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An Intramolecularly Hydrogen Bonded Dihydrotripyrrinone

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Summary. A yellow tripyrrole analog (**1**) of bilirubin has been synthesized, and its lone propionic acid group is found to engage in conformation determining, intramolecular hydrogen bonding in solution and in the crystal. Molecular modelling and X-ray crystallography reveal an abbreviated ridge-tile or L-shape conformation in which an essentially planar dipyrrinone is hydrogen bonded to the single opposing propionic acid group. In the (arbitrary) (*P*)-helicity ridge-tile, the torsion angles about C(10) are computed to be 55° and 61° by molecular dynamics and found to be 66° and 53° in the crystal. Such torsion angles lead to an interplanar dihedral angle (∼93°) between the dipyrrinone and its adjoining pyrrole that is very close to the dihedral angle (∼98°) found in intramolecularly hydrogen bonded bilirubin.

Keywords. Bile pigments; X-Ray structure; Molecular dynamics.

Ein Dihydrotripyrrinon mit intramolekularer Wasserstoffbrückenbindung

Zusammenfassung. Ein gelbes Tripyrrinanaloges (**1**) des Bilirubins wurde synthetisiert; es wurde gefunden, daß in Lösung und im Kristall seine Propionsäuregruppe an einer konformationsbestimmenden intramolekularen Wasserstoffbrückenbindung beteiligt ist. Molekülrechnungen und Röntgenstrukturanalyse zeigen eine verkürzte Firstziegel- oder L-Typ-Konformation, in der ein im wesentlichen ebenes Dipyrrinon an die gegenüberliegende Propionsäuregruppe gebunden ist. Für die (beliebige) (*P*)-helikale Firstziegelkonformation ergeben Kraftfeldrechnungen Torsionswinkel von 55° und 61° um C(10); im Kristall werden 66° und 53° gemessen. Diese Torsionswinkel haben einen Interplanarwinkel von etwa 93° zwischen dem Dipyrrinon und dem benachbarten Pyrrolring zur Folge, welcher nahe an dem für das ebenfalls intramolekular wasserstoffbrückengebundene Bilirubin (∼98°) liegt.

Introduction

Bilirubin, the neurotoxic yellow pigment of jaundice, is comprised of two dipyrrinone chromophores conjoined to a methylene group. The dipyrrinone skeleton β-carbons are substituted by vinyl, methyl, and propionic acid groups (Fig. 1), and by varying the order of the β-substituents, a large array of bilirubin analogs can be formulated. Only one pigment, however, is usually found in

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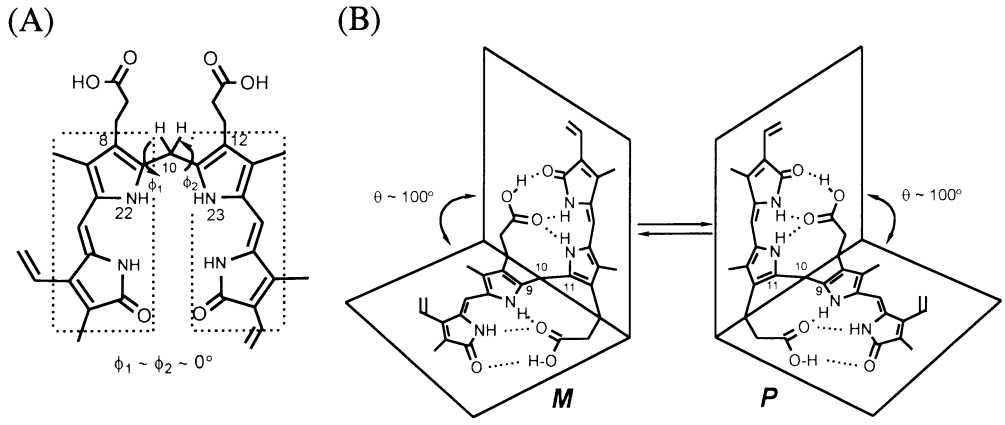


Fig. 1. (A) Porphyrin-like conformation of bilirubin with N(22)–C(9)–C(10)–C(11) and C(9)–C(10)–C(11)–N(23) torsion angles (ϕ_1 and ϕ_2, respectively) of approx. 0°; the dipyrrinone chromophores are enclosed in the dashed boxes. (B) Interconverting folded, intramolecularly hydrogen bonded conformations ($\phi_1 = \phi_2 \sim -60°$ (*M*), $\phi_1 = \phi_2 \sim +60°$ (*P*)) shaped like ridge-tiles and corresponding to global energy minimum conformations; the interplanar dihedral angle θ is about 100°; hydrogen bonds are indicated by dotted lines

mammals: bilirubin (bilirubin-IXα), which is formed at the rate of $\sim$300 mg/day from the breakdown of $\sim 10^{11}$ red blood cells per day [1–3]. The location of the propionic acid groups has a profound influence on the spectroscopic, solution, and metabolic properties of bilirubin [1, 4], but the location of the remaining β-substituents is less important. When the propionic acid groups are moved from their natural positions at C(8) and C(12), the resulting bilirubin pigments are much more polar and much less soluble in nonpolar organic solvents such as chloroform or benzene (in which the UV/Vis λ_{max} are blue shifted). Such pigments are also more soluble in dilute alkali and more excretable across the liver into bile [4, 5]. On the other hand, when the vinyl groups are reduced to ethyl, as in mesobilirubin, these properties of the pigment remain relatively unchanged.

The propionic acid groups at C(8) and C(12) play a unique role in stabilizing a particular bilirubin conformation, one where the two dipyrrinones are rotated about the C(9)–C(10) and C(10)–C(11) bonds so as to bring the propionic CO_2H and the dipyrrinone pyrrole NH and lactam –NH–C=O groups into sufficiently close proximity for intramolecular hydrogen bonding (Fig. 1B) [6–9]. With tetrahedral hybridization at C(10), the molecule is bent across the middle to form either of two enantiomeric conformers shaped like ridge-tiles [9] and seen in equal numbers in crystals of bilirubin and its dicarboxylate salts [10] – to the exclusion of other conformations [9–10]. In the crystalline state, bilirubin molecules can stretch and vibrate but are otherwise restrained. However, when dissolved in organic solvents, bilirubin is potentially more flexible and might be expected to exhibit more conformational freedom, forming hydrogen bonds to solvent molecules, to other bilirubin molecules, or intramolecularly as it does in the crystal [11–14]. Despite a multitude of conformational possibilities, it now seems clear that intramolecularly hydrogen bonded structures like those in Fig. 1B prevail in non-polar solvents such

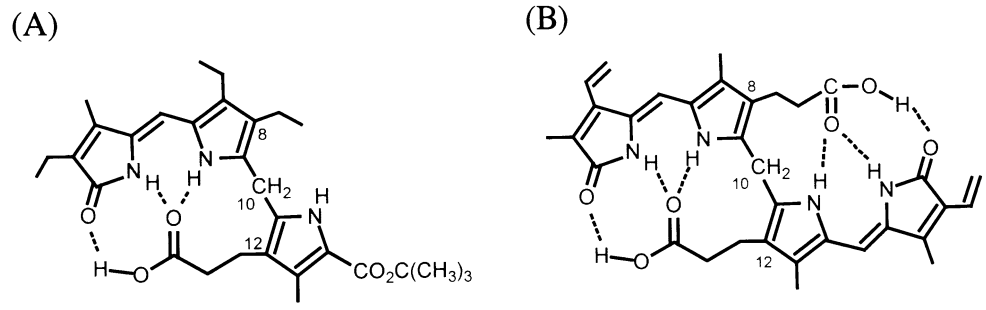


Fig. 2. Planar representation of (A) tripyrrinone (**1**), an analog of intramolecularly hydrogen bonded bilirubin (B). Hydrogen bonds are indicated by dashed lines

as chloroform, in polar solvents such as acetone and ethanol, and even in water at high *pH* (where bilirubin is present as the dicarboxylate dianion) [7, 15].

