Intermolecular Hydrogen Bonding in π Facial Dipyrrinone Dimers as Molecular Capsules

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Abstract: (4*Z*)-Dipyrrinones, which are the component chromophores of yellow pigment of jaundice, are known to self-associate strongly in nonpolar solvents ($K_{assoc} \simeq 25\,000$ M at 25 °C in $CHCl_3$), forming *planar* dimers in which the monomers are linked tightly by four intermolecular hydrogen bonds. When the chromophore has an attached propionic or longer chain acid group, it forms a new type of *stacked* dimer through a network of six hydrogen bonds in which the carboxyl group of one dipyrrinone is tethered to the other dipyrrinone. Thus, xanthobilirubic acid and its homologs strongly self-associate as stacked dimers in contrast to its methyl ester, which forms planar dimers. The stacked dimers are recognized by large (1 ppm) shieldings of their N*H* resonances in their ^{1}H-NMR spectra, as compared with planar dimers. They are also recognized by unusually large optical rotations and exciton coupling in the circular dichroism spectra when a stereogenic center is present in the alkanoic acid chain. In $CHCl_3$, (β*S*)-methylxanthobilirubic acid (**1**) has $[\alpha]^{20}_D = -314°$ and $\Delta\epsilon^{max}_{434} = -10.9$, $\Delta\epsilon^{max}_{388} = +5.7$, whereas its methyl ester (**6**) has $[\alpha]^{20}_D = +62°$; $\Delta\epsilon^{max}_{370} < 1$.

Introduction

Dipyrrinones are typically bright yellow compounds exhibiting an intense UV−visible absorption near 400 nm ($\epsilon \simeq 30\,000$ L mol^{-1} cm^{-1}) associated with a long axis-polarized $\pi \rightarrow \pi^*$ excitation in the 14π-electron-conjugated chromophore (Figure 1).[1] The dipyrrinone chromophore is found in nature in tetrapyrrole bile pigments, especially in (4*Z*,15*Z*)-bilirubin-IXα, the yellow-orange pigment of jaundice.[1,2] Bilirubin is a dicarboxylic acid comprised of two dipyrrinones conjoined at and capable of independent rotations about a $-CH_2-$ group at C(10). It is through such rotations that the carboxyl group of one dipyrrinone is brought into sufficiently close proximity to engage the other dipyrrinone's lactam and pyrrole moieties in a matrix of intramolecular hydrogen bonds (Figure 1). Collectively, these six hydrogen bonds act as a potent stabilizer of the conformation of bilirubin, seen in three dimensions as a ridge-tile shape.[3] Whether in bilirubin or as independent units, dipyrrinones are known to be avid participators in hydrogen bonding.[1] They have also served as useful adjuncts in studies of jaundice phototherapy[4] and in bilirubin structure−biological function relationships.[5]

Dipyrrinones are known from X-ray crystallography[1,6] and molecular mechanics calculations[1,7] to prefer the lactam tautomer and the *Z*-configuration C=C at C(4) and to show substantial double-bond and single-bond character in the C(4)=C(5) and C(5)−C(6) bonds, respectively (Figure 2). They adopt essentially planar conformations ($\psi \simeq 0°$) in the crystal, where

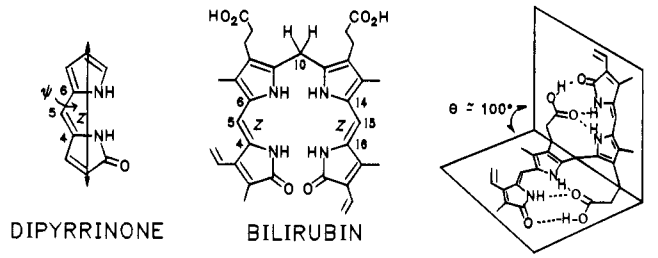

Figure 1. (left) Dipyrrinone chromophore. The double-headed arrow approximates the long axis polarization of the intense ~400 nm electronic transition. (center) Bilirubin in a porphyrin-like representation composed of two dipyrrinone chromophores. (right) Stable ridge-tile bilirubin conformation with hydrogen bonding between carboxylic acid groups and opposing dipyrrinones.

they are present as intermolecularly hydrogen-bonded planar dimers (Figure 2).[1,6] Most of these characteristics persist in nonpolar solutions. In $CHCl_3$, for example, dipyrrinones are strongly associated with dimerization constants of 1700 M (37 °C) for kryptopyrromethenone[8] and 25 000 M (22 °C) for methyl xanthobilirubinate[9] measured by vapor phase osmometry and ^{1}H-NMR spectroscopy, respectively. The dimers are held together by a matrix of four intermolecular hydrogen bonds, with a calculated stabilization enthalpy of 20−30 kcal/mol.[10] In methyl xanthobilirubinate, two intermolecularly hydrogen-

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(10) Molecular mechanics calculations and molecular modeling were carried out on an Evans and Sutherland ESV-10 workstation using version 6.0 of SYBYL (Tripos Assoc., St. Louis, MO) as described in ref 3. The ball and stick drawings were created from the atomic coordinates of the molecular dynamics structures using Müller and Falk's "Ball and Stick" program (Cherwell Scientific, Oxford, U.K.) for the Macintosh.

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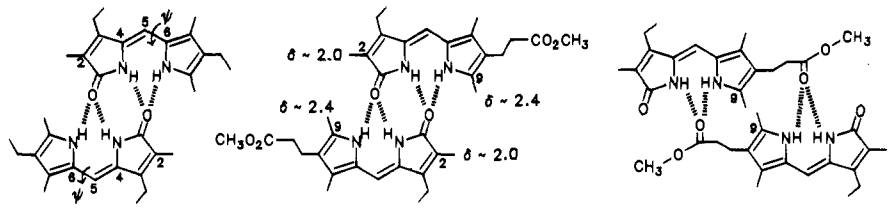


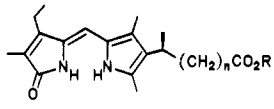
Figure 2. Dipyrrinone dimers. (left) Kryptopyrromethenone dimer proposed by Falk *et al.* (ref 8). An analog with ethyl at C(2) rather than methyl is found in the crystal as essentially the same intermolecularly hydrogen-bonded dimer, with $\psi \simeq 4°$ (ref 13a). (center) Methyl xanthobilirubinate traditional dimer. Consistent with this dimeric representation, in $CDCl_3$ ^{1}H-NMR NOE's are found between the methyls at C(2) and C(9) (ref 9). (right) Hypothetical alternative dimeric representation not observed in methyl xanthobilirubinate.

bonded dimers are conceivable (Figure 2); however, the traditional dimer is calculated by molecular dynamics[10] to be 3.1 kcal/mol more stable than the alternative. And, in support of the traditional dimer, ^{1}H-NMR NOE's are found between the methyls at C(2) and C(9).[9]

The type of dipyrrinone to dipyrrinone dimer shown at the left and center of Figure 2 is thought to be the most common type of hydrogen-bonded dipyrrinone dimer.[1] It is found even in bilirubin dimethyl ester,[1,11a,12] but in bilirubin and its analogs, the component dipyrrinones participate in a unique type of hydrogen bonding involving the carboxylic acids (Figure 1) found in the solid by X-ray crystallography,[6e,13] in solution by ^{13}C{^{1}H} heteronuclear Overhauser effects[14] and ^{1}H-NMR,[11,12] and in general by molecular orbital and molecular dynamics computations.[15] Until recently,[16] it represented the only well-established example of carboxylic acid to amide hydrogen bonding. The potential for such hydrogen bonding is present in dipyrrinone acids, but this has never been examined. In the following, we show by ^{1}H-NMR and circular dichroism spectroscopy that dipyrrinone acids (below) form stable dimers, as expected, but the dimers are not the traditional planar dimers; rather, they are an entirely new type and shape of dimer involving carboxylic acid to dipyrrinone intermolecular hydrogen bonds.

Results and Discussion

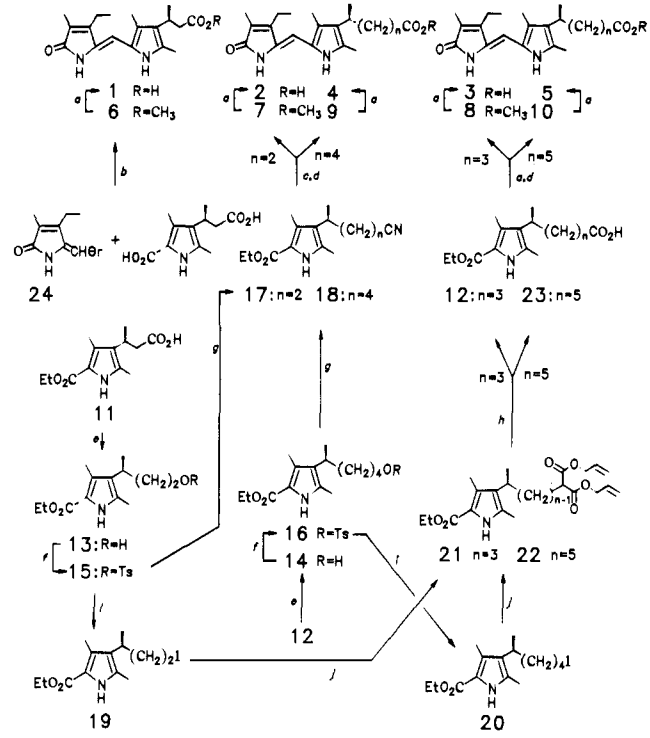
Synthesis. Various analogs of xanthobilirubic acid and its methyl ester were available from earlier studies on the total synthesis of bilirubins with varying alkanoic acid chain lengths.[17] Optically active dipyrrinones **1**−**10** were prepared as outlined



R=H	R=CH$_3$
1: n=1	6: n=1
2: n=2	7: n=2
3: n=3	8: n=3
4: n=4	9: n=4
5: n=5	10: n=5

in Scheme 1. Methyl (βS)-methylxanthobilirubinate (**6**) and the

Scheme 1



[a] Aqueous NaOH, then HCl. [b] CH_3OH, reflux. [c] 10 N KOH, then HNO_3 at 0 °C. [d] Heat at reflux in CH_3OH with **24**. [e] BH_3−THF. [f] *p*-TsCl/Et_3N. [g] NaCN/$(CH_3)_2SO$. [h] $Pd(OAc)_2$, PPh_3, $Et_3NH^+{}^-O_2CH$. [i] NaI/$(CH_3)_2CO$. [j] $CH_2(CO_2CH_2CH{=}CH_2)_2$, K_2CO_3/Cs_2CO_3.

key optically active monopyrrole intermediate **11** were available from an earlier total synthesis.[18] All dipyrrinone esters were prepared in the final by condensation of bromomethylenepyrrolinone **24** with various monopyrrole diacids derived from **11** by one- or two-carbon homologation sequences. Thus, while **11** could convert to **6** without homologation, **7** and **8** required one- and two-carbon homologated analogs, respectively. The

