic stirrer, an argon inlet, and a rubber septum, ethyl 3-ethyl-4-methylpyrrole-2-carboxylate (**11**) (12.55 g, 69.3 mmol) was dissolved in 200 mL of dry CH_2Cl_2. Propionyl chloride (7.23 mL, 83.2 mmol) was then added, and the reaction mixture was cooled in an ice water bath to 0–5 °C. $SnCl_4$ (6.5 mL, 55.6 mmol) was then added over 5 min with a syringe. After the addition of the $SnCl_4$ was complete, the deep red reaction mixture was stirred at room temperature for 15 min. Water (100 mL) was added to quench the reaction and the mixture stirred until the red color disappeared. The CH_2Cl_2 layer was separated off in a separatory funnel and washed with 1 N HCl (2 × 100 mL), 10% aqueous NaOH (1 × 100 mL), and water (1 × 100 mL). The organic layer was dried over Na_2SO_4, and the solvent removed in vacuo on a rotary evaporator to afford a light yellow oil. The oil was dissolved in *n*-hexane (50 mL) and placed in the freezer overnight. Filtration and washing with cold *n*-hexane afforded a white to off-white solid. Second and third crops of clean product were obtained by concentrating the mother liquor, and placing it in the freezer. Yield: 14.12 g (86%). M.p.: 54–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.20 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.36 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.29 (s, 3H, CH_3), 2.75 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.80 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.33 (q, J = 7.1 Hz, 2H, CH_2CH_3), 9.53 (br, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 7.8, 11.0, 14.3, 15.0, 17.7, 33.9, 60.5, 121.5, 124.1, 130.4, 133.9, 160.9, 191.9; LRMS (CI +): *m/e* : 238 (100); HRMS (CI +) *m/e* calcd for $C_{13}H_{19}NO_3$ (M)$^+$: 237.1365, found 237.1370; Analysis calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90; found: C, 65.89; H, 8.10; N, 5.93.

20 and **21** (*meso*- and *d,l*-1,4-Bis(5-ethoxycarbonyl-4-ethyl-3-methyl-2-pyrryl)-2,3-dimethyl-1,4-butanedione): In a three-neck, 500 mL round-bottomed flask equipped with an argon inlet and a dropping funnel, *n*-butyllithium (69.0 mL, 110.2 mmol; 1.6 M in *n*-hexane) was mixed with 70 mL of dry THF and cooled to 0 °C in an ice water bath. Diisopropylamine (15.45 mL, 110.2 mmol) was added dropwise through an addition funnel (addition time about 10 min) and the mixture stirred at 0 °C for 15 min. A solution of **16** (12.44 g, 52.5 mmol) in 25 mL of dry THF was added dropwise over 10 min. The resulting yellow reaction mixture was allowed to stir at room temperature for 45 min. This yielded a yellow suspension that, in turn, was cooled to 0 °C. Copper(II) triflate (21.31 g, 57.7 mmol), previously dissolved in 60 mL of dry DMF was then added rapidly through an addition funnel (addition time ca. 1 min.). The resulting dark green solution was stirred at 0 °C for 15 min, and then at room temperature for 45 min. HCl (0.5 N, 200 mL) was added to quench the reaction. The two phase mixture that resulted was stirred for 10 min. The flask contents were transferred to a separatory funnel and extracted with $CHCl_3$ (5 × 50 mL). The combined organic layers were then washed with 1 N HCl (1 × 100 mL) and brine (1 × 100 mL) and dried over Na_2SO_4. The solvent was removed in vacuo on a rotary evaporator to give a brown oil. Ethanol (10 mL) and *n*-hexane (50 mL) were added to the oil and the flask placed in the freezer overnight. The white solid that resulted was filtered off, washed first with ethanol and then with *n*-hexane, and then dried in vacuo to afford 3.08 g (25%) of the *meso* compound **20**. The *d,l* mixture of isomers was isolated chromatographically from the mother liquor on silica gel with $CHCl_3$ as eluent. Recrystallization from $CHCl_3$ layered with *n*-hexane afforded 1.95 g (16%) of the *d,l* mixture of isomers **21** as an off-white solid. Overall diketone yield: 5.03 g (41%). *meso* material (**20**): M.p.: 220–222 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.4 Hz, 6H, CH_2CH_3), 1.14 (d, J = 6.2 Hz, 6H, $CHCH_3$), 1.38 (t, J = 7.1 Hz, 6H, CH_2CH_3), 2.39 (s, 6H, CH_3), 2.77 (q, J = 7.5 Hz, 4H, CH_2CH_3), 3.71 (m, 2H, $CHCH_3$), 4.36 (q, J = 7.1 Hz, 4H, CH_2CH_3), 9.61 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.0, 14.4, 15.0, 17.0, 17.8, 44.7, 60.7, 122.4, 125.7, 130.0, 134.2, 160.8, 194.4; LRMS (FAB +) *m/e*: 473 (28), 472 (20), 427 (5), 293 (31), 292 (100), 264 (20), 246 (60), 208 (35), 162 (77); HRMS (FAB +) *m/e* calcd for $C_{26}H_{36}N_2O_6$: 472.2573, found 472.2560. *d,l* material (**21**): M.p.: 131–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.1 Hz, 6H, CH_2CH_3), 1.37 (t, J = 7.1 Hz, 6H, CH_2CH_3), 1.69 (d, J = 6.8 Hz, 6H, $CHCH_3$), 2.78 (q, J = 7.0 Hz, 4H, CH_2CH_3), 4.37 (q, J = 7.0 Hz, 4H, CH_2CH_3), 4.97 (q, J = 6.9 Hz, 2H, $CHCH_3$), 9.68 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.5, 14.2, 14.9, 17.6, 19.5, 53.9, 60.8, 123.2, 126.6, 127.7, 133.8, 160.6, 184.7.