In order to explore the importance and location of a single propionic acid in stabilizing the ridge-tile conformation, we synthesized and determined the properties of a novel tripyrrinone analog (**1**) of bilirubin (Fig. 2). Its conformation in solution has been analyzed by NMR spectroscopy, and its three-dimensional structure in the solid is revealed by X-ray crystallography.

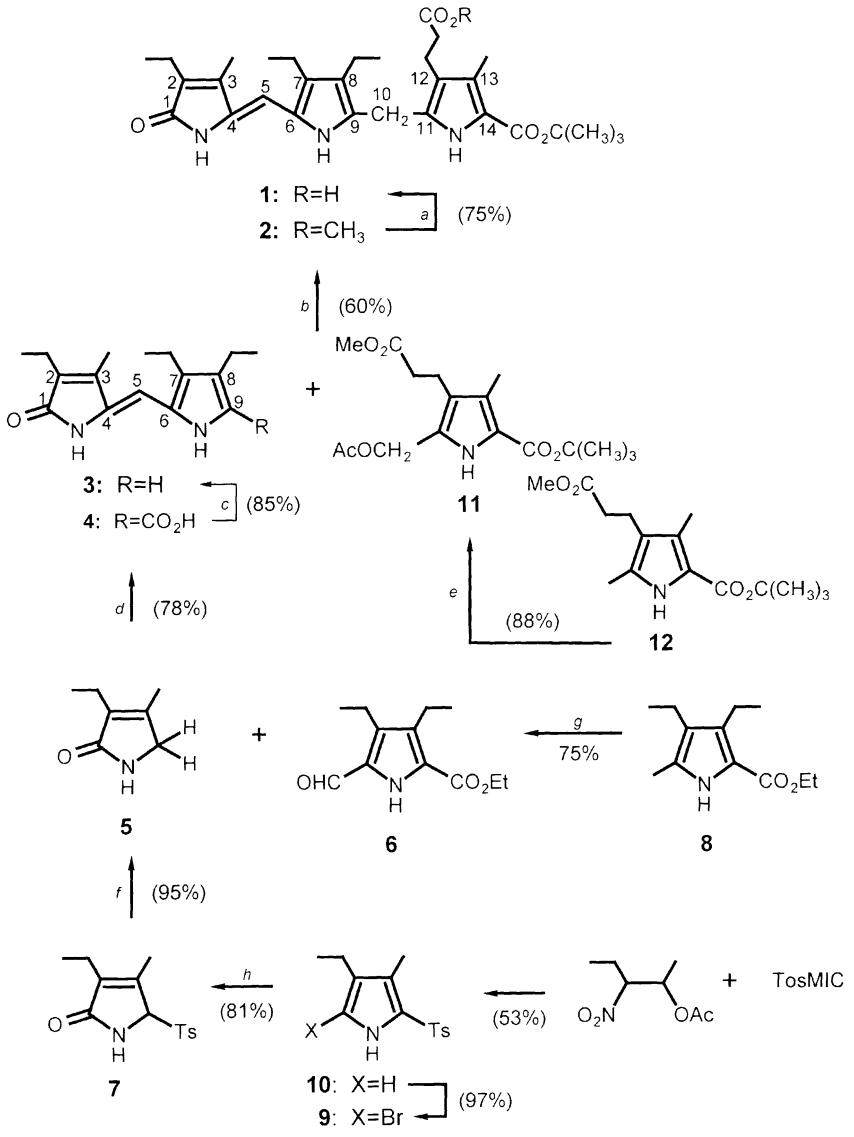
Results and Discussion

Synthetic aspects

Our approach towards the synthesis of **1** focussed on an acid-catalyzed solvolytic coupling reaction used to prepare dipyrrylmethanes [16, 17]. Thus, solvolysis of α-acetoxymethylpyrrole **11** in the presence of the α-free dipyrrinone **3** afforded a 60% yield of tripyrrinone ester **2**. Simple saponification of **2** afforded pure **1**. The monopyrrole coupling partner (**11**) was prepared by lead tetraacetate oxidation of the known pyrrole **12** [18]. The dipyrrinone coupling partner with the three β-ethyls (**3**) was designed to have improved solubility in nonpolar organic solvents. It was synthesized by condensing ethyl 5-formyl-3,4-diethylpyrrole-2-carboxylate (**6**) with 3-ethyl-4-methylpyrrolinone (**5**). The former was prepared in good yield by ceric ammonium nitrate oxidation of the known pyrrole ester **8** [19–21], the latter in excellent yield from α-tosylpyrrole **10**, which was synthesized by reaction of *p*-toluenesulfonylmethyl isocyanide (*TosMIC*) with 3-nitropentan-2-ol acetate according to the *Barton-Zard* method [22].

Structure from ^{13}C NMR

The constitutional structures of tripyrrinones **1** and **2** follow from their syntheses and are confirmed by their ^{13}C NMR spectroscopic data (Table 1). The carbon chemical shifts, determined in $CDCl_3$ and assigned by HMBC and HMQC methods, as expected are nearly identical for **1** and **2**. The chemical shifts assigned to their dipyrrinone cores are quite similar to those of the dipyrrinone parent (**3**) and differ only in a few notable instances: the lactam carbonyl resonances of **1** and



[a] Ascorbic acid/0.2 *M* NaOH/MeOH/*THF*, then 10% aq. HCl; [b] *pTSA*/HOAc/*THF*, 40°C; [c] KOAc/NaOAc, 130°C; [d] 4 *M* KOH/MeOH, refl., then HCl; [e] $Pb(OAc)_4$/HOAc; [f] $NaBH_4$/EtOH; [g] *CAN*/HOAc/*THF*/H_2O; [h] *TFA*/H_2O; [i] $Br_2/MeCl_2$; guanidine/*THF*/isopropanol

2 are markedly shielded relative to that of **3**, and somewhat different shieldings in the dipyrrinone pyrrole ring carbons (probably due to the absence of a C(9) alkyl substituent in **3**) are observed. In $CDCl_3$ the corresponding chemical shifts are qualitatively similar to those measured in $(CD_3)_2SO$. The notable differences lie in the generally more deshielded resonances of **1** relative to those of **2**, indicative perhaps of different conformations.

