Exciton Coupling from Dipyrrinone Chromophores

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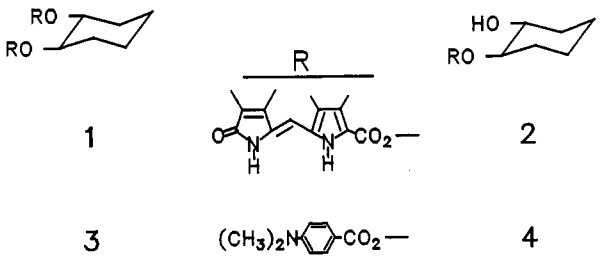
2,3,7,8-Tetramethyl-(10*H*)-dipyrrin-1-one-9-carboxylic acid and *p*-(dimethylamino)benzoic acid are reacted separately with (1*R*,2*R*)-cyclohexanediol to form the corresponding diesters (1 and 3, respectively). These diesters exhibit intense bisignate circular dichroism (CD) spectra characteristic of exciton coupling and show a negative exciton chirality: $\Delta\epsilon_{408}^{max}$ −122.5, $\Delta\epsilon_{360}^{max}$ +95 (1 in CH_2Cl_2) and $\Delta\epsilon_{318}^{max}$ −88.5, $\Delta\epsilon_{292}^{max}$ +41.5 (3 in CH_2Cl_2). In $(CH_3)_2SO$ solvent the Cotton effect signs become inverted for the bis(dipyrrinone ester) but remain unchanged for the bis[*p*-(dimethylamino)benzoate ester].

Introduction

The yellow-orange tetrapyrrole bilirubin (Figure 1) consists of two dipyrrinone chromophores conjoined at a $-CH_2-$ group (C_{10}). This bichromophoric pigment is produced in copious quantities during the normal metabolism of heme and is responsible for the yellow coloration of jaundice.[1,2] Its shape and properties are governed principally by rotations about the C=C double bonds at C_4 and C_{15} and the C–C single bonds at C_5–C_6, C_9–C_{10}, C_{10}–C_{11}, and C_{14}–C_{15}. The most stable arrangement is one with the *Z* configuration double bonds and syn-periplanar or synclinal conformations at the C_5–C_6 and C_{14}–C_{15} single bonds.[3,4] Rotations of the dipyrrinone chromophores about the C_9–C_{10} and C_{10}–C_{11} single bonds generate a large array of propeller-like bilirubin conformational isomers, ranging from a planar linear representation to a planar porphyrin-like representation, with many possible three-dimensional conformations lying in between.[4,5] In one of the last, a folded conformation with $\phi_1 \simeq \phi_2 \simeq 60°$ (relative to $\phi_1 \simeq \phi_2 \simeq 0°$ in the porphyrin-like conformation), the propionic acid groups can easily reach out to the opposing dipyrrinone N—H and C=O groups and enter into intramolecular hydrogen bonding, which greatly stabilizes the structure (Figure 2).[5,6] The resulting ridge-tile structure is important because it renders an erstwhile polar molecule lipophilic and thus controls its binding and hepatic excretion.[1,2,7] It is also interesting because two enantiomeric ridge-tile conformers are possible, and they interconvert by breaking all six hydrogen bonds, rotating about C_9–C_{10} and C_{10}–C_{11} and then remaking the hydrogen bonds. Displacement of the enantiomeric equilibrium toward the *M* or *P* isomer through the action of chiral binding agents or through intramolecular allosteric action generates bilirubin optical activity as seen by usually intense bisignate circular dichroism (CD) Cotton effects, e.g., $\Delta\epsilon_{475}^{max}$ −245, $\Delta\epsilon_{419}^{max}$ +197 $L \cdot mol^{-1} \cdot cm^{-1}$ for the bilirubin–chicken serum albumin complex in pH 7.4 aqueous buffer,[8] $\Delta\epsilon_{469}^{max}$ + 210, $\Delta\epsilon_{418}^{max}$ −143 $L \cdot mol^{-1} \cdot cm^{-1}$ for the bilirubin with (−)-ψ-ephedrine methyl ether in benzene,[9] and $\Delta\epsilon_{436}^{max}$ −250, $\Delta\epsilon_{391}^{max}$ +142 for (αS,$\alpha' S$)-dimethylmesobilirubin XIIIα in chloroform.[10] The bisignate nature of the CD for the long wavelength UV–vis transition(s) has been interpreted in terms of molecular exciton theory, with the maximum observed $|\Delta\epsilon|$ values predicted to approach 270.[11]

Since much of our understanding of the stereochemistry of bilirubin is derived from CD and treatment of the pigment as a molecular exciton, we initiated a program to enhance our understanding of exciton interaction between two dipyrrinone chromophores. In the following, we describe a unique exciton model for bilirubin: a dipyrrinone diester of (1*R*,2*R*)-cyclohexanediol (**1**), which is shown to have an intense bisignate CD spectrum, comparable to that of the diester analogue **3** with *p*-(dimethylamino)benzoate chromophores. This finding is important for its confirms that strong exciton interaction can be obtained from two nonconjugated dipyrrinones and supports the thesis that bilirubin optical activity is derived mainly through exciton chirality.



Results and Discussion

The expectation that the dipyrrinone derivative **1** would serve as a suitable model for exciton coupling is based on the benzoate chirality rule derived from steroid diol systems.[12] For example, the bis[*p*-(dimethylamino)benzoate] of the diequatorial *vic*-diol, 5α-cholestane-3β,4α-diol gives $\Delta\epsilon_{322}^{max}$ +91.3, $\Delta\epsilon_{297}^{max}$ −52.5 in ethanol.[12] As reference compounds for the cyclohexanediol system, the mono- and bis[*p*-(dimethylamino)benzoates] of (1*R*,2*R*)-cyclohexanediol (**4** and **3**, respectively) were prepared, and their CD spectra were recorded (Table I). As expected, the mono ester gives only a weak, monosignate CD spectrum in the vicinity of the long wavelength aromatic transition,