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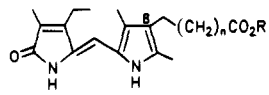
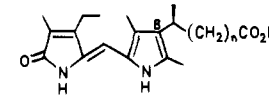
Table 1. Comparison of Pyrrole and Lactam NH ^{1}H-NMR Chemical Shifts in Dipyrrinone Acids and Esters[a]





	R = CH_3		R = H				R = CH_3		R = H			
n	lactam	pyrrole	lactam	pyrrole	$\Delta\delta^b$ lactam	$\Delta\delta^b$ pyrrole	lactam	pyrrole	lactam	pyrrole	$\Delta\delta^b$ lactam	$\Delta\delta^b$ pyrrole
1	10.92	10.13	9.90	8.84	1.02	1.29	10.89	10.03	9.70	8.54	1.19	1.49
2	10.93	10.12	10.60	8.84	0.33	1.28	10.87	10.02	10.20	8.92	0.67	1.10
3	10.84	10.05	10.47	8.90	0.37	1.15	10.87	10.01	10.52	8.81	0.35	1.20
4	10.85	10.06	10.53	8.94	0.32	1.12	10.86	9.99	10.52	8.88	0.34	1.11
5							10.85	9.98	10.59	8.91	0.26	1.07
KRP[c]	10.81	10.02										
9	10.86	10.05	10.45	8.64	0.41	1.41						
18	10.70	9.94	10.70	9.01	0.00	0.93						

[a] δ (ppm) downfield from $(CH_3)_4Si$ at 500 MHz. Solutions are all 1×10^{-3} M ± 10% in $CDCl_3$. [b] $\delta_{ester} - \delta_{acid}$. [c] Kryptopyrromethenone (Figure 2) behaves more like the esters than the acids.

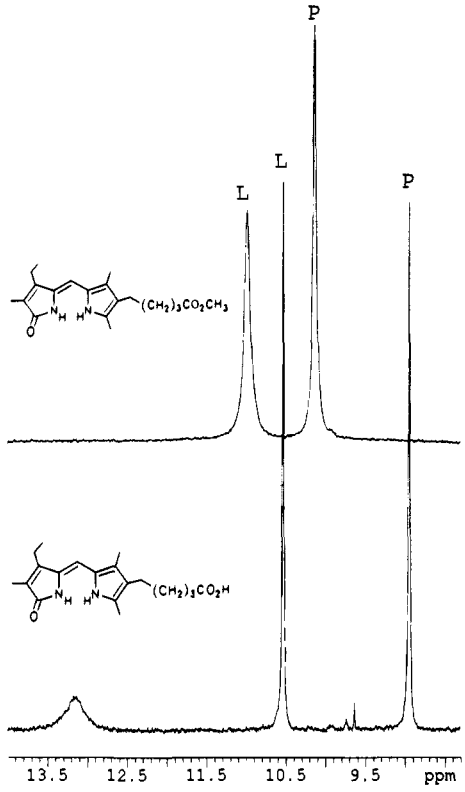


Figure 3. Pyrrole (P) and lactam (L) N-*H* chemical shifts in the partial ^{1}H-NMR spectra of 1×10^{-3} M methyl bishomoxanthobilirubinate (upper) and bishomoxanthobilirubic acid (lower) in $CDCl_3$ at 23 °C.

two-carbon monopyrrole homolog **12** could be further homologated by one or two carbons, thus providing entry into dipyrrinones **9** and **10**, respectively. The synthesis of **12** was achieved by reaction of iodide **19** with diallyl malonate anion to give **21**, which was smoothly deprotected at the malonic ester site and decarboxylated. Iodide **19** was prepared from tosylate **15** derived from **13**, the product of diborane reduction of **11**. Tosylate **15** gave nitrile **17** upon displacement with cyanide, and **17** could be converted to its diacid by base-catalyzed hydrolysis. Thus, **11** could be converted to dipyrrinones **7** and **8**. Similarly, **12** could be converted to **9** and **10**, as outlined in Scheme 1. The methyl esters **6**−**10** were readily saponified to the corresponding acids **1**−**5**.

^{1}H-NMR and Hydrogen Bonding. Dipyrrinones are avid hydrogen bonders. Consistent with this behavior and typical of hydrogen bonding, their intrinsic N−H ^{1}H-NMR chemical shifts ($\delta \simeq 8$)[9] become strongly deshielded in nonpolar solvents, to approximately 10 and 11 ppm[12] for the pyrrole and lactam hydrogens, respectively. These chemical shifts, found in a wide variety of dipyrrinones with hydrocarbon, ester, and amide substituents, are characteristic of the traditional dipyrrinone to dipyrrinone dimer (Figure 2).[1,9,12] In clear but unexpected contrast, however, the pyrrole and lactam N-*H*'s of dipyrrinone acids experience a large shielding relative to their esters. This is found in xanthobilirubic acid (Table 1) and may also be seen in analogs with longer acid chains (Figure 3). It appears to be general for dipyrrinone acids; yet, the behavior is difficult to reconcile with either the traditional or alternative dimer (Figure 4). The N-*H* chemical shifts of the dipyrrinone acids (Table 1) mitigate against the traditional dimer found in dipyrrinone esters—unless one assumes an implausible weakening of the intermolecular hydrogen bonding. The alternative dimer, with its six intermolecular hydrogen bonds (Figure 4), is more attractive, and the observed N-*H* shieldings are consistent with those found in bilirubin, where intramolecular dipyrrinone to carboxylic acid hydrogen bonding yields N-*H* chemical shifts near 9 ppm (pyrrole) and 10.5 ppm[12,18] (lactam). Yet, it still suffers from an apparent destabilizing nonbonded methyl−methyl interaction. Such steric destabilization can be alleviated by rotating the dipyrrinone components above and below each other in a stacked orientation. Such stacking would leave the N-*H*'s above or below the pyrrole or dipyrrinone π-system, thus accounting for their shielding. One can visualize a lock and key arrangement in dipyrrinone acids, where the carboxylic acid

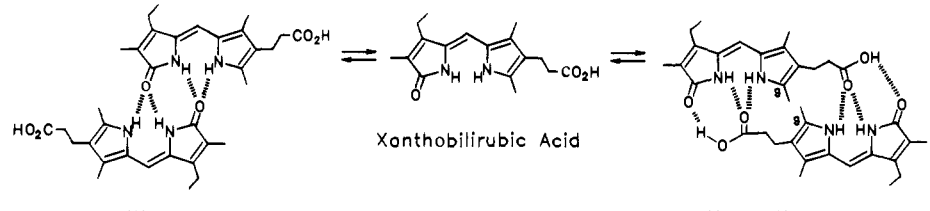
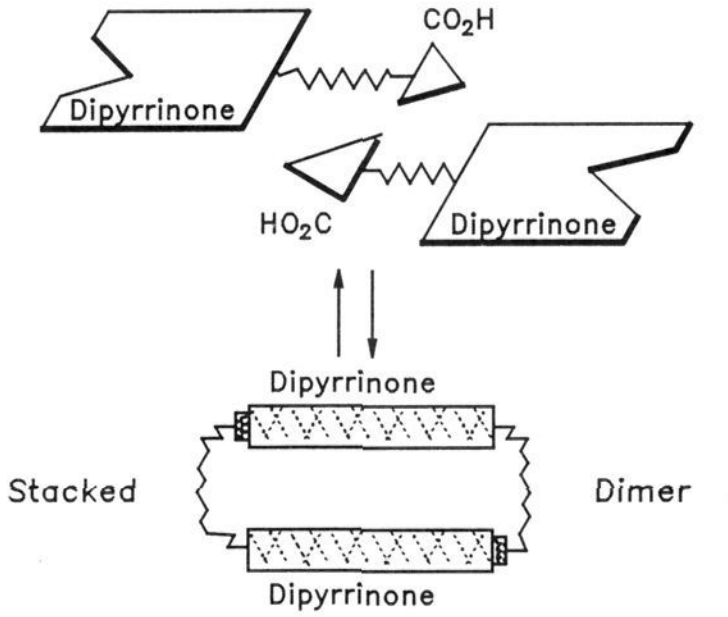


Figure 4. Dimerization of xanthobilirubic acid to form (left) the traditional planar dimer with four hydrogen bonds and (right) an alternative dimer represented in planar form with six hydrogen bonds.



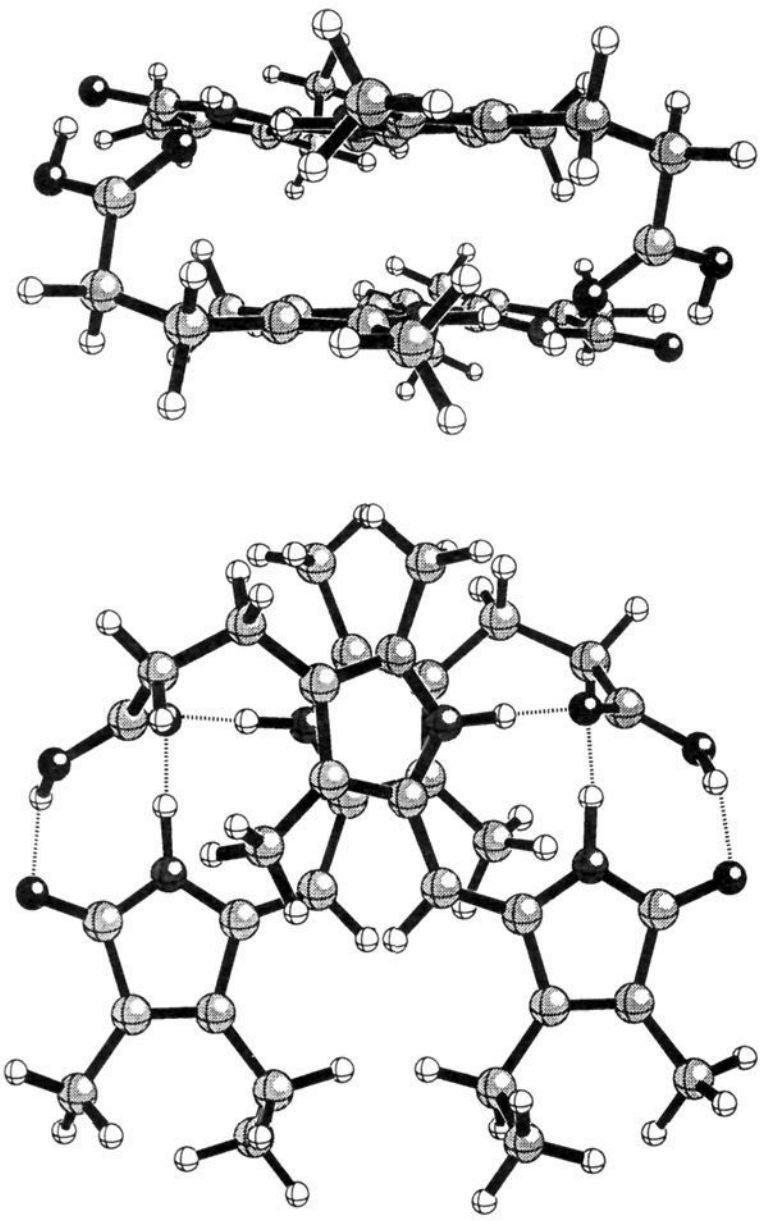


Figure 5. (upper) Schematic representation for planar dipyrrinone and its appended carboxylic acid that fit together, lock and key fashion, in a stacked dimeric arrangement. Ball and stick representation of the stacked hydrogen-bonded dimer of xanthobilirubic acid in edge view (middle) and in top view (lower). The dimer shown has a ***P***-helical arrangement of the long-wavelength electric transition dipole moments oriented along the long axis of each dipyrrinone chromophore (Figure 1).

key is chained to a planar dipyrrinone lock (Figure 5). If the chain is sufficiently long, two units can be tethered in a stacked arrangement by a matrix of six intermolecular hydrogen bonds. Surprisingly, stacked dimers are apparently assembled even with very long alkanoic acid chains (Table 1). These dimers resemble small open-ended boxes with dipyrrinone tops and bottoms and two hydrocarbon walls (Figure 5) that can be expanded (according to chain length) to accommodate or encapsulate guest molecules.

