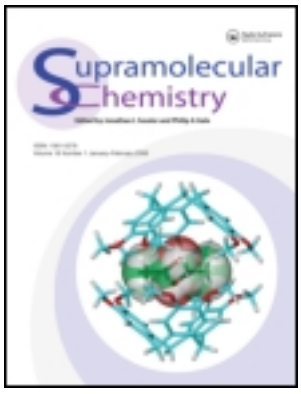

Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsch20

Amide to carboxylic acid hydrogen bonding. The dipyrrinone receptor

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Available online: 13 Apr 2011

To cite this article: Michael T. Huggins, Nicholas T. Salzameda & David A. Lightner (2011): Amide to carboxylic acid hydrogen bonding. The dipyrrinone receptor, Supramolecular Chemistry, 23:03-04, 226-238

To link to this article: http://dx.doi.org/10.1080/10610278.2010.521836

Supramolecular Chemistry
Vol. 23, Nos. 3–4, March–April 2011, 226–238

Amide to carboxylic acid hydrogen bonding. The dipyrrinone receptor

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(*Received 8 July 2010; final version received 24 August 2010*)

Hydrogen bonding between carboxylic acid and amide groups was demonstrated for a series of amides called [*n*]-semirubins consisting of a dipyrrinone attached to the end of an *n*-carbon alkanoic acid. Such hydrogen bonding is more effective than the alternative amide to amide or acid to acid types for all of the semirubins studied: $n = 1, 3–7, 10$ and 20. As determined by ^{1}H NMR and vapour pressure osmometry, [*n*]-semirubins, where $n = 5–20$, are intramolecularly hydrogen bonded in $CHCl_3$ or $CDCl_3$; [4]-semirubin is intermolecularly hydrogen bonded as a dimer; [3]-semirubin is a tetramer; and [1]-semirubin is a dimer – all with carboxylic acid to amide hydrogen bonding. The dipyrrinone amide and adjacent pyrrole constitute an efficacious receptor for the carboxylic acid group.

Keywords: dipyrrinones; hydrogen bonding; vapour pressure osmometry

1. Introduction

Molecular associations consolidated by hydrogen bonding (*1*) are found in organic and biochemistry, e.g. molecular recognition supramolecular chemistry (*2*), protein conformation (*3*), nucleic acid structure (*4*), etc., with amides and carboxylic acids being among the most important functional groups involved. Amide to amide hydrogen bonding (Figure 1(A)) (*5*) has been recognised and studied for decades (*1*, *6*) as an important determinant of the peptide secondary structure (*1b*,*c*, *3*) and often found as a key binding component in molecular recognition constructs (*2*). Typical self-association constants, K_A, are of the order of 10–100 in hydrogen bond-promoting solvents such as CCl_4 and $CHCl_3$ (*1*). Carboxylic acid to carboxylic acid hydrogen bonding has also seen a long period of investigation, and hydrogen-bonded carboxylic acid dimers (Figure 1(B)) have been shown to exhibit even larger K_As ($\sim 10^3$) for self-association in favourable solvents (*1*). In contrast, the mixed type, amide to carboxylic acid hydrogen bonding (Figure 1(C)) has received far less attention (*7*), except in co-crystals (*8*), and usually in connection with molecular recognition/self-assembly studies (*9*, *10*). In one of the handful of such studies, borrowing from the α-pyridone-based amide–amide association (Figure 1(D)) model of Wuest (*11*) (Figure 1(E)), a strongly hydrogen-bonded amide to acid dimer (Figure 1(F)) was found in $CDCl_3$ (*12*). But perhaps nature's best example of strong amide to carboxylic acid hydrogen bonding was found long ago in crystals of bilirubin (*13*) and, subsequently, in its solutions (*14*, *15*).

Bilirubin (Figure 2(A)) is the yellow pigment of jaundice and the end-product of haem metabolism in mammals (*15*). Structural studies have shown that bilirubin consists of two dipyrrinones, each with an attached propionic acid that is intramolecularly hydrogen-bonded to an opposing

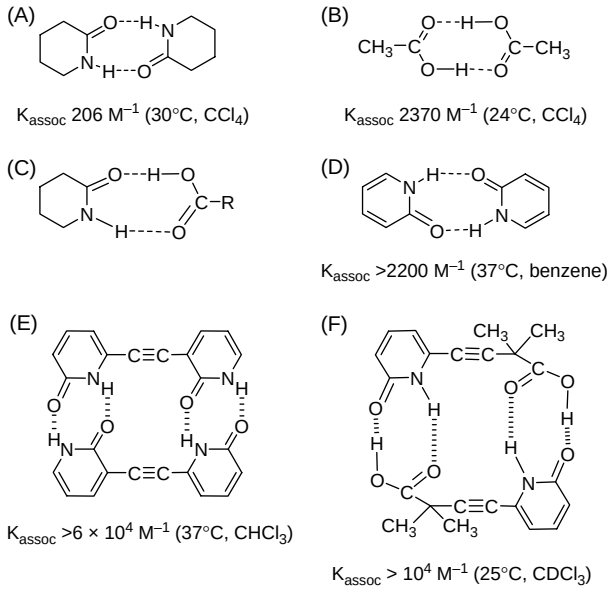

Figure 1. Intermolecularly hydrogen-bonded dimers of (A) δ-valerolactam, (B) acetic acid, (C) amide–acid hydrogen-bonded pair, (D) α-pyridone, (E) bis-α-pyridonylacetylene and (F) α-pyridone acid.

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ISSN 1061-0278 print/ISSN 1029-0478 online

DOI: 10.1080/10610278.2010.521836
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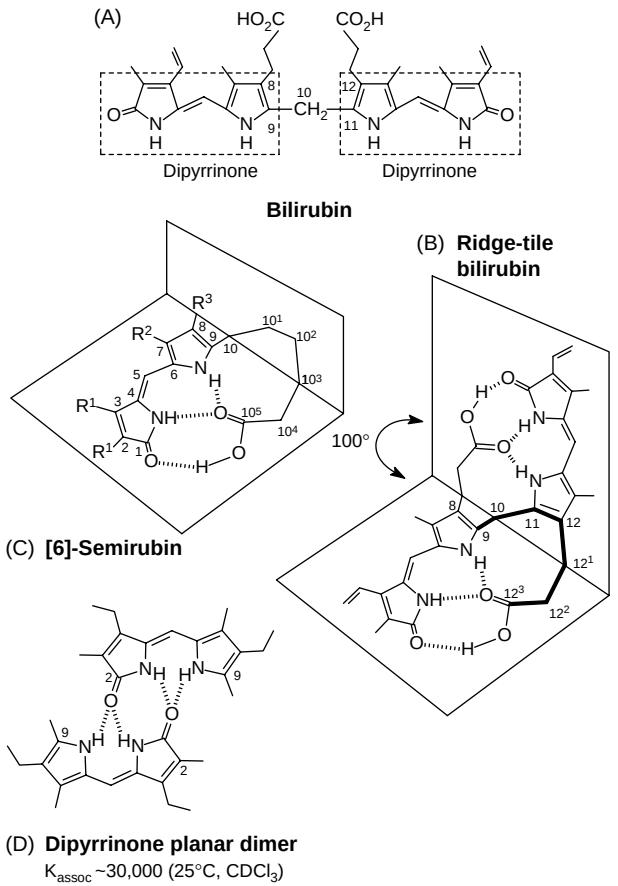
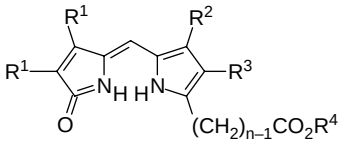


Figure 2. (A) Constitutional structure of bilirubin, composed of two dipyrrinones, each with a propionic acid. (B) The most stable bilirubin conformation is shaped like a ridge tile, with hydrogen bonds (shown by dashed lines) between the carboxylic acid groups and the opposing dipyrrinones. The bold lines show the characteristic six-carbon connectivity for intramolecular hydrogen bonding between the dipyrrinone and carboxylic acid of bilirubin and [6]-semirubin. (C) [6]-Semirubin in its favoured intramolecularly hydrogen-bonded conformation. The shape of [6]-semirubin is similar to that of one-half of bilirubin. (D) Dipyrrinones in solution form planar dimers with four intermolecular hydrogen bonds. Hydrogen bonds are represented by dashed lines.

dipyrrinone amide: nature's example *par excellence* of carboxylic acid to amide hydrogen bonding (Figure 2(B)) (*14*, *16*). Such hydrogen bonding is strongly preferred to intermolecular hydrogen bonding of the acid–amide, amide–amide or acid–acid types – or to other intramolecular hydrogen bonding possibilities (*14f*). Bilirubin esters, on the other hand, exhibit intermolecular hydrogen bonding of the amide to amide type (*14f*).

The dipyrrinone unit is an intriguing construct with interesting spectroscopic properties and a well-established propensity to self-associate by forming planar hydrogen-bonded dimers (Figure 2(D)) (*14b*, *16*, *17*). Previously, we showed by ^{1}H NMR spectroscopy that simple dipyrrinones are strongly hydrogen-bonded as dimers (Figure 2(D)) ($K_{assoc} \sim 30{,}000$ at 25°C) in $CDCl_3$ (*18*), and more recently confirmed this by vapour pressure osmometry (VPO) (*19*). The results showed that dipyrrinones form stable dimers in $CHCl_3$ through intermolecular hydrogen bonding, preferring *not* to be monomeric at concentrations $> 10^{-4}$ M (*18*). They suggest that something more than simple amide to amide hydrogen bonding is involved in the dipyrrinone planar dimer and implicate participation by the pyrrole N—H, which in the crystal is within the proper contact distance for hydrogen bonding (N—H to O distance – 1.97 Å) (*16*, *17*).