25 (2,5-Bis(5-ethoxycarbonyl-4-ethyl-3-methyl-2-pyrryl)-3,4-dimethylpyrrole): In a 100 mL round-bottomed flask, **20** and **21** (2.89 g, 6.1 mmol) were suspended in 20 mL of glacial acetic acid under an argon blanket. Acetic anhydride (1 mL) was added, followed by ammonium carbonate (5.86 g, 61.0 mmol), at a rate such that excessive effervescence was avoided. The mixture was then heated to 120–130 °C for 16 h. The greenish solution was allowed to cool to 80 °C and then poured over 30 mL of ice water with vigorous stirring. After 30 min stirring, the greenish solid that resulted was collected by filtration and washed with water. This solid was taken up in 50 mL of CH_2Cl_2, washed with sat. $NaHCO_3$ (2 × 50 mL) before the organic layer was dried over Na_2SO_4. The resulting pink solid was recrystallized from $CHCl_3$ layered with *n*-hexane. Drying in vacuo afforded the product **25** as a light purple crystalline solid. Yield: 1.97 g (71%). M.p.: 196–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.4 Hz, 6H, CH_2CH_3), 1.30 (t, J = 7.1 Hz, 6H, CH_2CH_3), 2.07 (s, 12H, $2\times CH_3$), 2.77 (q, J = 7.3 Hz, 4H, CH_2CH_3), 4.22 (q, J = 7.0 Hz, 4H, CH_2CH_3), 8.24 (br, 1H, NH), 8.93 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.8, 10.3, 14.4, 15.0, 18.5, 59.9, 117.6, 117.9, 118.4, 120.9, 126.2, 134.2, 161.7; UV/Vis (CH_2Cl_2) λ_{max} [nm] (log ε): 337.5 (4.47); LRMS (FAB +) *m/e*: 453 (100), 407 (83), 361 (46); HRMS (FAB +) *m/e* calcd for $C_{26}H_{35}N_3O_4$: 453.2628, found: 453.2620; Analysis calcd for $C_{26}H_{35}N_3O_4$: C, 68.85; H, 7.78; N, 9.26; found: C, 68.63; H, 7.72; N, 9.18.