Table 1. Comparison of ^{13}C NMR chemical shifts[a] and assignments[b] of dihydro-tripyrrinone acid **1**, its ester **2**, and dipyrrinone **3**

Carbon position	Chemical shift[a] in *DMSO*-d_6			Chemical shift[a] in $CDCl_3$		
	1	**2**	**3**	**1**	**2**	**3**
1 C=O	161.9	161.2	171.9	161.9	160.9	173.8
2 =C–	129.7	129.3	130.3	130.4	129.5	130.0
2^1 CH_2	16.87	16.80	16.66	17.34	16.72	16.27
2^2 CH_3	13.91	13.82	13.71	14.20	13.65	14.10
3 =C–	141.4	141.2	141.3	142.4	142.3	141.7
3^1 CH_3	9.77	9.64	9.59	10.26	9.71	9.43
4 –C=	130.0	129.8	128.0	130.7	128.6	129.4
5 –CH=	98.20	98.01	97.98	101.5	101.5	101.8
6 –C=	121.8	121.9	125.5	123.5	122.6	123.5
7 –C=	122.2	122.0	129.3	123.9	122.7	129.7
7^1 CH_2	17.21	17.13	18.06	17.68	17.35	18.10
7^2 CH_3	17.13	16.22	13.71	17.85	16.10	13.23
8 –C=	131.6	131.8	124.9	131.4	131.8	125.7
8^1 CH_2	17.56	17.40	17.32	18.48	17.79	17.55
8^2 CH_3	16.46	16.82	16.77	17.86	16.90	16.82
9 –C=	130.1	130.0	119.2	131.8	130.7	120.1
10 CH_2	23.08	23.00		22.82	22.82	
11 –C=	118.5	119.4		120.7	119.1	
12 –C=	119.6	118.2		120.6	119.0	
12^1 CH_2	19.67	19.53		19.18	19.61	
12^2 CH_2	35.19	34.51		33.46	35.10	
12^3 CO_2R	174.4	173.1		179.9	174.0	
12^4 OCH_3	–	51.41		–	51.6	
13 –C=	139.3	129.3		131.1	129.8	
13^1 CH_3	10.83	10.60		11.94	10.50	
14 –C=	125.3	125.3		125.9	126.0	
14^1 $–CO_2–$	174.4	171.9		175.2	173.1	
$OC(CH_3)_3$	79.75	76.62		81.16	80.02	
$OC(CH_3)$	28.77	28.61		29.18	28.38	

[a] Chemical shifts in δ (ppm, 125 MHz) downfield from *TMS* for 1×10^{-3} *M* solutions of pigment; [b] carbon assignments from NOE, HMQC, and HMBC measurements; for pigment numbering see synthetic scheme

Conformation from ^1H NMR

In bilirubins, ^1H NMR chemical shifts of the dipyrrinone NH and the propionic acid OH have been shown to be useful diagnostics for detecting the intramolecular hydrogen bonding that stabilizes the ridge-tile conformation depicted in Fig. 1B [7, 14, 23]. Hydrogen bonding causes large deshieldings of the dipyrrinone NHs, from ~7.5 ppm (lactam) and ~8 ppm (pyrrole) in the monomer to ~11 and 10 ppm, respectively, in the intramolecularly hydrogen bonded planar dimer [16, 24] in $CDCl_3$ [25]. A large number of NMR studies have shown that the pyrrole NH chemical shift is ~1 ppm more shielded (to ~9.2 ppm) in $CDCl_3$ when dipyrrinone

Table 2. Comparison of lactam and pyrrole NH and propionic CO_2H ^1H NMR chemical shifts[a] in dihydro-tripyrrinones **1** and **2**, dipyrrinone **3**, and the tetra-*n*-butylammonium salt (**13**)[b] of **1**

	Chemical shift[a] in *DMSO*-d_6				Chemical shift[a] in $CHCl_3$			
	Dipyrrinone		Pyrrol		Dipyrrinone		Pyrrol	
	lactam NH	pyrrol NH	NH	CO_2H	lactam NH	pyrrol NH	NH	CO_2H
1	10.16	10.76	9.69	11.96	10.41	9.02	8.17	13.48
2	10.21	10.83	9.69	–	10.71	10.22	9.22	–
3	10.45	11.15	–	–	10.50	9.81	–	–
13	11.76	12.30	9.57	–	11.73	11.43	8.07	–

[a] Chemical shift in δ (ppm) downfield from *TMS* for 1×10^{-3} *M* solutions;
[b] prepared according to Lightner DA, Ma JS. Wu XX (1986) *Spectrosc. Lett.* **19**: 311

and carboxylic acid groups are linked by intramolecular hydrogen bonding [7, 11–14, 23]. The difference may be attributed to a positioning of the pyrrole NH above the opposing pyrrole or dipyrrinone π-system when the pigment adopts a ridge-tile shape (Fig. 1B). Similarly, even larger shieldings are found in dipyrrinone stacked dimers [26]. In **1**, the dipyrrinone pyrrole NH chemical shift in $CDCl_3$ (Table 2) is shielded to $\sim$9 ppm, whereas it appears near 10.2 ppm in its methyl ester (**2**). Similarly, the second pyrrole NH of **1** is $\sim$1 ppm more shielded than in **2**. These data are consistent with different conformations in **1** and **2**, with **1** behaving more like bilirubin and **2** behaving more like its dimethyl ester.

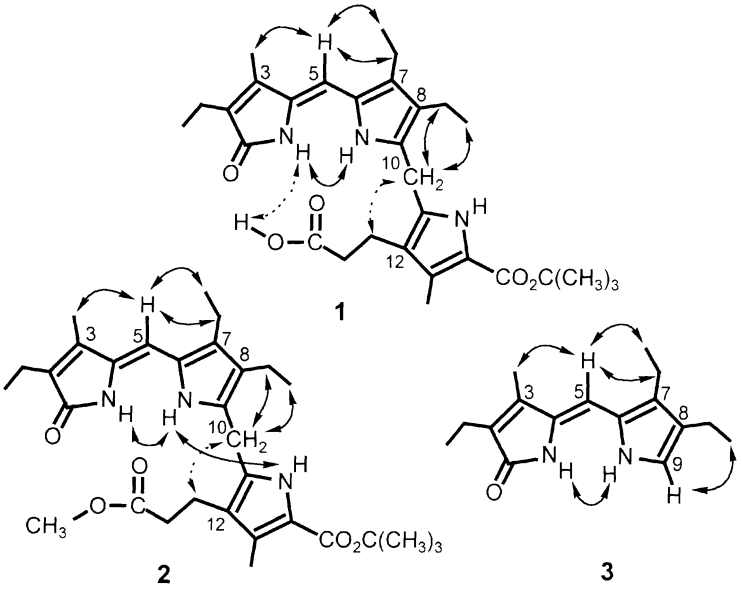


Fig. 3. Nuclear *Overhauser* enhancements of stereochemical relevance (indicated by curved arrows) found in tripyrroles **1** and **2** and dipyrrinone **3** in $CDCl_3$

Additional evidence for an intramolecularly hydrogen bonded conformation in **1** comes from an examination of the proton coupling constants in the propionic acid chain. In $CDCl_3$ the observed ABCX coupling pattern ($^2J_{AX} = 3.2$ Hz, $^3J_{AB} = 0.5$ Hz, $^3J_{AC} = 3.4$ Hz, $^2J_{BC} = 9.6$ Hz, $^3J_{BX} = 3.7$ Hz, $^3J_{CX} = 0.3$ Hz) is characteristic of restricted mobility [11–13] in the $-CH_AH_X-CH_BH_C-COOH$ segment which, when intramolecularly hydrogen bonded (Fig. 2A), is constrained to adopt a fixed staggered geometry. In $(CD_3)_2SO$, however, the less complicated A_2B_2 pattern ($^3J_{AB} = 7.3$ Hz) observed signifies more motional freedom in the propionic acid chain, whose COOH group is thought to be linked to the dipyrrinone *via* bound solvent molecules [12].

The stereochemical conclusions drawn above were confirmed by $^1H\{^1H\}$-homonuclear *Overhauser* effect (NOE) experiments in $CDCl_3$ (Fig. 3). The *syn-Z*-dipyrrinone conformation of **1–3** is confirmed by the moderately strong NOEs observed between the dipyrrinone NHs and between the vinylic C(5)–H and the $C(3)-CH_3$ and $C(7)-CH_2CH_3$ groups. Significantly, in **1** an NOE is found between the COOH and the lactam NH, whereas in **2** this is not observed. Rather, in **2** an NOE is observed between the dipyrrinone pyrrole NH and the second pyrrole ring NH.