In bilirubin, the dipyrrinones prefer to be hydrogen bonded to the propionic carboxylic acid group, even when the carboxylic acid is ionised to carboxylate (*14d*,*f*); whereas, in its diester, dipyrrinone to dipyrrinone hydrogen bonding prevails (*14a*,*b*). Recently, external guests have been shown to be effective at disrupting the dipyrrinone–dipyrrinone self-assembled dimer in favour of intermolecular hydrogen bonding with the guest (*20*). This was particularly true for guests that possess both hydrogen bond acceptor and donor groups, i.e. carboxylic acids and hydrogen sulphate. In order to explore the details of the role of dipyrrinones as hydrogen



Acids					Esters	
R^4=H	[n]	R^1	R^2	R^3	R^4	
1	1	Et	*i*-Bu	Me	Me	**1e**
2	3	Me	Et	Et	Me	**2e**
3	4	Me	Et	Et	Me	**3e**
4	5	Me	Me	Me	Me	**4e**
5	6	Me	Me	Me	Me	**5e**
6	7	Me	Me	Me	Me	**6e**
7	10	Me	Me	Me	Me	**7e**
8	20	Me	Me	Me	Me	**8e**

Structures

bonding receptors for the carboxylic acid group, we constructed a series of dipyrrinone carboxylic acids based on the essential components shown in bilirubin (Figure 2(B)). We named these designed and engineered dipyrrinone acids, '[*n*]-semirubins', where *n* is the number of carbons in the alkanoic acid chain. [6]-Semirubin has a 6-carbon acid emanating from C(9) of the dipyrrinone that corresponds to the 6-carbon acid chain (Figure 2(B)) found in bilirubin. One might thus consider $n = 6$ to be the 'ideal' alkanoic acid

chain length (**5** of Structures). Variants with both shorter (**1**–**4**) and longer (**6**–**8**) acid chains (see Structures) were synthesised to learn (i) whether the dipyrrinone slips over to the planar dimer of Figure 2(D) when the alkanoic acid chain is too short to engage it and (ii) whether the dipyrrinone will 'find' the carboxylic acid terminus of very long alkanoic acids. For comparison of hydrogen bonding in bilirubin esters, we also prepared [*n*]-semirubin methyl or ethyl esters (**1e**–**8e**).

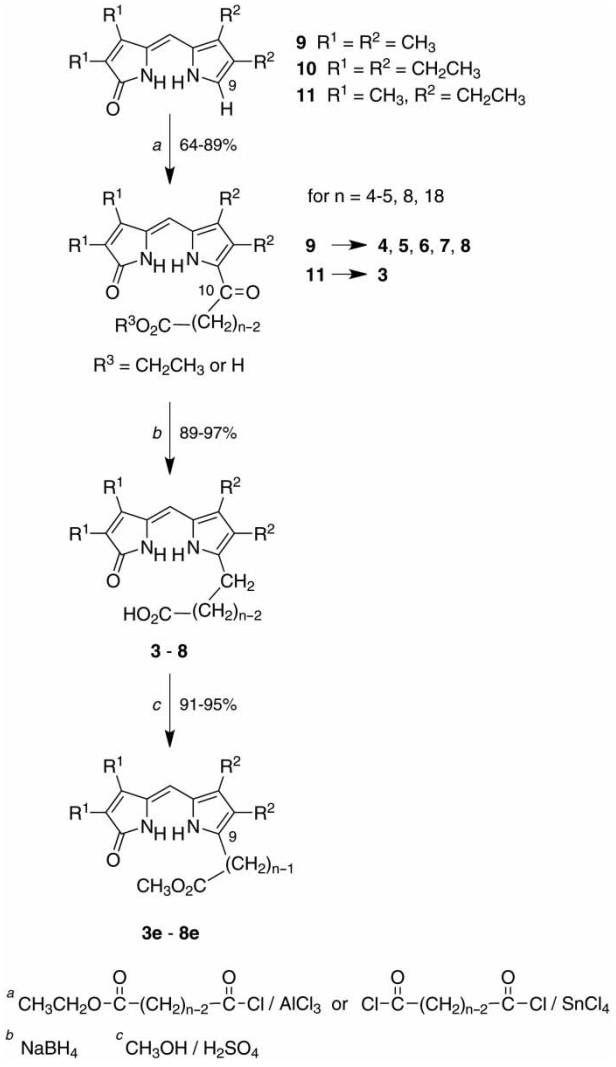
2. Results and discussion

2.1 Synthesis

The preparation of the majority of the [*n*]-semirubins of this work (**3**–**8**) follows the general procedure outlined in Scheme 1, as described previously for **5**, **7** and **8** (*21*). Thus, 9-H dipyrrinones, **9**, **10** or **11**, were acylated under Friedel–Crafts conditions with a dibasic acid mono-ester acid chloride or diacid chloride to give a 10-*oxo*-[*n*]-semirubin ester or acid that was reduced (and saponified) directly to the [*n*]-semirubin with $NaBH_4$. The corresponding semirubin methyl esters were obtained by Fischer esterification.

The syntheses of [1]-semirubin (**1**) and [3]-semirubin (**2**) were accomplished via different routes. [1]-Semirubin, with a CO_2H group attached at C-9 of the dipyrrinones, was prepared by condensation of diethylpyrrolinone **12** and pyrrole aldehyde ester **13** (Scheme 2). The latter was prepared by cerium (IV) ammonium nitrate (CAN) oxidation of the pyrrole α-CH_3 of **14**, which was synthesised by hydroxide-catalysed condensation of ethyl 3,5-dimethylpyrrole-2-carboxylate (**15**) with isobutyraldehyde (*22*). The larger pyrrole β-substituent of **1** was required for improved solubility of **1** in the $CHCl_3$ solvent.

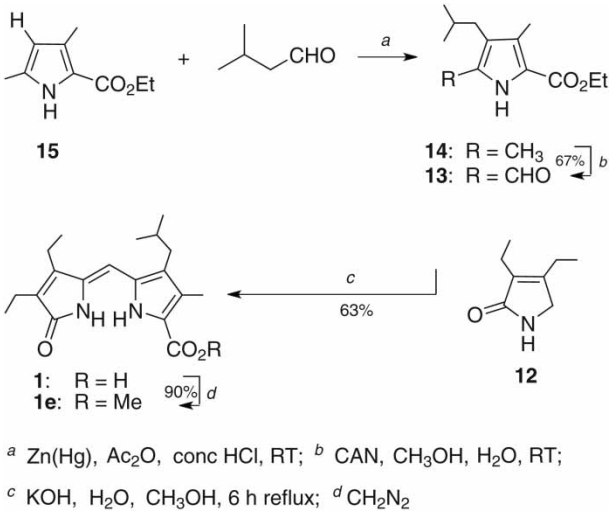
Following a failed attempt to make 10-*oxo*-[3]-semirubin via the procedure of Scheme 1, an alternative route was sought (Scheme 3). Thus, the known dipyrrinone 9-carboxylic acid (**16**) (*22*) was converted efficiently to the 9-formyl analogue (**17**) in methyl orthoformate–trifluoroacetic acid (TFA). Condensation of **17** with mono-ethyl malonate in the presence of the piperidinium acetate catalyst afforded a high yield of α,β-unsaturated ester **18**, which was reduced to **2** by $NaBH_4$ in isopropyl alcohol at reflux. Conversion of **2** to **2e** in 96% was achieved by Fischer esterification.



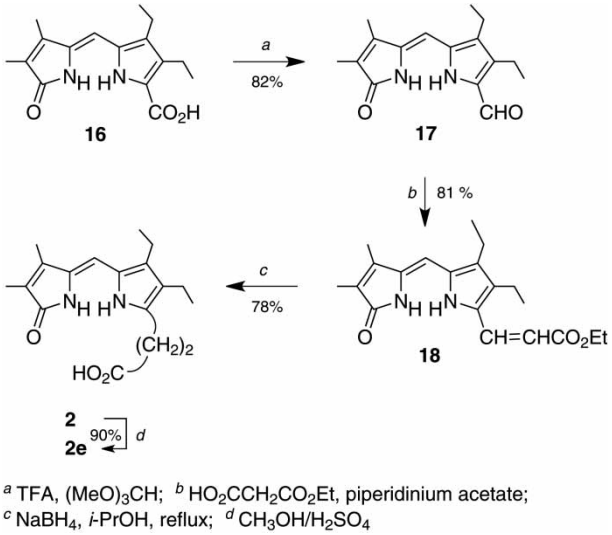
Scheme 1. Synthesis of semirubins **3**–**8**.