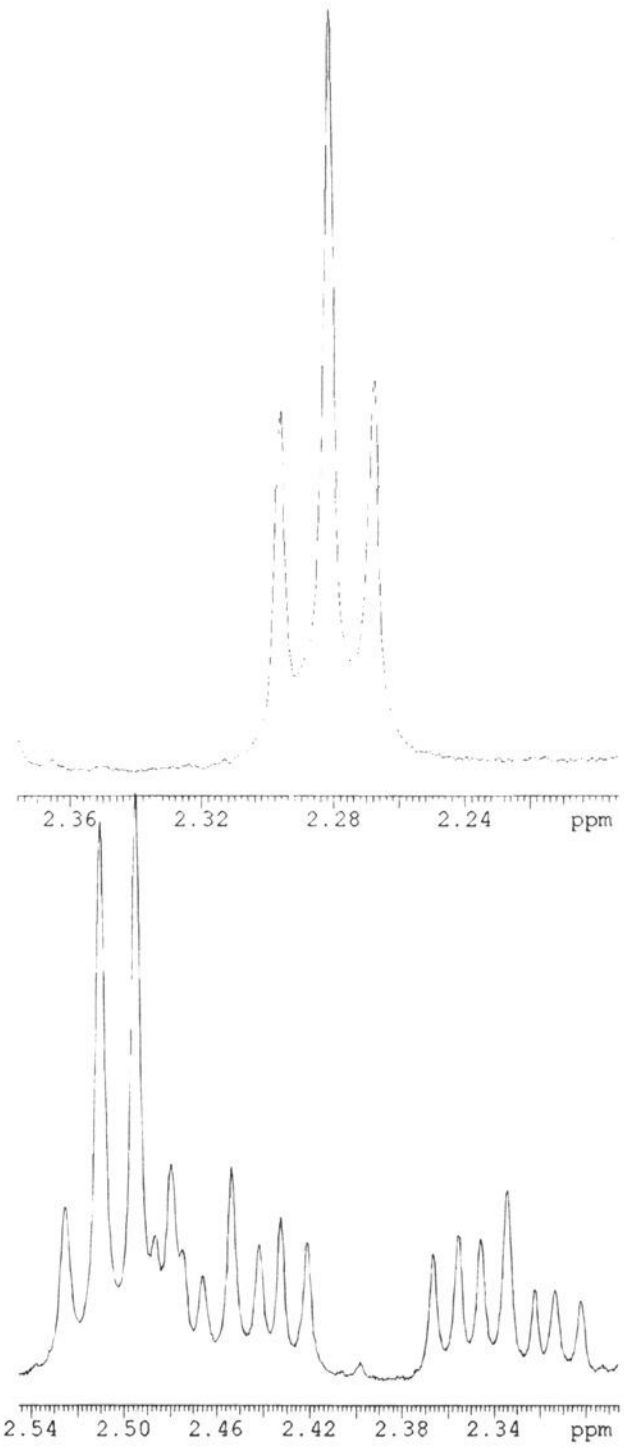


Figure 6. ^{1}H-NMR splittings of the α-CH_2 group in dipyrrinone acid **3** (lower) and its methyl ester **8** (upper).

Further support for a stacked dimer in dipyrrinone acids **1**−**5** may be found in the ^{1}H-NMR signals of the hydrogens α to their carboxyl groups. The α-CH_AH_B hydrogen splitting (Figure 6) is characteristic of an ABXX′ spin system. The chemical shift difference between the diastereotopic A and B protons is *0.1*−*0.2 ppm, with* H_A *and* H_B *being a ddd. This strong* evidence for restricted motion in the carboxylic acid chain is in keeping with the intermolecularly hydrogen-bonded stacked dimer. In marked contrast, the α-CH_2 signals in the ^{1}H-NMR spectra of esters **6**−**10** are simple triplets with ordinary coupling constants, as is typical of free rotation in the ester chain.

Optical Activity and Dipyrrinone Stacking. Optically active xanthobilirubic acid analogs (**1**−**10**), with alkanoic acid chains ranging from propionic to heptanoic, were prepared with an *S*-configuration stereogenic center adjacent to the pyrrole ring. All were synthesized (Scheme 1) from monopyrrole **11**, which was crystallized to 100% diastereomeric excess as its brucine salt, and from this salt the absolute configuration of **11** was determined by X-ray crystallography.[18] Although the optical rotations of the dipyrrinone esters (**6**−**10**) are unexceptional (all are positive in $CHCl_3$ and CH_3CN, with $[\alpha]_D$ values ranging from +28° to +62°), rotations of the acids (**1**−**5**) are unusual. In $CHCl_3$ they are consistently larger than those of the corresponding esters while varying in sign (Table 2). But in the more polar CH_3CN they become weaker, with magnitudes comparable to those of the esters. This behavior was unexpected

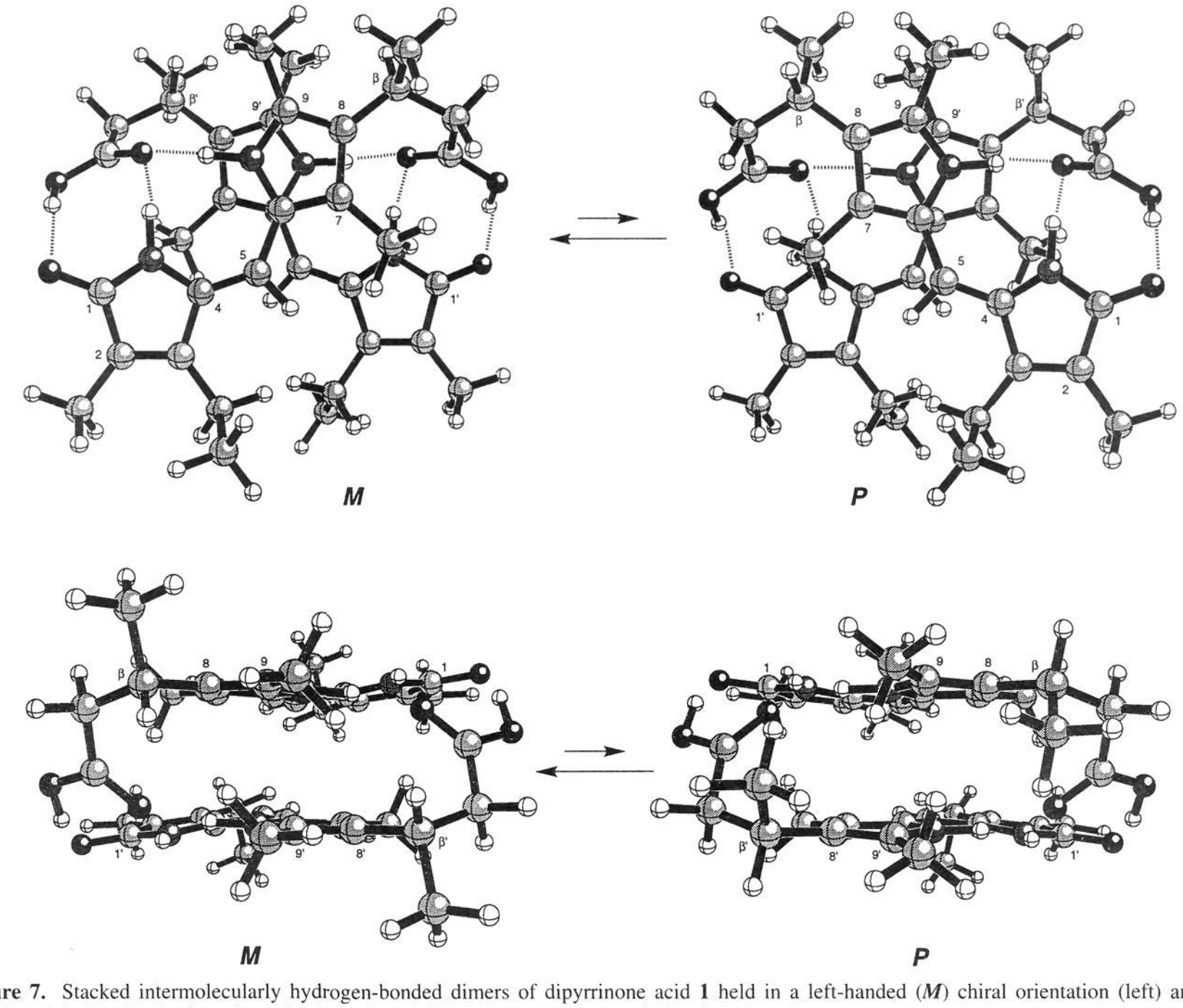


Figure 7. Stacked intermolecularly hydrogen-bonded dimers of dipyrrinone acid **1** held in a left-handed (***M***) chiral orientation (left) and in a right-handed (***P***) chiral orientation (right) as viewed from the top (upper) and the edge (lower).

Table 2. Comparison of Optical Rotations, $[\alpha]^{20}_{D}$ (deg), of Dipyrrinone Acids (**1**−**5**) and Corresponding Esters (**6**−**10**) in $CHCl_3$ and CH_3CN

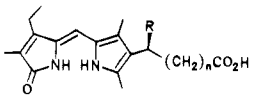
solvent	dipyrrinone	**1** and **6** ($n = 1$)	**2** and **7** ($n = 2$)	**3** and **8** ($n = 3$)	**4** and **9** ($n = 4$)	**5** and **10** ($n = 5$)
$CHCl_3$	ester	+62	+40	+40	+48	+28
	acid	−314	+104	−560	+224	−85
CH_3CN	ester	+44	+29	+28	+33	+16
	acid	−35	+12	+11	−8	−11

and indicates that (i) dipyrrinone acids and esters adopt different dimer structures and (ii) the stability of the acid dimer is greater in nonpolar solvents such as $CHCl_3$ than in polar solvents such as CH_3CN. Since dipyrrinone esters are known to adopt the planar traditional dimeric structure of Figure 2, the acid dimer must adopt a very different structure, such as the stacked dimer of Figure 5. This stacking arrangement imparts a new element in addition to the stereogenic centers of **1**−**5**.

