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LONG-RANGE EXCITON COUPLING FROM DIPYRRINONE CHROMOPHORES

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Abstract. Dipyrrinone chromophores, attached by their acid termini to give (1*R*,2*R*)-cyclohexanediol dipropionate and diacetate esters (xanthobilirubinate and nor-xanthobilirubinate, respectively), interact through exciton coupling, as evidenced by intense bisignate circular dichroism Cotton effects for the pigment's long wavelength transition. The bis-xanthobilirubinate exhibits the expected negative exciton chirality ($\Delta\epsilon^{max}_{439}$ -16, $\Delta\epsilon^{max}_{382}$ +22, CH_2Cl_2) but the bis-norxanthobilirubinate exhibits positive exciton chirality ($\Delta\epsilon^{max}_{420}$ +38, $\Delta\epsilon^{max}_{367}$ -46, CH_2Cl_2).

INTRODUCTION

Dipyrrinones are the parent chromophoric units of (4*Z*,15*Z*)-bilirubin-IXα (Fig. 1A), the yellow cytotoxic pigment of jaundice that is produced in copious amounts in normal heme metabolism.[1,2] Like bilirubins, dipyrrinones are typically colored yellow to orange. They have a strongly allowed UV-visible absorption ($\epsilon \simeq$ 30,000) near 400 nm which originates from a π-π^* type electronic excitation with the electric dipole transition moment oriented along the long axis of the chromophore.[3-5] Although they may adopt dissymmetric conformations by rotation about ψ (Fig. 1B) and are thus potentially chiral molecules, there is only a small (<1 kcal/mole) energy difference between (i) the nearly *syn*-periplanar conformation ($\psi \simeq 4°$) seen in the crystal or in non-polar solvents (where dimers persist) and (ii) the *syn*-clinal conformation ($\psi \simeq$ 20-50°) found in highly dilute solutions or in polar solvents.[3,5a,6]

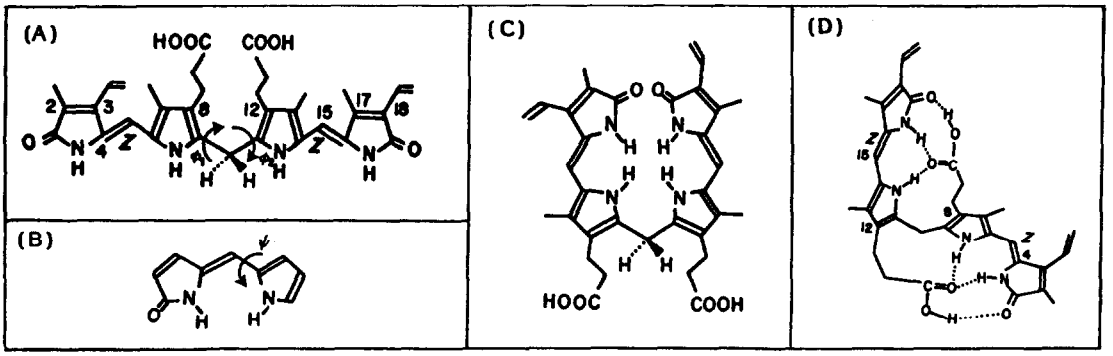


FIGURE 1. (A) Linear representation for bilirubin, whose two dipyrrinone chromophores are conjoined by the central -CH_2- group. (B) Dipyrrinone chromophore. Rotation about torsion angle ψ generates an array of conformational isomers. (C) Porphyrin-like representation for bilirubin. These conformations represented in (A) and (C) may be interconverted by rotation of each dipyrrinone by 180° about torsion angles ϕ_1 and ϕ_2. (D) Ridge-tile conformation of bilirubin stabilized by intramolecular hydrogen bonding. In (D) $\phi_1 \simeq \phi_2 \simeq 60°$, and the dihedral angle between the two (planar) dipyrrinones ($\psi = 0°$) is $\sim 100°$.

When in contact with chiral solvents or chiral complexation agents, dipyrrinones exhibit optical activity (detected by circular dichroism) associated with the long wavelength transition.[7,8] For example, a weak CD Cotton effect can be seen for kryptopyrromethenone in optically active mesophases[8] and for xanthobilirubic acid under special conditions, *e.g.*, bound to human serum albumin in pH 7.33 aqueous buffer ($\Delta\epsilon^{max}_{426}$ +12),[7a] complexed with quinine in CH_2Cl_2 ($\Delta\epsilon^{max}_{412}$ -5)[7b] or covalently linked as in the amide made with (*R*)-phenethylamine ($\Delta\epsilon^{max}_{413}$ -1.3 in $(CH_3)_2SO$).[9] However, more often only a far weaker or vanishingly small CD is observed, *e.g.*, for xanthobilirubic acid salts with optically active amines in sodium deoxycholate micelles (pH 7.7-8.0 buffer) or in the presence of β-cyclodextrin.[10] Furthermore, where dipyrrinone optical activity is detected, it is unclear how much is due to dissymmetric vicinal perturbation of a (planar) inherently symmetric chromophore or to an excess of a dissymmetric conformation (non-planar chromophore by rotation ψ, Fig. 1B) produced by dissymmetric vicinal action.

When two dipyrrinones come close to one another, the possibility for coupling of their locally excited states increases, as in exciton interaction. Nature provides an example for potential exciton coupling in the bile pigment, bilirubin, whose two dipyrrinone chromophores are attached to and may, in principle, rotate freely (propeller fashion) about the central -CH_2- group. Such rotations (ϕ_1, ϕ_2, Fig. 1) generate a large array of conformational isomers, ranging from the planar linear (Fig. 1A) to the planar porphyrin-like (Fig. 1C), with many different 3-dimensional conformations lying in between.[3,11,12] In one such conformation (Fig. 1D), with $\phi_1 \simeq \phi_2 \simeq 60°$ (relative to $\phi_1 = \phi_2 = 0°$ in the porphyrin-like conformation), the propionic acid groups are brought into sufficiently close contact with the opposing dipyrrinone C=O and N-H groups to engage in very

effective, energy-lowering, intramolecular hydrogen bonding.[11-13] The resulting markedly stabilized ridge-tile structure is probably an important factor in bilirubin binding and hepatic excretion since intramolecular hydrogen bonding changes the pigment from polar and hydrophilic to nonpolar and lipophilic.[14]