(1) For leading references, see: Ostrow, J. D., Ed. *Bile Pigments and Jaundice*; Marcel-Dekker: New York, 1986.
(2) McDonagh, A. F. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1979; Vol. 6, pp 293–491.
(3) See: Lightner, D. A. In *Bilirubin*; Heirwegh, K. P. M., Brown, S. B., Eds.; CRC Press, Boca Raton, FL, 1982; Vol. 1, Chapter 1.
(4) Falk, H. *The Chemistry of Linear Oligopyrroles and Bile Pigments*; Springer Verlag: New York, 1989.
(5) Molecular mechanics calculations indicate a global minimum for the (folded) conformation with $\phi_1 \simeq \phi_2 \simeq 62°$ (where ϕ_1 and ϕ_2 are defined as 0° in the porphyrin-like conformation of Figure 1). Intramolecular hydrogen bonding is computed to lower the total energy of the folded conformation by an addition 16 kcal/mol. Lightner, D.; Person, R.; Peterson, B.; Puzicha, G.; Pu, Y.-M.; Bojadziev, S. *Biomolecular Spectroscopy II*; Nafie, L. A.; Birge, R. R., Eds.; Proc. SPIE 1432: Seattle, WA, 1991; pp 2–13.
(6) (a) Bonnett, R.; Davies, J. E.; Hursthouse, M. B.; Sheldrick, G. M. *Proc. R. Soc. London, Ser. B* **1978**, *202*, 249–268. (b) LeBas, G.; Allegret, A.; Mauguen, Y.; DeRango, C.; Bailly, M. *Acta Crystallogr., Sect. B* **1980**, *B36*, 3007–3011. (c) Becker, W.; Sheldrick, W. S. *Acta Crystallogr., Sect B* **1978**, *B34*, 1298–1304.
(7) McDonagh, A. F.; Lightner, D. A. *Pediatrics* **1985**, *75*, 443–455.
(8) (a) Blauer, G. *Isr. J. Chem.* **1983**, *23*, 201–209, and references therein. (b) Harmatz, D.; Blauer, G. *Arch. Biochem. Biophys.* **1975**, *170*, 375–386.
(9) Pu, Y.-M.; Lightner, D. A. *Croat. Chem. Acta* **1989**, *62*, 301–324.
(10) Puzicha, G.; Pu, Y.-M.; Lightner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 3583–3592.
(11) Lightner, D. A.; Gawroński, J.; Wijekoon, W. M. D. *J. Am. Chem. Soc.* **1987**, *109*, 6354–6362.
(12) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

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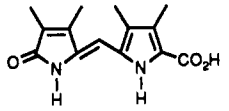
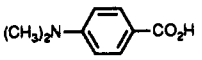
Table I. Circular Dichroism and UV-vis Spectral Data[a] for Esters of (1*R*,2*R*)-Cyclohexanediol

acid component	solvent	$\Delta\epsilon_{max}$ (λ_1)	λ_2 at $\Delta\epsilon$=0	$\Delta\epsilon_{max}$ (λ_3)	ϵ_{max} (λ)
	CH_2Cl_2	−122.5 (408)	382	85.0 (370)[sh]	51 500 (380)
		−55.0 (393)[sh]		+95.0 (360)	32 800 (404)[sh]
	CH_3CN	−95.2 (403)	377	+62.0 (365)[sh]	51 400 (375)
		−52.0 (388)[sh]		+75.2 (354)	33 200 (400)[sh]
	CH_3OH	−21.6 (408)	378		51 800 (380)
		−16.0 (393)[sh]		+18.4 (357)	41 200 (400)[sh]
	$(CH_3)_2SO$	+63.5 (407)	381	−22.0 (370)[sh]	54 300 (385)
		+25.0 (391)[sh]		−25.1 (359)	46 000 (406)[sh]
2 (mono)	CH_2Cl_2			+0.5 (367)	18 600 (398)[sh]
				−0.5 (396)[sh]	24 100 (380)
	CH_3CN			−0.7 (377)	19 200 (396)[sh]
				−0.3 (398)	25 200 (375)
	CH_3OH			−0.3 (382)	23 500 (400)[sh]
					27 600 (382)
	$(CH_3)_2SO$			+0.2 (385)	20 100 (403)[sh]
				+0.6 (400)	23 600 (385)
	CH_2Cl_2	−88.5 (318)	305	+41.5 (292)	53 600 (311)
	CH_3CN	−90.3 (317)	304	+43.5 (292)	52 500 (309)
	CH_3OH	−83.5 (320)	307	+44.3 (295)	52 900 (310)
	$(CH_3)_2SO$	−69.0 (322)	310	+34.1 (298)	51 700 (313)
4 (mono)	CH_2Cl_2	−0.6 (308)			27 200 (312)
	CH_3CN	−0.9 (311)			27 400 (308)
	CH_3OH	−0.7 (311)			26 500 (310)
	$(CH_3)_2SO$	−0.7 (310)			26 200 (310)

[a] Run on 2.0×10^{-5} M solutions at 25 °C.

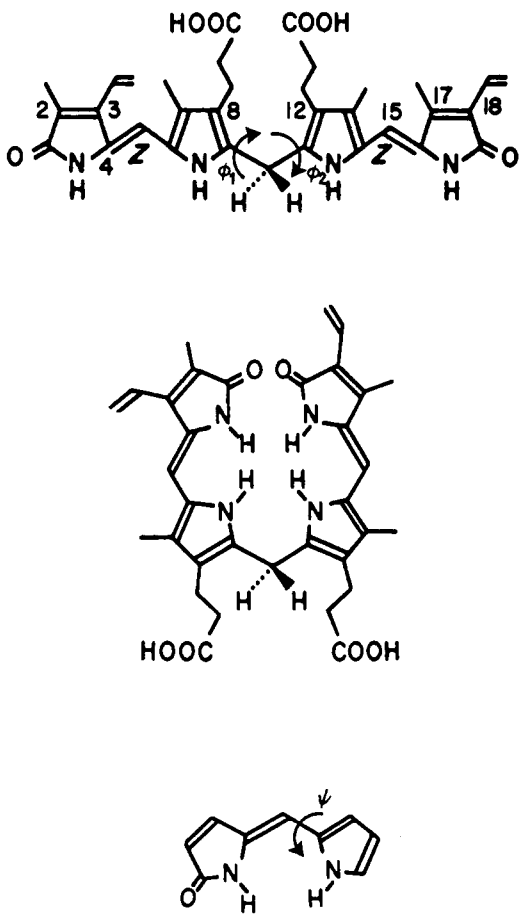


Figure 1. Linear (top) and porphyrin-like (middle) representations for (4*Z*,15*Z*)-bilirubin IXα. These conformations may be interconverted through rotation of each dipyrrinone by 180° about torsion angles ϕ_1 and ϕ_2. (Bottom) Dipyrrinone chromophore in the *syn*-*Z* conformation, ψ = 0°. Rotation about torsion angle ψ generates an array of conformational isomers.

but the diester gives an intense negative chirality bisignate CD spectrum, with the two exciton components flanking the long wavelength UV transition(s) (Figure 3). The CD intensities of **3** and **4** are fairly insensitive to solvent effects, although the values for **3** drop ~15% in dimethyl sulfoxide. Thus, *trans*-cyclohexanediol would appear to be an excellent template on which to attach a dipyrrinone chromophore.

Dipyrrinones are usually bright yellow compounds, with an intense ($\epsilon \simeq 30\,000$) UV-vis absorption near 400 nm originating from the conjugated π-electron system.[4] Although these pigments may adopt a twisted (dissymmetric) conformation (by rotation about ψ, Figure 1) and are potentially chiral molecules, there is only a small (<1 kcal/mol) energy difference between the essentially planar syn-periplanar conformation seen in the crystal and in nonpolar solvents (where intermolecularly hydrogen-bonded dimers persist) and the syn-clinal conformation found in highly dilute solutions or polar solvents ($\psi \simeq$ 20–50°).[4] Consequently, their solutions in isotropic media exhibit no optical activity. However, when covalently linked to an optically active ester or amine, weak monosignate CD Cotton effects ($|\Delta\epsilon| \simeq 1$) have been seen in polar solvents such as dimethyl sulfoxide and weak bisignate Cotton effects ($|\Delta\epsilon| \simeq$ 1–3) are seen in nonpolar solvents such as dichloromethane.[13] The latter are assumed to originate from exciton interaction in the intermolecularly hydrogen-bonded dimer.