In the stacked dimer of xanthobilirubic acid, the dipyrrinones are held in a dissymmetric orientation—either in the right-handed helical orientation shown in Figure 5 or in its mirror image, isoenergetic dimer with left-handed helicity. The dimer of (*βS*)-methylxanthobilirubic acid (**1**) exhibits similar left and right-handed stacking arrangements (Figure 7). However, here the stacked dimers are diastereomeric and not of equal energy. Consequently, solutions of **1** and its homologs (**2**−**5**) in nonpolar solvents may be expected to exhibit spectral characteristics of the predominant stacked dimer where the dipyrrinone chromophores are held in a dissymmetric relative orientation. This sort of dissymmetry is not available in the traditional dimer (Figure 4), where the component dipyrrinone chromophores lie in the same plane.

Dimer Stability and Stacking Stereochemistry. The stability of the traditional planar dipyrrinone dimer (Figure 2) relative to two separate monomeric dipyrrinones has been determined experimentally from temperature-dependent equilibrium studies ($\Delta H^\circ_{eq} \simeq 17$ kcal/mol, $\Delta S^\circ_{eq} \simeq 38$ eu) of kryptopyrromethenone, methyl xanthobilirubinate, and other dipyrrinone esters.[9] The data are supported by molecular mechanics calculations[10] that predict the traditional planar methyl xanthobilirubinate dimer (Figure 2) to be 20 kcal/mol more stable than two well-separated monomers. In dipyrrinone acids, such as xanthobilirubic acid and its homologs (Table 3), the stacked dimer is even more stable than the traditional dimer (Figure 4). Of course, the ***M***- and ***P***-helical stacked dimers (Figure 5) are enantiomeric and thus isoenergetic. However, when the dipyrrinones have a stereogenic center in the alkanoic acid chain (**1**−**5**), the ***M***- and ***P***-helical stacked dimers (Figure 7) are diastereomeric and thus not isoenergetic. Molecular mechanics calculations predict the ***M***-helical stacked dimer to be more stable than the ***P*** in **1**−**3** and **5** example by 1.7−5.6 kcal/mol,

Table 3. Computed Energy Differences ($\Delta\Delta H_f$)[a] between Stacked and Planar Traditional Dimers of Xanthobilirubic Acid (R = H, n = 1) and Its Homologs (R = H, n = 2–5, 10, and 19), and (βS)-Methylxanthobilirubic Acid (R = CH_3, n = 1) and Its Homologs (R = CH_3, n = 2–5)



R	n		relative stability ($\Delta\Delta H_f$, kcal/mol) M-helical stacked dimer[b]	P-helical stacked dimer[b]	$M - P$
H	1		−11.8	−11.8	0.0
H	2		−18.3	−18.3	0.0
H	3		−15.2	−15.2	0.0
H	4		−11.6	−11.6	0.0
H	5		−12.2	−12.2	0.0
H	10		−15.0	−15.0	0.0
H	19		−15.9	−15.9	0.0
CH_3	1	**1**	−16.4	−10.8	−5.6
CH_3	2	**2**	−25.2	−21.3	−3.9
CH_3	3	**3**	−20.7	−17.8	−2.9
CH_3	4	**4**	−13.7	−14.3	+0.6
CH_3	5	**5**	−15.2	−13.5	−1.7

[a] Computed by molecular mechanics using SYBYL ver. 6.0. [b] ΔH_f (stacked dimer) − ΔH_f (traditional planar dimer) (Figure 4).

but in **4**, the ***P***-helical dimer is estimated to be 0.6 kcal/mol more stable than the ***M*** (Table 3).

Circular Dichroism and Dimer Stereochemistry. The distinctions between dipyrrinone acid (**1**–**5**) and ester (**6**–**10**) rotations (Table 2) are even more clearly evident in their circular dichroism (CD) spectra (Figure 8). When measured in nonpolar solvents, which promote dimer formation, optically active dipyrrinone acids (**1**–**5**) are observed to give moderately strong bisignate CD Cotton effects near the ~400 nm dipyrrinone long-wavelength electronic transition. However, when measured in polar solvents such as CH_3OH and $(CH_3)_2SO$, which disrupt dimers, the Cotton effects are weak to vanishingly small and monosignate. In contrast, optically active dipyrrinone esters (**6**–**10**) give weak to vanishingly small monosignate CD Cotton effects in all solvents (as in Figure 8, center). The bisignate Cotton effects observed with dipyrrinone acids (summarized in Table 4) and attributed to dimers are characteristic of exciton coupling[3,19] between (the relevant electric transition dipole transition moments of) two dissymmetrically-oriented proximal chromophores. The ~400 nm π–π^* transition is polarized along the long axis of each dipyrrinone chromophore (Figure 1)[1] held in close proximity in the intermolecularly hydrogen-bonded stacked dimers (Figure 5). It may be noted that the dipyrrinones of the dimer shown in Figure 5 are dissymmetrically oriented and that the component transition moments are oriented in a right-handed (***P***) helical sense, with positive exciton chirality.[19] The mirror image dimer with a left-hand (***M***) helicity is equally probable. It is this dimer stacking dissymmetry and the interaction between the component dipyrrinone chromophores that explains the CD spectra (Figure 8) and rotation data (Table 2) of dipyrrinone acids **1**–**5**.

According to exciton coupling theory,[19,20] excited state dipole–dipole interaction between two dipyrrinone chromophores should lead to a splitting of the ~400 nm transition and two oppositely-signed CD Cotton effects for the resultant two excitonic transitions. Exciton chirality theory[19] predicts that a CD coupled with long-wavelength positive, short-wavelength negative components can be expected from a right-handed

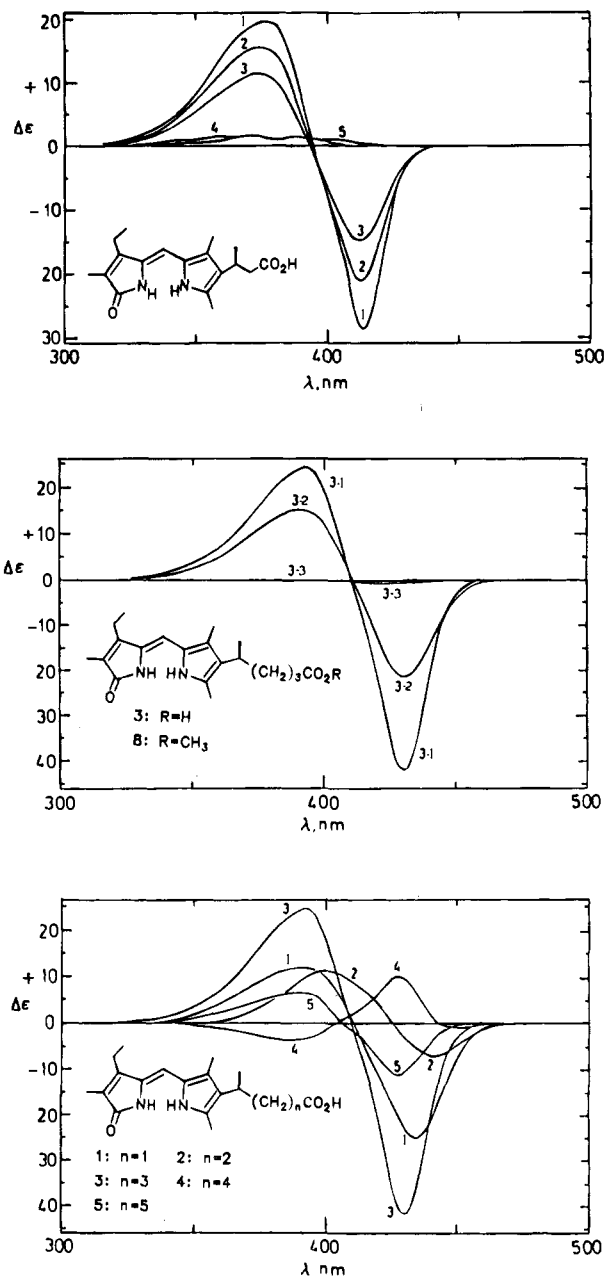


Figure 8. Circular dichroism spectra. (upper) Dipyrrinone acid **1** in (1) CCl_4, (2) benzene, (3) $CHCl_3$, (4) CH_3CN, and (5) CH_3OH. (middle) Dipyrrinone acid **3** in (1) CCl_4, (2) $CHCl_3$, and (3) CH_3CN. Dipyrrinone acid **3** in CH_3OH lies in the $\Delta\epsilon = 0$ line, as do the CD spectra of its methyl ester (**8**) in CCl_4, $CHCl_3$, CH_3CN, and CH_3OH. (lower) Dipyrrinone acids **1**–**5** in CCl_4. Spectra were obtained from 5×10^{-5} M solutions at 23 °C.

helical orientation of the electric transition dipole moments (Figure 1) of the two interacting chromophores. And a left-handed helical orientation can be expected to give a bisignate CD couplet signed long--wavelength negative, short-wavelength positive. Accordingly, the absolute conformation of the dimer can be determined from its CD spectrum. Dipyrrinone **1** may stack in either of two diastereomeric dimers (Figure 7), one with a left-handed (***M***) helicity, the other right-handed (***P***). The CD of **1** in nonpolar solvents (Table 4, Figure 8) predicts a predominance of the dimer with left-handed (***M***) helicity. The same qualitative conclusion may be reached from inspection of molecular models, which show a greater nonbonded steric repulsion in the dimer with right-handed (***P***) helicity—particularly between the β-methyl of one dipyrrinone and a C(9) methyl in the other. In the ***M***-helicity dimer, the β-methyls lie nearly

(19) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(20) Kasha, M.; El-Bayoumi, M. A.; Rhodes, W. *J. Chim. Phys. Phys.-Chim. Biol.* **1961**, *58*, 916–925.