It is important to note that intramolecular hydrogen bonding stabilizes *two enantiomeric* ridge-tile conformers, which interconvert by breaking and reforming all six hydrogen bonds (Fig. 2).[15] Displacement of the conformational enantiomeric equilibrium toward the **P** or the **M** isomer through the action of chiral complexation agents or through intramolecular allosteric action generates bilirubin optical activity, as seen from variably intense bisignate CD Cotton effects, *e.g.*, $\Delta\epsilon^{max}_{469}$ +210, $\Delta\epsilon^{max}_{418}$ -143 L · mole^{-1} · cm^{-1} for bilirubin with (-)-ψ-ephedrine methyl ether in benzene,[16] $\Delta\epsilon^{max}_{463}$ +11, $\Delta\epsilon^{max}_{413}$ -7 L · mole^{-1} · cm^{-1} for bilirubin with *R*-(+)-methyl *p*-tolylsulfoxide in CH_2Cl_2,[17] $\Delta\epsilon^{max}_{463}$ -275, $\Delta\epsilon^{max}_{411}$ +161 L · mole^{-1} · cm^{-1} for the bilirubin-porcine serum albumin complex in pH 4.0 aqueous buffer,[18] and $\Delta\epsilon^{max}_{436}$ -250, $\Delta\epsilon^{max}_{391}$ +142 for (αS,$\alpha' S$)-dimethylmesobilirubin-XIIIα in $CHCl_3$.[19] The bisignate nature of the CD spectra has been ascribed to exciton behavior, with the theoretical maximum | $\Delta\epsilon$ | values approaching 300.[7]

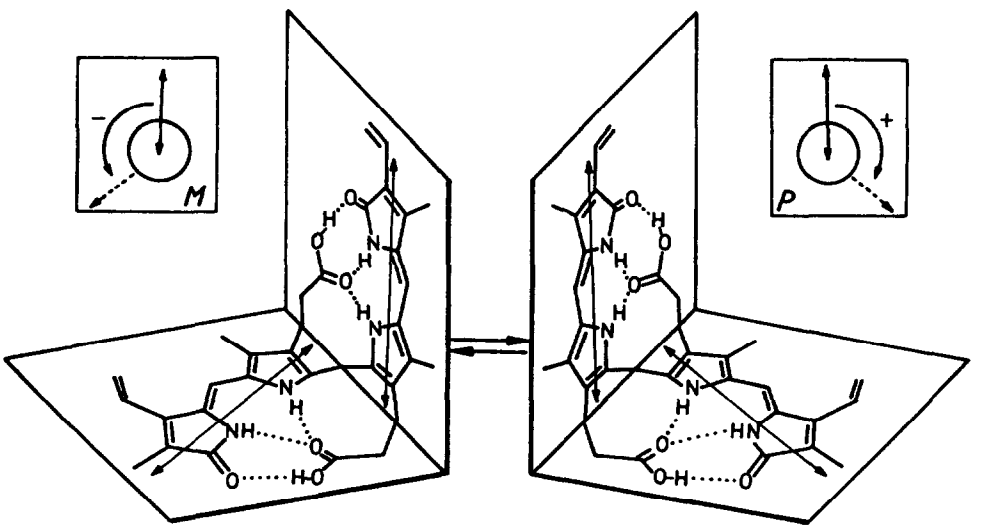
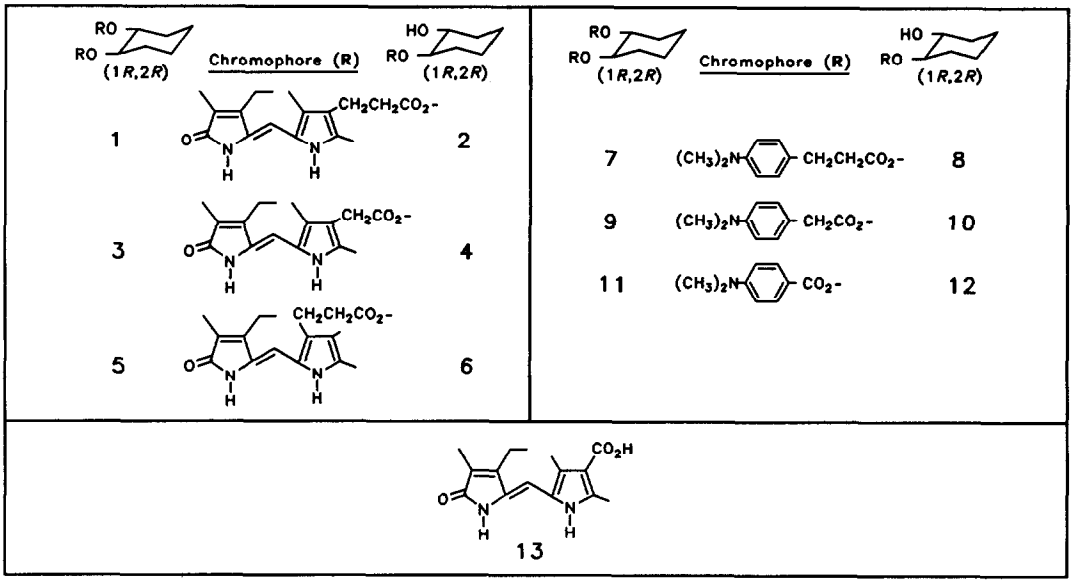


FIGURE 2. Interconverting enantiomeric conformers of intramolecularly hydrogen bonded bilirubin. The interplanar angle between the two planar dipyrrinone chromophores is defined as θ, and the chirality of their respective electric dipole transition moments (shown by double-headed arrows and passing lengthwise through the chromophores) is defined as **M** (minus chirality) or **P** (plus chirality).

As part of a program pointed toward understanding the bisignate CD spectra of bilirubins, we undertook a study of select optically active bis-dipyrrinones where exciton interaction might be expected. The results are important for they show that exciton interaction between dipyrrinones can occur over potentially large distances and give large $\Delta\epsilon$ magnitudes.