26 (2,5-Bis(5-ethoxycarbonyl-4-ethyl-3-methyl-2-pyrryl)-3,4-dimethylfuran): Obtained as a by-product from the reaction sequence used to prepare **25**. It was isolated as the first fraction during the course of column chromatographic separation (silica gel, $CHCl_3$ as eluent) of **25** (glows blue under UV light on silica gel TLC plate). Yield: ca. 5%. M.p.: 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.4 Hz, 6H, CH_2CH_3), 1.35 (t, J = 7.1 Hz, 6H, OCH_2CH_3), 2.10 (s, 6H, CH_3), 2.13 (s, 6H, CH_3), 2.79 (q, J = 7.4 Hz, 4H, CH_2CH_3), 4.31 (q, J = 7.1 Hz, 4H, OCH_2CH_3), 8.87 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.5, 9.9, 14.4, 14.9, 18.3, 59.9, 118.7, 199.6, 123.9, 134.0, 142.0, 161.3, 191.9; LRMS (FAB +) *m/e*: 362 (23), 408 (61), 454 (100); HRMS (FAB +) *m/e* calcd for $C_{26}H_{34}N_2O_5$ (M$^+$): 454.2468, found: 454.2464.

29 (2,5-Bis(4-ethyl-3-methyl-2-pyrryl)-3,4-dimethylpyrrole): In a 100 mL round-bottomed flask equipped with a reflux condenser and an argon inlet, **25** (1.08 g, 2.4 mmol) and excess NaOH (2 g) were suspended in 20 mL ethylene glycol. While under an argon sweep, the flask was immersed in a silicon oil bath held at 180 °C for 30 min. The light green solution was allowed to cool to 100–120 °C. Degassed water (30 mL) was then added. The resulting, somewhat air-sensitive precipitate was collected by vacuum filtration under an argon sweep. Drying in vacuo afforded product **29** as a white to light green powder. The terpyrrolic product may be recrystallized, if desired, from CH_2Cl_2/*n*-hexane on the rotary evaporator to remove any traces of furan-containing compound arising from **26**. Yield: 78.6 mg (96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 6H, CH_2CH_3), 2.08 (s, 12H, $2\times CH_3$), 2.52 (q, J = 7.3 Hz, 4H, CH_2CH_3), 6.59 (s, 2H, CH), 7.63 (br, 1H, NH), 7.72 (br, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.8, 10.1, 14.2, 18.7, 77.4, 113.8, 115.2, 116.6, 121.2, 121.8, 126.1; LRMS (FAB +) *m/e*: 309 (100); HRMS (FAB +) *m/e* calcd for $C_{20}H_{27}N_3$: 309.2205, found: 309.2189.

31 (Orangarin): In a 500 mL round-bottomed flask equipped with an argon inlet and a magnetic stirrer, 4,4'-diethyl-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole (**30**) (53.4 mg, 1.96×10^{-4} mol) was dissolved in 20 mL EtOH. CH_2Cl_2 (250 mL) was added, followed by 2,5-bis(3,4-dimethyl-2-pyrryl)-3,4-dimethylpyrrole (**28**) (55.2 mg, 1.96×10^{-4} mol). Six drops conc. aq. HCl was then added and the reaction was allowed to stir at room temperature overnight. The solvent was removed with the aid of a rotary evaporator and the residue was purified chromatographically on silica gel (3 × 15 cm, 1% MeOH in $CHCl_3$ as eluent). The first orange fraction was concentrated to ca. 25 mL, transferred to a separatory funnel, and washed with 1 N