Molecular geometry from molecular dynamics calculations and X-ray crystallography

As determined from molecular dynamics calculations using Sybyl [6], the global minimum energy conformations of **1** are two mirror image intramolecularly hydrogen bonded structures shaped like truncated ridge-tiles (Fig. 4). The

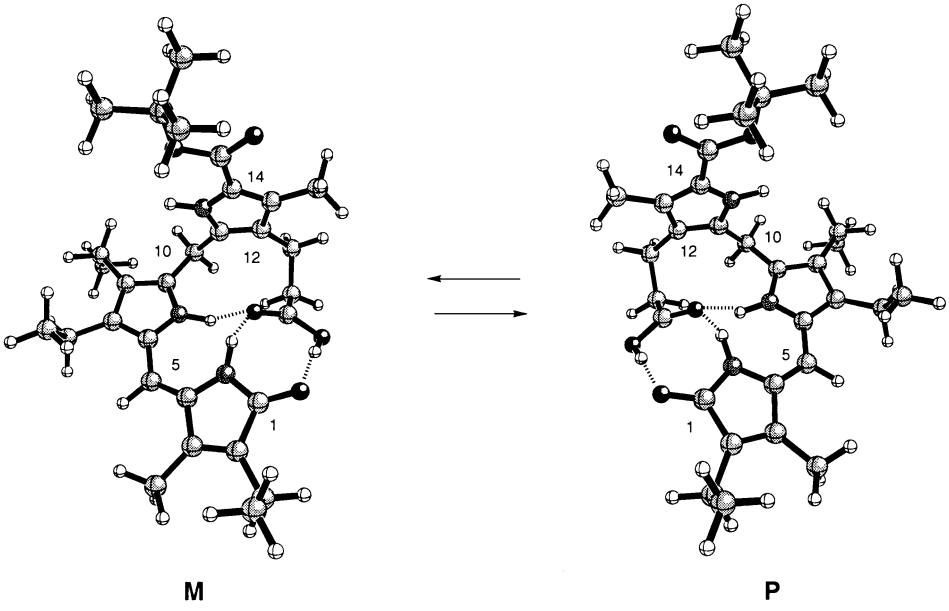


Fig. 4. Ball and stick representations for the enantiomeric global minimum energy conformations of tripyrrinone **1** found by molecular dynamics computations; the pigment adopts a truncated ridge-tile shape fixed by intramolecular hydrogen bonds; hydrogen bonds are indicated by dashed lines

Table 3. Crystallographic data for tripyrrole **1**

Formula weight	523.3
Crystallized from	CH_2Cl_2/acetone
Temperature (K)	298
Crystal size (mm)	$0.5\times0.3\times0.4$
Formula	$C_{31}H_{41}O_5N_3$
Space group	C2
Z	4
Cell dimensions:	$a = 27.099(3)$ Å
	$b = 11.616(9)$ Å
	$c = 9.414(8)$ Å
	$\alpha = 90°$
	$\beta = 99.51(12)°$
	$\gamma = 90°$
	$V = 2922.8(5)$ Å
Nr/v range of Refs. used for cell refinement	$38/10.08° < \theta < 24.91°$
Calc. density d_x (g/cm^3)	1.188
Data collection range	$3.5 < 2\theta < 50°$
Scan type/scan range	$\omega/1.2°$
Nr. Total data recorded	3205
Nr. Unique data	3003
Weighting scheme[a]	$a = 0.0534$, $b = 0$
No. Obs./ no. parameters	2583/354
R_1^b, wR_2^c ($I > 2\sigma(I)$)	$R_1 = 0.0605$, $wR_2 = 0.1137$
e.s.d. of C–C bond length	0.009
Highest peak in final ΔF map (e · Å^{-3})	0.0208
Anisotropic non-H atoms	all
Isotropic non-H atoms	none
μ(Mokα) (mm^{-1})	0.081
Radiation (λ (Å))	0.71073
Transm. factors	0.78–0.99

[a] $w^{-1} = (\sigma^2(F_\circ^2) + (aP)^2 + bP)$ where $P = (F_\circ^2 + wF_c^2)/3$; Goodness of Fit (GOOF): $(\Sigma(w(F_\circ^2 - F_c^2)^2)/(M-N))^{0.5}$ where M is the number of reflections and N is the number of parameters refined; [b] $R_1 = \Sigma\|Fo| - |Fc\|/\Sigma|Fo|$; [c] $wR_2 = (\Sigma(w(F_o^2 - F_c^2)^2)/\sigma(w(F_o^2)^2)^{0.5}$

interconversion energy between these conformational enantiomers is computed by molecular dynamics to be ~9 kcal/mol. These results were completely in accordance with the structures found by X-ray crystallography.

Previously, only two related tripyrrole structures had been established by X-ray analysis, one a red protonated tripyrrene salt [27], the other a planar, completely conjugated, red tripyrrinone derived from etiobiliverdin-IV$_\gamma$ [28]. These structures resemble biliverdin, whereas the structure of yellow **1** is more like that of bilirubin. Crystal and refinement data for **1** are summarized in Table 3, the final main atom coordinates angles are listed in Table 4. The systematic numbering system for bile pigments has been used throughout (Fig. 5).

The dipyrrinone unit in **1** displays an essentially planar *syn-Z* conformation (Table 5), and the flanking pyrrole ring is held at an interplanar angle of 93°, thus giving the structure a truncated ridge-tile shape. The pigment is thus quite similar

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for the non-hydrogen atoms of tripyrrinone **1**; *U*(eq) is defined as one third of the trace of the orthogonalized *U*ij tensor

Atom label	*x*	*y*	*z*	*U*(eq)	Atom label	*x*	*y*	*z*	*U*(eq)
N(21)	−159(2)	3541(4)	2431(5)	60(1)	C(13)	2054(2)	3010(5)	4164(6)	48(2)
N(22)	571(2)	5279(4)	4054(5)	54(1)	C(14)	2127(2)	3999(6)	3459(7)	50(2)
N(23)	1874(2)	4856(4)	4026(5)	53(1)	C(21)	−1170(3)	2278(7)	−203(7)	86(2)
O(1)	−356(2)	1612(4)	2314(5)	75(2)	C(22)	−942(3)	1570(9)	−1195(9)	145(4)
O(123)	596(2)	2855(3)	4765(4)	62(1)	C(31)	−1041(2)	5048(6)	−370(8)	91(2)
O(124)	474(2)	1014(4)	4107(5)	69(1)	C(71)	257(3)	8164(7)	2510(10)	106(3)
O(141)	2421(2)	5333(4)	1926(5)	80(2)	C(72)	−199(4)	8543(9)	2800(10)	105(3)
O(142)	2613(2)	3456(3)	1756(3)	64(1)	C(81)	1246(3)	7983(7)	4955(7)	77(2)
C(1)	−429(2)	2605(6)	1876(6)	58(2)	C(82)	1596(2)	8362(7)	3904(8)	104(3)
C(2)	−803(2)	3058(6)	714(7)	63(2)	C(121)	1573(2)	2458(7)	6268(6)	59(2)
C(3)	−745(2)	4198(6)	648(7)	61(2)	C(122)	1234(2)	1480(5)	5606(7)	62(2)
C(4)	−330(2)	4560(6)	1757(7)	55(2)	C(123)	735(2)	1853(6)	4782(7)	57(2)
C(5)	−149(2)	5619(5)	2056(7)	64(2)	C(131)	2267(2)	1853(6)	3943(7)	72(2)
C(6)	265(2)	5987(6)	3122(7)	57(2)	C(141)	2402(2)	4338(7)	2327(7)	58(2)
C(7)	468(2)	7082(6)	3352(7)	64(2)	C(143)	2879(3)	3605(6)	515(7)	71(2)
C(8)	894(2)	7016(6)	4390(7)	59(2)	C(144)	2518(3)	4024(8)	−768(7)	125(4)
C(9)	956(2)	5880(5)	4840(7)	55(2)	C(145)	3315(3)	4399(7)	927(8)	109(3)
C(10)	1336(2)	5236(5)	5838(6)	58(2)	C(146)	3054(4)	2390(7)	282(9)	142(4)
C(11)	1644(2)	4426(5)	5102(6)	48(2)	C(72A)	433(12)	8456(28)	1204(32)	105(3)
C(12)	1751(2)	3269(5)	5206(6)	51(2)					