2.2 Constitutional structure

The constitutional structures of acids **1**–**8** and their esters (**1e**–**8e**) follow logically from the method of synthesis and from previous literature reports (on **5**, **7** and **8**) (*21*). All ^{13}C NMR assignments were confirmed by a combination of 1H{1H}-nuclear Overhauser enhancement spectroscopy (NOESY or 1D NOE), HSQC and heteronuclear multiple bond correlation (HMBC) techniques. The ^{13}C NMR chemical shifts of the corresponding dipyrrinone skeletal carbons C(1)—C(9) vary little among **2**–**8** and **2e**–**8e** and correspond generally well to other well-studied dipyrrinones such as kryptopyrromethenone (3,8-diethyl-2,7,9-triethyl-(10*H*)-dipyrrin-1-one) and xanthobilirubic acid [8-(2-carboxyethyl)-3-ethyl-2,7,9-trimethyl-(10*H*)-dipyrrinone] and its methyl ester (*19*, *21*, *23*). The corresponding chemical shifts of **1** and **1e** differ more substantially, as might be expected for this dipyrrinone with its carboxyl group directly attached to C(9), where it is better able to perturb the electronic structure of the molecule. The *Z*-configuration of the C(4)—C(5) exocyclic double bond of the dipyrrinone cores was confirmed by the observation of a moderate NOE between the C(5)—H and the C(3) alkyl group (CH_3 or CH_2CH_3) as well as the C(7) alkyl group (CH_3 or CH_2CH_3) in $CDCl_3$.



Scheme 2. Synthesis of semirubin **1**.



Scheme 3. Synthesis of semirubin **2**.

2.3 Aggregation and hydrogen bonding

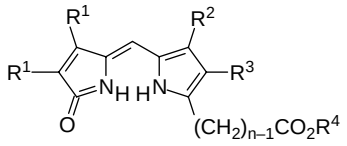
VPO has been found to be an effective technique to study the aggregation properties of dipyrrinones in non-polar organic solvents (*19–22*). From such studies, the average molecular weight (MW) of the species in solution is measured providing insight into how many molecules have assembled in the aggregate. It has been well established that the hydrogen bonding pattern of dipyrrinones can be discerned from the analysis of the NH chemical shifts in the ^{1}H NMR spectrum (*18–22*). In $CDCl_3$, dipyrrinones hydrogen bonded to a carboxylic acid have the pyrrole and lactam NH signals at 8.1–9.2 and 10.5–11.0 ppm, respectively. In the dipyrrinone planar dimer, the pyrrole and lactam NH signals appear at 10.0–10.7 and 10.9–11.5 ppm, respectively. However, both NH resonances are generally located below 8.0 ppm when the dipyrrinone is not participating in hydrogen bonding or it is only weakly hydrogen bonded (*18–20*).

The VPO data show that the [*n*]-semirubin esters, **1e–8e,** were found to be dimeric except for [1]-semirubin ester in $CHCl_3$ at 45°C (see Table 1). Specifically, the semirubin esters were found to have MW in the chloroform solution near double their formula weights (FW). Based on the NH chemical shifts in ^{1}H NMR in $CDCl_3$, shown in Table 2, the esters exist in the dipyrrinone planar dimer with four intermolecular hydrogen bonds between the lactam C═O and the pyrrole and lactam NHs, as shown in Figure 2(D). As previously discussed, the dipyrrinone planar dimer is the traditional arrangement observed for dipyrrinone analogues not possessing a carboxylic acid moiety (*13*). The [1]-semirubin ester, **1e,** was found to be monomeric by VPO, which was not surprising since it had been previously shown that 9-acyl dipyrrinones participate in intermolecular hydrogen bonding to a much lesser extent than other dipyrrinones (*19*).

[5]-Semirubin acid **4** was found to be monomeric by VPO in $CHCl_3$, as the measured MW in chloroform is near its calculated FW (Table 1). As previously shown for [*n*]-semirubin acids **5–8,** these semirubin analogues adopt an intramolecular hydrogen-bonded conformation with the carboxylic acid hydrogen bonded to the dipyrrinone via three hydrogen bonds, as shown in Figure 2(C) (*21*). This was confirmed **4** by ^{1}H NMR analysis of the NH chemical shifts in $CDCl_3$ (see Table 2). The lactam and pyrrole NH chemical shifts for **4–8** were found at 10.48–10.83 and 8.79–8.95 ppm, respectively. In these semirubin analogues (**4–8**), the alkanoic acid chains have sufficient length to facilitate intramolecular hydrogen bonding between the carboxylic acid moiety and the dipyrrinone receptor.

[4]-Semirubin acid **3** gave a measured MW by VPO in $CHCl_3$ of 633 ± 25 g/mol which corresponds to a dimeric aggregation state (FW = 330 g/mol, Table 1). Interestingly, the ^{1}H NMR chemical shifts of the lactam and pyrrole NHs correspond to a dipyrrinone that is participating in hydrogen bonding with a carboxylic acid group at 10.71 and 8.92 ppm, respectively (Table 2). Molecular mechanics calculations for **3** suggest that the alkanoic acid chain is too short for the CO_2H moiety to intramolecularly hydrogen bond with dipyrrinone.[1] Thus, the carboxylic acid to dipyrrinone hydrogen bonding must be of the intermolecular motif. The molecular mechanics calculations suggested a stacked dimer as the lowest energy conformation where the dipyrrinones are aligned above/below each other and the alkanoic acid groups act as straps connecting the two dipyrrinones with a total of six intermolecular hydrogen bonds (Figure 3). Stacked dipyrrinone dimers displaying dipyrrinone to carboxylic acid hydrogen bonding have been observed in xanthobilirubinic acid and other dipyrrinone analogues containing the alkanoic acid chain at C(8) (*23b*), also

Table 1. MW of [*n*]-semirubins **1**–**8** and their esters (**1e**–**8e**), determined at 45°C in $CHCl_3$ by VPO.[a]



Compound	[*n*]	R^1	R^2	R^3	R^4	FW[b]	MW[c]	Conc. range[d]
1	1	Et	*i*-Bu	Me	H	330	652 ± 20	$2.2–7.4 \times 10^{-3}$
2	3	Me	Et	Et	H	316	1225 ± 30	$2.1–6.9 \times 10^{-3}$
3	4	Me	Et	Et	H	330	633 ± 25	$2.3–6.8 \times 10^{-3}$
4	5	Me	Me	Me	H	316	332 ± 20	$2.1–6.6 \times 10^{-3}$
5	6	Me	Me	Me	H	330	337 ± 20	$2.1–6.6 \times 10^{-3}$
6	7	Me	Me	Me	H	344	356 ± 13	$1.8–5.7 \times 10^{-3}$
7	10	Me	Me	Me	H	386	394 ± 20	$1.7–5.7 \times 10^{-3}$
8	20	Me	Me	Me	H	526	533 ± 20	$1.6–4.1 \times 10^{-3}$
1e	1	Et	*i*-Bu	Me	Me	344	372 ± 10	$2.1–6.2 \times 10^{-3}$
2e	3	Me	Et	Et	Me	330	620 ± 10	$2.0–6.4 \times 10^{-3}$
3e	4	Me	Et	Et	Me	344	595 ± 25	$1.2–9.8 \times 10^{-3}$
4e	5	Me	Me	Me	Me	330	537 ± 25	
5e	6	Me	Me	Me	Me	344	584 ± 30	$1.7–6.1 \times 10^{-3}$
6e	7	Me	Me	Me	Me	358	718 ± 20	$1.8–5.5 \times 10^{-3}$
7e	10	Me	Me	Me	Me	400	691 ± 25	$2.2–5.2 \times 10^{-3}$
8e	20	Me	Me	Me	Me	540	902 ± 30	$1.5–4.1 \times 10^{-3}$

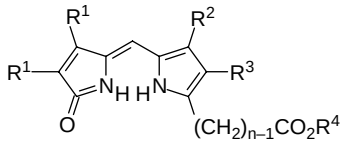
[a] Calibrated with benzil (FW = 210, measured MW = 220 ± 15).
[b] Formula weight.
[c] Molecular weight in g/mol.
[d] mol/kg.

indicative of a position which forbids intramolecular hydrogen bonding between the dipyrrinone and carboxylic acid groups.

By VPO in $CHCl_3$ at 45°C, [3]-semirubin acid **2** was found to have a measured MW of 1225 ± 30 g/mol which corresponds to a tetrameric aggregation state (FW: 316 g/mol; Table 1). In addition, the lactam and pyrrole NH signals were found at 10.82 and 8.96 ppm, respectively, in $CDCl_3$. As previously discussed, this is indicative of dipyrrinone to carboxylic acid hydrogen bonding. In $CDCl_3$, the methylenes of the propionic acid moiety in **2** showed an AA′XX′ coupling pattern in the proton NMR which is indicative of an *anti*-conformation for the dipyrrinone and carboxylic acid groups. Both methylenes were observed as triplets in DMSO-d_6. Molecular mechanics calculations predicted that the propionic acid chain was not only too short for intramolecular hydrogen bonding, but was also too short for the formation of the stacked dimer observed for the [3]-semirubin acid **3**.[1] A tetrameric arrangement where the propionic acids linked from one dipyrrinone to another in a cyclic fashion and contained two stacked dimers was found as the lowest energy conformation by molecular mechanics calculations (Figure 4). The predicted tetramer allows for the observed dipyrrinone to carboxylic acid hydrogen bonding, the *anti*-conformation of the propionic acids and maintaining the ~3.5 Å distance between dipyrrinones. The overall conformation of the aggregate is very similar to the stacked dimer arrangement observed for xanthobilirubic and [4]-semirubin. In the tetramer, the two stacked dimer subunits are aligned ~90° out of plane from each other.