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HCl (2 × 25 mL). The organic layer was separated off, and dried over Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting residue recrystallized from $CHCl_3$ layered with *n*-hexane. Yield: 58.5 mg (59%). M.p.: decomp. > 225 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = -0.02$ (br, 2H, N*H*), 0.07 (br, 1H, N*H*), 0.11 (br, 2H, N*H*), 0.26 (t, $J = 7.2$ Hz, 6H, CH_2CH_3), 0.41 (s, 6H, CH_3), 0.42 (s, 6H, CH_3), 0.58 (s, 6H, CH_3), 0.68 (s, 6H, CH_3), 0.99 (q, $J = 7.4$ Hz, 4H CH_2CH_3), 2.37 (s, 2H, *meso-H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 8.0, 8.1, 8.2, 8.6, 13.2, 16.2, 122.9, 126.9, 129.6, 134.5, 134.7, 139.2, 146.3, 146.5, 151.6, 159.6.; UV/Vis (CH_2Cl_2) λ_{max} [nm] (logε): 366.8 (4.14), 462.8 (4.52), 551.8 (4.26); LRMS (FAB +) *m/e*: 518 (100); HRMS (FAB +) *m/e* calcd for $C_{34}H_{40}N_5$ $(M-2HCl+1)^+$: 518.3284, found: 518.3293. For the free base of **31** (**31b**), prepared by washing a CH_2Cl_2 solution of **31a** with 10% NaOH (2 × 50 mL): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.72$ (t, $J = 7.6$ Hz, 6H, CH_2CH_3), 1.13 (s, 6H, CH_3), 1.23 (s, 12H, 2 × CH_3), 1.35 (s, 6H, CH_3), 1.60 (q, $J = 7.6$ Hz, 4H CH_2CH_3), 4.09 (s, 2H, *meso-H*). (no NH peaks could be observed in this experiment.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 8.6, 10.2, 10.4, 10.7, 14.8, 16.7, 117.4, 122.3, 124.2, 125.4, 129.7, 136.8, 138.8, 140.5, 140.7, 148.7, 160.7.

37 (Amethyrin): In a 2000 mL round-bottomed flask, **29** (684.7 mg, 2.2 mmol) was dissolved in 1000 mL of CH_2Cl_2 under an argon blanket. Formaldehyde (165.8 mL, 2.2 mmol, 37% aq.) was added and the mixture stirred vigorously for 5 min. TFA (0.5 mL) was added, and the solution was stirred at room temperature for 3 h. *p*-Cloranil (1.19 g, 4.8 mmol) was added and the mixture was allowed to stir overnight. The solvent was removed in vacuo with the aid of a rotary evaporator. The residue was taken up in CH_2Cl_2 (50 mL) and washed with 10% NaOH (2 × 50 mL). The organic phase was dried over Na_2SO_4 and the solvent removed. The resulting solid material was purified chromatographically on a pre-basified silica gel column (4 × 30 cm, made basic by bubbling NH_3 through a CH_2Cl_2 slurry of silica gel). The first orange fraction off the column with CH_2Cl_2 as the eluent was collected, concentrated in vacuo, and washed with 1 N HCl (3 × 50 mL). The organic layer was dried over Na_2SO_4 before the solvent was removed in vacuo. Recrystallization from $CHCl_3$ layered with *n*-hexane afforded the dihydrochloric acid salt of amethyrin (**37c**) as green crystals with a metallic luster. Yield: 502 mg (64%). M.p.: decomp. > 280 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.59$ (t, $J = 7.4$ Hz, 12H, CH_2CH_3), 0.74 (s, 12H, CH_3), 0.89 (s, 12H, CH_3), 1.27 (q, $J = 7.3$ Hz, 8H, CH_2CH_3), 3.40 (s, 2H, *meso-H*), 23.57 (br, 4H, N*H*), 24.63 (br, 2H, N*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 8.9, 9.8, 14.0, 16.9, 120.7, 125.1, 126.5, 132.2, 134.7, 149.6, 152.2; UV/Vis (CH_2Cl_2) λ_{max} [nm] (logε): 384 (4.46), 493 (5.04), 597 (4.75); LRMS (FAB +) *m/e*: 639 (100); HRMS (FAB +) *m/e* calcd for $C_{42}H_{50}N_6$ $(M-2HCl)^+$: 638.4097, found: 638.4097. For the free base form (**37b**) (prepared by washing a CH_2Cl_2 solution of **37c** with 10% NaOH (2 × 50 mL)): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.05$ (t, $J = 7.1$ Hz, 12H, CH_2CH_3), 1.69 (s, 12H, CH_3), 1.87 (s, 12H CH_3), 2.38 (q, 8H, CH_2CH_3), 5.72 (s, 2H, *meso-H*), 10.95 (br, 2H, N*H*), 12.20 (br, 2H, N*H*); UV/Vis (CH_2Cl_2) λ_{max} [nm] (logε): 467.8 (4.66).