STRUCTURES

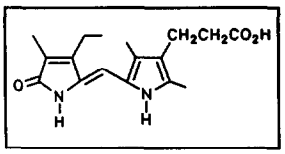
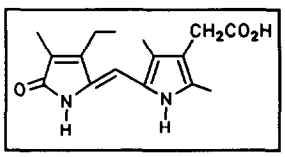
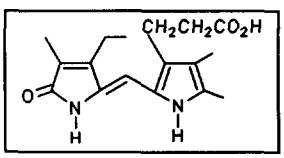
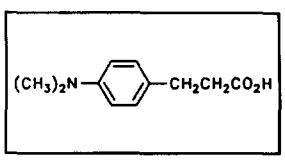
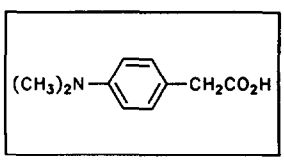
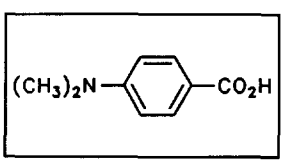


Results and Discussion

The optically active template, (1*R*,2*R*)-cyclohexanediol, was esterified with xanthobilirubic acid and its analogs to give the mono and diesters **1-6**. For purposes of comparison, mono and diesters **7-12**, derived from *p*-dimethylaminobenzoic acid and its homologs, were also prepared. The *p*-dimethylaminohydrocinnamate esters **7** and **8** were chosen as analogs of xanthobilirubinate esters **1** and **2** and ψ-xanthobilirubinate esters **5** and **6**, and *p*-dimethylaminophenylacetate esters **9** and **10** were chosen as analogs of nor-xanthobilirubinate esters **3** and **4**. We could not prepare cyclohexane diol esters with the bisnor-xanthobilirubic acid **13**,[20] apparently due to steric hindrance from the "ortho" methyl groups flanking the CO_2H. The esters (**11** and **12**) of *p*-dimethylaminobenzoic acid were readily formed.

The CD data for the esters of this work are summarized in Table 1. As expected, the bis-*p*-dimethylaminobenzoate (**11**) gives a strong bisignate CD with negative exciton chirality — as predicted by the exciton chirality rule;[21] whereas, the mono-ester (**12**) shows only a weak monosignate CD Cotton effect for the long wavelength transition. The magnitudes of the bisignate CD of **11** compares very favorably with those observed for the bis-*p*-dimethylaminobenzoate of diequatorial *trans-vic*-diol 5α-cholestan-3β,4α-diol ($\Delta\epsilon_{322}^{max}$ +91.3, $\Delta\epsilon_{297}^{max}$ -57.5 in ethanol).[21] Thus, *trans*-cyclohexanediol would appear to be an excellent template on which to attach dipyrrinone chromophores and look for exciton coupling. However, when the aromatic chromophore is removed by one or two -CH_2- groups from the cyclohexanediol (as in **9** and **7**), the CD intensity drops sharply by an

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

Acid Component	Compound	Solvent	$\Delta\epsilon_{max}$ (λ_1)	λ_2 at $\Delta\epsilon$=0	$\Delta\epsilon_{max}$ (λ_3)	ϵ_{max} (λ)
	1 (di)[b]	CH_2Cl_2	-16.0 (439)	404	+22.3 (382)	61,350 (389)
		$(CH_3)_2SO$	-12.6 (419)	397	+ 6.7 (382)	51,900 (408)
	2 (mono)	CH_2Cl_2	« 0.1 (400)	—	—	26,710 (400)
	3 (di)	CH_2Cl_2	+37.5 (420)	389	-45.8 (367)	42,700 (376)
		CH_3CN	+28.6 (414)	386	-33.0 (361)	40,500 (375)
		CH_3OH	+ 2.4 (395)	385	- 4.0 (362)	40,500 (390)
		$(CH_3)_2SO$	+ 2.2 (396)	384	- 3.6 (363)	39,200 (390)
	4 (mono)	CH_2Cl_2	« 0.1 (390)	—	—	29,920 (390)
	5 (di)	CH_2Cl_2	-36.3 (430)	400	+45.7 (375)	60,700 (383)
		CH_3OH	- 3.9 (432)	385	+ 7.8 (364)	58,600 (408)
		$(CH_3)_2SO$	+ 2.3 (422)	—	« 0.1 (360)	53,600 (409)
	6 (mono)	CH_2Cl_2	+ 0.5 (367)	—	—	27,000 (390)
	7 (di)	CH_2Cl_2	- 1.9 (262)	—	« 0.1	29,700 (259)
		CH_3CN	- 1.5 (262)	—	« 0.1	31,800 (257)
		CH_3OH	- 1.0 (256)	—	« 0.1	30,200 (256)
	8 (mono)	CH_3CN	« 0.1 (257)	—	—	15,500 (257)
	9 (di)	CH_2Cl_2	+ 3.1 (267)	—	« 0.1	29,690 (263)
		CH_3CN	+ 2.6 (259)	—	« 0.1	30,170 (260)
		CH_3OH	+ 2.0 (263)	—	« 0.1	28,340 (259)
	10 (mono)	CH_3CN	« 0.1 (260)	—	—	15,260 (259)
	11 (di)	CH_2Cl_2	-88.5 (318)	305	+41.5 (292)	53,610 (311)
		CH_3CN	-90.3 (317)	304	+43.5 (292)	52,500 (309)
		CH_3OH	-83.5 (320)	307	+44.3 (295)	52,870 (310)
		$(CH_3)_2SO$	-69.0 (322)	310	+34.1 (298)	51,700 (313)
	12 (mono)	CH_3CN	- 0.9 (311)	—	—	27,370 (308)

[a] Run on 1-2 x 10^{-5} *M* solutions at 20°C.

[b] Insoluble in CH_3CN and CH_3OH.

order of magnitude (for a 50% drop in UV ϵ^{max}), and the bisignate Cotton effects characteristic of exciton coupling can no longer be seen. Thus, the effectiveness of exciton coupling in these systems falls off sharply as the distance from the chiral templates increases modestly and the rotational or orientational degrees of freedom increase. One might think, therefore, that exciton coupling would also not be seen for the dipyrrinones of this study. However, this is not the case.