[1]-Semirubin, **1,** was found to have a measured MW of 652 ± 20 g/mol in $CHCl_3$ at 45°C by VPO (FW: 330 g/mol; Table 1), indicative of a dimeric structure. In $CDCl_3$, [1]-semirubin displayed unique ^{1}H NMR chemical shifts for the lactam and pyrrole NHs at 11.82 and 10.02 ppm, respectively (Table 2). The chemical shifts seem to pinpoint carboxylic acid to dipyrrinone hydrogen bonding, but the NHs are shielded by approximately 1 ppm in comparison to the range normally observed for this hydrogen bonding pattern. Additionally, the NH chemical shifts were found to be concentration independent over the range 10^{-2}–10^{-5} M in $CDCl_3$. Molecular mechanics calculations found a unique planar dipyrrinone dimer as the lowest energy conformation for [1]-semirubin (Figure 5).[1] The new planar dipyrrinone dimer has six intermolecular hydrogen bonds between the two dipyrrinones and the carboxylic acid on the neighbouring dipyrrinone. Surprisingly, [1]-semirubin **1** showed no solubility in DMSO-d_6. Typically, [*n*]-semirubin acids and

Table 2. Dipyrrinone NH and COOH ^{1}H NMR chemical shifts of [*n*]-semirubins **1**–**8** and their esters (**1e**–**8e**) at 25°C in $CDCl_3$ and $(CD_3)_2SO$ solvents.



		δ (ppm) in $CDCl_3$			δ (ppm) in $(CD_3)_2SO$		
Semirubin	[*n*]	Lactam NH	Pyrrole NH	CO_2H	Lactam NH	Pyrrole NH	CO_2H
1	1	11.82	10.03	14.37	9.13	9.44	–[a]
2	3	10.82	8.96	14.62	9.78	10.13	12.15
3	4	10.71	8.92	14.17	9.83	10.12	11.97
4	5	10.73	8.91	14.32	9.81	10.13	11.97
5	6	10.48	8.89	13.22	9.81	10.12	11.98
6	7	10.75	8.79	13.90	9.81	10.11	11.96
7	10	10.83	8.83	13.52	9.78	10.09	11.88
8	20	10.75	8.95	13.22	9.78	10.10	11.84
1e	1	9.13	9.44	–	–	–	–
2e	3	10.84	10.09	–	9.75	10.12	–
3e	4	11.04	10.08	–	9.81	10.11	–
4e	5	11.06	10.08	–	9.82	10.12	–
5e	6	11.17	10.11	–	9.78	10.12	–
6e	7	11.14	10.1	–	9.80	10.11	–
7e	10	11.34	10.18	–	9.81	10.10	–
8e	20	11.17	10.00	–	9.79	10.09	–

[a] Not observed in DMSO-d_6.

other dipyrrinone acids are strongly solvated by DMSO-d_6 and give lactam and pyrrole NH chemical shifts in ^{1}H NMR that are indicative of hydrogen bonding to the solvent. In the [1]-semirubin acid, **1**, the lack of solubility in DMSO suggests that the dimerisation is not disrupted by the solvent and an unusually large K_{assoc} for the system.

2.4 Nuclear Overhauser effects

Analysis of the ^{1}H{^{1}H}-nuclear Overhauser effect (NOE) data in $CDCl_3$ also provided additional insight into the structure of the aggregates for the [*n*]-semirubin acids **1**–**8** and esters **1e**–**8e**. Significantly, bilirubin and mesobilirubin (*24*) were found to give weak NOEs between the carboxylic

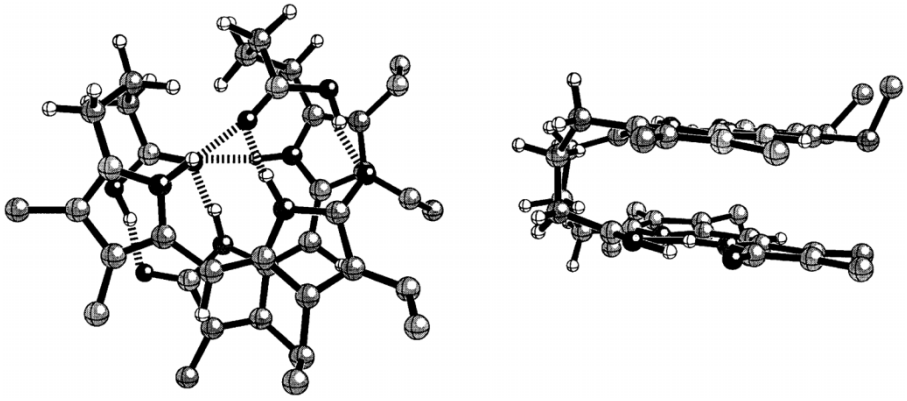


Figure 3. Ball and stick representation of [4]-semirubin acid in the stacked dimer predicted by molecular mechanics calculations – left: top view; right: side view. Dipyrrinone to dipyrrinone distances were measured at ~3.5 Å, indicating π–π stacking between the conjugated systems. The six intermolecular hydrogen bonds between the carboxylic acid and dipyrrinone moieties are indicated by the dashed bonds. Hydrogen atoms on the alkyl substituents have been omitted for clarity.

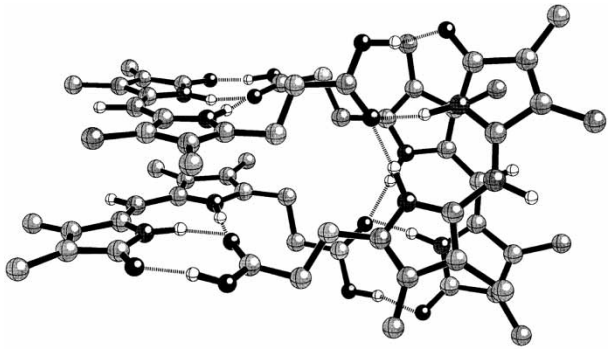


Figure 4. Ball and stick representation of the computed global minimum tetrameric conformation of the propionic acid semirubin **2**. Non-essential hydrogen has been omitted, and ethyls were replaced with methyls along the dipyrrinone backbone.

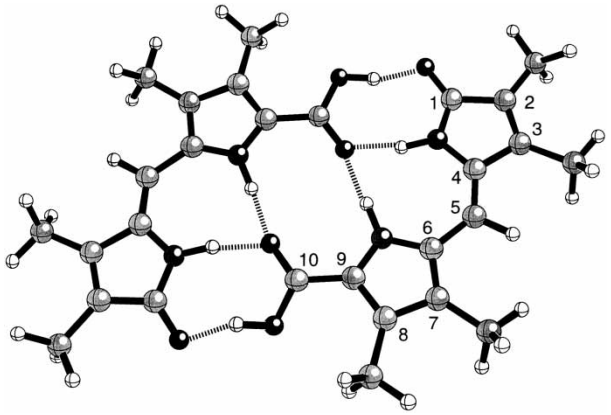


Figure 5. Ball and stick structure of the computed global minimum dimeric conformation for [1]-semirubin acid **1**. All substituents along the dipyrrinone backbone were replaced with methyls to simplify the picture.

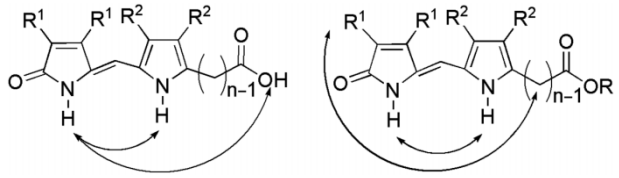


Figure 6. $^{1}H\{^{1}H\}$-NOEs found in [*n*]-semirubins in $CDCl_3$ solvent are indicated by curved double-headed arrows.

acid hydrogen and the lactam hydrogen showing the close proximity of the two groups. The presence of this key NOE provides additional evidence for the dipyrrinone to carboxylic acid hydrogen bonding motif, however it does not provide insight into the aggregation state of the molecule. In [*n*]-semirubin acids **1**–**8**, weak NOEs between the lactam NH and carboxylic acid OH were found (Figure 6, left). Supporting intermolecular hydrogen bonding in [*n*]-semirubin esters **1e**–**8e**, an NOE was detected between the C(10) hydrogens and the C(2) methyl, as is expected from a dipyrrinone planar dimer (Figure 6, right) (*18*).

2.5 Conclusions

The dipyrrinone moiety has been found to be a natural receptor for carboxylic acids where dipyrrinone to acid hydrogen bonding patterns are preferred over other stable molecular arrangements. Specifically, the [*n*]-semirubin acids, **1**–**8**, were found to adopt conformations involving the dipyrrinone receptor containing three hydrogen bonds to the carboxylic acid, while the [*n*]-semirubin esters, **2e**–**8e**, adopted the traditional planar dipyrrinone dimer motif. Thus, the hydrogen bonding pattern is controllable via relatively modest changes in substituents on the dipyrrinone and has potential uses as a supramolecular building block for sensor development, supramolecular polymers, anion transport systems and much more.