Table 4. Solvent Dependence of UV–Visible and Circular Dichroism Data for Dipyrrinone Acids[a]

		1		2		3		4		5	
solvent	ϵ	ϵ^{max} (λ^{max})	$\Delta\epsilon_1$ (λ_1) λ at $\Delta\epsilon = 0$ $\Delta\epsilon_2$ (λ_2)	ϵ^{max} (λ^{max})	$\Delta\epsilon_1$ (λ_1) λ at $\Delta\epsilon = 0$ $\Delta\epsilon_2$ (λ_2)	ϵ^{max} (λ^{max})	$\Delta\epsilon_1$ (λ_1) λ at $\Delta\epsilon = 0$ $\Delta\epsilon_2$ (λ_2)	ϵ^{max} (λ^{max})	$\Delta\epsilon_1$ (λ_1) λ at $\Delta\epsilon = 0$ $\Delta\epsilon_2$ (λ_2)	ϵ^{max} (λ^{max})	$\Delta\epsilon_1$ (λ_1) λ at $\Delta\epsilon = 0$ $\Delta\epsilon_2$ (λ_2)
CCl_4	2.2	30 400 (415)	+12.0 (392)		+11.3 (401)	32 800 (416)^{sh}	+24.5 (393)	33 100 (419)^{sh}	−3.7 (389)	33 100 (418)^{sh}	+6.5 (393)
			411	30 900 (425)	426		410		404		407
		28 800 (430)^{sh}	−25.0 (435)		−7.2 (441)	33 900 (429)	−41.9 (430)	33 600 (430)	+10.0 (429)	33 800 (430)	−11.4 (428)
C_6H_6	2.3		+11.6 (391)		+8.6 (399)		+24.0 (392)		−5.8 (386)		+4.9 (389)
		29 300 (413)	412	30 600 (424)	423	32 700 (426)	410	31 100 (419)	407	31 200 (424)	406
			−18.6 (434)		−8.4 (441)		−38.6 (431)	30 800 (425)^{sh}	+12.3 (429)		−8.9 (428)
$CHCl_3$	4.7		+5.7 (388)		+6.2 (405)		+15.2 (390)		−2.7 (394)		+2.3 (388)
		30 000 (410)	410	30 900 (416)	422	31 900 (416)	411	30 500 (413)	412	31 400 (415)	407
			−10.9 (434)		−2.6 (446)		−21.3 (431)		+4.7 (432)		−4.3 (430)
THF	7.3	32 200 (403)	0.00	33 000 (405)	0.00	33 600 (407)	0.00	33 100 (399)^{sh}	0.00	33 000 (400)^{sh}	0.00
								33 600 (409)	0.00	33 500 (410)	
CH_3OH	32.6	36 100 (412)	+0.4 (388)	38 300 (414)	0.00	38 000 (413)	0.00	37 800 (415)	0.00	38 000 (415)	0.00
CH_3CN	36.2	32 400 (398)	+0.7 (380)	33 300 (397)	0.00	33 500 (402)	+0.6 (370)	33 000 (403)	+0.8 (386)	32 200 (403)	0.00
							404				
							−0.9 (425)				
DMSO	49	34 400 (409)	0.00	36 600 (410)	0.00	36 300 (413)	0.00	36 300 (413)	0.00	35 800 (413)	0.00

[a] Data obtained at 22 °C on 5 × 10^{-5} M solutions.

perpendicular to the plane of each dipyrrinone and point away from the C(9) methyls. Similarly, the negative exciton chirality CD spectra of **2**, **3**, and **5** (Table 4, Figure 8) predict a predominance of the ***M***-helicity dimer, a prediction supported (as in **1**) by steric constraints. In contrast, predominance of a ***P***-chirality dimer is predicted for **4**.

A more detailed understanding of relative stability of dipyrrinone dimers and their CDs comes from computational methods. Exciton chirality calculations in the coupled oscillator formalism[3,19] predict $\Delta\epsilon_{453}^{max}$ −179, $\Delta\epsilon_{368}^{max}$ +179 for the ***M***-helicity dimer of **1** (Figure 7) and $\Delta\epsilon_{448}^{max}$ +181, $\Delta\epsilon_{371}^{max}$ −181 for the ***P***. Using these values and the observed CD, one would estimate a 57:43 ratio of ***M***:***P*** helicity dimers. This is a far smaller difference in the relative stability of these two dimers than that estimated by molecular mechanics calculations (Table 3). However, the data of Table 3 neglect solvation effects and thus probably have only a qualitative usefulness in being able to predict (correctly) the relative stability of the ***M***- and ***P***-helical dimers.

Dipyrrinone Dimers as Capsules. The stacked dimers of dipyrrinone acids have a cleftlike shape, with the two dipyrrinone units forming the floor and ceiling and the carboxylic acid chains forming two sides (Figure 5). Molecular mechanics calculations[10] on the unsolvated stacked dimers predict inner dimensions of ~8 × 8 × 3 Å. Although the ~3 Å gap in the cleft of the dimer is small, it can expand, accordion-like, in xanthobilirubic acids with long alkanoic acid chains. For example, dipyrrinones with pentanoic acids are capable of encapsulating simple planar guest molecules such as naphthalene and pyrene (Figure 9) or the planar antineoplastic agents 5-fluorouracil and methoxsalen. The computed binding energies ($\Delta\Delta H_f \simeq$ 26, 19, 16, and 27 kcal/mol, respectively)[10] undoubtedly overstate the binding affinities expected in nonpolar solvents, probably by a factor of 3 or 4. However, the computations suggest that encapsulation of the guest molecules above actually stabilizes the dimer (*cf.* R = H, n = 3 of Table 3). Since dipyrrinone acids are very insoluble in water, even at pH 7.4, but bind tightly to serum albumin, one can easily imagine stacked dimers of dipyrrinone acids serving as capsule vehicles for delivering pharmacophore guests. Work on this potentially useful instrument is currently under study in our laboratory.

Experimental Section

General Methods. All UV–visible spectra were recorded on a Perkin Elmer model 3840 diode array or Cary 219 spectrophotometer, and all circular dichroism (CD) spectra were recorded on a JASCO J-600 instrument. NMR spectra were obtained on a GE GN-300 or Varian Unity Plus spectrometer operating at 300 or 500 MHz, respectively, in $CDCl_3$ solvent (unless otherwise noted). Chemical shifts are reported in δ (ppm) referenced to the residual $CHCl_3$ ^{1}H signal at 7.26 ppm and ^{13}C signal at 77.00 ppm. A *J*-modulated spin-echo experiment (attached proton test) was used to assign ^{13}C-NMR spectra. Mass spectra (EI) were measured on a Finnigan MAT SSQ 710 instrument. Optical rotations were measured on a Perkin Elmer model 141 polarimeter. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. 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). Combustion analyses were carried out by Desert Analytics, Tucson, AZ. Dipyrrinone acids **1**–**5** form hydrates and were analyzed as their methyl ester derivatives **6**–**10** and by mass spectrometry.

Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). Borane–tetrahydrofuran solution, *p*-toluenesulfonyl chloride, triethylamine, cesium carbonate, and palladium(II) acetate were from Aldrich. Tetrahydrofuran, dichloromethane, chloroform, methanol, hexane, acetone, dimethyl sulfoxide, ethyl acetate, 1,4-dioxane, and dimethylformamide were HPLC grade from Fisher. Tetrahydrofuran was dried by distillation from $LiAlH_4$; dimethylformamide and triethylamine were distilled and dried over 3 Å molecular sieves.

(+)-(*S*)-3-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)butanoic Acid (11) was obtained as previously described via resolution of the 1:1 salt with brucine by fractional crystallization from acetone.[18] It had $[\alpha]^{20}_D$ +30.5° (*c* 0.8, ethanol).

(+)-(*S*)-3-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)butanol (13). Alcohols **13** and **14** were prepared by the following general procedure. Acid **11** or **12** (10 mmol) was dissolved in 80 mL of dry THF under N_2. The solution was cooled to −20 °C, and 1 M BH_3–THF (13 mL, 13 mmol) was added by syringe over 30 min. The mixture was stirred for 16 h, allowing the temperature to reach ambient. The reaction was then quenched with 10 mL of water, and the THF was removed under vacuum. The residue was partitioned between 50 mL of CH_2Cl_2 and 50 mL of H_2O. The organic extract was washed with successively 15 mL of 1 N NaOH, 15 mL of 2% HCl, and water until neutral. Then it was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum to give a quantitative yield of **13** or **14**, whose purity was satisfactory for use in the next step. Alcohol **13** was obtained from **11** in 96% yield. It had mp 77–79 °C (after recrystallization from ethyl acetate/hexane) and $[\alpha]^{20}_D$ +22.6° (*c* 1.1, ethanol). ^{1}H-NMR: δ 1.25 (3H, d, *J* = 7.2 Hz), 1.34 (3H, t, *J* = 7.2 Hz), 1.86 (2H, m), 2.24 (3H, s), 2.33 (3H, s), 2.91 (1H, m, *J* = 7.2 Hz), 3.56 (2H, m), 4.28 (2H, q, *J* = 7.2 Hz), 8.54 (1H, br s) ppm. ^{13}C-NMR: δ 11.10, 12.53, 14.54, 20.80, 27.17, 39.08, 59.60, 61.74, 116.85, 124.95, 126.72, 129.15, 161.75 ppm. MS: *m*/*z* (relative

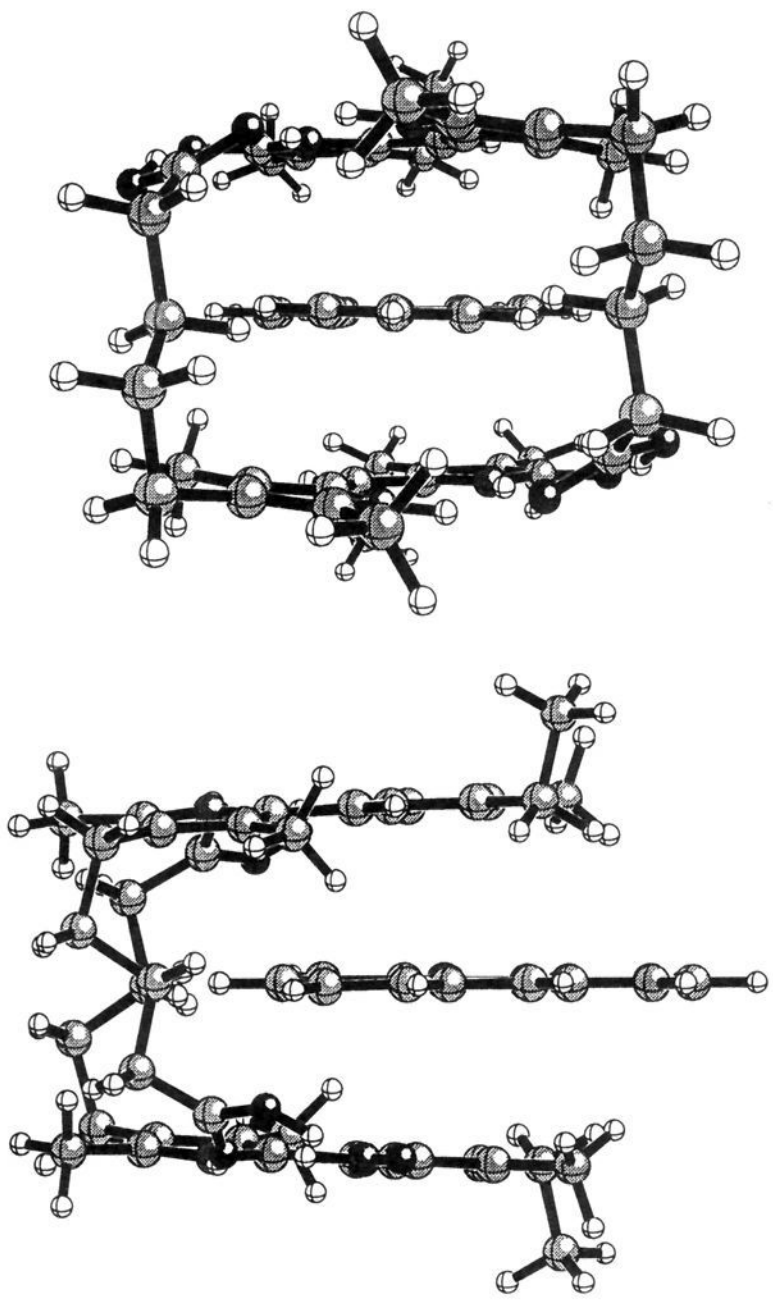


Figure 9. Ball and stick models for the stacked dimer of a xanthobilirubic acid analog with pentanoic acid replacing propionic (R = H, n = 3, Table 3), encapsulating pyrene. (top) Doughnut view. (middle) Cleft view. (bottom) Top view.

intensity) 239 [$M^{+\bullet}$] (16), 194 (70), 180 (8), 148 (100). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.50; H, 8.82; N, 5.78.