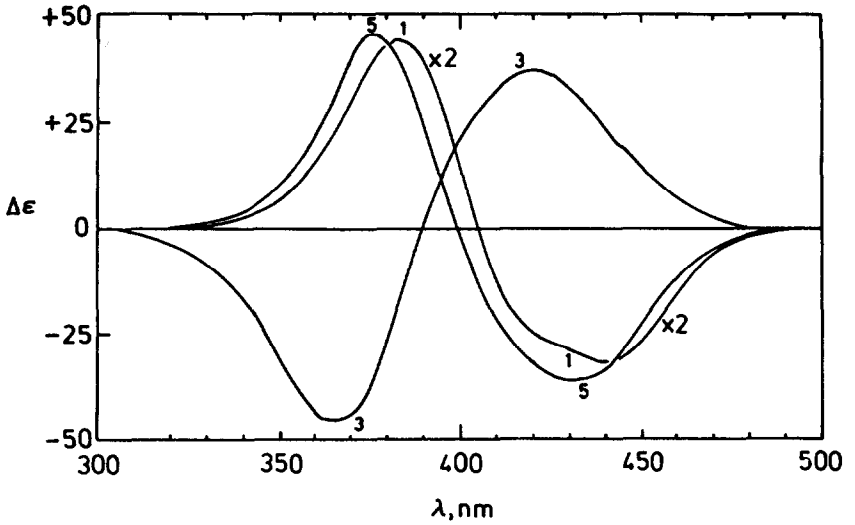


FIGURE 3. Circular dichroism spectra of 2.04 x 10^{-5} *M* **1** (scaled x 2), 6.09 x 10^{-6} *M* **3** and 9.92 x 10^{-6} *M* **5** in CH_2Cl_2 solvent at 21°C. The analog of **1** prepared from (1*S*,2*S*)-cyclohexanediol gave exactly the mirror image CD spectrum compared to that of **1**.

Surprisingly, strong bisignate CD is seen for **1**, **3** and **5** in CH_2Cl_2 (Fig. 3). Further evidence for exciton interaction in **1**, **3** and **5** may be found in their UV-vis spectra in CH_2Cl_2 (Fig. 4), where a short wavelength intense transition near 385 nm is followed by a much less intense shoulder near 410 nm. In contrast, mono-esters **2**, **4** and **6** have UV-vis spectra where the shape of the band is much more symmetric, with no shoulder on the long wavelength side. Structural information can be extracted from the shape and relative intensity of the UV-vis curves of the bis-dipyrrinones. The apparently large exciton splitting and skewing of excitation intensity toward the higher energy exciton transition is consistent with small (<30°) dihedral angles between the transition moments of the two dipyrrinones.[11,16,22]

In polar, hydrogen bonding solvents, CH_3OH and $(CH_3)_2SO$, the $\Delta\epsilon$ values decrease substantially (Table 1). The decreases seen would appear to reflect changes in the relative orientation of the dipyrrinone electric dipole transition moments caused by the additional steric requirements of these solvents, which are known to coordinate with dipyrrinones. A marked bathochromic shift and broadening of the UV-vis spectra (Fig. 4) are seen for **1**, **3** and **5** in $(CH_3)_2SO$ solvent (*cf.* CH_2Cl_2), an indication of possible solvent perturbation on the geometry of the exciton. At present a clearer definition of the decreased $\Delta\epsilon$ values is unavailable; however, the exciton origin of the CD of the bis-dipyrrinones seems clear since only weak or vanishingly small monosignate Cotton effects are seen with the mono-esters for the dipyrrinone long wavelength transition.

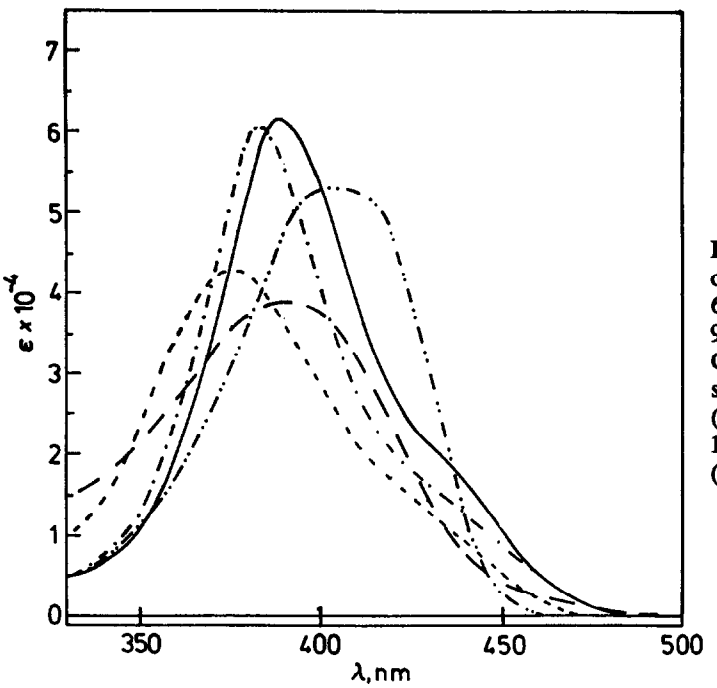


FIGURE 4. UV-visible spectra of 2.04 x 10^{-5} *M* **1** (———), 6.09 x 10^{-6} *M* **3** (- - - -) and 9.92 x 10^{-6} *M* **5** (— · — ·) in CH_2Cl_2 at 21°C, and at the same concentrations in $(CH_3)_2SO$: **3** (— — — —) and **1** and **5** essentially the same (— ·· — ··).

More surprising is the fact that the bisignate CD Cotton effect signs are inverted for **3** (in all solvents) relative to **1**, **5** and **11**. Thus, by shortening the carboxylic acid chain length by one -CH_2- unit in **1**, the expected negative exciton chirality is inverted to positive for the diesters of (1*R*,2*R*)-cyclohexanediol. This unexpected phenomenon can only occur from a change of orientation of the relevant electric dipole transition moments from negative to positive helicity. Space-filled (CPK) molecular models indicate that the steric influence of the "ortho" methyl groups in **3** orients the dipyrrinones so that the long axis of the chromophores (hence the transition moments oriented along these axes) form a positive helicity, effectively inverting[23] the negative helicity orientation adopted by the dipyrrinones in **1** and **5**, and the *p*-dimethylaminobenzoates of **11**. It is relevant to note that the preferred relative orientation of the relevant transition moments gives a negative chirality bisignate CD in both the bis-*p*-dimethylaminobenzoate and the bis-xanthobilirubinate esters of (2*R*,3*R*)-butanediol.