3. Experimental section

NMR spectra were obtained on a GE QE-300 spectrometer operating at 300 MHz, or on a Varian Unity Plus 500 MHz spectrometer in the $CDCl_3$ solvent (unless otherwise specified). Chemical shifts were reported in δ ppm referenced to the residual $CHCl_3$ ^{1}H signal at 7.26 ppm and ^{13}C signal at 77.0 ppm. To ensure anhydrous samples and solvent in ^{1}H NMR experiments, the samples were dried under vacuum in a drying pistol at refluxing toluene temperature, using P_2O_5 desiccant. The $CDCl_3$ solvent was stored over CaH_2 after having been passed through a column of Woelm basic Al_2O_3 (super Act 1). Heteronuclear multiple quantum coherence (HMQC) and HMBC spectra were used to assign ^{13}C NMR spectra. All UV–vis spectra were recorded on a Perkin-Elmer λ-12 spectrophotometer, and VPO measurements were performed using an Osmomat 070 (Gonotec, Berlin, Germany) in $CHCl_3$ at 45°C with benzil used for calibration. Melting points were taken on a MelTemp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ, USA. Fast atom bombardment high-resolution mass spectra (FAB-HR-MS) were obtained from the University of Minnesota Mass Spectrometry Facility. Analytical thin layer chromatography was carried out on JT Baker silica gel IB-F plates (125 μ layers). Flash column chromatography was carried out using Woelm silica gel F, thin layer chromatography grade. Radial chromatography was carried out on Merck silica gel PF_{254} with gypsum preparative layer grade, using a Chromatotron (Harrison Research, Palo Alto, CA, USA). Spectral data were obtained in spectral grade solvents (Aldrich, St Louis, MO, USA or Fisher, Pittsburgh, PA, USA). The dibasic acids, mono-ethyl oxalyl chloride and sebacoyl chloride, were from Aldrich, and eicosanedioc acid

was from TCI America. Dichloromethane, methanol, tetrahydrofuran, hexane and 2-propanol were from Fisher, and sodium borohydride, anhydrous aluminium chloride and stannic chloride were from Acros.

The various dibasic acid mono-ester acid chlorides and diacid chlorides were prepared by standard methods. 2,3,7,8-Tetramethyl-(10*H*)-dipyrrin-1-one (**9**) (*21a*, *22*, *25*) was prepared according to literature procedures, as were dipyrrinones **10** (*26*) and **11** (*22*). [6]-Semirubin **5** and its methyl ester (**5e**) were available from earlier work (*21a*), as were [10]-semirubin **7** and its methyl ester (**7e**), [20]-semirubin **8** and its methyl ester (**8e**) (*21b*).

3.1 2,3-Diethyl-7-isobutyl-8-methyl-(10H)-dipyrrin-1-one-9-carboxylic acid (1)

Pyrrole **15** (1.9 g, 8.0 mmol), pyrrolinone **12** (1.3 g, 9.4 mmol) and 50 ml of CH_3OH were placed in a 500 ml round-bottom flask equipped for magnetic stirring. Two hundred millilitres of 4 M aq. KOH was added, and the reaction mixture was heated at reflux for 6 h. The reaction mixture was chilled in an ice bath for 30 min followed by acidification with conc. HCl to $\sim$ pH 3. The resulting solid product was collected by filtration (vacuum), washed with water (100 ml) and dried *in vacuo* to give **1** (1.7 g, 63%). It has mp 226–227°C; IR (KBr): ν 3360, 3055, 2956, 2922, 1683, 1678, 1465, 1371, 1270, 1167, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.94 (6H, d, $J = 6.5$ Hz), 1.17 (3H, t, $J = 7.5$ Hz), 1.23 (3H, t, $J = 7.5$ Hz), 1.75 (1H, sept, $J = 6.5$ Hz), 2.33 (3H, s), 2.40 (2H, q, $J = 7.5$ Hz), 2.42 (2H, d, $J = 6.5$ Hz), 2.56 (2H, q, $J = 7.4$ Hz), 6.11 (1H, s), 10.03 (1H, s), 11.82 (1H, s), 14.37 (1H, s) ppm; FAB-MS: *m/z* 330.4 [M^+] amu; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{19}H_{26}N_2O_3$ (330.4): C, 69.06; H, 7.93; N, 8.48. Found: C, 69.17; H, 7.84; N, 8.56.

3.2 2,3-Diethyl-7-isobutyl-8-methyl-9-carbomethoxy-(10H)-dipyrrin-1-one (1e)

In a 50 ml Erlenmeyer flask (clean and no scratches) were placed 20 ml of ether and 10 ml of 40% KOH (aq.). The mixture was placed in an ice bath and was stirred for 10 min. *N*-Methyl-*N*-nitrosourea (0.5 g) was added, and the reaction mixture was stirred for 10–15 min at 0°C. The ethereal diazomethane layer was separated and added to a solution of 0.25 g (0.76 mmol) dipyrrinone acid **1** in 50 ml of MeOH over a 5 min period. The resulting solution was stirred at room temperature for 30 min followed by cooling in an ice bath. Glacial acetic acid was added dropwise with the evolution of gases until the evolution ceased. The mixture was added to 100 ml of CH_2Cl_2 and washed with water (3 × 100 ml), sat. aq. $NaHCO_3$ (2 × 200 ml), and dried over Na_2SO_4 (anh.). The solvent was removed (rotovap), and the resulting residue was purified by radial chromatography (97:3 by vol. CH_2Cl_2: CH_3OH eluent) and recrystallised from CH_2Cl_2–*n*-hexane to give **1e** (235 mg) in a 90% yield. It has mp 172–173°C; IR (KBr): ν 3328, 2959, 2874, 1704, 1672, 1454, 1381, 1269, 1217, 1158, 1079, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.91 (6H, d, $J = 7.0$ Hz), 1.12 (3H, t, $J = 7.5$ Hz), 1.20 (3H, t, $J = 7.5$ Hz), 1.74 (1H, sept, $J = 7.0$ Hz), 2.28 (3H, s), 2.36 (2H, d, $J = 7.0$ Hz), 2.42 (2H, q, $J = 7.5$ Hz), 2.53 (2H, q, $J = 7.5$ Hz), 3.83 (3H, s), 5.97 (1H, s), 9.13 (1H, s), 9.44 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{20}H_{28}N_2O_3$ (344.4): C, 69.74; H, 8.19; N, 8.13. Found: C, 69.39; H, 8.50; N, 8.13.

3.3 9-(2-Carboxyethyl)-7,8-diethyl-2,3-dimethyl-(10H)-dipyrrin-1-one (2)

To a 100 ml round-bottom flask equipped with the magnetic stirring were placed 170 mg (0.5 mmol) of semirubin **20** and 50 ml of 2-propanol. Sodium borohydride (150 mg) was added, and the reaction mixture was heated at reflux for 4 days. The hot reaction mixture was poured into ice water (100 ml/50 g), and the solution was acidified with 10% HCl (aq.). The suspension was extracted with dichloromethane (3 × 75 ml). The combined extracts were washed with water (3 × 100 ml), dried over Na_2SO_4 (anh.) and the solvent removed (rotovap). The crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2:MeOH eluent) and recrystallised from CH_2Cl_2–hexane to give 123 mg (78%) of pure **2**. It has mp 243–244°C; IR (KBr): ν 3337, 2953, 2925, 2887, 1710, 1693, 1668, 1615, 1455, 1367, 1250, 1158, 1042, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.13 (3H, t, $J = 7.5$ Hz), 1.16 (3H, t, $J = 7.5$ Hz), 1.91 (3H, s), 2.12 (3H, s), 2.44 (2H, q, $J = 7.5$ Hz), 2.56 (2H, q, $J = 7.5$ Hz), 2.75 (3H, ddd, $J = -13.7$, 13.9, 5.8 Hz), 2.76 (1H, ddd, $J = -13.7$, 13.2, 3.1 Hz), 3.08 (1H, ddd, $J = -14.2$, 13.2, 3.1 Hz), 3.09 (1H, ddd, $J = -14.2$, 13.2, 5.8 Hz), 6.14 (1H, s), 8.96 (1H, s), 10.82 (1H, s), 14.62 (1H, s) ppm; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.01 (3H, t, $J = 7.5$ Hz), 1.04 (3H, t, $J = 7.5$ Hz), 1.76 (3H, s), 2.04 (3H, s), 2.32 (2H, q, $J = 7.5$ Hz), 2.46 (2H, q, $J = 7.5$ Hz), 2.50 (2H, t, $J = 7.5$ Hz), 2.76 (2H, t, 7.5 Hz), 5.89 (1H, s), 9.78 (1H, s), 10.13 (1H, s), 12.15 (1H, br s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{18}H_{24}N_2O_3$ (316.4): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.13; H, 7.41; N, 8.89.

3.4 9-(2-Carbomethoxyethyl)-7,8-diethyl-2,3-dimethyl-10H-dipyrrin-1-one (2e)

To a 100 ml round-bottom flask equipped with magnetic stirring were added 35 mg (0.1 mmol) of [3]-semirubin

acid **2** and 50 ml of methanol. To this solution was added 10 ml of 10% aq. H_2SO_4, and the solution was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, taken up in 50 ml of CH_2Cl_2, washed with water (2 × 100 ml), sat. aq. $NaHCO_3$ (2 × 100 ml) and dried over Na_2SO_4 (anh.). The solvent was removed at reduced pressure (rotovap) and the residue was purified by radial chromatography (97:3 by vol. CH_2Cl_2:MeOH) and recrystallised (CH_2Cl_2–hexane) to give 31 mg (96%) of the desired ester **2e**. It has mp 198–199°C; IR (KBr): ν 3350, 2960, 2921, 1738, 1673, 1634, 1464, 1432, 1371, 1282, 1250, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.10 (3H, t, $J = 7.5$ Hz), 1.1 (3H, t, $J = 7.5$ Hz), 1.89 (3H, s), 2.11 (3H, s), 2.42 (2H, q, $J = 7.5$ Hz), 2.55 (2H, q, $J = 7.5$ Hz), 2.72 (2H, t, $J = 8.0$ Hz), 3.06 (2H, t, $J = 8.0$ Hz), 3.67 (3H, s), 6.10 (1H, s), 10.09 (1H, s), 10.84 (1H, s) ppm; ^1H NMR (DMSO-d_6, 300 MHz): δ 0.98 (3H, t, $J = 7.5$ Hz), 1.00 (2H, t, $J = 7.5$ Hz), 1.73 (3H, s), 2.01 (3H, s), 2.31 (2H, q, $J = 7.5$ Hz), 2.43 (2H, q, $J = 7.5$ Hz), 2.59 (2H, t, $J = 7.5$ Hz), 2.76 (2H, t, $J = 7.5$ Hz), 3.57 (3H, s), 5.86 (1H, s), 9.75 (1H, s), 10.11 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online; FAB-MS 330.4 [M^+], 353.4 [+Na^+] *m/z*. Anal. Calcd for $C_{19}H_{26}N_2O_3$ (330.4): C, 69.06; H, 7.93; N, 8.48. Calcd for $C_{19}H_{26}N_2O_3 \cdot 0.25H_2O$ (334.4): C, 68.14; H, 7.97; N, 8.36. Found: C, 68.06; H, 8.06; N, 8.42.