38 (*p*-Nitrophenylamethyrin): In a 250 mL round-bottomed flask equipped with an argon inlet and a magnetic stirrer, **29** (37.0 mg, 1.2×10^{-4} mol) was dissolved in 150 mL of CH_2Cl_2. *p*-NO_2-benzaldehyde was added (18.1 mg, 1.2×10^{-4} mol) followed by 4 drops of TFA. The resulting dark solution was stirred at room temperature for 4 h. DDQ was then added (54.3 mg, 2.4×10^{-4} mol) and the solution stirred for 1 h. The solvent was removed with the aid of a rotary evaporator. The residue was taken up in 25 mL of $CHCl_3$ and washed with 10% NaOH (2 × 25 mL). The organic layer was separated off and dried over Na_2SO_4. The solvent was removed in vacuo on the rotary evaporator. The resulting solid was purified chromatographically on a 3 × 10 cm column of basic silica gel (achieved by bubbling NH_3 through a CH_2Cl_2 slurry of silica) with NH_3 saturated CH_2Cl_2 as the eluent. The first orange band off the column was washed with 1 N HCl (2 × 50 mL) and dried over Na_2SO_4. It was then taken to dryness with the aid of a rotary evaporator to afford a green solid with a metallic luster. The product, compound **38c**, was recrystallized from $CHCl_3$/*n*-hexane to afford green metallic crystals. Yield: 33.1 mg (29%). M.p.: decomp. > 250 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.50$ (t, $J = 7.3$ Hz, 12H, CH_2CH_3), 0.85 (m, 4H, CH_2CH_3), 0.97 (m, 4H, CH_2CH_3), 1.12 (s, 12H, CH_3), 1.23 (s, 12H, CH_3), 2.16 (s, H_2O), 7.10 (d, $J = 8.5$ Hz, 4H, phenyl-*H*), 8.06 (d, $J = 8.5$ Hz, 4H, phenyl-*H*), 20.09 (s, 4H, N*H*), 21.71 (s, 2H, N*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.4, 9.8, 13.9, 19.1, 123.7, 125.3, 130.4, 130.8, 132.0, 134.0, 139.0, 143.2, 149.1, 150.9, 151.4; UV/Vis (CH_2Cl_2) λ_{max} [nm] (logε): 395.5 (4.44), 503.5 (4.86), 544.0 (4.77), 644.0 (4.63); LRMS (FAB +) *m/e*: 881 (100), 882 (84); HRMS (FAB +) *m/e* calcd for $C_{54}H_{57}N_8O_4$ $(M-2HCl+1)^+$: 881.4503, found: 881.4514.

41 [Zn_2(amethyrin)]: In a 100 mL round-bottomed flask, amethyrin **37c** (26.4 mg, 3.71×10^{-5} mol) was dissolved in 50 mL methanol. Triethylamine (2 mL) was added to the bright red solution. The color immediately turned yellow-brown. At this juncture, $ZnCl_2$ (51.0 mg, 3.71×10^{-4} mol) was added and the reaction mixture turned bright red. After ca. 30 s, the reaction mixture became light gray as the product precipitated out. This suspension was stirred at room temperature overnight. The gray-green precipitate was filtered off on a fritted funnel and washed with MeOH. The product was recrystallized from CH_2Cl_2 layered with MeOH to afford green crystals with a metallic luster. Yield: 20.0 mg. M.p.: decomp. > 300 °C; ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 0.92$ (t, $J = 7.3$ Hz, 12H, CH_2CH_3), 1.51 (br, 12H, CH_3) 1.67 (br, 12H, CH_3), 2.07 (q, $J = 7.0$ Hz, 8H, CH_2CH_3), 3.43 (s, 2H, *meso-H*), 16.31 (br 1H, N*H*?), 16.49 (br, 1H, N*H*?), 16.56 (br, 0.5H, O*H*?); ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ = 10.3, 10.4, 10.5, 10.6, 10.8, 10.9, 15.3, 15.5, 17.6, 50.9, 120.7, 121.0, 123.4, 123.5, 123.6, 125.9, 126.0, 127.7, 127.9, 139.2, 139.4, 139.5, 142.2, 146.1, 146.2, 146.4, 154.2; UV/Vis (CH_2Cl_2) λ_{max} [nm] (logε): 355.5 (4.36), 412.0 (4.35), 497.0 (4.96), 555.5 (4.86). This complex was further characterized by X-ray diffraction analysis.