(+)-(*S*)-5-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)hexanol (14). As above, alcohol **14** was obtained from **12** in 96% yield. It was an oil (purified by radial chromatography, using hexane/acetone (9:1−8:2) as the eluent), $[\alpha]^{20}_D$ +13.1° (*c* 1.5, ethanol). ^{1}H-NMR: δ 1.21 (3H, d, J = 7.1 Hz), 1.34 (3H, t, J = 7.1 Hz), 1.48−1.70 (6H, m), 2.22 (3H, s), 2.30 (3H, s), 2.70 (1H, m, J = 7.1 Hz), 3.60 (2H, t, J = 6.6 Hz), 4.28 (2H, q, J = 7.1 Hz), 8.67 (1H, br s) ppm. ^{13}C-NMR: δ 11.08, 12.57, 14.49, 20.72, 24.29, 30.48, 32.74, 36.27, 59.53, 62.74, 116.44, 125.60, 126.76, 129.23, 161.94 ppm. MS: *m/z* (relative intensity) 267 [$M^{+\bullet}$] (14), 222 (4), 194 (100), 148 (91). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.28; H, 9.62; N, 5.11.

(+)-(*S*)-3-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)butanol *p*-Toluenesulfonate (15). Tosylates **15** and **16** were obtained by the following general procedure. Alcohol **13** or **14** (10 mmol) was dissolved in 20 mL of dry CH_2Cl_2 and 2.7 mL (20 mmol) of dry Et_3N. The solution was cooled with an ice bath, and 2.86 g (15 mmol) of *p*-toluenesulfonyl chloride was added in small portions over 30 min. The mixture was stirred for 1 h at 0 °C and then for 15 h while the temperature was slowly raised to ambient. Water (100 mL) was added, and the product was extracted with 2 × 50 mL of CH_2Cl_2. The organic extracts were washed with 2% HCl (50 mL), then water until neutral (4 × 50 mL), and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum. Tosylate **15** was obtained in 84% yield after being purified by recrystallization from ethyl acetate/hexane. It had mp 85−87 °C (ethyl acetate/hexane) and $[\alpha]^{20}_D$ +12.6° (*c* 1.0, ethanol). ^{1}H-NMR: δ 1.19 (3H, d, J = 7.1 Hz), 1.34 (3H, t, J = 7.2 Hz), 1.92 (2H, m), 2.16 (3H, s), 2.22 (3H, s), 2.43 (3H, s), 2.85 (1H, m), 3.84 and 3.97 (1H each, m), 4.28 (2H, q, J = 7.2 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.73 (2H, d, J = 8.1 Hz), 8.56 (1H, br s) ppm. ^{13}C-NMR: δ 11.06, 12.34, 14.55, 20.48, 21.55, 26.66, 35.08, 59.60, 69.34, 116.94, 123.38, 126.51, 127.73, 129.22, 129.69, 133.05, 144.58, 161.56 ppm. Anal. Calcd for $C_{20}H_{27}NO_5S$: C, 61.04; H, 6.92; N, 3.56. Found: C, 61.17; H, 6.95; N, 3.53.

(+)-(*S*)-5-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)hexanol *p*-Toluenesulfonate (16). Tosylate **16** was obtained from **14** in 84% yield after radial chromatography (hexane/acetone (10:1−10:3.5)). It was an oil, $[\alpha]^{20}_D$ +10.4° (*c* 2.1, ethanol). ^{1}H-NMR: δ 1.17 (3H, d, J = 7.1 Hz), 1.18 (2H, m), 1.34 (3H, t, J = 7.1 Hz), 1.42−1.65 (4H, m), 2.19 (3H, s), 2.26 (3H, s), 2.44 (3H, s), 2.62 (1H, m), 3.97 (2H, t, J = 6.5 Hz), 4.28 (2H, q, J = 7.1 Hz), 7.32 (2H, d, J = 8.2 Hz), 7.75 (2H, d, J = 8.2 Hz), 8.48 (1H, br s) ppm. ^{13}C-NMR: δ 11.05, 12.66, 14.58, 20.69, 21.59, 23.95, 28.84, 30.41, 35.79, 59.55, 70.55, 116.58, 125.32, 126.71, 127.81, 128.80, 129.76, 133.01, 144.61, 161.58 ppm. Anal. Calcd for $C_{22}H_{31}NO_5S$: C, 62.68; H, 7.41; N, 3.32. Found: C, 62.64; H, 7.58; N, 3.32.

(+)-(*S*)-4-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)valeronitrile (17). Nitriles **17** and **18** were synthesized by the following general procedure. A mixture of 10 mmol of tosylate **15** or **16**, 2.45 g (50 mmol) NaCN, and 15 mL of dry $(CH_3)_2SO$ was stirred for 20 h. Water (100 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with water (3 × 100 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under vacuum. The yield is quantitative, and the purity is satisfactory for use in the next step. From **15**, an analytical sample was obtained in 88% yield by recrystallization from ethyl acetate/hexane. It had mp 88−89 °C and $[\alpha]^{20}_D$ +81.6° (*c* 1.7, ethanol). ^{1}H-NMR: δ 1.28 (3H d, J = 7.1 Hz), 1.35 (3H, t, J = 7.1 Hz), 1.95 (2H, dt, J = 7.0, 6.7 Hz), 2.16 (2H, m), 2.25 (3H, s), 2.31 (3H, s), 2.89 (1H, m, J = 7.1 Hz), 4.29 (2H, q, J = 7.1 Hz), 8.73 (1H, br s) ppm. ^{13}C-NMR: δ 11.14, 12.46, 14.56, 15.71, 20.44, 29.76, 31.69, 59.73, 117.28, 119.87, 122.65, 126.47, 129.42, 161.63 ppm. MS: *m/z* (relative intensity) 248 [$M^{+\bullet}$] (20), 203 (10), 194 (69), 148 (100). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 68.07; H, 8.01; N, 11.07.

(+)-(*S*)-6-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)heptanenitrile (18). As above, **16** gave **18** in 82% yield. It had mp 72−73 °C (ethyl acetate/hexane) and $[\alpha]^{20}_D$ +32.4° (*c* 1.1, ethanol). ^{1}H-NMR: δ 1.22 (3H, d, J = 7.2 Hz), 1.33 (3H, t, J = 7.1 Hz), 1.34 (2H, m), 1.51−1.69 (4H, m), 2.22 (3H, s), 2.30 (3H, s), 2.31 (2H, t, J = 6.7 Hz), 2.70 (1H, m), 4.29 (2H, q, J = 7.1 Hz), 8.68 (1H, br s) ppm. ^{13}C-NMR: δ 11.08, 12.58, 14.52, 17.04, 20.73, 25.43, 27.28, 30.37, 35.61, 59.55, 116.66, 119.74, 125.10, 126.54, 128.95, 161.70 ppm. MS: *m/z* (relative intensity) 276 [$M^{+\bullet}$] (29), 231 (11), 194 (100), 148 (93). Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.79; H, 8.94; N, 10.13.

(+)-(*S*)-3-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)butyl Iodide (19). Iodides **19** and **20** were obtained by the following general procedure. A mixture of 10 mmol of tosylate **15** or **16**, 4.50 g (30 mmol) NaI, and 120 mL of dry acetone was heated at reflux for 3 h. The solvent was removed almost completely under vacuum, and

the product was partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The extract was washed with H_2O (3 × 100 mL), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under vacuum. The yield was quantitative, and the purity was satisfactory for use in the next step. Analytical samples were obtained by recrystallization from ethanol. Thus, **15** gave **19** in 95% yield. It had mp 106−107 °C (ethyl acetate/hexane) and $[\alpha]^{20}_D$ +69.6° (*c* 1.1, ethanol). ^{1}H-NMR: δ 1.24 (3H, d, *J* = 7.0 Hz), 1.33 (3H, t, *J* = 7.1 Hz), 2.07 and 2.17 (1H each, m), 2.26 (3H, s), 2.33 (3H, s), 2.89 (1H, m), 2.98 and 3.14 (1H each, 2 × dt, *J* = 8.1, 9.4 Hz; *J* = 6.4, 9.4 Hz), 4.29 (2H, q, *J* = 7.1 Hz), 8.57 (1H, br s) ppm. ^{13}C-NMR: δ 5.91, 11.27, 12.75, 14.59, 20.23, 31.22, 39.80, 59.66, 117.00, 123.58, 126.76, 129.21, 161.56 ppm. MS: *m/z* (relative intensity) 349 [$M^{+\bullet}$] (9), 304 (3), 194 (70), 148 (100). Anal. Calcd for $C_{13}H_{20}INO_2$: C, 44.71; H, 5.77; N, 4.01. Found: C, 44.66; H, 5.79; N, 3.99.

(+)-(*S*)-5-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)hexyl Iodide (20). As above, **20** was obtained from **16** in 90% yield. It had mp 41−42 °C (ethanol) and $[\alpha]^{20}_D$ +29.2° (*c* 2.2, ethanol). ^{1}H-NMR: δ 1.21 (3H, d, *J* = 7.1 Hz), 1.30 (2H, m), 1.34 (3H, t, *J* = 7.1 Hz), 1.59 (2H, m), 1.79 (2H, m), 2.23 (3H, s), 2.31 (3H, s), 2.69 (1H, m), 3.14 (2H, dt, *J* = 7.1, 7.1 Hz), 4.28 (2H, q, *J* = 7.1 Hz), 8.60 (1H, br s) ppm. ^{13}C-NMR: δ 7.04, 11.12, 12.66, 14.55, 20.76, 29.06, 30.38, 33.59, 35.31, 59.53, 116.59, 125.37, 126.64, 129.03, 161.78 ppm. MS: *m/z* (relative intensity) 377 [$M^{+\bullet}$] (22), 332 (5), 250 (24), 194 (86), 148 (100). Anal. Calcd for $C_{15}H_{24}INO_2$: C, 47.75; H, 6.41; N, 3.71. Found: C, 47.87; H, 6.30; N, 3.66.