The dipyrrinone carboxylic acid **11** used to prepare the di (**1**) and mono (**2**) esters of (1*R*,2*R*)-cyclohexanediol was synthesized in eight steps from 2-butanone and diethyl (hydroxyimino)malonate as outlined in Scheme I. Since this previously unknown dipyrrinone has an intense UV-vis long wavelength absorption ($\epsilon \simeq 25\,000$) near 380 nm (Figure 4), it would appear to be an excellent chromophore equivalent to *p*-(dimethylamino)benzoic acid (ϵ_{311}^{max} 30 400). As accomplished with the latter chromophore, **11** was reacted with (1*R*,2*R*)-cyclohexanediol to afford both the monoester and the diester. Monoester **2** (Table I) gave only extremely weak monosignate CD Cotton effects, of the same order of magnitude as those from the monoester with *p*-(dimethylamino)benzoic acid. Interestingly, there

(13) Lightner, D. A.; Reisinger, M.; Wijekoon, W. M. D. *J. Org. Chem.* 1987, *52*, 5391–5395.

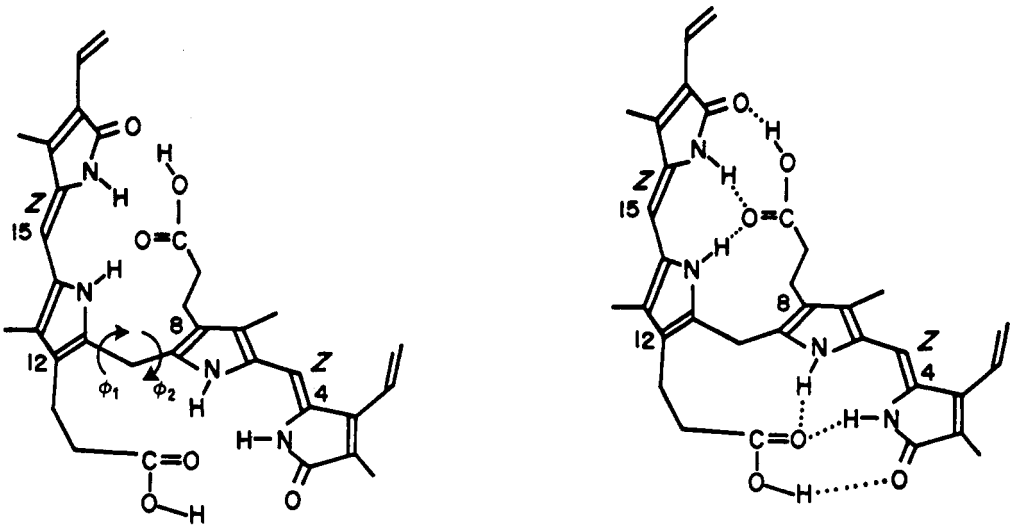


Figure 2. (Left) Folded, energy-minimum conformation of bilirubin with torsion angles $\phi_1 \simeq \phi_2 \simeq 60°$ (refs 4 and 5). The torsion angles are defined as 0° in the porphyrin-like conformation of Figure 1 and 180° in the linear representation. (Right) Folded conformation with intramolecular hydrogen bonding; the "ridge-tile" conformation found in certain crystals of bilirubin (ref 6).

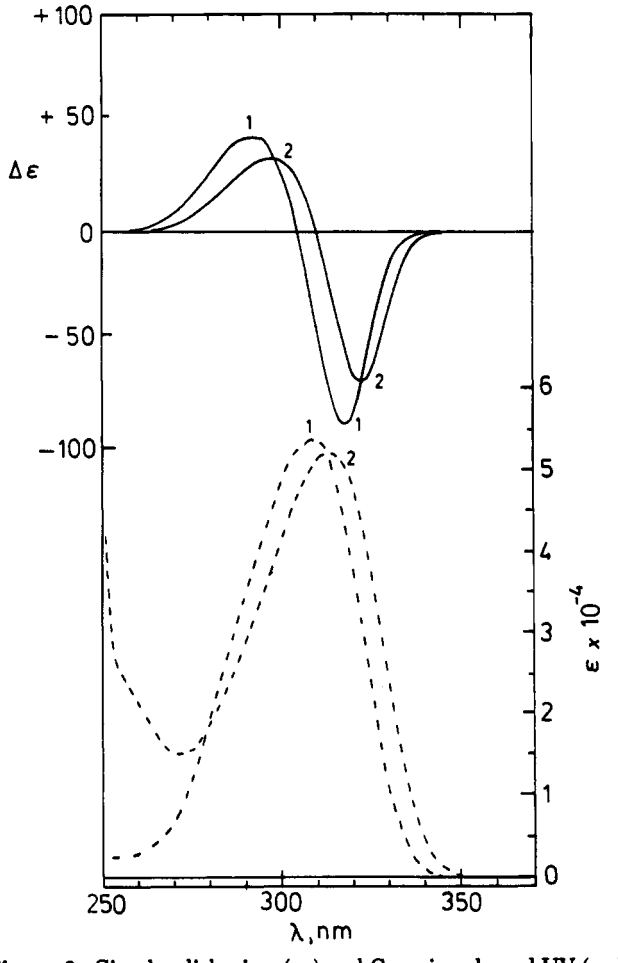


Figure 3. Circular dichroism (—) and Gaussian-shaped UV (---) spectra of 1.21×10^{-5} M (1*R*,2*R*)-cyclohexanediol bis[(*p*-dimethylamino)benzoate] in CH_3CN (1) and $(CH_3)_2SO$ (2) at 21 °C.

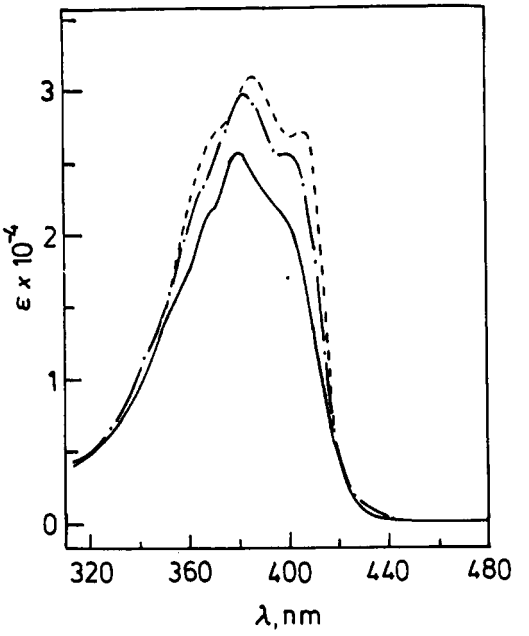


Figure 4. Visible region absorption spectra of 11 methyl ester in CH_2Cl_2 (6.9×10^{-6} M) (—), CH_3OH (6.9×10^{-6} M) (-·-), and $(CH_3)_2SO$ (1.0×10^{-6} M) (---) at 21 °C.