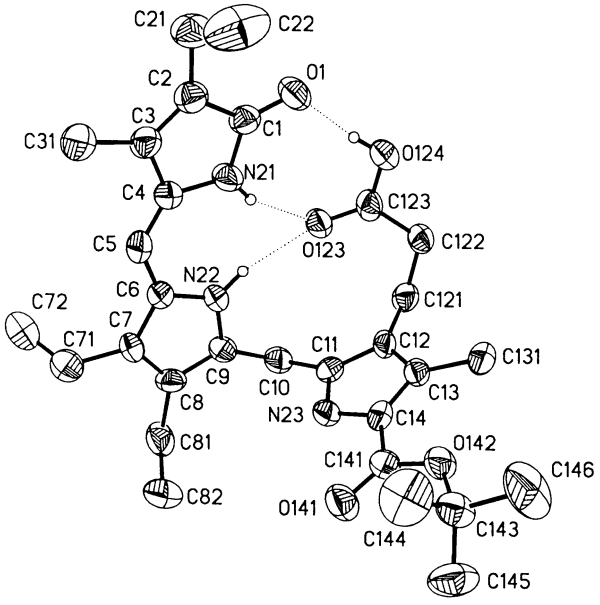


Fig. 5. Perspective drawing of the (*P*)-helical enantiomer of tripyrrinone **1** with ring and atom labelling; hydrogen bonds are denoted by dotted lines

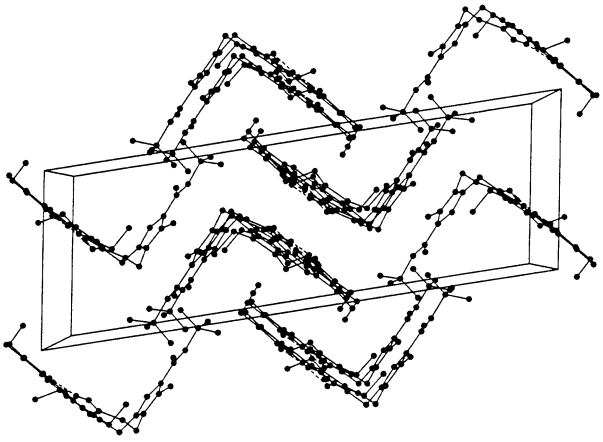
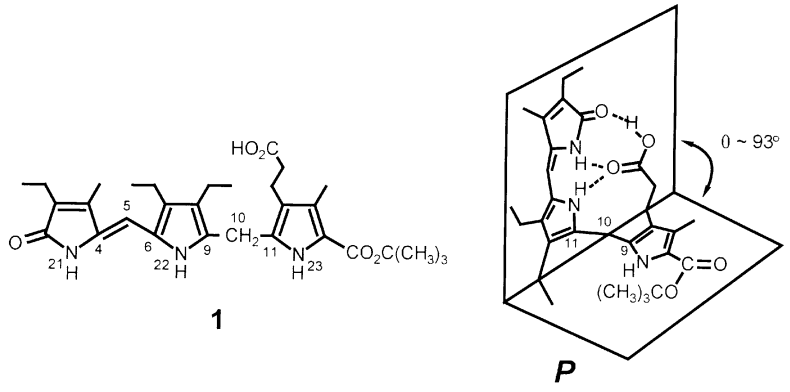


Fig. 6. Molecular packing of **1** in the projection (010), viewed down the *b* axis; contains stacked (*M*) and (*P*) helicity ridge-tile enantiomers

Table 5. Comparison of selected torsion and interplanar angles in the structure of dihydro-tripyrrinone **1** from X-ray crystallography and molecular dynamics calculations, as compared with those from the bilirubin crystallographic structure



Angle (°) Distance (Å)	X-Ray	Molecular dynamics	Bilirubin X-ray
N(21)-C(4)-C(5)-C(6)	−0.5	1.4	17.5
C(4)-C(5)-C(6)-N(22)	1.7	13.0	−2.7
N(22)-C(9)-C(10)-C(11)	66.0	54.9	60°
C(9)-C(10)-C(11)-N(23)	52.5	60.5	60°
Interplanar Dihedral Angle	92.5	93.3	98°
N(21)–H···O=C(OH)	2.0	1.54	1.75
N(22)–H···O=C(OH)	2.0	1.58	1.78
C(1)=O···HO–C(=O)	1.9	1.56	1.52

in overall shape to that of bilirubin, whose planar dipyrrinone moieties are held at an interplanar angle of 98°. The following main atom non-bonding distances are observed for the propionic acid carboxyl: N(21)···O(123) 2.0 Å, N(22)···O(123) 2.0 Å, O(1)···O(124) 1.9 Å. This suggests that the hydrogen bond (for distances,

see Table 5) to the pyrrole is about as strong as that to the lactam [29]. These mirror image (*M*) and (*P*)-helical intramolecularly hydrogen bonded molecules of **1** are stacked with their dipyrrinone systems parallel to one another. The stacking pattern (Fig. 6) is very similar to that found in bilirubin [8, 9].

Experimental

All UV/Vis spectra were recorded on a Perkin-Elmer λ-12 spectrophotometer, and all nuclear magnetic resonance (NMR) spectra were obtained on GE QE-300 300 MHz or Varian Unity Plus 500 MHz spectrometers. Chemical shifts are reported in δ (ppm) referenced to the residual $CHCl_3$ ^1H signal at 7.26 ppm and to the ^{13}C signal at 77.5 ppm. Melting points were taken on a mel-temp capillary apparatus and are uncorrected. Combustion analyses were carried out for **1**, **2**, **3** (including 0.5 equivalents of H_2O), and **9** by Desert Analytics, Tucson, AZ. Their data were in satisfactory agreement with the calculated values. Analytical thin layer chromatography was carried out on J.T. 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, Inc., Palo Alto, CA). HPLC analyses were carried out on a Perkin-Elmer series 4 high performance liquid chromatography with an LC-95 UV/Vis spectrophotometric detector (set at 410 nm) equipped with a Beckman-Altex ultrasphere IP 5 µm C(18) ODS column (25×0.46 c) and a Beckman ODS precolumn (4.5×0.46 cm). The flow rate was 1.0 ml/min, and the elution solvent was 0.1 *M* di-*n*-octylamine acetate in 5% aqueous methanol (*pH* 7.7, 31°C). Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). Trifluoroacetic acid, 3-nitropropane, and guanidine were purchased from Acros Organics, dichloromethane, methanol, acetic acid, tetrahydrofuran, bromine, ceric ammonium nitrate, lead tetraacetate, and phosphorus pentoxide from Fisher.