3.5 9-(3-Carboxypropyl)-7,8-diethyl-2,3-dimethyl-(10H)-dipyrrin-1-one (3)

To a 500 ml round-bottom flask equipped with magnetic stirring were added dipyrrinone **11** (*26*) (0.50 g, 2.0 mmol) and 100 ml of dichloromethane. The solution was stirred in an ice bath for 20 min. A solution of mono-methyl succinate acid chloride (0.812 g, 6.2 mmol) and $AlCl_3$ (3.0 g, 22.5 mmol) in 100 ml of dichloromethane was added all at once, and the reaction mixture stirred for 1.5 h at room temperature. The reaction mixture was then poured into 250 ml of ice water and stirred for 2 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 100 ml). The combined extracts were washed with sat. aq. $NaHCO_3$ (2 × 200 ml) and water (400 ml), and then dried over Na_2SO_4. The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2:MeOH) and recrystallised from CH_2Cl_2–hexane to afford 9-(3-carboxypropanoyl)-7,8-diethyl-2,3-dimethyl-(10*H*)-dipyrrin-1-one (0.44 g, 60%). It has mp 166–168°C; IR (KBr): ν 3376, 3125, 2969, 2954, 1740, 1675, 1436, 1260, 1166, 693 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 1.01 (3H, t, $J = 7.0$ Hz), 1.03 (3H, t, $J = 7.0$ Hz), 1.77 (3H, s), 2.05 (3H, s), 2.50 (2H, q, $J = 7.0$ Hz), 2.58 (2H, t, $J = 7.5$ Hz), 2.64 (2H, q, $J = 7.0$ Hz), 3.17 (2H, t, $J = 7.5$ Hz), 3.56 (3H, s), 5.91 (1H, s), 10.36 (1H, s), 10.66 (1H, s) ppm; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.14 (3H, t, $J = 7.5$ Hz), 1.21 (3H, t, $J = 7.5$ Hz), 1.93 (3H, s), 2.11 (3H, s), 2.53 (2H, q, $J = 7.5$ Hz), 2.75 (4H, m), 3.18 (2H, t, $J = 6.5$ Hz), 3.70 (3H, s), 5.95 (1H, s), 9.05 (1H, s), 9.53 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.60, 9.93, 15.90, 16.41, 17.22, 18.64, 28.39, 34.11, 51.96, 96.78, 128.19, 128.91, 129.93, 130.11, 133.30, 136.26, 142.06, 173.80, 173.86, 187.78 ppm; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{20}H_{26}N_2O_4$ (358.4): C, 67.02; H, 7.31; N, 7.82. Found: C, 66.64; H, 7.43; N, 7.86.

To a 250 ml round-bottom flask equipped with the magnetic stirring were placed 300 mg (0.85 mmol) of 10-*oxo*-semirubin from above and 100 ml of 2-propanol. Sodium borohydride (100 mg) was added, and the reaction mixture was heated at reflux for 2 h. The hot reaction mixture was poured into 100 ml of ice water, and the solution was acidified with 10% HCl (aq.). The suspension was extracted with dichloromethane (3 × 50 ml), and the combined extracts were washed with water (3 × 100 ml), dried over Na_2SO_4 (anh.), and the solvent was removed (rotovap). The crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2:MeOH) to give [4]-semirubin **3** (257 mg, 93%). It has mp 204–206°C; IR (KBr): ν 3350, 2959, 2921, 2852, 1711, 1679, 1637, 1467, 1370, 1275, 1177, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.11 (3H, t, $J = 7.5$ Hz), 1.15 (3H, t, $J = 7.5$ Hz), 1.88 (3H, s), 2.10 (3H, s), 2.13 (2H, m), 2.43 (2H, q, $J = 7.5$ Hz), 2.41 (2H, t, $J = 7.0$ Hz), 2.55 (2H, q, $J = 7.5$ Hz), 2.73 (2H, t, $J = 6.5$ Hz), 6.11 (1H, s), 8.92 (1H, s), 10.71 (1H, s), 14.17 (1H, br s) ppm; ^1H NMR (DMSO-d_6, 500 MHz): δ 1.00 (3H, t, $J = 7.5$ Hz), 1.04 (3H, t, $J = 7.5$ Hz), 1.76 (5H, m), 2.04 (3H, s), 2.21 (2H, t, $J = 7.0$ Hz), 2.31 (2H, q, 7.5 Hz), 2.46 (2H, q, $J = 7.5$ Hz), 2.51 (2H, t, $J = 7.5$ Hz), 5.90 (1H, s), 9.83 (1H, s), 10.12 (1H, s), 11.97 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{19}H_{26}N_2O_3$ (330.4): C, 69.06; H, 7.93; N, 8.48. Found: C, 68.81; H, 8.08; N, 7.62.

3.6 9-(3-Carbomethoxypropyl)-7,8-diethyl-2,3-dimethyl-(10H)-dipyrrin-1-one (3e)

To a 100 ml round-bottom flask equipped with magnetic stirring were added 88 mg (0.27 mmol) of semirubin acid **3** and 50 ml of methanol. To this solution was added 10 ml of 10% H_2SO_4, and the solution was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, taken up in 50 ml of dichloromethane, washed with water (2 × 100 ml), sat. aq. $NaHCO_3$ (2 × 100 ml) and dried over Na_2SO_4. The solvent was removed (rotovap), and the residue was purified by radial chromatography (97:3 by

vol. CH_2Cl_2:MeOH) to give pure **3e** (4 mg, 92%). It has mp 206–208°C; IR (KBr): ν 3448, 3348, 2953, 2919, 2863, 1736, 1670, 1638, 1473, 1436, 1371, 1177, 942, 394 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.11 (3H, t, $J = 7.5$ Hz), 1.16 (3H, t, $J = 7.5$ Hz), 1.93 (3H, s), 2.02 (2H, pentet, $J = 7.5$ Hz), 2.12 (3H, s), 2.34 (2H, t, 7.0 Hz), 2.41 (2H, q, $J = 7.5$ Hz), 2.56 (2H, q, $J = 7.5$ Hz), 2.81 (2H, t, $J = 7.0$ Hz), 3.64 (3H, s), 6.11 (1H, s), 10.08 (1H, s), 11.04 (1H, s) ppm; ^1H NMR (DMSO-d_6, 500 MHz): δ 1.01 (3H, t, $J = 7.5$ Hz), 1.04 (3H, t, $J = 7.5$ Hz), 1.76 (3H, s), 1.81 (2H, quintet, $J = 7.5$ Hz), 2.04 (3H, s), 2.31 (4H, m), 2.46 (2H, q, $J = 7.5$ Hz), 2.53 (2H, t, $J = 7.5$ Hz), 3.58 (3H, s), 5.90 (1H, s), 9.81 (1H, s), 10.11 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{20}H_{28}N_2O_3$ (344.2): C, 69.74; H, 8.19; N, 8.13. Found: C, 69.64; H, 8.17; N, 8.17.

3.7 9-(4-Carboxybutyl)-2,3,7,8-tetramethyldipyrrin-1-one (4)

To a 500 ml round-bottom flask equipped with magnetic stirring were added 0.500 g (2.3 mmol) of dipyrrinone **9** (*21a*, *25*) and 100 ml of dichloromethane. The solution was stirred in an ice bath for 20 min. A solution of 0.916 g (5.5 mmol) of mono-methyl glutarate acid chloride and 4.5 g (31.7 mmol) of $AlCl_3$ in 100 ml of dichloromethane was added all at once and the reaction mixture was stirred for 1.5 h at room temperature. The reaction mixture was then poured into a mixture of conc. HCl (200 ml) and 100 g of ice and stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 100 ml). The combined extracts were washed with aq. $NaHCO_3$ (2 × 200 ml), water (400 ml) and dried over Na_2SO_4. The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2: MeOH), and then recrystallised from CH_2Cl_2–hexane to afford 9-(4-carboethoxybutanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (0.41 g, 60%). It has mp 173–174°C; IR (KBr): ν 3355, 3133, 2999, 2917, 1732, 1656, 1436, 1362, 1251, 1167, 942, 763, 692 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 1.16 (2H, t, $J = 7.5$ Hz), 1.59 (2H, m), 1.79 (3H, s), 2.01 (3H, s), 2.07 (3H, s), 2.22 (3H, s), 2.32 (2H, t, $J = 6.5$ Hz), 2.82 (2H, t, $J = 7.5$ Hz), 5.95 (1H, s), 10.32 (1H, s), 10.74 (1H, s) ppm; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.93 (3H, s), 2.03 (3H, s), 2.11 (3H, s), 2.33 (3H, s), 2.74 (2H, t, $J = 6.5$ Hz), 3.13 (2H, t, $J = 6.5$ Hz), 3.70 (3H, s), 5.94 (1H, s), 8.64 (1H, s), 9.41 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online: δ 8.58, 9.39, 9.90, 11.93, 28.25, 34.83, 51.92, 96.79, 123.66, 127.05, 128.39, 129.52, 130.18, 136.83, 141.87, 173.43, 173.74, 187.64 ppm; UV–vis data in Table 2 of the Supporting Information, available online