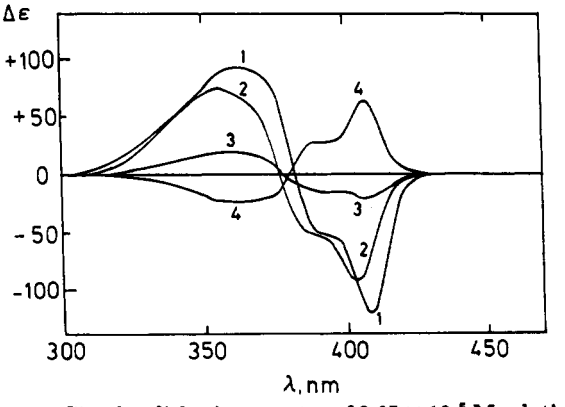
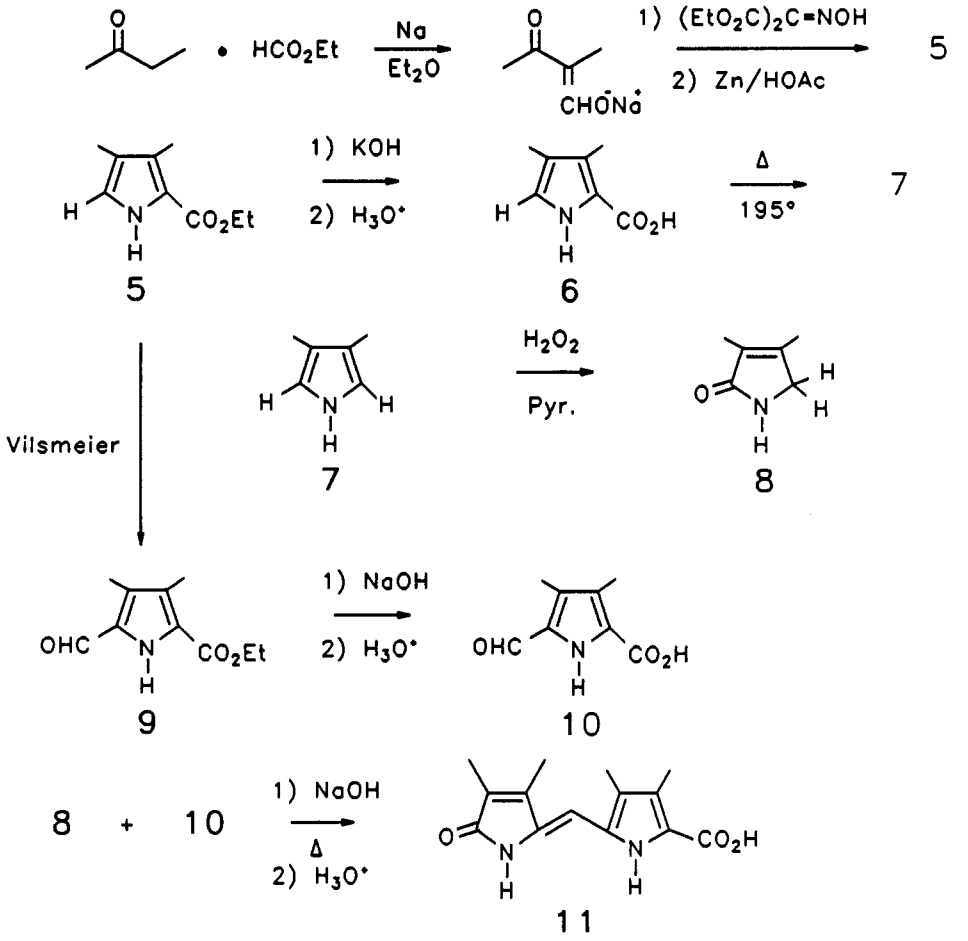


Figure 5. Circular dichroism spectra of 9.65×10^{-5} M solutions of bis(dipyrrinone ester) 1 in CH_2Cl_2 (1), CH_3CN (2), CH_3OH (3), and $(CH_3)_2SO$ (4) at 21 °C.

appear to be two, nearly overlapping UV–vis transitions in the 380–400 nm band of the dipyrrinone monoester (see also Figure 4), and they have the same CD signs (in a given solvent). Other dipyrrinones not having a carboxyl group attached directly to the pyrrole α-carbon exhibit only one long wavelength electronic transition.

In contrast to the CD of monoester **2**, the CD spectra of the diester (**1**) are far different (Table I). The dipyrrinone diester exhibits *intense bisignate* Cotton effects (Figure 5). Here again the distorted shape of the CD spectra suggests overlapping spectra arising from two

Scheme I



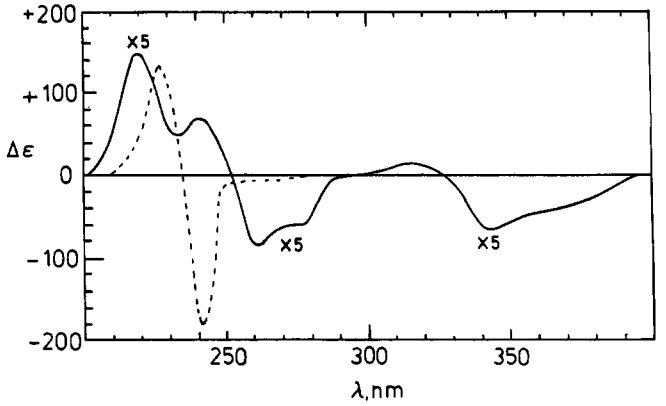


Figure 6. Circular dichroism spectra of 2.17×10^{-5} M (1*R*,2*R*)-cyclohexanediol bis[6-(dimethylamino)-2-naphthoate] (—) and 1.22×10^{-5} M (1*R*,2*R*)-cyclohexanediol bis[(2-naphthoate) (- - -) in CH_3CN solvent at 21 °C.

different types of transitions in the dipyrrinone chromophore. Each transition is apparently electronically coupled to the corresponding transition of the neighboring dipyrrinone of the diester with the result that the observed CD spectra take on the appearance of two overlapping bisignate CD curves, with each curve having the same signed order of the exciton couplets.