4-Ethyl-3-methyl-2-p-toluenesulfonyl-pyrrole (**10**; $C_{14}H_{17}NO_2S$)

The pyrrole synthesis followed that described by *Barton*, *Kervagoret*, and *Zard* [22] for the isomeric 2-*p*-toluenesulfonyl-3-ethyl-4-methyl-pyrrole. A solution of *p*-(toluenesulfonyl)methyl isocyanate (*TosMIC*) [30] (21.8 g, 112 mmol), 2-propanol (40 ml), *THF* (40 ml), and guanidine (40 g, 43.7 ml, 340 mmol) was added dropwise to 3-nitro-pentan-2-ol acetate [31] dissolved in 2-propanol (150 ml) and *THF* (150 ml). After the addition was complete, the solution was stirred for 1 h; then the solvent was evaporated (rotovap). The remaining oily residue was dissolved in CH_2Cl_2 (300 ml), washed with water (4×100 ml), and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the remaining oil was flash chromatographed using CH_2Cl_2 as eluent. After evaporation of the solvent, the remaining solid was crystallized from methylene chloride/hexane.

Yield: 15.5 g (53%); m.p.: 112–113°C (Ref. [32]: 117–118°C); IR (KBr): $\nu = 3303$, 2973, 2940, 2927, 2897, 1494, 1450, 1367, 1300, 1179, 1138, 1084, 1055, 807, 795 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.11 (t, $J = 7.4$ Hz, 3H), 2.16 (s, 3H), 2.34 (s, 3H), 2.38 (s, 3H), 6.69 (d, $J = 2.4$ Hz, 1H), 7.26 (d, $J = 8.3$ Hz, 2H), 7.78 (d, $J = 8.3$ Hz, 2H), 9.2 (bs, 1H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 9.04, 14.0, 18.2, 21.4, 119.7, 123.6, 123.9, 126.5, 127.9, 129.6, 140.2, 143.3 ppm.

2-Bromo-3-ethyl-4-methyl-5-p-toluenesulfonyl-pyrrole (**9**; $C_{14}H_{16}NO_2SBr$)

4-Ethyl-3-methyl-2-*p*-toluenesulfonyl-pyrrole (**10**; 23.4 g, 89 mmol) was dissolved in CH_2Cl_2 (200 ml) and cooled to 0°C. A solution of bromine (4.6 ml, 14.3 g, 89 mmol) in CH_2Cl_2 (200 ml) was added dropwise to the pyrrole solution. After the addition was complete, the solution was stirred

for 1 h, washed with 5% aqueous hydroxide (2×100 ml), and dried over anhyd. Na_2SO_4. After evaporation of the solvent (rotovap), the remaining solid was dried under high vacuum (0.7 mm Hg).

Yield: 29.35 g (97%); m.p.: 170–172°C; IR (KBr): $\nu = 3287$, 3064, 2970, 1690, 1592, 1311, 1159, 1127, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.02 (t, $J = 7.6$ Hz, 3H), 2.18 (s, 3H), 2.34 (q, $J = 7.6$ Hz, 2H), 2.41 (s, 3H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.78 (d, $J = 8.5$ Hz, 2H), 8.99 (bs, 1H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 9.55, 14.1, 18.13, 21.44, 104.7, 124.8, 125.1, 126.7, 127.1, 129.8, 139.7, 143.7 ppm.

3-Ethyl-4-methyl-5-p-toluenesulfonyl-3-pyrrolin-2-one (**7**; $C_{14}H_{17}NO_3S$)

7 was prepared according to the procedure of *Barton*, *Kervagoret*, and *Zard* [22] for the isomeric 4-ethyl-3-methyl-5-p-toluenesulfonyl-pyrrolin-2-one. 2-Bromo-3-ethyl-4-methyl-5-p-toluenesulfonylpyrrole (**9**; 19.5 g, 85 mmol) was combined with trifluoroacetic acid (250 ml) and water (50 ml) and stirred overnight. The trifluoroacetic acid was removed by distillation under water aspirator pressure, and the remaining solution was dissolved in CH_2Cl_2 (200 ml) and washed with saturated sodium bicarbonate (3×100 ml). The organic layer was dried (anhyd. Na_2SO_4), and the solvent was evaporated (rotovap). The remaining solid was crystallized from hexane/ethyl acetate.

Yield: 12.82 g (81%); m.p.: 148–149°C; (Ref. [20]: 137–139°C); IR (KBr): $\nu = 3266$, 3064, 2970, 1690, 1592, 1311, 1159, 1127, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 300 MHz): 0.59 (t, $J = 7.3$ Hz, 3H), 2.00 (m, $J = 7.3$ Hz, 2H), 2.15 (s, 3H), 2.39 (s, 3H), 5.02 (s, 1H), 6.96 (bs, 1H), 7.29 ($J = 7.6$ Hz, 2H), 7.66 (d, $J = 7.6$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 11.89, 12.73, 16.50, 21.5, 79.0, 129.6, 130.5, 139.4, 142.5, 145.8, 172.7 ppm.

3-Ethyl-4-methyl-3-pyrrolin-2-one (**5**; $C_7H_{11}NO$)

The tosyl group of **5** was reductively cleaved according to the procedure of *Murata*, *Kinoshita*, and *Inomata* [33] for 4-ethyl-3-methyl-pyrrolin-2-one. 3-Ethyl-4-methyl-5-*p*-toluenesulfonyl-pyrrolin-2-one (**7**; 4.7 g, 0.017 mol) was dissolved in absolute ethanol (75 ml). To the solution sodium borohydride (1.314 g, 35 mmol) was added in two portions over thirty minutes. The solution was stirred overnight, after which it was filtered; the ethanol was removed by evaporation (rotovap). The remaining solid was dissolved in CH_2Cl_2 (100 ml), washed with water (2×50 ml), and dried over anhyd. Na_2SO_4. Removal of the solvent (rotovap) afforded pure **5**.

Yield: 2.0 g (95%); m.p.: 89–92°C (Ref. [34]: 102°C); IR (KBr): $\nu = 3202$, 2947, 2908, 1675, 1432, 1178, 1111, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.05 (t, $J = 7.2$ Hz, 3H), 1.97 (s, 3H), 2.15 (q, $J = 7.2$ Hz, 2H), 3.78 (s, 1H), 7.4 (bs, 1H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 12.81, 12.89, 16.45, 49.96, 134.0, 148.4, 176.2 ppm.

Ethyl 3,4-diethyl-5-formyl-pyrrole-2-carboxylate (**6**; $C_{12}H_{17}NO_3$)

According to *Thyrann* and *Lightner* [35], in a 3-neck 2 l round bottom flask equipped with a thermometer and a mechanical stirrer 2-carboethoxy-3,4-diethyl-5-methyl-pyrrole (**8** [19–21]; 8.2 g, 39 mmol) was added to a solution of *THF* (328 ml), acetic acid (648 ml), and water (200 ml). The solution was cooled to 0°C for thirty minutes, and ceric ammonium nitrate (90 g, 164 mmol) was added in two portions over a period of 15 min. The solution was stirred for 2 h at room temperature followed by extraction with CH_2Cl_2 (2×500 ml). The organic layer was washed with water (2×500 ml), saturated sodium bicarbonate (2×500 ml), and saturated sodium chloride (2×350 ml). After drying over anhyd. Na_2SO_4, the solvent was removed (rotovap) to afford a yellow-orange oil. The oil was flash chromatographed using CH_2Cl_2 as the eluent to give an off-white solid.

Yield: 6.7 g (75%); m.p.: 49–50°C (Ref. [20]: 53°C); IR (KBr): $\nu = 3259$, 2964, 2921, 2867, 1692, 1666, 1547, 1479, 1462, 1364, 1338, 1253, 1132, 1021, 766 cm^{-1}; ^1H NMR ($CDCl_3$, δ,

300 MHz): 1.15 (t, $J = 7.3$ Hz, 3H), 1.23 (t, $J = 7.3$ Hz, 3H), 1.37 (t, $J = 7.3$ Hz, 3H), 2.73 (q, $J = 7.3$ Hz, 4H), 4.36 (q, $J = 7.3$ Hz, 2H), 9.52 (s, 1H), 9.77 (bs, 1H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 14.0, 15.2, 16.1, 17.4, 18.6, 60.8, 124.1, 130.0, 132.5, 137.2, 160.0, 179.0 ppm.