CONCLUDING COMMENTS

Dipyrrinones exhibit a strong tendency to participate in exciton coupling through the interaction of their long wavelength electric dipole transition moments oriented along the long axis of the molecule. The intense bisignate CD Cotton effects seen in CH_2Cl_2 solvent for the bis-dipyrrinones of this work do not find a ready counterpart in the homologated bis-*p*-dimethylaminobenzoates. Polar, hydrogen-bonding solvents strongly

perturb the CD of the bis-dipyrrinones, typically inducing markedly reduced $\Delta\epsilon$ magnitudes. Although the xanthobilirubinate diester of (1*R*,2*R*)-cyclohexanediol, with the dipyrrinone chromophores attached to ω-carbon of the propionic acids, shows a strong bisignate CD with the expected *negative* chirality, the corresponding nor-xanthobilirubinate, with the same chromophore attached to the ω-carbon of the acetic acid chains shows an even stronger bisignate CD with a positive chirality. This behavior serves as a caution in the application of exciton chirality rule to the determination of absolute configuration: the relative orientation of the relevant electric dipole transition moments must be known with certainty. The results of this study indicate that exciton interaction can occur over what might be viewed as large distances, and they provide useful analogs for considerations of exciton coupling in bilirubin conformational isomers.

EXPERIMENTAL

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 on a GE QE-300 300 MHz spectrometer in $CDCl_3$ solvent unless otherwise noted. HPLC analyses were carried out on a Perkin-Elmer high pressure liquid chromatograph with a LC-95 UV/vis spectrophotometer detector (set at 410 nm) equipped with a Beckman-Altex ultrasphere-IP 5 mm C-18 ODS column (25 x 0.46 cm) and Beckman ODS precolumn (4.5 x 0.46 cm). The flow rate was 1.0 mL/minute. 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-Hoover Uni-Melt capillary apparatus or Mel-Temp capillary apparatus and are uncorrected. Spectral grade solvents for UV-vis and CD were purchased from Aldrich, Eastman, MCB, and Fisher. Deuterated chloroform, deuterated methylsulfoxide, deuterated benzene, *p*-dimethylaminobenzoic acid, *p*-(dimethylamino)-phenethyl alcohol, diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,1′-carbonyldiimidazole were from Aldrich. *p*-(Dimethylamino)phenylacetic acid was from Polysciences, Inc. Xanthobilirubic acid, ψ-xanthobilirubic acid and nor-xanthobilirubic acid were prepared as described earlier.[24] Dimethylsulfoxide (DMSO) from Eastman was dried over 4Å molecular sieves. (1*R*,2*R*)-*trans*-Cyclohexanediol with >99% purity and $[\alpha]_D^{20}$ = -39 ± 1° (c = 1.6, H_2O) and (1*S*,2*S*)-*trans*-cyclohexanediol with >99% purity and $[a]_D^{20}$ = +39 ± 1° (c = 1.6, H_2O) were from Fluka. Analytical thin layer chromatography (TLC) was carried out on J. T. Baker silica gel IB-F plates (125 μ layer) or Analtech silica gel G plates (250 μ layer, 5 x 20 cm). Preparative TLC was performed on Analtech silica gel G plates (500 μ, 20 x 20 cm).

General Procedure. Conversions to the esters[25] 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 dimethylsulfoxide (DMSO) and stirred magnetically for 20-30 min at 40°C. Then (1*R*,2*R*)-cyclohexanediol (0.5 mmol for synthesis of the mono-ester; 0.25 mmol for the di) was added, along with 0.5 mmol of diazabicyclo[5.4.0]undec-7-ene (DBU) and a few 4Å molecular sieves, and the reaction mixture was blanketed with nitrogen and stirred for 16-20 hours (for di-derivative) or 10-15 h (for mono) while maintaining

the reaction temperature at 40-50° (**7-12**), or 80-100° (for **1-6**). 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 by the addition of 3 mL of water. At this point a precipitate or gum (**7-10**) came out of solution. The precipitate was filtered and washed well with water and dissolved in 15 mL of dichloromethane. The gum was extracted into 15 mL of dichloromethane, which was then washed several times with 15 mL aliquots of water. In either case, 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% aq. sodium bicarbonate (8 mL) and sat. aq. sodium chloride (8 mL). After drying the solution over anhydrous sodium sulfate, the dichloromethane was removed on a roto-vap. The residue was chromatographed by preparative TLC (Analtech 20 x 20 cm plates coated with 500 μ of silica gel G). The plates were irrigated with 20:1 CH_2Cl_2:CH_3OH (vol/vol) for **1**, **3** and **5**, 10:1 CH_2Cl_2:CH_3OH (vol/vol) for **2**, **4** and **6**, or 9:1 benzene:ethyl acetate (vol/vol) for **7-12** to afford pure products with their characteristic spectral and physical properties delineated below. A specific procedure (for **11**) follows.

(1*R*,2*R*)-*trans*-Cyclohexanediol bis-4-dimethylaminobenzoate (11): 4-Dimethylaminobenzoic 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 4Å molecular sieves and DBU (0.092 mL, 0.605 mmol), and the mixture was kept at 40°C for 6 hours (very little further reaction was achieved after an additional 11 hours 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), washed with dilute acetic acid (8 mL), water (10 mL), 5% aq. $NaHCO_3$ (8 mL) and saturated aq. 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. It had mp 153.5-155°C; IR (nujol) ν: 1704, 1686 cm^{-1}; ^{1}H-NMR δ: 1.40-1.65 (m, 4H), 1.70-1.85 (m, 2H), 2.15-2.25 (m, 2H), 2.95 (s, 12H), 5.05-5.23 (m, 2H), 6.54 (d, 4H, J=9.0 Hz), 7.83 (d, 4H, J=9.0 Hz) ppm; ^{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) ppm; UV-vis and CD data in Table 1; mass spectra *m/z* (rel. intens.): 410 (54%) [$M^{\bullet+}$], 246 (59%) [M - $O_2C_6H_5N(CH_3)_2$], 164 (30%) [$O_2CC_6H_5N(CH_3)_2$], 148 (100%) [$O{=}CC_6H_5N(CH_3)_2$] amu.