To a 100 ml round-bottom flask equipped with magnetic stirring were placed 97 mg (0.3 mmol) of 10-*oxo*-semirubin (above) and 50 ml of 2-propanol. Sodium borohydride (50 mg, 0.85 mmol) was added and the reaction mixture was heated at reflux for 2 h. The hot reaction mixture was poured into 100 ml of ice water, and the solution was acidified with 10% HCl (aq.). The suspension was extracted with dichloromethane (3 × 50 ml), and the combined extracts were washed with water (3 × 100 ml) and dried over Na_2SO_4. The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2:MeOH) to give **4** (85 mg, 98%). It has mp 200–202°C; IR (KBr): ν 3424, 3343, 2915, 2848, 1653, 1635, 1384, 1266, 1174, 938, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.71 (2H, m), 1.83 (2H, m), 1.90 (3H, s), 1.95 (3H, s), 2.10 (3H, s), 2.12 (3H, s), 2.44 (2H, t, $J = 8.0$ Hz), 2.69 (2H, t, $J = 8.0$ Hz), 6.14 (1H, s), 8.91 (1H, s), 10.73 (1H, s), 14.32 (1H, br s) ppm; ^1H NMR (DMSO-d_6, 500 MHz): δ 1.52 (4H, m), 1.77 (3H, s), 1.86 (3H, s), 2.01 (3H, s), 2.06 (3H, s), 2.23 (2H, t, $J = 7.0$ Hz), 2.52 (2H, t, $J = 6.5$ Hz), 5.93 (1H, s), 9.81 (1H, s), 10.13 (1H, s), 11.97 (1H, s) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 8.32, 8.80, 9.40, 9.56, 24.19, 25.25, 29.23, 33.47, 97.91, 114.74, 121.63, 122.67, 123.32, 128.85, 133.55, 141.37, 171.74, 174.39 ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{18}H_{24}N_2O_3$ (316.2): C, 68.33; H, 7.64; N, 8.85. Calcd for $C_{18}H_{24}N_2O_3 \cdot 0.5H_2O$ (325.2): C, 66.42; H, 7.75; N, 8.61. Found: C, 66.51; H, 7.54; N, 8.88.

3.8 9-(4-Carbomethoxybutyl)-2,3,7,8-tetramethyl-(10H)-dipyrrin-1-one (4e)

To a 100 ml round-bottom flask equipped with magnetic stirring were added 88 mg (0.26 mmol) of semirubin acid **4** and 50 ml of methanol. To this solution was added 10 ml of 10% H_2SO_4, and the solution was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, taken up in 50 ml of dichloromethane, washed with water (2 × 100 ml), sat. aq. $NaHCO_3$ solution (2 × 100 ml) and dried over Na_2SO_4 (anh.). The solvent was removed (rotovap), and the residue was purified by radial chromatography (97:3 by vol. CH_2Cl_2:MeOH) to give pure **4e** (85 mg, 98%). It has mp 192–194°C; IR (KBr): ν 3400, 3355, 1736, 1670, 1637, 1436, 1371, 1333, 1268, 941, 752, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.92 (3H, s), 1.95 (3H, s), 2.00 (2H, p, $J = 7.0$ Hz), 2.10 (3H, s), 2.12 (3H, s), 2.32 (2H, t, $J = 7.0$ Hz), 2.81 (2H, t, $J = 7.0$ Hz), 3.63 (3H, s), 6.12 (1H, s), 10.08 (1H, s), 11.06 (1H, s) ppm; ^1H NMR (DMSO-d_6, 500 MHz): δ 1.52 (4H, m), 1.77 (3H, s), 1.85 (3H, s), 2.00 (3H, s), 2.05 (3H, s), 2.32 (2H, t, $J = 7.5$ Hz), 2.51 (2H, t, $J = 7.5$ Hz), 3.57 (3H, s), 5.92 (1H, s), 9.82 (1H, s), 10.12 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz in Table 1

of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{19}H_{26}N_2O_3$ (330.2): C, 69.05; H, 7.94; N, 8.48. Found: C, 69.19; H, 7.81; N, 8.74.

3.9 9-(6-Carboxyhexyl)-2,3,7,8-tetramethyl-(10H)-dipyrrin-1-one (6)

A suspension of anh. $AlCl_3$ (3.00 g, 22.5 mmol) in 300 ml of dichloromethane in a 1 litre round-bottom flask with a drying tube ($CaCl_2$) was cooled to 0°C by an ice bath. To the mixture, freshly distilled 6-carboethoxyhexanoyl chloride (1.33 g, 0.75 mmol) was added in one portion. The mixture was stirred for an additional 10 min in the ice bath, at which time **9** (1.0 g, 4.6 mmol) in 200 ml of CH_2Cl_2 was added in one portion to the mixture. The mixture was stirred at room temperature for 15 h and then poured into 300 ml of ice water and stirred for 30 min. The solution was extracted with CH_2Cl_2 (3 × 125 ml), and the combined extracts were washed with water (3 × 100 ml). After drying over anh. Na_2SO_4 and evaporation of the solvent, the residue was subjected to radial chromatography using CH_2Cl_2–methanol (98:2 by vol.) as the eluent. After evaporating the solvent, the residue was recrystallised from hexane–CH_2Cl_2 to yield 9-(6-carboethoxyhexanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (670 mg, 40%). It has mp 129–130°C; IR (NaCl, film): ν 3341, 2939, 1735, 1656, 1436, 1247, 1171, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, $J = 7.32$ Hz), 1.42 (2H, m), 1.69 (4H, m), 1.93 (3H, s), 2.07 (3H, s), 2.11 (3H, s), 2.3 (5H, m), 2.79 (2H, t, $J = 7.33$ Hz), 4.11 (2H, q, $J = 7.33$ Hz), 5.94 (1H, s), 8.8 (1H, br), 9.39 (1H, br) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 8.8, 9.7, 10.1, 11.9, 14.5, 24.3, 25.1, 29.2, 34.4, 40.1, 60.4, 124.1, 126.3, 128.3, 129.3, 131.3, 136.4, 142.2, 174.2, 173.9, 190.3 ppm.

In a 100 ml round-bottom flask equipped with a stirring bar, the *oxo*-semirubin above (0.10 g, 0.26 mmol) was dissolved in 2-propanol (60 ml). The solution was stirred while sodium borohydride (0.15 g, 4.05 mmol) was added in one portion to the solution. The solution was held at reflux for 3 h, when the hot solution was poured into a 250 ml beaker containing 100 g of ice water. The solution was acidified with 10% aq. hydrochloric acid. The acidified solution was extracted with CH_2Cl_2 (3 × 30 ml), and the combined organic layers were washed with water (100 ml), dried with Na_2SO_4, and the solvent was removed by rotovap. The residue was dissolved in CH_2Cl_2 (30 ml) and anh. $AlCl_3$ (1 g) was added to the solution and the mixture was stirred for 2 h. The solution was poured into a beaker containing 100 g of ice water. The mixture was stirred for 30 min and extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were washed with water (2 × 50 ml) and dried (Na_2SO_4). The solvent was removed by rotovap and the residue was crystallised by hexane–dichloromethane to yield **7** (56 mg, 63%). It has mp 150–152°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (2H, m), 1.56 (4H, m), 1.68 (2H, m), 1.9 (3H, s), 2.0 (3H, s), 2.1 (3H, s), 2.11 (3H, s), 2.44 (2H, t, $J = 6.22$ Hz), 2.59 (2H, m, $J = 7.69$ Hz), 6.12 (1H, s), 8.79 (1H, br s), 10.75 (1H, br s), 13.9 (1H, br s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{20}H_{28}N_2O_3$ (344.2): C, 69.74; H, 8.19; N, 8.13. Found: C, 69.52; H, 8.07; N, 8.08.

3.10 9-(6-Carbomethoxyhexyl)-2,3,7,8-tetramethyl-(10H)-dipyrrin-1-one (6e)

[7]-Semirubin **6** (20 mg, 0.058 mmol) was dissolved in methanol (25 ml), 10% sulphuric acid (5 ml) was added slowly and the solution was heated at reflux for 1 h while stirring. The solution was cooled to room temperature and taken up in CH_2Cl_2 and washed with sat. aq. sodium bicarbonate (2 × 25 ml). The organic layer was separated and dried (Na_2SO_4), and the solvent was removed. The residue was crystallised with hexane–dichloromethane to give pure **6e** (16 mg, 77%). It has mp 169–170°C; IR (NaCl, film): ν 3343, 2923, 1740, 1654, 1372.6, 1174, 722.32, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33 (2H, m), 1.62 (6H, m), 1.92 (3H, s), 1.95 (3H, s), 2.11 (3H, s), 2.13 (3H, s), 2.74 (2H, t, $J = 7.3$ Hz), 2.73 (2H, m), 3.65 (3H, s), 6.13 (1H, s), 10.07 (1H, br s), 11.14 (1H, br s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) in Table 1 of the Supporting Information, available online; UV–vis data in Table 2 of the Supporting Information, available online. Anal. Calcd for $C_{21}H_{30}N_2O_3$ (358.2): C, 70.36; H, 8.44; N, 7.81. Found: C, 70.28; H, 8.28; N, 7.72.