42 [$CoCl_2$(amethyrin)]: In a 50 mL round-bottomed flask equipped with an argon inlet and a magnetic stirrer, amethyrin **37c** (40 mg, 5.6×10^{-5} mol) was dissolved in methanol. Triethylamine (2 mL) was added to the bright red solution; the color immediately turned yellow-brown. $CoCl_2$ (73 mg, 5.6×10^{-4} mol) was then added and the mixture heated at reflux for 1 h. After cooling, the solvent was removed from the deep red solution with the aid of a rotary evaporator. The resulting residue was purified chromatographically on a column of 3 × 15 cm basic silica gel (achieved by treating a CH_2Cl_2 slurry of silica gel with 5 drops triethylamine) and obtained as the first red fraction to elute from the column with CH_2Cl_2 as the eluent. The solvent was removed in vacuo and the resulting greenish solid recrystallized from CH_2Cl_2 layered with *n*-hexane. Yield: 14 mg. M.p.: decomp. > 300 °C. This complex was further characterized by X-ray diffraction analysis; UV/Vis (CH_2Cl_2) λ_{max} [nm] (logε): 394.0 (4.44), 503.0 (4.91), 580.0 (4.56). HRMS (FAB +) *m/e* calcd for $C_{42}H_{50}N_6Cl_2Co$ (M^+): 767.2806, found: 767.2800.

43 [UO_2(amethyrin)]: In a 25 mL round-bottomed flask equipped with a reflux condenser, an argon inlet, and a magnetic stirrer, amethyrin **37c** (10.9 mg, 1.53×10^{-5} mol) was dissolved in 50 mL absolute methanol and 4 mL triethylamine. To this brown solution, $UO_2Cl_2 \cdot 3H_2O$ (70 mg, 10 equiv) was added. The reaction mixture was then stirred at reflux in an oil bath for 36 h. During this time, the reaction mixture gradually became a red suspension. This suspension was allowed to cool to room temperature before being filtered through a plug of Celite on a fritted funnel. After washing the Celite with methanol until the washings were colorless, the washings were combined and taken to dryness with the aid of a rotary evaporator. The resulting residue was taken up in CH_2Cl_2 and layered with *n*-hexane. The green crystals that precipitated out in this way were collected by vacuum filtration. Yield: 2.3 mg. M.p.: decomp. > 300 °C; UV/Vis (CH_2Cl_2) λ_{max} [nm]: 515, 825; HRMS (FAB +) *m/e* calcd for $C_{42}H_{46}N_6O_2{}^{238}U$ $(M-2H)^+$: 904.4190, found: 904.4179.