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-3-ethyl-2,7,9-trimethyl-(10*H*)-dipyrrin-1-one 8-propionate (1): The diester decomposes without melting at 270°C and had IR (film): 3350, 2930, 1735, 1672, 1633, 1462, 1374, 1268, 1171, 1058 cm^{-1}; ^{1}H-NMR δ: 1.10 (t, 6H, J=7.5 Hz, CH_2CH_3), 1.22-1.45 (m, 4H), 1.75 (s, 6H, CH_3), 2.02 (s, 6H, CH_3), 2.28 (s, 6H, CH_3), 2.20-2.55 (m, 16 H), 4.85 (m, 2H, O-CH), 5.84 (s, 2H, =CH), 10.24 (s, 2H, NH), 11.20 (s, 2H, NH) ppm; ^{13}C-NMR δ: 8.40 (q), 9.53 (q), 11.51 (q), 15.12 (q), 17.88 (t), 19.38 (t), 23.84 (t), 30.63 (t), 35.55 (t), 73.68 (d), 100.48 (d), 119.02 (s), 122.03 (s), 122.28 (s), 124.11 (s), 126.61 (s), 131.49 (s), 147.16 (s), 172.80 (s), 173.25 (s) ppm; UV-vis and CD data in Table 1.

Anal. Calcd for $C_{40}H_{52}N_4O_6$ (684.87): C, 70.15; H, 7.65; N, 8.18.
Found: C, 70.16; H, 7.41; N, 7.93.

(1*R*,2*R*)-*trans*-Cyclohexanediol mono 3-ethyl-2,7,9-trimethyl-(10*H*)-dipyrrin-1-one 8-propionate (2): The mono ester decomposes without melting at 210°C and had IR (film) ν: 3340 (NH), 3500-3200 (OH), 2971, 2935, 2860, 1736, 1667, 1635, 1451, 1369, 1271, 1244, 1201, 1169, 1060 cm^{-1}; ^{1}H-NMR δ: 1.15 (t, 3H, J=7.5 Hz, CH_2CH_3), 1.20-1.75 (m, 4H), 1.91 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.40-2.58 (m, 4H), 2.73 (t, 2H, J=8.2 Hz, CH_2CO), 3.50 (m, 1H, HC-OH), 4.55 (m, 1H, HC-O-), 4.81 (br s, 1H, OH), 6.09 (s, 1H, =CH), 10.19 (s, 1H, NH), 11.08 (s, 1H, NH) ppm; ^{13}C-NMR δ: 8.51 (q), 9.67 (q), 11.63 (q), 15.03 (q), 17.95 (t), 19.95 (t), 23.76 (t), 23.90 (t), 29.94 (t), 32.91 (t), 35.47 (t), 72.74 (d), 78.30 (d), 100.90 (d), 118.97 (s), 122.41 (s), 122.62 (s), 124.39 (s), 127.40 (s), 131.50 (s), 148.31 (s), 173.62 (s), 174.08 (s) ppm; UV-vis data in Table 1.

Anal. Calcd for $C_{23}H_{32}N_2O_4$ (400.52): C, 68.97; H, 8.05; N, 6.99.
Found: C, 68.87; H, 7.84; N, 7.04.

(1*R*,2*R*)-*trans*-Cyclohexanediol bis-3-ethyl-2,7,9-trimethyl-(10*H*)-dipyrrin-1-one 8-acetate (3): The diester had mp 210-220°C (first softened then melted); IR (film) ν: 3347, 2926, 1736, 1677, 1635, 1570, 1436, 1271 cm^{-1}; ^{1}H-NMR δ: 1.13 (t, 6H, J=7.5 Hz, CH_3), 1.20-1.40 (m, 4H), 1.60-1.80 (m, 2H), 1.90-2.20 (m, 2H), 1.77 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.43 (q, 4H, J=7.5 Hz), 3.19 (s, 4H, O-CH_2), 4.77 (m, 2H), 6.00 (s, 2H, =CH), 10.37 (s, 2H, NH), 11.23 (s, 2H, NH) ppm; ^{13}C-NMR δ: 8.50 (q), 9.74 (q), 10.94 (q), 15.01 (q), 17.85 (t), 23.76 (t), 30.23 (t), 30.70(t), 74.33 (d), 100.68 (d), 112.94 (s), 122.30 (s), 122.42 (s), 124.97 (s), 127.27 (s), 132.86 (s), 147.60 (s), 171.50 (s), 173.60 (s) ppm; UV-vis and CD data in Table 1.

Anal. Calcd. for $C_{38}H_{48}N_4O_6$ (656.83): C, 69.49; H, 7.37; N, 8.53.
Found: C, 69.18; H, 7.84; N, 8.26.

(1*R*,2*R*)-*trans*-Cyclohexanediol mono 3-ethyl-2,7,9-trimethyl-(10*H*)-dipyrrin-1-one 8-acetate (4): The mono ester had mp 218-219°C; IR (film) ν: 3355, 2965, 2932, 2864, 1733, 1675, 1634, 1456, 1270, 1162 cm^{-1}; ^{1}H-NMR δ: 1.17 (t, 3H, J=7.5 Hz), 1.20-1.40 (m, 4H), 1.60-1.75 (m, 2H), 1.95-2.10 (m, 2H), 1.94 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.55 (q, 2H, J=7.5 Hz), 3.43 (s, 2H, CH_2), 3.54 (m, 1H, -CH-O-), 4.53 (m, 1H, -CH-O-), 6.12 (s, 1H, =CH), 10.42 (s, 1H, NH), 11.22 (s, 1H, NH) ppm; ^{13}C-NMR δ: 8.55 (q), 9.77 (q), 11.70 (q), 15.03 (q), 17.96 (t), 23.76 (t), 23.88 (t), 29.94 (t), 30.88 (t), 32.87 (t), 72.94 (d), 78.56 (d), 101.07 (d), 113.51 (s), 122.58 (s), 122.69 (s), 124.85 (s), 127.46 (s), 132.44 (s), 148.42 (s), 172.36 (s), 174.15 (s) ppm; UV-vis and CD data in Table 1.

Anal. Calcd. for $C_{22}H_{30}N_2O_4$ (395.51): C, 66.81; H, 7.64; N, 7.08.
Found: C, 67.12; H, 7.66; N, 7.28.

