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Synthesis of an optically active dipyrrinone sulfide and sulfoxide

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Abstract

Optically active dipyrrinone sulfide **2** and its sulfoxide **1** have been synthesized as potential precursors to tetrapyrrole analogs of bilirubin with sulfoxide groups replacing the natural carboxylic acids. Dipyrrinones **1** and **2** show weak exciton coupling in their circular dichroism spectra, with $\Delta\varepsilon_{427}^{max}$ −0.44, $\Delta\varepsilon_{398}^{max}$ +0.50 from **1**, and $\Delta\varepsilon_{442}^{max}$ –0.67, $\Delta\varepsilon_{404}^{max}$ +1.20 from **2**, but no evidence for inter- or intramolecular hydrogen bonding between the dipyrrinone NHs and the sulfoxide group of **1**.

1. Introduction

Dipyrrinones (Fig. 1A) are typically yellow chromophores with intense UV–visible absorption (ε ~30 000) near 400 nm.[1] They are the principal components of the important natural bile pigment bilirubin (Fig. 1B), the end product of heme metabolism in mammals and the colorful herald of hepatobiliary disease.[2,3] (4*Z*)-Dipyrrinones are avid hydrogen bonders and are strongly associated in solutions of nonpolar solvents.[4] In $CHCl_3$, for example, kryptopyrromethenone and methyl xanthobilirubinate show dimerization constants of 1700 M^{-1} (37°C)[5] and 25 000 M^{-1} (22°C)[4] measured by vapor pressure osmometry and ^{1}H NMR spectroscopy, respectively. The dimers are clamped together by four intermolecular hydrogen bonds, with a molecular mechanics-computed stabilization enthalpy of 20–30 kcal/mol.[6,7]

The type of dipyrrinone to dipyrrinone dimer shown in Fig. 1C is thought to be the most common type of hydrogen-bonded dipyrrinone dimer and is found even in bilirubin dimethyl ester.[1,8,9] However, in bilirubin and its analogs with propionic acids at C(8) and C(12), the component dipyrrinones participate in a unique type of hydrogen bonding involving the carboxylic acids (Fig. 1B), as found in the crystal by X-ray crystallography,[10–14] in solution by $^{13}C\{^1H\}$ heteronuclear Overhauser effects[15,16] and ^{1}H NMR,[8,9] and by molecular orbital and molecular dynamics computations.[17–20] Until recently,[6,21] 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, such as xanthobilirubic acid, but

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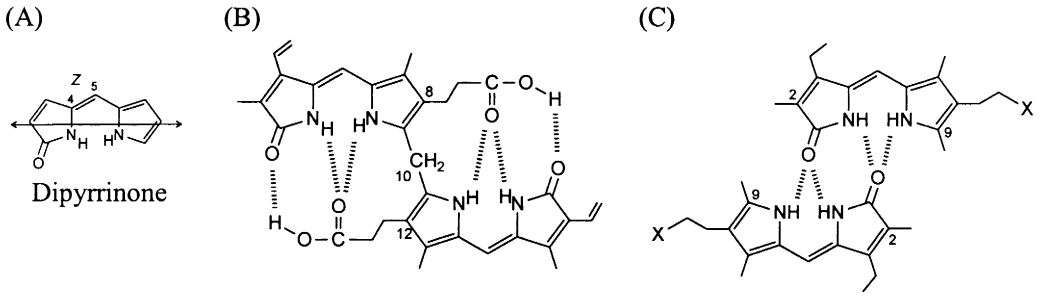


Fig. 1. (A) (4*Z*)-Dipyrrinone chromophore. The double-headed arrow approximates the long-axis polarization of the intense ($\varepsilon \sim 30\,000$) long wavelength electronic transition near 400 nm. (B) Intramolecularly hydrogen-bonded bilirubin with hydrogen bonding between carboxylic acids and dipyrrinones. (C) Intermolecularly hydrogen-bonded dipyrrinone dimer of kryptopyrromethenone (X=H) and methyl xanthobilirubinate ($X=CO_2CH_3$)

it had not been detected until recent work established by ^{1}H NMR and circular dichroism spectroscopy that dipyrrinone acids form a new type of π-stacked stable dimers (Fig. 2).[6,7]