44 [Cu_2^I(amethyrin)]: In a 100 mL round-bottomed flask equipped with an argon inlet and a magnetic stirrer, amethyrin **37c** (45.5 mg, 6.42×10^{-5} mol) was dissolved in 20 mL absolute methanol (through which argon was had been bubbled for 5 min) and 1 mL triethylamine. To the resulting dark brown solution was added CuCl (130 mg, 20 equiv). The solution became immediately deep red and after 1 min became a suspension. The reaction mixture was stirred at room temperature overnight. The suspension was filtered through a plug of Celite on a fritted funnel, and the Celite was washed with methanol until the washings were colorless. The light pink mother liquor was discarded, and now the Celite was washed with CH_2Cl_2. The dark orange-red filtrate was transferred to a round-bottomed flask and the solvent removed with the aid of a rotary evaporator. The resulting residue was recrystallized from CH_2Cl_2 layered with methanol. The dark green crystals so obtained were collected by vacuum filtration and dried in vacuo. Yield: 51 mg. M.p.: decomp. > 300 °C; ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 1.52$ (s, H_2O), 2.00 (t, $J = 7.6$ Hz, 12H, CH_2CH_3), 3.22 (s, 12H, CH_3), 3.74 (s, 12H, CH_3), 4.00 (q, $J = 7.5$ Hz, 8H, CH_2CH_3), 10.30 (s, 2H, *meso-H*); ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ = 14.9, 15.7, 17.6, 20.6, 110.2, 126.9, 136.1, 148.1, 148.2, 151.1, 151.9; UV/Vis (CH_2Cl_2) λ_{max} [nm]: 448, 516, 870. LRMS (FAB +) *m/e*: 639 (1.7), 760 (2.1), 761 (1.9), 762 (2.1), 763 (1.5), 860 (1.1), 861 (1.3), 862 (1.1), 863 (1.1), 893 (1.3), 907 (1.4), 908 (1.1), 909 (1.2), 920 (1.4), 921 (2.6), 922 (2.5), 923 (4.2), 924 (3.3), 925 (3.5), 958 (1.6), 959 (1.8), 960 (2.1), 961 (1.5); HRMS (FAB +) *m/e* calcd for $C_{42}H_{47}N_6Cu_2$: 761.2454, found: 761.2436; for $C_{48}H_{58}N_7Cu_3$: 921.2642, found: 921.2587.

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$$R(F^2)_w = \{\sum w(|F_o|^2 - |F_c|^2)^2/\sum w(|F_o|)^4\}^{1/2} \quad \text{(a)}$$

$$R(F^2) = \sum(|F_o| - |F_c|)/\sum|F_o| \quad \text{(b)}$$

for all reflections having $F_o > 4(\sigma(F_o))$

$$S(F^2) = (\sum w(|F_o|^2 - |F_c|^2)^2/(n-p))^{1/2} \quad \text{(c)}$$

where n is the number of reflections and p is the number of refined paramters.

For **37c**, the function $\sum w(|F_o| - |F_c|)^2$ was minimized, where $w = 1/(\sigma(F_o))^2$ and $\sigma(F_o) = \{0.5kI^{-1/2}((\sigma(I))^2 + (0.02I)^2)^{1/2}\}$. The intensity I is given by $(I_{peak} - I_{background}) \times$ (scan rate); where 0.02 is a factor to downweight intense reflections and to account for instrument instability and k is the correction due to Lp effects and decay. Sigma(I) was estimated from counting statistics; $\sigma(I) = ((I_{peak} + I_{background})^{1/2} \times$ (scan rate)). The following definitions [Eq. (d)–(f)] apply to these structures:

$$R(F) = \sum(|F_o| - |F_c|)/\sum|F_o| \quad \text{(d)}$$

$$R(F)_w = \{\sum w(|F_o| - |F_c|)^2/\sum w(|F_o|)^2\}^{1/2} \quad \text{(e)}$$

$$S(F) = \{\sum w(|F_o| - |F_c|)^2/(m-n)\}^{1/2} \quad \text{(f)}$$

where m is the number of reflections and n is the number of refined parameters.

Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992) [26]. Other computer programs used in this work are listed elsewhere [27]. All figures were generated using SHELXTL-Plus [24]. Tables of positional and thermal parameters, bond lengths, angles and torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary material. For all figures, thermal ellipsoids are scaled to the 30% probability level, and hydrogen atoms are drawn to an arbitrary scale. Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ (UK), on quoting the full journal citation.
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[31] Recent work from the Vogel group on sterically modulated porphycenes has demonstrated the likely contribution of NHN hydrogen bonds to large changes in internal NH chemical shifts. See ref. [3b].
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[34] The systematic name for amethyrin **37** is: 3,9,12,13,16,22,25,26-octamethyl-4,8,17,21-tetraethyl-27,28,29,30,31,32-hexaazaheptacyclo-(22.2.1.1^{2,5}.1^{7,10}.1^{11,14}.1^{15,18}.1^{20,23})-hexacosa-1(26),2(27),3,5,7,9,11,13,15(30),16,18,20,22,24-tetradecene.
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