3.11 2-Formyl-3-isobutyl-4-methyl-5-(ethoxycarbonyl)-1H-pyrrole (13)

To a 500 ml round-bottom flask equipped with magnetic stirring were added 7.0 g (31.0 mmol) of 2,4-dimethyl-3-isobutyl-5-carboethoxypyrrole (**14**), 250 ml of methanol and 20 ml water. The reaction mixture was placed in an ice bath for 30 min, and then 70.0 g of CAN was added all at once and stirring was continued at room temperature for 3 h. The reaction mixture was taken up in dichloromethane (500 ml) and washed with water (3 × 400 ml), saturated sodium bicarbonate (2 × 300 ml), and dried over Na_2SO_4. The solvent was removed (rotovap) to yield an oily product, which was recrystallised from methanol to give the desired pyrrole aldehyde **13** (4.95 g, 67%). It has mp 63–64°C; IR (KBr): ν 3284, 2957, 2921, 2867, 1700, 1659, 1463, 1258, 1228, 1129, 1075 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (6H, d, $J = 6.5$ Hz), 1.23 (2H, t, $J = 7.5$ Hz), 1.79 (1H, sept, $J = 6.5$ Hz), 2.17 (3H, s), 2.51 (2H, d, $J = 6.5$ Hz), 4.22 (2H, q, $J = 7.5$ Hz), 9.76 (1H, s), 9.92 (1H, br s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.87, 14.13, 22.11, 30.19, 32.25, 60.60, 124.36, 126.52, 130.28, 133.58, 160.76, 179.24 ppm; GC-MS: *m/z* 237 [M^+], 194, 176, 148 (100%), 121, 92, 65 amu.

Anal. Calcd for $C_{13}H_{19}N_2O_3$ (237.3): C, 65.80; H, 8.07; N, 5.90. Found: C, 65.55; H, 8.19; N, 5.99.

3.12 2,4-Dimethyl-3-isobutyl-5-carboethoxypyrrole (14)

To a 2 litres three-neck round-bottom flask equipped with a mechanical stirrer and thermometer was added 100 g (0.60 mol) of diethyl oximinomalonate, 55.6 g (0.56 mol) of 2,4-pentanedione and 1.1 litre of glacial acetic acid. The reaction mixture was heated to ~90°C and 47.2 g of zinc dust was added at such a rate that the temperature was maintained between 85 and 90°C. After the addition was complete, the reaction mixture was heated at reflux for 2 h. The hot mixture was then poured into 8 litres of ice water and placed in a cold room for 4 h. The crude product was collected by vacuum filtration, washed with water (3 × 500 ml), and air dried to give 75.9 g (82%) of 5-carboethoxy-2,4-diethylpyrrole **15** (*27*). It was sufficiently pure for the next step and had ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34 (3H, t, $J = 7.0$ Hz), 2.24 (3H, s), 2.30 (3H, s), 4.28 (2H, q, $J = 7.0$ Hz), 5.79 (1H, d, $J = 2.5$ Hz), 8.73 (1H, br s) ppm.

Acetic anhydride (20 ml) was slowly added to 5 ml of conc. HCl with stirring and cooling, and 6.1 g (36.5 mmol) of **15** was dissolved in the resulting solution. Amalgamated zinc (100 g) and 7.5 ml of isobutyraldehyde were then added at 20°C, and the mixture was stirred for 20 min at 20–25°C. The zinc was separated by filtration, washed with acetic acid, and the liquid was poured into water to precipitate the crude product. The crude product was recrystallised from methanol–water to give **14**. It has mp 114–115°C (lit. (*28*) 115–117°C) and GC-MS: *m/z* 223 [M^+], 182, 180, 134 (100%), 107, 77, 65 amu.

3.13 9-Formyl-7,8-diethyl-2,3-dimethyl-(10H)-dipyrrin-1-one (17)

To a 200 ml round-bottom flask equipped with magnetic stirring were added 1.8 g (6.3 mmol) of 7,8-diethyl-2,3-dimethyl-dipyrrin-1-one-9 carboxylic acid (**16**) (*22*) and 40 ml of TFA. The reaction mixture was stirred for 30 min at room temperature, followed by cooling to 0°C in an ice-salt bath. Triethyl orthoformate (5 ml) was added dropwise, followed by stirring for 10 min. The reaction mixture was then poured onto ice water (100 ml/100 g) and stirred for 30 min. The crude product was collected by filtration (vacuum) and purified by trituration with cold CH_2Cl_2 (20 ml) to give pure **17** (1.4 g, 82%). It has mp 256–257°C; IR (KBr): ν 3338, 2970, 2903, 1708, 1687, 1658, 1601, 1558, 1463, 1252, 1175, 756, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (3H, t, $J = 7.5$ Hz), 1.26 (3H, t, $J = 7.5$ Hz), 2.00 (3H, s), 2.13 (3H, s), 2.57 (2H, q, $J = 7.5$ Hz), 2.78 (2H, q, $J = 7.5$ Hz), 5.96 (1H, s), 9.70 (1H, s), 10.69 (1H, s), 10.91 (1H, s) ppm; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.05 (3H, t, $J = 7.5$ Hz), 1.07 (3H, t, $J = 7.5$ Hz), 1.79 (3H, s), 2.07 (3H, s), 2.50 (2H, q, $J = 7.5$ Hz), 2.67 (2H, q, $J = 7.5$ Hz), 5.90 (1H, s), 10.57 (1H, s), 10.96 (1H, s), 12.36 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.66, 9.93, 16.27, 17.11, 17.36, 95.65, 128.42, 130.19, 130.57, 132.72, 136.82, 138.71, 141.99, 174.12, 177.23 ppm. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.2): C, 70.55; H, 7.41; N, 10.29. Found: C, 70.51; H, 7.42; N, 10.42.

3.14 9-(2-Carboethoxyethenyl)-7,8-diethyl-2,3-dimethyl-(10H)-dipyrrin-1-one (18)

To a 250 ml round-bottom flask equipped with magnetic stirring were added dipyrrinone aldehyde **17** (0.5 g, 1.8 mmol), ethyl hydrogen malonate (2.0 g, 15 mmol), 100 ml toluene, 100 ml pyridine, 0.5 ml acetic acid (glacial) and 0.5 ml of piperidine. The reaction mixture was heated at reflux for 6 h followed by pouring onto 10% HCl (aq.)/ice (100 ml/50 g). After stirring for 30 min, the suspension was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were washed with 10% aq. HCl (2 × 150 ml), water (1 × 200 ml), and dried over anh. Na_2SO_4. The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2:CH_3OH eluent) and recrystallised from CH_2Cl_2–hexane to give 0.51 g (81%) of pure **18**. It has mp 201–202°C; IR (KBr): ν 3337, 2953, 2925, 2887, 1710, 1693, 1668, 1615, 1455, 1367, 1250, 1158, 1042, 976 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.17 (3H, t, $J = 7.5$ Hz), 1.18 (3H, t, $J = 7.5$ Hz), 1.30 (3H, t, $J = 7.5$ Hz), 1.94 (3H, s), 2.12 (3H, s), 2.57 (2H, q, $J = 7.5$ Hz), 2.61 (2H, q, $J = 7.5$ Hz), 4.23 (2H, q, $J = 7.5$ Hz), 6.09 (1H, s), 6.55 (1H, d, $J = 16.0$ Hz), 7.67 (1H, d, $J = 1.0$ Hz), 10.22 (1H, s), 11.20 (1H, s) ppm; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.05 (3H, t, $J = 7.5$ Hz), 1.06 (3H, t, $J = 7.5$ Hz), 1.24 (3H, t, $J = 7.5$ Hz), 1.80 (3H, s), 2.07 (3H, s), 2.52 (4H, q, $J = 7.5$ Hz), 4.15 (2H, q, 7.5 Hz), 5.91 (1H, s), 6.37 (1H, d, $J = 15.5$ Hz), 7.42 (1H, d, $J = 15.5$ Hz), 10.17 (1H, s), 10.38 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.76, 9.27, 14.5, 16.5, 16.9, 17.5, 60.0, 99.2, 112.7, 126.3, 127.7, 129.5, 131.3, 131.5, 131.9, 132.3, 142.5, 168.2, 174.9 ppm. Anal. Calcd for $C_{20}H_{26}N_2O_3$ (342.4): C, 70.15; H, 7.65; N, 8.18. Calcd for $C_{20}H_{26}N_2O_3 \cdot 0.5CH_3OH$ (358.4): C, 69.40; H, 7.77; N, 7.99. Found: C, 69.21; H, 7.40; N, 7.64.

Note

1. Molecular mechanics calculations and molecular modelling was carried out on an SGI Octane workstation using version 6.6 of Sybyl (Tripos Associates, Inc., St Louis, MO, USA) as described in Ref. (*20*). The ball and stick drawings were created from the atomic coordinates of the molecular

dynamics structures using Muller and Falk's 'Ball and Stick' program for the Macintosh.

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