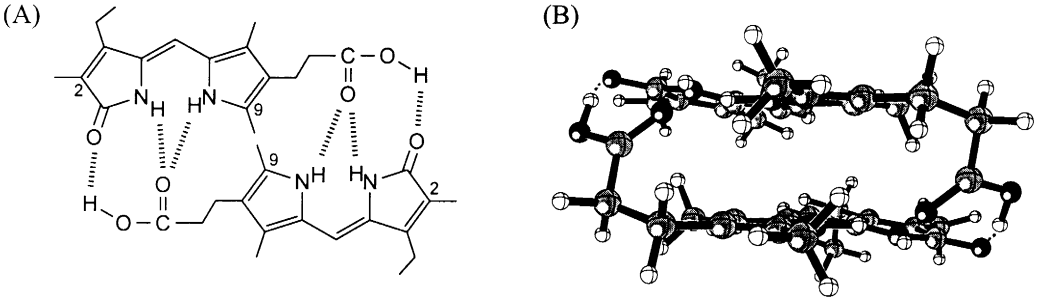


Fig. 2. (A) Dimeric xanthobilirubic acid (XBR), stabilized by six intermolecular hydrogen bonds linking dipyrrinones to propionic acid carboxyls. The dimer is actually π-stacked to avoid nonbonded steric interactions between the C(9) methyls. (B) Ball and Stick representation of the π-stacked XBR dimer of (A), shown in an edge view orientation. The dipyrrinone planes are orthogonal to the plane of the paper

Although dipyrrinones form intermolecularly hydrogen-bonded dimers in nonpolar solvents, the dimers are disrupted in polar solvents, especially in dimethylsulfoxide, which is thought to participate in hydrogen bonding to the NHs (Fig. 3A).[1,9] In the following, we explore the possibility that a sulfoxide analog of xanthobilirubic acid (XBR, Fig. 2A) might participate in intermolecular hydrogen bonding involving sulfoxide and NH groups (Fig. 3B), with π-stacking akin to that of Fig. 2. For such purpose we synthesized optically active sulfoxide **1** and its sulfide analog **2**.

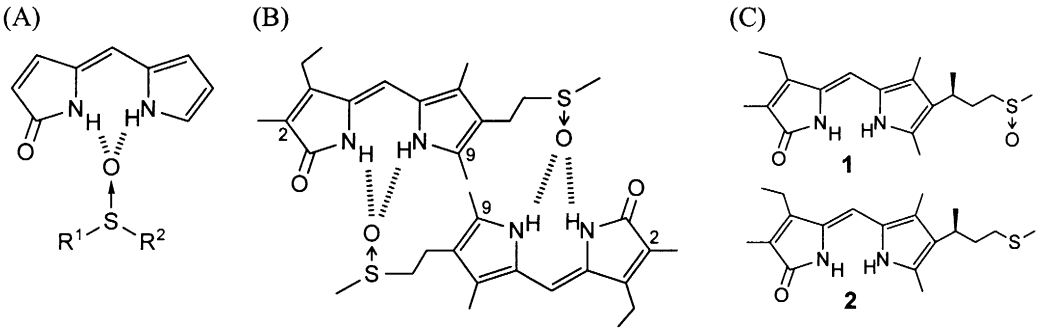


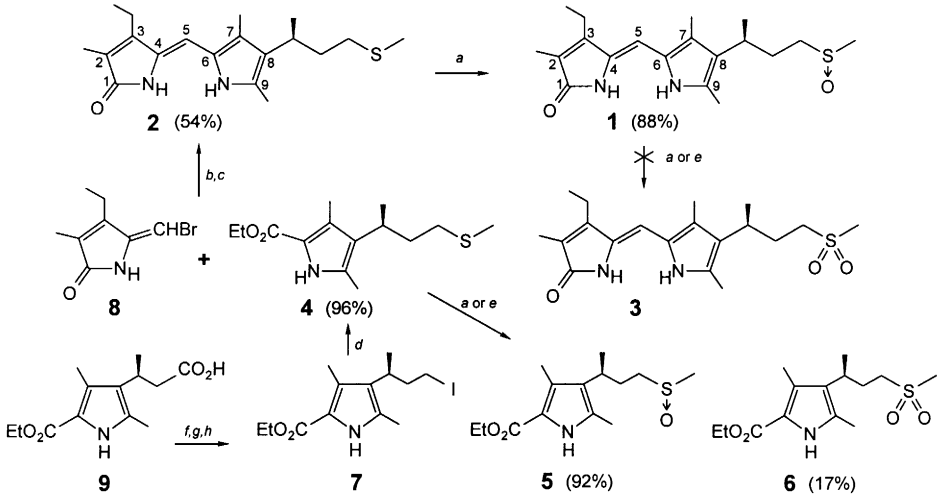
Fig. 3. (A) Dipyrrinone to sulfoxide hydrogen bonding. (B) Intermolecularly hydrogen-bonded dimer of a sulfoxide analog of XBR (see Fig. 2A). (C) Target optically active dipyrrinone sulfoxide **1** and sulfide **2**