This type of behavior has been reproduced in a substituted naphthalene chromophore, in the bis[6-(dimethylamino)-2-naphthoate ester] of (1*R*,2*R*)-cyclohexanediol (Figure 6), prepared from the known 6-(dimethylamino)-2-naphthoic acid.[14] Unlike the parent

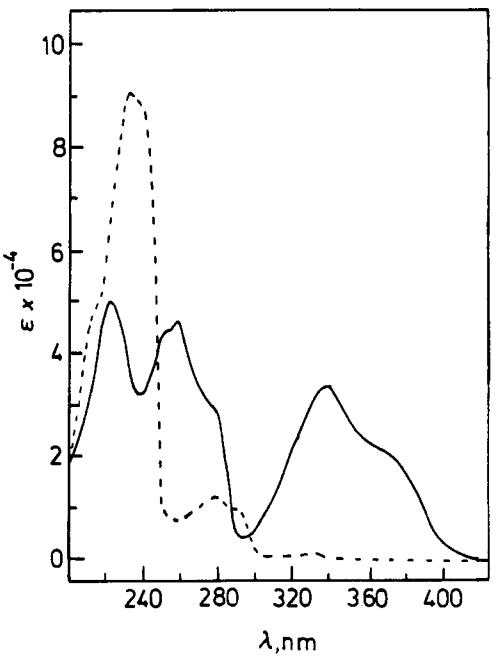


Figure 7. Ultraviolet spectra of 4.5×10^{-5} M (1*R*,2*R*)-cyclohexanediol bis[6-(dimethylamino)-2-naphthoate] (—) and 1.22×10^{-5} M (1*R*,2*R*)-cyclohexanediol bis(2-naphthoate) (- - -) in CH_3CN at 21 °C.

bis(2-naphthoate ester), overlapping "doubled" bisignate CD curves are seen with the 6-dimethylamino derivative—corresponding to the two shorter wavelength transitions seen in the UV spectrum (cf. only one short wavelength UV transition in the parent, Figure 7). The

(14) Adcock, W.; Wells, P. R. *Aust. J. Chem.* **1965**, *18*, 1351.

spectroscopic designations of the two short wavelength transitions of 6-(dimethylamino)-2-naphthoic acid remain uncharacterized.

Like the bis[*p*-(dimethylamino)benzoate] (3), the bis(dipyrrinone ester) 1 shows a strong negative exciton chirality in CH_2Cl_2 and CH_3CN solvents. In fact the observed $\Delta\epsilon$ values are even larger in the dipyrrinone spectra (Table I). Unlike the bis[*p*-(dimethylamino)benzoate], however, the CD of the bis(dipyrrinone) in CH_3OH shows a substantial drop in $\Delta\epsilon$ magnitude relative to the spectra in CH_2Cl_2 and CH_3CN. And, surprisingly, in $(CH_3)_2SO$ the Cotton effect signs become inverted (to positive chirality). In a simplistic view of the exciton chirality rule, this would imply an unprecedented change of (diol) absolute configuration with change of solvent. An alternative and probably better interpretation is that the dipyrrinone electric dipole transition moments have changed their relative orientation. Like *p*-(dimethylamino)benzoic acid, the relevant electric dipole transition moment of dipyrrinones lies along the long axis of the molecule.[4,15] Unlike the former, however, the acid carbonyl carbon of 11 does not lie on (or nearly so) this axis. Consequently, whereas rotation about the C_1–COOR bond of the *p*-(dimethylamino)benzoate does not alter the orientation of the ~310 nm electric transition dipole moment relative to the cyclohexanediol template, rotation about the C_9–COOR bond of the dipyrrinone in 1 (or 2) can (and apparently does) lead to major changes in electric dipole vector orientation. Other soruces of rotational degrees of freedom that would affect the orientation of the transition dipoles come from ester C–O–C bond rotations; however, for *p*-(dimethylamino)benzoates this has not been a problem in applying the exciton chirality rule. That the relevant transition dipoles of 1 might reorient upon changes in solvent is not altogether surprising, given the factor that dipyrrinones hydrogen bond strongly to $(CH_3)_2SO$ (and probably CH_3OH) solvent through their pyrrole and lactam hydrogens.[16] Such strong association with solvent thus imposes additional steric constraints not pertinent to CH_2Cl_2 and CH_3CN solvents. Presently it is difficult to draw firm conclusions on the conformation of 1 in CH_2Cl_2 and in $(CH_3)_2SO$. The significant presence of diaxial isomers seems remote, given the conformational preference of 1,2-dihydroxy- or 1,2-diacetoxycyclohexane for the diequatorial configuration. Considering only diequatorial conformers, one possibility, shown in Figure 8, orients the ester carbonyl oxygen anti-periplanar or anti-clinal to the pyrrole nitrogen into a compact structure with a predicted negative exciton chirality, the same as that observed in CH_2Cl_2, CH_3CN, and CH_3OH. Another possibility orients the ester carbonyl oxygen syn-periplanar or syn-clinal to the pyrrole nitrogen in order to accommodate hydrogen bonding to $(CH_3)_2SO$. This orientation has a positive helicity of the transition dipoles, as predicted by exciton chirality rules for the major contributing conformer in $(CH_3)_2SO$.

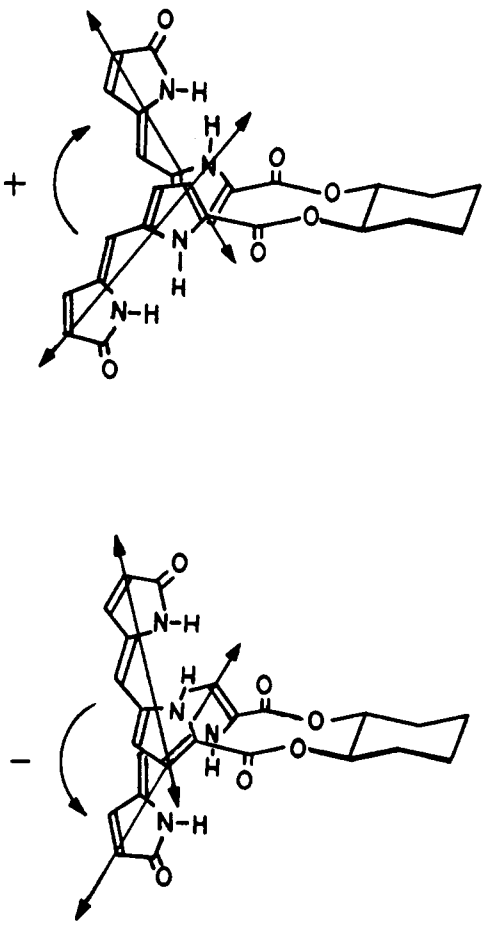


Figure 8. Probable conformations of bis(dipyrrinone ester) 1 in $(CH_3)_2SO$ (upper) and CH_2Cl_2 (lower) showing solvent-induced reorientation of the dipyrrinone chromophores (and their long wavelength electric dipole transition moments represented as double-headed arrows) from *P*-(+) helicity (upper) to *M*-(−) helicity (lower). Conformational changes are achieved by rotations about the C_9–COOR bonds. Alkyl substituents are removed for clarity.

Summary

Optical activity due to exciton coupling can be detected for the bis(dipyrrinone esters) of (1*R*,2*R*)-cyclohexanediol by CD spectroscopy. Intense bisignate CD is seen for the long wavelength transition(s), as in the bis[*p*-(dimethylamino)benzoate ester]. In contrast, only very weak monosignate CD can be detected for the monoesters. Unlike the *p*-(dimethylamino)benzoate exciton, in the dipyrrinone exciton studied here, the relative orientation of the chromophores changes in going from CH_2Cl_2 or CH_3CN solvent to $(CH_3)_2SO$ solvent in such a way that the relevant electric dipole transition moments are reoriented from a negative to a positive exciton chirality. These results are important because they support the explanation that bilirubin, which has two dipyrrinone chromophores, behaves as a molecular exciton in giving intense CD and because they offer a cautionary note that one must know the orientation of the transition dipoles when applying exciton chirality rules.[26]

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(16) (a) Trull, F. R.; Ma, J.-S.; Landen, G. L.; Lightner, D. A. *Isr. J. Chem.* **1983**, *23*, 211–218. (b) Gawroński, J. K.; Polonski, T.; Lightner, D. A. *Tetrahedron* **1990**, *46*, 8053–8066.