(4Z)-3-Methyl-2,7,8-triethyl-dipyrrin-1(10H)-3-one (**3**; $C_{16}H_{22}N_2O$)

3-Ethyl-4-methyl-3-pyrrolin-2-one (**5**; 1.32 g, 10 mmol) was combined with 2-carboethoxy-3,4-diethyl-2-formyl pyrrole (**6**; 2.32 g, 10 mmol), and the mixture was dissolved in methanol (64 ml) and 4 M aqueous potassium hydroxide (40 ml). The resulting solution was heated at reflux for 1 h, and the methanol was removed (rotovap). The remaining solution was acidified with concentrated hydrochloric acid until a precipitate formed. The precipitated dipyrrinone acid (**4**) was cooled and filtered to give a green solid (2.49 g, 78%). 2.49 g (8.2 mmol) of the precipitate were suspended in an intimate mixture of potassium acetate (12.5 g, 127 mmol) and sodium acetate (10.45 g, 127 mmol) at 130°C [36]. The mixture was stirred and heated to 180°C for twenty minutes and then quenched with water. The resulting precipitate was collected by filtration and washed with water repeatedly to afford a yellow-green solid (1.98 g, 85%), which was purified by flash chromatography using methylene chloride/methanol (97:3 (v/v)) as the eluent to afford pure **3**.

Yield: 1.98 g (85%); m.p.: 198–200°C; IR (KBr): $\nu = 3361$, 3188, 3149, 2966, 2920, 2868, 1616, 1512, 1449, 1419, 1399, 1374, 1274, 1171, 1054, 986, 939, 897, 804, 776, 717, 686 cm^{-1}; UV/Vis $\varepsilon_{max} = 34800$ (*DMSO*, 399 nm), 38000 ($CHCl_3$, 397 nm), 37700 (CH_3OH, 405 nm), 34500 ($(CH_3)_2CO$, 399 nm), 37100 (C_6H_6, 392 nm); ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.17 (t, $J = 7.5$ Hz, 3H, H-22), 1.19 (t, $J = 7.5$ Hz, 3H, H-82), 1.21 (t, $J = 7.5$ Hz, 3H, H-72), 2.16 (s, 3H, H-31), 2.46 (q, $J = 7.5$ Hz, 2H, H-21), 2.48 (q, $J = 7.5$ Hz, 2H, H-71), 2.58 (q, $J = 7.5$ Hz, 2H, H-81), 6.16 (s, 1H, H-5), 6.82 (d, $J = 2.5$ Hz, 1H, H-9), 10.23 (s, H-1, NH-22), 11.05 (s, 1H, H-21) ppm; ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 0.958 (t, $J = 7.8$ Hz, 3H, H-72), 0.995 (t, $J = 7.5$ Hz, H-82), 1.090 (t, $J = 7.2$ Hz, 3H, H-22), 2.025 (s, 3H, H-31), 2.20 (q, $J = 7.2$ Hz, 2H, H-21), 2.33 (q, $J = 7.5$ Hz, 2H, H-81), 2.44 (q, $J = 7.8$ Hz, 2H, H-71), 590 (s, 1H, H-5), 6.69 (s, 1H, H-9), 9.70 (s, 1H, NH-21), 10.46 (s, 1H, NH-22) ppm; for ^{13}C NMR data, see Table 1.

tert-Butyl 4-(2-Methoxycarbonylethyl)-3,5-dimethyl-pyrrole-2-carboxylate (**12**; $C_{15}H_{23}NO_4$)

Ester **12** was prepared according to *Smith* and *Pandey* [18] in 51% yield.

M.p.: 98°C (Ref. [18]: 100°C); ^{13}C NMR ($CDCl_3$, δ. 75 MHz): 10.45, 11.13, 19.52, 28.39, 34.87, 51.24, 79.90, 118.2, 119.6, 125.8, 129.3, 161.4, 173.3 ppm.

tert-Butyl 5-Acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methyl-pyrrole-2-carboxylate (**11**; $C_{18}H_{20}NO_6$)

tert-Butyl 4-(2-methoxycarbonylethyl)-3,5-dimethyl-pyrrole-2-carboxylate (**12** [18]; 6.0 g, 21.4 mmol) was dissolved in acetic acid (576 ml). Lead tetraacetate (9.8 gm, 22.0 mmol) was added in three portions over 30 min. The reaction mixture was stirred for 3 h at room temperature. The acetic acid was removed (rotovap), and the remaining oil was dissolved in CH_2Cl_2 (300 ml) and washed with water (2×200 ml), saturated sodium bicarbonate (2×200 ml), and saturated sodium chloride (1×200 ml). The solution was dried over anhyd. Na_2SO_4, the solvent removed (rotovap), and the remaining orange oil passed through a thin layer of silica gel using CH_2Cl_2 as eluent. The resulting oil was dried under high vacuum (0.7 mm Hg) and crystallized from dichloromethane/hexane to give a white crystalline solid.

Yield: 6.4 g (88%); m.p.: 80°C (Ref. [18]: 80°C); ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 10.14, 19.16, 20.68, 28.30, 35.09, 51.35, 56.83, 80.59, 120.7, 122.6, 125.0, 126.6, 171.2, 173.0, 216.0 ppm.

(4Z)-14-tert-Butoxycarbonyl-10,17-dihydro-3,13-dimethyl-12-(2-ethoxycarbonyl)-2,7,8-triethyl-tripyrrin-1(15H)-one (**2**; $C_{31}H_{43}N_3O_5$)

Dipyrrinone **3** (1.34 g, 5.0 mmol) was combined with α-acetoxymethylpyrrole **11** [18] (1.7 g, 5.0 mmol) in a solution of acetic acid (100 ml) and *THF* (53 ml). *p*-Toluenesulfonic acid (80 mg, 0.5 mmol) was added in one portion and the solution was stirred at 40°C for 3 h. The solution was extracted with CH_2Cl_2 (3×100 ml) and dried over anhyd. Na_2SO_4. After removal of the solvent (rotovap) the remaining solid was flash chromatographed with CH_2Cl_2/methanol (97:3 (v/v)) to afford 2.2 g (75%) of a yellow solid which was crystallized from acetone/water to give pure **2**.