Allyl (*S*)-2-((Allyloxy)carbonyl)-5-(2,4-dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)hexanoate (21). Diallyl malonate esters **21** and **22** were prepared by the following general procedure. A mixture of 10 mmol of iodide **19** or **20**, 2.76 g (15 mmol) of diallyl malonate,[21] 2.07 g (15 mmol) of K_2CO_3, 207 mg (10% w/w) of Cs_2CO_3, and 15 mL of dry DMF was stirred for 24 h at room temperature. Water (100 mL) was added, and the product was extracted with diethyl ether (2 × 100 mL). The extracts were washed with H_2O (6 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under vacuum to give a quantitative yield of crude products containing 8−12% (by GC) of starting diallyl malonate. The crude material was used directly in decarboxylation reaction. Purified samples for spectroscopy were obtained after radial chromatography (hexane/acetone (10:1.5−10:3.5)). From **19**, **21** was obtained as an oil. ^{1}H-NMR: δ 1.21 (3H, d, *J* = 7.2 Hz), 1.34 (3H, t, *J* = 7.1 Hz), 1.61 (2H, m), 1.81 (2H, m), 2.21 (3H, s), 2.29 (3H, s), 2.72 (1H, m), 3.35 (1H, t, *J* = 7.4 Hz), 4.28 (2H, q, *J* = 7.1 Hz), 4.61 (4H, ddd, *J* = 5.7, 1.1, 1.2 Hz), 5.22 (2H, ddt, *J* = 10.4, 1.2, 1.2 Hz), 5.30 (2H, ddt, *J* = 17.2, 1.4, 1.2 Hz), 5.87 (2H, ddt, *J* = 10.4, 17.2, 1.2 Hz), 8.52 (1H, br s) ppm. ^{13}C-NMR: δ 10.93, 12.28, 14.36, 20.55, 27.31, 30.26, 33.72, 51.66, 59.35, 65.58, 116.57, 118.25, 124.47, 126.36, 129.26, 131.41, 161.78, 168.71 ppm. MS: *m/z* (relative intensity) 405 [$M^{+\bullet}$] (14), 360 (3), 348 (3), 206 (6), 194 (100), 148 (61).

Allyl (*S*)-2-((Allyloxy)carbonyl)-7-(2,4-dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)octanoate (22). From **20**, **22** was obtained as an oil. ^{1}H-NMR: δ 1.20 (3H, d, *J* = 7.1 Hz), 1.28 (4H, m), 1.34 (3H, t, *J* = 7.1 Hz), 1.57 (2H, m), 1.87 (2H, m), 2.21 (3H, s), 2.29 (3H, s), 2.67 (1H, m), 3.36 (1H, t, *J* = 7.5 Hz), 4.28 (2H, q, *J* = 7.1 Hz), 4.62 (4H, br d, *J* = 5.6 Hz), 5.22 (2H, dd, *J* = 10.5, 1.0 Hz), 5.31 (2H, dd, *J* = 17.2, 1.3 Hz), 5.88 (2H, m), 8.50 (1H, br s) ppm. ^{13}C-NMR: δ 10.99, 12.41, 14.40, 20.66, 27.19, 27.59, 28.57, 30.26, 36.00, 51.68, 59.35, 65.61, 116.39, 118.29, 125.34, 126.46, 129.19, 131.42, 161.81, 168.85 ppm. MS: *m/z* (relative intensity) 433 [$M^{+\bullet}$] (11), 194 (100), 148 (48).

(+)-(*S*)-5-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)hexanoic Acid (12). Monopyrrole monoacids **12** and **23** were prepared by the following general procedure. To a mixture of 10 mmol of diallyl ester **21** or **22**, 67 mg (0.3 mmol) of palladium(II) acetate, 341 mg (1.3 mmol) of triphenylphosphine, and 25 mL of dry freshly distilled 1,4-dioxane was added a solution of 7.0 mL (50 mmol) of triethylamine and 1.5 mL (40 mmol) of formic acid in 5 mL of 1,4-dioxane. The mixture was heated at reflux for 8 h; then, the dioxane was removed under vacuum. The residue was partitioned between 5% aqueous NaOH (2 × 50 mL) and $CHCl_3$ (2 × 20 mL). The alkaline aqueous solution was partially evaporated under vacuum to remove traces of $CHCl_3$ and was then acidified at 0 °C with 10% HCl. The liquid was decanted, and the semisolid crude product was recrystallized from methanol/water (added dropwise). This gave **12** (from **21**) in 89% yield. It had mp 94−96 °C (methanol/water) and $[\alpha]^{20}_D$ +19.3° (*c* 0.7, ethanol). ^{1}H-NMR: δ 1.22(3H, d, *J* = 7.2 Hz), 1.34 (3H, t, *J* = 7.1 Hz), 1.56 (2H, m), 1.62 (2H, m), 2.22 (3H, s), 2.30 (3H, s), 2.31 (2H, t, *J* = 7.3 Hz), 2.71 (1H, m), 4.28 (2H, q, *J* = 7.1 Hz), 9.00 (1H, br s), 11.1 (1H, very br s) ppm. ^{13}C-NMR: δ 11.14, 12.59, 14.51, 20.72, 23.38, 30.35, 34.02, 35.80, 59.80, 116.54, 125.25, 126.95, 129.74, 162.37, 179.27 ppm. MS: *m/z* (relative intensity) 281 [$M^{+\bullet}$] (18), 236 (5), 220 (5), 194 (100), 148 (86). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.24; H, 8.49; N, 4.85.

(+)-(*S*)-7-(2,4-Dimethyl-5-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)octanoic Acid (23). Using the procedure above, ester **22** gave acid **23** in 91% yield. It had mp 77−78 °C (methanol/water) and $[\alpha]^{20}_D$ +20.0° (*c* 0.5, ethanol). ^{1}H-NMR: δ 1.20 (3H, d, *J* = 7.1 Hz), 1.20−1.35 (4H, m), 1.34 (3H, t, *J* = 7.1 Hz), 1.58 (4H, m), 2.22 (3H, s), 2.29 (3H, s), 2.32 (2H, t, *J* = 7.4 Hz), 2.68 (1H, m, *J* = 7.1 Hz), 4.28 (2H, q, *J* = 7.1 Hz), 8.83 (1H, br s), 11.1 (1H, very br s) ppm. ^{13}C-NMR: δ 11.17, 12.62, 14.50, 20.76, 24.65, 27.77, 29.09, 30.43, 34.00, 36.25, 59.79, 116.36, 125.79, 127.00, 129.81, 162.45, 179.46 ppm. MS: *m/z* (relative intensity) 309 [$M^{+\bullet}$] (12), 264 (2), 248 (3), 194 (100), 148 (70). Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.95; H, 8.64; N, 4.47.

5-(Bromomethylene)-4-ethyl-3-methyl-2-oxo-1*H*-pyrrole (24). This compound was synthesized as described previously.[22]

(+)-(*S*)-Methyl 3-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)butanoate (6). This dipyrrinone was synthesized from **11** and **24** as described previously.[18] It had $[\alpha]^{20}_D$ +61.8° (*c* 0.8, $CHCl_3$), $[\alpha]^{20}_D$ +44.3° (*c* 0.1, CH_3CN).

(+)-(*S*)-Methyl 4-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)pentanoate (7). Dipyrrinones **7** and **9** were obtained by the following general procedure. A mixture of 5 mmol of nitrile **17** or **18**, 12.5 mL of ethanol, and 17.5 mL of 10 N KOH was heated at vigorous reflux for 40 h. The solvents were completely removed under vacuum. To the residue was added methanol (50 mL), and the mixture was cautiously acidified at 0 °C by dropwise addition of concentrated HNO_3. The mixture was filtered, then poured into a flask containing 5.5 mmol of **24**. The volume was reduced under vacuum to ~25 mL, and the inorganic precipitates were removed by filtration. Then, filtrate was heated at reflux for 7 h. After cooling the mixture for 18 h at −25 °C, the precipitated crude product (contaminated with inorganic salt) was collected by filtration. The dipyrrinone was redissolved in $CHCl_3$, filtered, and purified by radial chromatography. Thus, **17** gave **7** in 52% yield. It had mp 161−162 °C ($CHCl_3$/CH_3OH) and $[\alpha]^{20}_D$ +39.7° (*c* 0.6, $CHCl_3$). ^{1}H-NMR: δ 1.17 (3H, t, *J* = 7.6 Hz), 1.28 (3H, d, *J* = 7.1 Hz), 1.92 (2H, m), 1.94 (3H, s), 2.14 (3H, s), 2.22 (2H, t, *J* = 7.6 Hz), 2.43 (3H, s), 2.54 (2H, q, *J* = 7.6 Hz), 2.76 (1H, m, *J* = 7.1 Hz), 3.62 (3H, s), 6.13 (1H, s), 10.30 (1H, br s), 11.30 (1H, br s) ppm. ^{13}C-NMR: δ 8.51, 10.30, 12.58, 15.02, 17.93, 20.77, 30.30, 31.54, 32.73, 51.35, 100.96, 122.23, 122.36, 123.34, 124.41, 127.00, 131.21, 148.31, 174.07, 174.33 ppm. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.76; H, 8.20; N, 8.22.

(+)-(*S*)-Methyl 6-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)heptanoate (9). Using the method above, **9** was obtained from **18** in 53% yield. It had mp 144−145 °C ($CHCl_3$/CH_3OH) and $[\alpha]^{20}_D$ +47.7° (*c* 0.5, $CHCl_3$). ^{1}H-NMR: δ 1.17 (3H, t, *J* = 7.6 Hz), 1.23 (3H, d, *J* = 7.1 Hz), 1.24 (2H, m), 1.61 (4H, m), 1.95 (3H, s), 2.15 (3H, s), 2.28 (2H, t, *J* = 7.6 Hz), 2.44 (3H, s), 2.55 (2H, q, *J* = 7.6 Hz), 2.71 (1H, m), 3.65 (3H, s), 6.15 (1H, s), 10.30 (1H, br s), 11.34 (1H, br s) ppm. ^{13}C-NMR: δ 8.52, 10.34, 12.69, 15.06, 17.92, 20.92, 25.05, 27.74, 30.59, 34.05, 36.23, 51.39, 101.06, 122.05, 122.13, 124.45, 124.70, 126.80, 131.01, 148.25, 174.02, 174.26 ppm. Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.93; H, 8.66; N, 7.52. Found: C, 70.57; H, 8.52; N, 7.28.

(+)-(*S*)-Methyl 5-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)hexanoate (8). Dipyrrinones **8** and **10** were obtained

(21) Vinokurov, D. M.; Khaikina, M. B.; *Izv. Vysshikh. Uchebn. Zaved. Khim. Khim Tekhnol.* **1963**, *6*, 83−86; *Chem. Abstr.* **1963**, *59*, 6250g.