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(24) Arndt, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 2, p 461.

Experimental Section

General. Circular dichroism (CD) spectra were recorded on a JASCO J-600 spectropolarimeter. Ultraviolet–visible (UV–vis) spectra were determined on a Cary 219 spectrophotometer or a Perkin-Elmer 3840 diode array spectrophotometer. Mass spectra were recorded on a Hewlett-Packard 5970 mass selective detector/8890 capillary gas chromatograph (70 eV), using a 30-m HP-1 column. Infrared (IR) spectra were recorded on a Perkin-Elmer 1610 Fourier transform spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ on a General Electric QE-300 300-MHz spectrometer. HPLC analyses were carried out on a Perkin-Elmer high pressure liquid chromatograph with a LC-95 UV–vis spectrometer detector (set at 410 nm) equipped with a Beckman-Altex ultrasphere-IP 5 mm C-18 ODS column (25 × 0.46 cm) and Beckman ODS precolumn (4.5 × 0.46 cm). The flow rate was 1.0 mL/min. The eluting solvent was 0.1 M di-*n*-octylamine acetate in 5% aqueous methanol (pH 7.7, at 31 °C). Melting points were determined either on a Thomas-Hooever Uni-Melt capillary apparatus or on a Mel-Temp capillary apparatus. Spectral grade solvents for UV–vis and CD were purchased from Aldrich, Eastman, MCB, and Fisher. Deuterated chloroform, deuterated methyl sulfoxide, deuterated benzene, *p*-(dimethylamino)benzoic acid, diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,1′-carbonyldiimidazole were from Aldrich. Dimethyl sulfoxide (DMSO) from Eastman was dried over 4-Å molecular sieves. (1*R*,2*R*)-*trans*-Cyclohexanediol with >99% purity and $[\alpha]^{20}_D = -39 \pm 1°$ (c = 1.6, H_2O) was obtained from Fluka. Analytical thin layer chromatography (TLC) was carried out on J. T. Baker silica gel IB-F plates (125 μm layer) or Analtech silica gel G plates (250 μm layer, 5 × 20 cm). Preparative TLC was performed on Analtech silica gel G plates (500 μm, 20 × 20 cm).

General Procedures. Conversions were typically carried out on a 0.5-mmol scale for the acid component. The acid component (0.5 mmol) and 1,1′-carbonyldiimidazole (0.55 mmol) were dissolved in 1.0–1.5 mL of dry dimethyl sulfoxide (DMSO) and stirred magnetically for 20–30 min at 40 °C. Then (1*R*,2*R*)-cyclohexanediol (0.5 mmol for synthesis of the monoester; 0.25 mmol for the diester) was added, along with 0.5 mmol of diazabicyclo[5.4.0]undec-7-ene (DBU) and a few 4-Å molecular sieves, and the reaction mixture was blanketed with nitrogen and stirred for 16–20 h (for the di derivative) or 10–15 h (for mono) while maintaining the reaction temperature at 40–50 °C (for **3** and **4**) or 80–100 °C (for **1** and **2**). The progress of the reaction was followed by TLC or HPLC. After the required reaction period, the mixture was cooled to room temperature and quenched with the addition of 3 mL of water. At this point a precipitate came out of solution. The precipitate was filtered and washed well with water and dissolved in 15 mL of dichloromethane. The dichloromethane solution was washed with dilute acetic acid (a few drops of glacial acetic acid in 10 mL of water), then water (8 mL) followed by 5% aqueous sodium bicarbonate (8 mL) and saturated aqueous sodium chloride (8 mL). After drying, the solution over anhydrous sodium sulfate, and the dichloromethane was removed on a Roto-vap. The residue was chromatographed by preparative TLC (Analtech 20 × 20 cm plates coated with 500 μm of silica gel G). The plates were irrigated with 20:1 CH_2Cl_2:CH_3OH (vol/vol) for **1**, 10:1 CH_2Cl_2:CH_3OH (vol/vol) for **2**, or 9:1 benzene:ethyl acetate (vol/vol) for **3** and **4** to afford pure products with their characteristic spectral and physical properties delineated below. A specific procedure (for **3**) follows.

(1*R*,2*R*)-*trans*-Cyclohexanediol Bis[4-(dimethylamino)benzoate] (3).[17] *p*-(Dimethylamino)benzoic acid (100.0 mg, 0.605 mmol) and 1,1′-carbonyldiimidazole (100.0 mg, 0.617 mmol) were dissolved in dry DMSO (1 mL). After 10 min at 40 °C, (1*R*,2*R*)-*trans*-cyclohexanediol (35 mg, 0.301 mmol) was added, along with 4-Å molecular sieves and DBU (0.092 mL, 0.605 mmol), and the mixture was kept at 40 °C for 6 h (very little further reaction was achieved after an additional 11 h at 40 °C). The clean, light blue reaction mixture was cooled to room temperature, then, water (3 mL) was added to afford a white precipitate. The precipitate was removed by filtration, washed with water, and dried in air. The solid was dissolved in CH_2Cl_2 (15 mL) and washed with dilute acetic acid (8 mL), water (10 mL), 5% aqueous $NaHCO_3$ (8 mL), and saturated aqueous NaCl (8 mL). After drying over anhyd Na_2SO_4, the CH_2Cl_2 was removed (rotary evaporator), and the residue was chromatographed by preparative TLC to give 65 mg (48%) of the pure diester: mp 153.5–155 °C; IR (Nujol) ν 1704, 1686 cm^{-1}; ^1H NMR δ 1.40–1.65 (m, 4 H), 1.70–1.85 (m, 2 H), 2.15–2.25 (m, 2 H), 2.95 (s, 12 H), 5.05–5.23 (m, 2 H), 6.54 (d, 4 H, J = 9.0 Hz), 7.83 (d, 4 H, J = 9.0 Hz); ^{13}C NMR δ 23.49 (t), 30.29 (t), 40.02 (q), 73.37 (d), 110.68 (d), 117.31 (d), 131.31 (s), 153.25 (s), 166.41 (s); UV–vis and CD data in Table I; mass spectrum m/z (rel intensity) 410 (54) [$M^{+\cdot}$], 246 (59) [M − $O_2CC_6H_5N(CH_3)_2$], 164 (30) [$O_2CC_6H_5N(CH_3)_2$], 148 (100) [$O{=}CC_6H_5N(CH_3)_2$].

Anal. Calcd for $C_{24}H_{30}N_2O_4$ (410.51): C, 70.22; H, 7.37; N, 6.82. Found: C, 69.82; H, 7.27; N, 6.77.