(1*R*,2*R*)-trans-Cyclohexanediol bis-3-ethyl-2,8,9-trimethyl-(10*H*)-dipyrrin-1-one-7-propionate (5): The diester had mp 225-230°C; IR (film) ν: 3350 (NH), 2959, 2932, 2860, 1741, 1690, 1641, 1586, 1450, 1373, 1276, 1172, 1058 cm^{-1}; ^{1}H-NMR δ: 1.09 (t, 6H, J=7.5 Hz), 1.20-1.45, 1.70-1.95, 2.0-2.70 (m), 1.85 (s, 6H, CH_3), 1.89 (s, 6H, CH_3), 2.11 (s, 6H, CH_3), 4.86 (m, 2H), 5.94 (s, 2H), 10.17 (s, 2H, NH), 11.23 (s, 2H, NH) ppm; ^{13}C-NMR δ: 8.62 (q), 8.80 (q), 11.09 (q), 15.11 (q), 17.66 (t), 19.87 (t), 23.89 (t), 30.66 (t), 36.17 (t), 73.76 (d), 100.41 (d), 114.73 (s), 121.84 (s), 121.91 (s), 127.12 (s), 127.38 (s), 130.94 (s), 147.86 (s),

172.49 (s), 173.53 (s) ppm; UV-vis and CD data in Table 1.

Anal. Calcd. for $C_{40}H_{52}N_4O_6$ (684.87): C, 70.15; H, 7.65; N, 8.18.
Found: C, 69.81; H, 7.56; N, 7.93.

(1*R*,2*R*)-*trans*-Cyclohexanediol bis-*p*-dimethylaminohydrocinnamate (7): The oily diester had IR (film) ν: 2939, 1732, 1665, 1520 cm^{-1}; ^{1}H-NMR δ: 1.20-1.45 (m, 4H), 1.57-1.80 (m, 2H), 1.90-2.10 (m, 2H), 2.50 (t, 4H, J=8.0 Hz), 2.80 (t, 4H, J=8.0 Hz), 2.88 (s, 12H, $N(CH_3)_2$), 4.81 (m, 2H), 6.66 (d, 4H, J=8.1 Hz), 7.04 (d, 4H, J=8.1 Hz) ppm; UV-vis and CD data in Table 1; mass spectra *m/z* (rel. intens.): 438 (19%) [$M^{+\bullet}$], 134 (100%) [$CH_2C_6H_5N(CH_3)_2$], 118 (11%) amu.

Anal. Calcd. for $C_{28}H_{38}N_2O_4$ (466.62): C, 72.07; H, 8.21; N, 6.00.
Found: C, 72.30; H, 8.45; N, 5.96.

(1*R*,2*R*)-*trans*-Cyclohexanediol mono *p*-dimethylaminohydrocinnamate (8): The oily monoester had IR (film) ν: 3442, 2938, 1732, 1616, 1523, 1450, 1347 cm^{-1}; ^{1}H-NMR δ: 1.15-1.38 (m, 4H), 1.57-1.77 (m, 2H), 1.90-2.05 (m, 2H), 2.19 (s, 1H, OH), 2.61 (t, 2H, J=7.8 Hz, CH_2), 2.83 (t, 2H, J=7.8 Hz, CH_2CO), 2.89 (s, 6H, $N(CH_3)_2$), 3.47 (m, 1H0), 4.54 (m, 1H, -HC-O-), 6.67 (d, 2H, J=8.7 Hz), 7.06 (d, 2H, J=8.7 Hz) ppm; ^{13}C-NMR δ: 23.75 (t), 23.88 (t), 29.94 (t), 30.15 (t), 32.90 (t), 36.51 (t), 40.78 (q), 72.56 (d), 78.11 (d), 113.05 (d), 128.47 (d), 128.81 (s), 149.43 (s), 173.29 (s) ppm; UV-vis data in Table 1; mass spectra *m/z* (rel. intens.): 291 (19%) [$M^{+\bullet}$], 134 (100%) [$CH_2C_6H_5N(CH_3)_2$] amu.

Anal. Calcd. for $C_{17}H_{25}NO_3$ (291.39): C, 70.07; H, 8.65; N, 4.81.
Found: C, 70.29; H, 8.65; N, 4.78.

(1*R*,2*R*)-*trans*-Cyclohexanediol bis *p*-dimethylaminophenylacetate (9): The diester was a sticky oil and had IR (film) ν: 3417 ($N(CH_3)_2$), 2988, 2866, 1732 (C=H), 1615, 1551, 1446 cm^{-1}; ^{1}H-NMR δ: 1.20-1.45 (m, 4H), 1.55-1.75 (m, 2H), 1.90-2.05 (m, 2H), 2.88 (s, 12 H, $N(CH_3)_2$), 3.31 (s, 4H, $OCCH_2$), 4.78 (m, 2H, -HC-O-), 6.65 (d, 4H, J=8.7 Hz), 7.07 (d, 4H, J=8.7 Hz) ppm; ^{13}C-NMR δ: 27.30 (t), 30.00 (t), 40.46 (t), 40.59 (q), 73.64 (d), 112.82 (d), 122.11 (d), 129.75 (s), 149.77 (s), [171.35, 171.45] (s) ppm; UV-vis and CD data in Table 1; mass spectra *m/z* (rel. intens.): 438 (15%) [$M^{+\bullet}$], 161 (85%) [$OCCH_2C_6H_5N(CH_3)_2$], 134 (100%) [$CH_2C_6H_5N(CH_3)_2$], 118 (11%) amu.

Anal. Calcd. for $C_{26}H_{34}N_2O_4$ (438.57): C, 71.21; H, 7.81; N, 6.39.
Found: C, 71.18; H, 7.86; N, 6.34.

(1*R*,2*R*)-*trans*-Cyclohexanediol mono *p*-dimethylaminophenylacetate (10): The mono-ester was a sticky oil and had IR (film) ν: 3441 (OH), 2938, 2862, 1732 (C=O)H, 1615, 1520, 1454 cm^{-1}; ^{1}H-NMR δ: 1.10-1.37 (m, 4H), 1.55-1.75 (m, 2H), 1.93-2.13 (m, 3H), 2.89 (s, 6H, $N(CH_3)_2$), 3.51 (s, 3H, OH, $OCCH_2$), 4.51 (m, 1H, -HC-O-), 6.66 (d, 2H, J=8.5 Hz), 7.12 (d, 2H, J=8.5 Hz) ppm; ^{13}C-NMR δ: 23.70 (t), 23.82 (t), 29.84 (t), 32.77 (t), 40.78 (q), 72.69 (d), 78.46 (d), 112.84 (d), 122.01 (d), 129.63 (s), 149.82 (s), 172.34 (s) ppm; UV-vis data in Table 1; mass spectra *m/z* (rel. intens.): 277 (10%) [$M^{+\bullet}$], 134 (100%) [$CH_2C_6H_5N(CH_3)_2$], 118 (11%), 77.05 (2%) [C_6H_5] amu.