Yield: 1.62 g (60%); m.p.: 194–195°C; IR (KBr): $\nu = 3348$, 2965, 1740, 1630, 1458, 1365, 1250, 1168, 1074 cm^{-1}; UV/Vis $\varepsilon_{max} = 29800$ (*DMSO*, 414 mm), 20000 (*DMSO*, 281 nm), 28000 ($CHCl_3$, 406 nm), 20400 ($CHCl_3$, 277 nm), 29500 (CH_3OH, 414 nm), 20200 (CH_3OH, 280 nm), 31500 ($(CH_3)_2CO$, 404 nm), 31800 (C_6H_6, 412 nm); ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 0.983 (t, $J = 7.5$ Hz, 3H, H-22), 1.08 (t, $J = 7.5$ Hz, 3H, H-72), 1.18 (t, $J = 7.5$ Hz, 3H, H-82), 1.46 (s, 9H, H-145, 146, 147), 2.14 (s, 3H, H-31), 2.26 (s, 3H, H-131), 2.29 (q, $J = 7.5$ Hz, 2H, H-21), 2.45 (q, $J = 7.5$ Hz, 2H, H-71), 2.48 (t, $J = 7.5$ Hz, 2H, H-121), 2.58 (q, $J = 7.5$ Hz, 2H, H-81), 2.82 (t, $J = 7.5$ Hz, 2H, H-122), 3.68 (s, 3H, H-124), 4.01 (s, 2H, H-10), 6.13 (s, 1H, H-5), 9.22 (s, 1H, NH-23), 10.2 (s, 1H, HN-22), 10.7 (s, 1H, NH-21) ppm; ^{1}H NMR (*DMSO*-d_6, δ, 500 MHz): 0.805 (t, $J = 7.0$ Hz, 3H, H-22), 1.02 (t, $J = 7.5$ Hz, 3H, H-72), 1.03 (t, $J = 7.5$ Hz, 3H, H-82), 1.51 (s, 9H, H-145, 146, 147), 2.03 (t, $J = 8.0$ Hz, 2H, H-121), 2.07 (s, 3H, H-31), 2.16 (s, 3H, H-131), 2.25 (q, $J = 7.0$ Hz, 2H, H-21), 2.27 (q, $J = 7.8$ Hz, 2H, H-71), 2.45 (q, $J = 7.0$ Hz, 2H, H-72), 2.53 (t, $J = 8.0$ Hz, 2H, H-122), 3.47 (s, 3H, H-124), 3.87 (s, 2H, H-10), 5.92 (s, 1H, H-5), 9.7 (s, 1H, NH-23), 10.23 (s, 1H, NH-21), 10.85 (s, 1H, NH-22) ppm; for ^{13}C NMR data, see Table 1.

(4Z)-14-tert-Butoxycarbonyl-12-(2-carboxyethyl)-10,17-dihydro-3,13-dimethyl-2,7,8-triethyl-tripyrrin-1(15H)-one (**1**; $C_{30}H_{41}N_3O_5$)

Tripyrrinone ester **2** (234 mg, 0.435 mmol) was combined with ascorbic acid (200 mg, 1.98 mmol) and dissolved in *THF* (128 ml). Methanol (128 ml) and sodium hydroxide (0.2 *M*, 256 ml) were added to the solution and stirred overnight under a nitrogen atmosphere. The solution was acidified with HCl (10%) until red on litmus paper. The tripyrrinone acid was extracted with CH_2Cl_2 (2×100 ml), washed with sodium chloride (2×100 ml), and dried over anhyd. Na_2SO_4. After removal of the solvent (rotovap), the remaining solid was flashed with dichloromethane/methanol (97:3 (v/v)) to afford 170 mg (75%) raw product. The yellow acid tripyrrole was crystallized from acetone to afford pure **1**.

Yield: 141 mg (64%); m.p.: 192–194°C; IR (KBr); $\nu = 3421$, 3268, 2964, 2931, 2870, 1251, 1170, 1102, 1057, 1007, 956, 871, 775, 690 cm^{-1}; UV/Vis: $\varepsilon_{max} = 20200$ (*DMSO*, 415 nm), 21200 (*DMSO*, 282 nm), 29400 ($CHCl_3$, 421 nm), 18300 ($CHCl_3$, 279 nm), 33100 (CH_3OH, 415 nm), 19700 (CH_3OH, 282 nm), 30700 ($(CH_3)_2CO$, 420 nm), 32000 (C_6H_6, 427 nm); ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.07 (t, $J = 7.5$ Hz, 3H, H-22), 1.18 (t, $J = 7.5$ Hz, 3H, H-72), 1.22 (t, $J = 7.5$ Hz, 3H, H-82), 1.51 (s, 9H, H-145, 146, 147), 2.17 (s, 3H, H-31), 2.26 (s, 3H, H-131), 2.35 (q, $J = 8.0$ Hz, 2H, H-21), 2.55 (q, $J = 7.5$ Hz, 2H, H-71), 2.56 (q, $J = 7.5$ Hz, 2H, H-81), 2.75 (ddd, $^3J_{BC} = 9.6$ Hz, $^3J_{CX} = 0.3$ Hz, $^3J_{AC} = 3.4$ Hz, 1H, H-121), 2.78 (ddd, $^3J_{BC} = 9.6$ Hz, $^3J_{Bx} = 3.7$ Hz, $J_{AB} = 0.5$ Hz, 1H, H-122), 2.80 (ddd, $^2J_{AX} = 3.4$ Hz, $^3J_{BX} = 3.7$ Hz, $^3J_{CX} = 0.3$ Hz, 1H, H-121), 2.81 (ddd, $^2J_{AX} = 3.4$ Hz, $^3J_{AB} = 0.5$ Hz, $^3J_{AC} = 3.4$ Hz, 1H, H-122), 3.94 (s, 2H, H-10), 6.07 (s, 1H, H-5), 8.17 (s, 1H, NH-23), 9.02 (s, 1H, NH-22), 10.4 (s, 1H, NH-21), 13.48 (s, 1H, H-123) ppm; ^{1}H NMR (*DMSO*-d_6, δ, 500 MHz): 0.849 (t, $J = 7.0$ Hz, 3H, H-22), 1.02 (t, $J = 7.5$ Hz, 3H, H-72), 1.03 (t, $J = 7.0$ Hz, 3H, H-82), 1.47 (s, 9H, H-145, 146, 147), 2.07 (t, $J = 7.3$ Hz, 2H, H-121), 2.09 (s, 3H, H-31), 2.12 (s, 3H, H-131), 2.26 (q, $J = 7.3$ Hz, 2H, H-21), 2.27 (q, $J = 7.5$ Hz, 2H, H-71), 2.45 (q, $J = 7.5$ Hz, 2H, H-81), 2.53 (t, $J = 7.3$ Hz, 2H, H-122), 3.87 (s, 2H, H-10), 5.93 (s, 1H, H-5), 9.70

(s, 1H, NH-23), 10.19 (s, 1H, NH-21), 10.75 (s, 1H, NH-22), 11.95 (s, 1H, H-123) ppm; ^{13}C NMR data, see Table 1.

X-Ray structure determination

Crystals of tripyrrinone **1** were grown by slow diffusion of acetone into a solution of CH_2Cl_2. Suitable crystals were coated with epoxy cement, mounted on a glass fiber, and placed on a Siemens P4 diffractomer. Unit cell parameters were determined by least squares analysis of 38 reflections with $10.08° < \theta < 24.91°$ using graphite monochromatized MoKα radiation (0.71073 Å). 3205 Reflections were collected between $3.5° < 2\theta < 50°$ yielding 3003 unique reflections ($R_{int} = 0.0361$). The data were corrected for *Lorentz* and polarization effects. Crystal data are given in Table 3. Scattering factors and corrections for anomalous dispersion were taken from a standard source [37].

Calculations were performed using Siemens SHELXTL PLUS, version 5.03, system of programs refining on F^2. The structure was solved by direct methods in the chiral space group C_2. The unit cell contains an ordered array of the molecule with no unusual contacts. The absolute configuration could not be accurately determined by refinement of the *Flack* parameter which is based on analysis of anomalous dispersion. The handedness of the molecule shown in Fig. 5 is therefore arbitrarily chosen. The structure contains one disordered ethyl group with the methyl portion (C(72)) occupying two positions.

All non-hydrogen atoms were refined with anisotropic thermal parameters. The refinement did not benefit from absorption corrections, and ultimately none was applied. Hydrogen atom positions were calculated using a riding model with a C–H distance fixed at 0.96 Å and a thermal parameter of 1.2 times of that of the host carbon atom. The largest peak in the final difference map corresponded to 0.157 e^-/Å^3 and was located 1.12 Å from C(31b).

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