(1*R*,2*R*)-*trans*-Cyclohexanediol bis[2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one-9-carboxylate] (1): mp 301–302 °C; IR (film) ν 3330, 2924, 2855, 1696, 1661, 1445, 1257, 1211, 1143, 1114 cm^{-1}; ^1H NMR δ 1.20–1.45 (m, 4 H), 1.50–2.40 (m, 4 H), 1.65 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 4.98 (br m, 2 H), 5.91 (s, 2 H, =CH), 9.20 (s, 2 H, NH), 11.29 (br s, 2 H, NH); ^{13}C NMR δ: 8.65 (q), 9.26 (q), 9.91 (q), 10.55 (q), 23.85 (t), 30.98 (t), 75.19 (d), 97.72 (d), 121.06 (s), 123.45 (s), 127.99 (s), 128.11 (s), 128.41 (s), 135.45 (s), 141.66 (s), 163.78 (s), 173.66 (s); UV–vis and CD data in Table I.

Anal. Calcd for $C_{34}H_{40}N_4O_6$ (600.71): C, 67.98; H, 6.71; N, 9.33. Found: C, 67.70; H, 6.59; N, 8.99.

(1*R*,2*R*)-*trans*-Cyclohexanediol mono[2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one-9-carboxylate] (2): mp 270–270.5 °C; IR (film) ν 3318, 2937, 2861, 1694, 1681, 1668, 1451, 1407, 1349, 1265, 1220, 1160, 1072, 1005, 947 cm^{-1}; ^1H NMR δ 1.15–1.45 (m, 4 H), 1.6–1.75 (m, 2 H), 1.95–2.50 (m, 2 H), 1.84 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 3.70 (m, 1 H), 4.57 (s, 1 H, OH), 4.65 (m, 1 H), 5.84 (s, 1 H, =CH), 9.25 (s, 1 H, NH), 9.81 (s, 1 H, NH); ^{13}C NMR δ 8.52 (q), 9.17 (q), 9.81 (q), 10.36 (q), 24.04 (t), 24.15 (t), 30.57 (t), 33.36 (t), 72.44 (d), 78.52 (d), 97.78 (d), 121.43 (s), 123.49 (s), 127.34 (s), 127.79 (s), 128.21 (s), 134.56 (s), 141.89 (s), 161.08 (s), 174.07 (s); UV–vis and CD data in Table I.

Anal. Calcd for $C_{20}H_{26}N_2O_4$ (358.44): C, 67.02; H, 7.31; N, 7.82. Found: C, 66.72; H, 7.27; N, 8.03.

(1*R*,2*R*)-*trans*-Cyclohexanediol mono[*p*-(dimethylamino)benzoate] (4): mp 180–181.5 °C; IR (Nujol) ν 3515, 2924, 1733, 1674, 1609 cm^{-1}; ^1H NMR δ 1.30–1.45 (m, 4 H), 1.70–1.80 (m, 2 H), 2.00–2.20 (m, 2 H), 2.62 (s, 1 H, OH), 3.67 (m, 1 H, O–CH), 4.74 (m, 1 H), 6.61 (d, 2 H, J = 8.7 Hz), 7.88 (d, 2 H, J = 8.7 Hz); ^{13}C NMR δ 23.72 (t), 23.94 (t), 30.14 (t), 32.97 (t), 32.97 (t), 39.97 (q), 73.01 (d), 77.93 (d), 110.75 (d), 117.16 (d), 131.37 (s), 153.52 (s), 167.24 (s); UV–vis and CD data in Table I.

Anal. Calcd for $C_{15}H_{21}NO_3$ (263.34): C, 68.41; H, 8.04; N, 5.32. Found: C, 68.31; H, 7.98; N, 4.97.

2-Carbethoxy-3,4-dimethyl-1*H*-pyrrole (5); mp 90–91 °C (lit.[18] mp 94–95 °C), was prepared in 24% yield according to the method of Kleinspehn:[18] FT-IR (Nujol) ν 3322 (NH), 2924, 1731, 1718, 1693, 1671, 1661, 1462 cm^{-1}; ^1H NMR δ 1.33 (t, 3 H, J = 7.2 Hz), 1.99 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 4.28 (q, CH_2, J = 6.9 Hz), 6.63 (d, 1 H, J = 2.7 Hz), 8.69 (s, 1 H, NH); ^{13}C NMR δ 9.84 (q), 10.19 (q), 14.51 (q), 59.73 (t), 119.30 (s), 120.02 (s), 120.51 (s), 126.54 (d), 161.72 (s); UV (methanol) ϵ^{max}_{272} = 14 420.

2-Carboxy-3,4-dimethyl-1*H*-pyrrole (6). 2-Carbethoxy-3,4-dimethyl-1*H*-pyrrole (3.6 g, 0.02 mol) was suspended in approximately 2 mL of 95% ethanol and 30% potassium hydroxide (400 mL) was added. The suspended solution was heated to reflux for 2 h, and then the resulting brown solution was cooled to room temperature and placed in an ice–water bath. Concentrated HCl was added dropwise to the cold brown solution to give a white

(25) (a) Reference 24, p 165. (b) Vogel, A. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Longman Scientific and Technical: England, 1978; p 291.

(26) **Note added in proof:** A similar instance of unexpected CD sign reversal of the exciton couplet ($\Delta\epsilon^{max}_{547}$ −241, $\Delta\epsilon^{max}_{476}$ +221) has been reported recently for the bis(cyanine) dye chromophore derived from (1*S*,2*S*)-(+)-*trans*-cyclohexanediamine and 7-piperidinohepta-2,4,6-trienal (merocyanine), where for steric reasons the long axis polarized transition dipoles of the chromophores are rotated away from the cyclohexyl C–N directionality, for which a positive exciton chirality is predicted. Gargiulio, D.; Derguini, F.; Berova, N.; Nakanishi, K.; Harada, N. *J. Am. Chem. Soc.* In press.

precipitate. The fine white solid was collected by filtration and washed with water. The solid was dried to give 2.99 g of product (quantitative yield). It did not melt but decomposed above 205 °C. **6**: IR (KBr) ν 3359, 3200–2350, 1648 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.93 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 6.71 (d, 1 H, J = 3.0 Hz, =CH), 9.30 (br s, 1 H, NH), 10.23 (s, 1 H, COOH); ^{13}C NMR (acetone-d_6) δ 9.04 (q), 9.43 (q), 118.90 (s), 119.44 (s), 120.65 (s), 125.89 (d), 161.85 (s); UV (methanol) ϵ_{270}^{max} = 12 870; mass spectrum m/z (rel intensity) 95 (64) [M - CO_2], 94 (100) [M - CO_2H], 67 (15).