Anal. Calcd. for $C_{16}H_{23}NO_3 \cdot 1/4\ H_2O$ (281.82): C, 68.18; H, 8.22; N, 4.97.
Calcd. for $C_{16}H_{23}NO_3 \cdot 1/8\ H_2O$ (279.62): C, 68.72; H, 8.38; N, 5.01.
Found: C, 68.72; H, 7.99; N, 5.40.

(1*R*,2*R*)-*trans*-Cyclohexanediol mono *p*-dimethylaminobenzoate (12): The mono ester had mp 180-181.5°C; IR (nujol) ν: 3515, 2924, 1733, 1674, 1609 cm^{-1}; ^{1}H-NMR δ: 1.30-1.45 (m, 4H), 1.70-1.80 (m, 2H), 2.00-2.20 (m, 2H), 2.62 (s, 1H, OH), 3.67 (m, 1H, O-CH), 4.74 (m, 1H), 6.61 (d, 2H, J=8.7 Hz), 7.88 (d, 2H, J=8.7 Hz) ppm; ^{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) ppm; UV-vis and CD data in Table 1.

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.

***p*-Dimethylaminohydrocinnamic acid.** This acid was prepared in four steps from commercially available (Polysciences) *p*-dimethylaminophenethyl alcohol as indicated in the following.

p-Dimethylaminophenethyl tosylate: *p*-Dimethylaminophenethyl alcohol (3.3 g, 0.02 mol) and pyridine (7.33 g, 0.09 mol) were added to a 50 mL three-necked round-bottom flask equipped with a thermometer and an efficient mechanical stirrer. The solution was cooled to -5°C by means of an ice-salt bath and then *p*-toluenesulfonyl chloride (4.2 g 0.022 mol) was added while maintaining the temperature below 0°C. Stirring was continued for 1 h at 0-2°C, cooling with an ice-water bath (while a precipitate formed). The reaction mixture was then mixed thoroughly with 60 g of ice and neutralized carefully with 10% aq. HCl. The precipitate was filtered and washed with ice-cold water (2 x 10 mL). The light yellowish-white product, which was still moist, was extracted into dichloromethane (50 mL) and washed with water (5 mL). After drying with sodium sulfate (anhydrous), the solvent was removed by rotary evaporation (temp < 20°C) to give an off-white product (4.55 g, 71.3 %) with mp 73-75°C. It had IR (nujol) ν: 1377 [S(=O)$_2$, asymmetric stretching], 1170 [S(=O)$_2$, symmetric stretching], 967, 904, 812, 774 (S-O-C stretching) cm^{-1}; ^{1}H-NMR δ: 2.41 (s, 3H, CH_3), 2.84 (t, 2H, J=7.5 Hz, CH_2), 2.89 (s, 6H, N(CH_3)$_2$), 4.12 (t, 2H, J=7.5 Hz, CH_2O-), 6.61 (d, 2H, J=8.7 Hz), 6.96 (d, 2H, J=8.7 Hz), 7.26 (d, 2H, J=7.8 Hz), 7.69 (d, 2H, J=7.8 Hz) ppm; ^{13}C-NMR δ: 21.54, 34.45, 40.63, 71.13, 112.88, 123.86, 127.82, 129.52, 129.69, 133.42, 144.41, 149.70 ppm.

p-Dimethylaminophenethylnitrile: To a 25 mL three-neck round bottom flask were added sodium cyanide (890 mg, 0.018 mol) and dimethylsulfoxide (5 mL). The temperature was increased to 70°C to dissolve the sodium cyanide and then the *p*-dimethylamino phenethyl tosylate (4.5 g, 0.014 mol) from above (dissolved in DMSO, 10 mL) was added with stirring. The reaction temperature was increased to 93°C and the reaction mixture stirred for 1.5 h to give a homogenous brown solution. After adding additional sodium cyanide (500 mg, 0.01 mol), the reaction temperature was increased to 100°C and the solution was stirred for 1 h. The brown solution was cooled to room temperature; then water (100 mL) was added to give a white precipitate. This precipitate was extracted into dichloromethane (1 x 50 mL, 3 x 25 mL), and the organic layer was washed with water (3 x 100 mL), then dried with sodium sulfate. After removing the solvent (roto-vap), a light orange oil was obtained (2.3 g, 93.7 %). It had IR (film) ν: 2926, 2802, 2244 (C≡N), 1615, 1523, 1349, 1226, 1164, 1062, 947 cm^{-1}; ^{1}H-NMR δ: 2.53 (t, 2H, J=7.5 Hz), 2.84 (t, 2H, J=7.2 Hz), 2.91 (s, 6H, N(CH_3)$_2$), 6.68 (d, 2H, J=8.4 Hz), 7.07 (d, 2H, J=7.8 Hz) ppm; ^{13}C-NMR δ: 19.66, 30.76, 40.58, 112.95, 119.39, 125.95, 128.89, 149.87 ppm.

p-Dimethylaminohydrocinnamic acid: To a 50 mL round-bottom flask was added 2.2 g (0.013 mol) of the *p*-dimethylaminophenethylnitrile from above. A solution of 7 mL (0.126 mol) concentrated sulfuric acid in 9 mL of water was prepared and added to the solution after cooling with an ice bath; then the solution was heated to reflux. After heating at reflux for 30 min., the brown solution was cooled to room temperature. The (acidic) solution was adjusted with 10% NaOH solution in an ice-water bath to pH = 6.0. The brown solution

turned cloudy as the solution pH increased. The neutralized solution was extracted with dichloromethane (5 x 30 mL), washed with water (3 x 70 mL) and saturated sodium chloride solution, and then dried with magnesium sulfate (anhydrous). The solvent was removed (rotary evaporator) to give a crystalline product (1.06 g, 43.4 %) with mp 100-103°C [lit[26] mp 104-106°C]. It had IR (nujol) ν: 2922, 2854, 1699 (COOH), 1520 cm^{-1}; ^{1}H-NMR δ: 2.63 (t, 3H, J=7.5 Hz, CH_2), 2.87 (t, 3H, J=7.5 Hz, CH_2), 2.90 (s, 6H), 6.72 (d, 2H, J=8.4 Hz), 7.08 (d, 2H, J=8.4 Hz), 10.57 (br s, 1H, COOH) ppm; ^{13}C-NMR δ: 29.28, 36.01, 40.95, 113.46, 128.81, 128.87, 149.40, 178.85 ppm.

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