(22) Shrout, D. P.; Lightner, D. A. *Synthesis* **1990**, 1062−1065.

by the following general procedure. A mixture of 5 mmol of monoacid **12** or **23**, 10 mL of ethanol, and a solution of 1.0 g (25 mmol) of NaOH in 8 mL of H_2O was heated at reflux for 4 h. Afterward the solvents were completely removed under vacuum. To the residue was added methanol (15 mL), and the mixture was cautiously acidified at 0 °C by dropwise addition of concentrated HNO_3. The mixture was filtered into a flask containing 5.5 mmol of **24** and heated at reflux for 7 h. Then the mixture was chilled for 18 h at −25 °C. The precipitated crude product (contaminated with inorganic salt) was collected by filtration. The dipyrrinone was redissolved in $CHCl_3$, filtered, and purified by radial chromatography. Thus **8** was obtained from **12** in 48% yield. It had mp 104−106 °C ($CHCl_3/CH_3OH$) and $[\alpha]^{20}_D$ +40.2° (*c* 0.5, $CHCl_3$). ^{1}H-NMR: δ 1.17 (3H, t, *J* = 7.5 Hz), 1.24 (3H, d, *J* = 6.9 Hz), 1.55−1.68 (4H, m), 1.94 (3H, s), 2.16 (3H, s), 2.29 (2H, t, *J* = 6.9 Hz), 2.44 (3H, s), 2.55 (2H, q, *J* = 7.5 Hz), 2.74 (1H, m), 3.65 (3H, s), 6.14 (1H, s), 10.32 (1H, br s), 11.35 (1H, br s) ppm. ^{13}C-NMR: δ 8.53, 10.34, 12.67, 15.03, 17.93, 20.87, 23.68, 30.59, 34.16, 36.06, 51.39, 101.04, 122.14, 122.23, 124.38 (int.), 126.92, 131.00, 148.29, 174.05, 174.18 ppm. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.82. Found: C, 70.50; H, 8.36; N, 7.75.

(+)-(*S*)-Methyl 7-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)octanoate (10). As above, **23** gave **10** in 37% yield. It had mp 126−128 °C ($CHCl_3/CH_3OH$) and $[\alpha]^{20}_D$ +28.4° (*c* 0.6, $CHCl_3$). ^{1}H-NMR: δ 1.17 (3H, t, *J* = 7.6 Hz), 1.23 (3H, d, *J* = 7.1 Hz), 1.26 (4H, m), 1.61 (4H, m), 1.95 (3H, s), 2.15 (3H, s), 2.28 (2H, t, *J* = 7.5 Hz), 2.44 (3H, s), 2.55 (2H, q, *J* = 7.6 Hz), 2.70 (1H, m), 3.65 (3H, s), 6.15 (1H, s), 10.29 (1H, br s), 11.31 (1H, br s) ppm. ^{13}C-NMR: δ 8.55, 10.36, 12.72, 15.07, 17.93, 20.93, 24.92, 27.86, 29.27, 30.70, 34.09, 36.47, 51.41, 101.10, 122.03, 122.10, 124.50, 124.89, 126.77, 131.03, 148.25, 174.01, 174.30 ppm. Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.43; H, 8.62; N, 7.22.

(−)-(*S*)-3-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)butanoic Acid (1). Dipyrrinone free acids (**1**−**5**) were prepared by the following general procedure. The methyl ester (**6**−**10**) (0.5 mmol) was heated at reflux for 7 h in 15 mL of 10% aqueous NaOH. Then the mixture was cooled, diluted with 50 mL of H_2O, and acidified with 10% HCl. In the case of butanoic acid **1**, the precipitate was collected by filtration, washed, and dried. In the others (**2**−**5**), the acid was extracted with $CHCl_3$ (2 × 100 mL), washed with H_2O (3 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by radial chromatography (3−5% CH_3OH/CH_2Cl_2) and recrystallized from $CHCl_3/CH_3OH$. Thus **6** gave **1** in 89% yield. It had mp 262−264 °C (dec), $[\alpha]^{20}_D$ −314° (*c* 0.07, $CHCl_3$), and $[\alpha]^{20}_D$ −35.8° (*c* 0.02, CH_3CN). ^{1}H-NMR: δ 1.11 (3H, t, *J* = 7.5 Hz), 1.34 (3H, d, *J* = 7.2 Hz), 1.86 (3H, s), 1.97 (3H, s), 2.40 (3H, s), 2.50 (2H, q, *J* = 7.5 Hz), 2.56 (1H, dd, *J* = 7.7, 12.6 Hz), 2.76 (1H, dd, *J* = 6.1, 12.6 Hz), 3.37 (1H, m), 5.87 (1H, s), 8.80 (1H, br s), 10.06 (1H, br s), 13.1 (1H, very br s) ppm. ^{1}H-NMR (DMSO-d_6): δ 1.07 (3H, t, *J* = 7.5 Hz), 1.16 (3H, d, *J* = 7.1 Hz), 1.77 (3H, s), 2.06 (3H, s), 2.21 (3H, s), 2.47 and 2.49 (1H each, AB), 2.50 (2H, q, *J* = 7.5 Hz), 3.13 (1H, m), 5.91 (1H, s), 9.77 (1H, s), 10.20 (1H, s), 11.94 (1H, br s) ppm. ^{13}C-NMR (DMSO-d_6): δ 8.13, 10.03, 12.05, 14.95, 17.23, 20.55, 27.14, 41.04, 97.56, 121.65, 121.83, 122.67, 122.98, 127.37, 128.81, 147.29, 171.99, 173.62 ppm. Calcd: MW ($C_{18}H_{24}N_2O_3$) 316. Found by MS: *m/z* (relative intensity) 316 [$M^{+\cdot}$] (100), 257 (73).

(+)-(*S*)-4-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)pentanoic Acid (2). As above, **7** gave **2** in 88% yield. It had mp 210−211 °C ($CHCl_3/CH_3OH$) and $[\alpha]^{20}_D$ +104.4° (*c* 0.1, $CHCl_3$). ^{1}H-NMR: δ 1.07 (3H, t, *J* = 7.6 Hz), 1.30 (3H, d, *J* = 7.0 Hz), 1.86 (3H, s), 1.99 (2H, m), 2.18 (3H, s), 2.26 (3H, s), 2.30 (1H, ddd, *J* = 7.6, 6.7, 14.8 Hz), 2.36 (2H, q, *J* = 7.6 Hz), 2.48 (1H, ddd, *J* = 7.6, 8.6, 14.8 Hz), 2.76 (1H, m), 5.92 (1H, s), 8.96 (1H, br s), 10.34 (1H, br s), 13.7 (1H, very br s) ppm. ^{13}C-NMR: δ 8.12, 10.67, 12.47, 14.93, 17.81, 20.65, 31.12, 32.19, 34.53, 100.87, 121.88, 122.63, 122.97, 125.41, 126.82, 131.82, 148.32, 174.17, 178.93 ppm. MS: *m/z* (relative intensity) 330 [$M^{+\cdot}$] (100), 257 (61). Calcd: MW ($C_{19}H_{26}N_2O_3$) 330.

(−)-(*S*)-5-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)hexanoic Acid (3). As above, **8** gave **3** in 65% yield. It had mp 212−215 °C (dec) ($CHCl_3/CH_3OH$) and $[\alpha]^{20}_D$ −560° (*c* 0.1, $CHCl_3$). ^{1}H-NMR: δ 1.13 (3H, t, *J* = 7.5 Hz), 1.23 (3H, d, *J* = 7.0 Hz), 1.57 (2H, m), 1.72 (2H, m), 1.88 (3H, s), 2.15 (3H, s), 2.27 (3H, s), 2.34 (1H, dd, *J* = 6.3, 9.4 Hz), 2.41 (1H, dd, *J* = 6.4, 9.4 Hz), 2.50 (2H, q, *J* = 7.5 Hz), 2.72 (1H, m), 6.10 (1H, s), 8.92 (1H, br s), 10.64 (1H, br s), 13.6 (1H, very br s) ppm. ^{13}C-NMR: δ 8.03, 10.74, 12.27, 14.94, 17.88, 21.25, 23.67, 30.87, 34.77, 35.72, 100.95, 122.48, 122.88, 124.07, 124.22, 127.31, 131.00, 148.44, 174.62, 179.47 ppm. Calcd MW ($C_{20}H_{28}N_2O_3$) 344. Found by MS: *m/z* (relative intensity) 344 [$M^{+\cdot}$] (100), 257 (57).

(+)-(*S*)-6-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)heptanoic Acid (4). As above, **9** gave **4** in 89% yield. It had mp 224−226 °C (dec) ($CHCl_3/CH_3OH$) and $[\alpha]^{20}_D$ +224° (*c* 0.1, $CHCl_3$). ^{1}H-NMR: δ 1.14 (3H, t, *J* = 7.6 Hz), 1.21 (3H, d, *J* = 7.1 Hz), 1.29 (2H, m), 1.62 (4H, m), 1.90 (3H, s), 2.12 (3H, s), 2.30 (3H, s), 2.37 and 2.41 (2H, AB, *J* = 7.3, 14.8 Hz), 2.50 (2H, q, *J* = 7.6 Hz), 2.70 (1H, m), 6.11 (1H, s), 8.99 (1H, br s), 10.64 (1H, br s), 13.4 (1H, very br s) ppm. ^{13}C-NMR: δ 8.09, 10.27, 12.91, 14.99, 17.89, 20.91, 24.75, 27.39, 30.61, 34.08, 36.35, 101.19, 122.30, 122.33, 124.91, 125.02, 127.16, 130.59, 148.39, 174.50, 179.39 ppm. Calcd: MW ($C_{21}H_{30}N_2O_3$) 358. Found by MS: *m/z* (relative intensity) 358 [$M^{+\cdot}$] (100), 257 (55).

(−)-(*S*)-7-(4-Ethyl-3,8,10-trimethyl-2-oxo-1,11-dihydrodipyrrin-9-yl)octanoic Acid (5). As above, **10** gave **5** in 66% yield. It had mp 163−166 °C ($CHCl_3/CH_3OH$) and $[\alpha]^{20}_D$ −85.3° (*c* 0.1, $CHCl_3$). ^{1}H-NMR: δ 1.15 (3H, t, *J* = 7.6 Hz), 1.23 (3H, d, *J* = 7.1 Hz), 1.33 (4H, m), 1.62 (4H, m), 1.90 (3H, s), 2.14 (3H, s), 2.33 (3H, s), 2.37 (2H, t, *J* = 7.6 Hz), 2.52 (2H, q, *J* = 7.6 Hz), 2.68 (1H, m), 6.13 (1H, s), 9.13 (1H, br s), 10.78 (1H, br s), 13.3 (1H, very br s) ppm. ^{13}C-NMR: δ 8.19, 10.46, 12.56, 15.01, 17.91, 20.81, 24.81, 28.08, 29.08, 30.89, 34.36, 36.39, 101.16, 122.29, 122.40, 124.68, 125.11, 127.02, 130.85, 148.36, 174.42, 179.58 ppm. Calcd: MW ($C_{22}H_{32}N_2O_3$) 372. Found by MS: *m/z* (relative intensity) 372 [$M^{+\cdot}$] (100), 328 (5), 257 (43).

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