3,4-Dimethyl-1*H*-pyrrole (7).[19,20] 2-Carboxy-3,4-dimethyl-1*H*-pyrrole (1.5 g, 0.01 mol) was added to a 15-mL round-bottom flask and heated on a Wood's metal bath. The acid was decarboxylated at a bath temperature between 180 and 195 °C. The pure decarboxylated product was obtained by using short path distillation apparatus. During the distillation, the compound solidified. Pure product (90 mg) was obtained in 88% yield. It had mp 30–31 °C and a benzene-like odor. **7**: ^1H NMR δ 2.03 (s, 6 H, 2 CH_3), 6.51 (d, 2 H, J = 2.4 Hz), 7.75 (s, 1 H, NH); ^{13}C NMR δ 9.93 (q), 115.51 (s), 118.16 (d); UV (methanol) ϵ_{214}^{max} = 4860; mass spectrum (rel intensity) m/z 95 (61) [$M^{+\cdot}$], 94 (100), 80 (19) [M - CH_3].

3,4-Dimethyl-3-pyrrolin-2-one (8).[21] 3,4-Dimethyl-1*H*-pyrrole (2.15 g, 0.023 mol) was dissolved in 6 mL of pyridine. Hydrogen peroxide (3 mL, 30%) was added slowly with magnetic stirring under argon. The temperature was kept below 35 °C. After stirring for 20 min, an additional 1.3-mL portion of hydrogen peroxide was added. The solution was heated to 85 °C for 20 min. The solvent was removed on a rotatory evaporator to give a light orange oil, which solidified on standing to afford 1.5 g (59% yield) of product: FTIR (Nujol) 3186 (NH), 2921, 1733 (lactam), 1684 cm^{-1}; ^1H NMR ($CDCl_3$) v 1.72 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 3.75 (s, 2 H), 7.55 (br s, 1 H), (DMSO-d_6) δ 1.61 (s, 3 H), 1.90 (s, 3 H), 3.70 (s, 2 H), 7.85 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 8.50 (q), 13.53 (q), 50.66 (t), 120.80 (s), 150.16 (s), 177.53 (s); mass spectrum m/z (rel intensity) 111 (100) [$M^{+\cdot}$], 96 (39) [M - CH_3].

2-Carbethoxy-3,4-dimethyl-5-formyl-1*H*-pyrrole (9) was prepared[22,23] in quantitative yield, using the Vilsmeier reaction on **5**. **9**: mp 100–103 °C; ^1H NMR δ 1.37 (t, 3 H, J = 7.2 Hz), 2.25 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 4.34 (q, 2 H, J = 7.2 Hz, OCH_2), 9.56 (br s, 1 H, NH), 9.77 (s, 1 H, CHO); ^{13}C NMR δ 8.41 (q), 9.55 (q), 14.23 (q), 60.77 (t), 124.43 (s), 126.88 (s), 129.92 (s), 129.98 (s), 160.90 (s), 179.12 (d); mass spectrum m/z (rel intensity) 195 (65) [$M^{+\cdot}$], 166 (30) [M - CHO], 121 (100) [M - $HCO_2C_2H_5$].

2-Carboxy-3,4-dimethyl-5-formyl-1*H*-pyrrole (10). 2-Carbethoxy-3,4-dimethyl-5-formyl-1*H*-pyrrole (2 g, 0.013 mmol) was added to a sodium hydroxide solution (200 mL, 25%) preheated to about 80 °C. After heating at reflux for 1 h, the pale brown solution was cooled to room temperature and carefully acidified with dilute HCl in an ice–salt bath. As the solution was acidifed, a white precipitate formed, which was filtered and washed with water. The white precipitate turned to light pink when it was filtered. After drying under vacuum 1.26 g of product (78.2% yield) was obtained, which decomposed at 188 °C. **10**: IR (KBr) ν 3299, 1690, 1656, 1560 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.12 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 9.40 (s, 1 H, NH), 9.70 (s, 1 H, CHO), 12.14 (br s, 1 H, COOH); ^{13}C NMR (DMSO-d_6) δ 9.10 (q), 9.35 (q), 124.98 (s), 125.45 (s), 126.47 (s), 130.10 (s), 162.17 (s), 181.54 (s); mass spectrum m/z (rel intensity) 123 (100) [M - CO_2], 94 (43) [M - CO_2 - CHO], 67 (22).

2,3,7,9-Tetramethyl-(10*H*)-dipyrrin-1-one-9-carboxylic Acid (11). To a 15-mL round-bottom flask were added a sodium hydroxide solution (20 mL, 4 N), 3,4-dimethyl-3-pyrrolin-2-one (**8**) (1.0 g, 9.01 mmol), 2-carboxy-3,4-dimethyl-5-formyl-1*H*-pyrrole (**10**) (1.0 g, 6.37 mmol), and methanol (12 mL). The mixture was heated for 1 h at reflux with magnetic stirring under argon. (A precipitate formed after 15 min into the reflux period.) The reaction mixture was cooled to room temperature and put in a cold room overnight to give more precipitate. The precipitate was filtered and washed with cold 4 N sodium hydroxide solution to give a light brown product. This sodium salt was dissolved in a small amount of water and carefully acidified with 10% HCl in an ice–salt bath. The resulting fine yellow precipitate was centrifuged and washed with water. After drying, 900 mg (54% yield) was obtained with mp 265–268 °C: IR (KBr) ν 3373, 3180, 2920, 1664 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 5.89 (s, 1 H, =CH), 10.43 (s, 1 H, NH), 10.93 (s, 1 H, NH), 12.32 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 8.81 (q), 9.59 (q), 10.01 (q), 10.78 (q), 96.61 (d), 121.97 (s), 123.05 (s), 126.35 (s), 126.76 (s), 127.87 (s), 134.68 (s), 142.30 (s), 162.70 (s), 173.12 (s).

The dipyrrinone acid was converted to its methyl ester for further analysis. Reaction with diazomethane afforded a yellow product, which was purified by preparative TLC (silica gel G, 500 μm, solvents; CH_2Cl_2/CH_3OH = 20/1, v/v) to give a pale yellow solid (45 mg, 85% yield) with mp 274–274.5 °C: IR (film) ν 3329, 1698, 1645, 1456, 1269 cm^{-1}; ^1H NMR δ 1.92 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 5.95 (s, 1 H, =CH), 9.01 (s, 1 H, NH), 9.30 (s, 1 H, NH); ^{13}C NMR δ 8.51 (q), 9.34 (q), 9.89 (q), 10.44 (q), 51.22 (q), 97.32 (d), 121.16 (s), 123.32 (s), 127.96 (s), 127.99 (s), 128.16 (s), 135.78 (s), 142.01 (s), 161.70 (s), 173.79 (s); UV-vis ϵ_{379}^{max} = 25 400 (CH_2Cl_2), ϵ_{381}^{max} = 29 650, ϵ_{400}^{max} = 25 450 (CH_3OH).

Anal. Calcd for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.72; H, 6.66; N, 10.22.

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Registry No. **1**, 135570-18-2; **2**, 135570-19-3; **3**, 135597-77-2; **4**, 135570-20-6; **5**, 938-75-0; **6**, 89776-55-6; **7**, 822-51-5; **8**, 4030-22-2; **9**, 4391-99-5; **10**, 135570-21-7; **11**, 92256-26-3; **11** (methyl ester), 92870-47-8; *p*-$Me_2NC_6H_4CO_2H$, 619-84-1; (1*R*,2*R*)-*trans*-cyclohexanediol, 1072-86-2.