Simple dipyrrinones containing sulfide or sulfoxide groups are scarce in the pyrrole literature, although dipyrrinthiones are known, as are their analogs used to make carbon–carbon bonds by sulfide contraction, and thiophene analogs of linear tetrapyrroles have been prepared, as have thia-hexapyrroles.[1] But sulfoxides and sulfides related to **1** and **2** are unknown.

2. Results and discussion

2.1. Synthesis

Synthesis of dipyrrinone sulfoxide precursor **2** was accomplished in two steps from optically pure pyrrole sulfide **4** and the known bromomethylenepyrrolinone **8** (Scheme 1),[22] first by saponifying **4** and reacting the acid with **8** in refluxing ethanol. Pyrrole **4** was prepared smoothly and in high yield from iodopyrrole **7** by reaction with sodium methylmercaptide in ethanol at room temperature. The iodopyrrole **7** was prepared as described previously[6] from the known pyrrole acid **9**,[23] first by selective reduction of the carboxylic acid group to the alcohol, then conversion of the alcohol to its tosylate followed by displacement of the tosylate with sodium iodide in acetone. Reaction of **4** with hydrogen peroxide gave a 92% yield of sulfoxide **5** (which is a diastereomeric mixture) while oxidation of **4** with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave both **5** and sulfone **6** in 83 and 17% yields, respectively. Attempted condensation of the acid of **5** or **6** with **8** by the route successfully followed in the synthesis of **2** gave no recognizable dipyrrinone. However, controlled reaction of **2** with *m*-chloroperoxybenzoic acid gave a high yield of sulfoxide **1** (which is a diastereomeric mixture). Attempts to oxidize **1** to sulfone **3** with *m*-CPBA or H_2O_2 did not give the desired product. When the syntheses of **1**–**6** were carried out using racemic **9**, racemic mixtures of **2**, **4** and **6**, and chromatographically inseparable diastereomeric mixtures of **1** and **5**, were obtained.

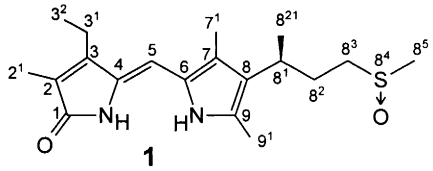


Scheme 1. [a]*m*-CPBA/$CHCl_3$ or CH_2Cl_2; [b]react **4** with NaOH/H_2O, Δ, then cold HNO_3; [c]condense **8** with **4**-acid in EtOH, Δ; [d]$CH_3S^-Na^+$/EtOH; [e]H_2O_2/EtOH; [f]$BH_3 \cdot THF$; [g]*p*-TsCl/Et_3N; [h]NaI/$(CH_3)_2CO$

2.2. ^{13}C NMR analysis and structure

The structures of **1** and **2** follow from their syntheses and are confirmed by spectroscopy. The ^{13}C NMR assignments are based on pulsed field gradient versions of HMQC and HMBC experiments. The ^{13}C NMR chemical shifts (Table 1) are consistent with those of related 4*Z*-dipyrrinones.[24] The distinctions found in spectra measured in $(CD_3)_2SO$ and $CDCl_3$ solvents are characteristic of sulfoxide-bound monomeric dipyrrinones in the former and intermolecularly hydrogen-bonded dimers in the latter. Interestingly, the sulfoxide **1** gives two sets of signals in both solvents, with the intensities being nearly1:1. These findings are to be expected from **1**, which, in contrast to **2,** is a mixture of diastereomers, with the *S*-stereochemistry at C(8^1) carbon and *R*- or *S*-stereochemistry at the sulfur center. We could not separate the diastereomers of **1** by chromatographic methods.

Table 1
Comparison of ^{13}C NMR chemical shifts[a] and assignments[b] of dipyrrinones **1** and **2**



1

Carbon Position	Chemical Shift in $(CD_3)_2SO$		Chemical Shift in $CDCl_3$	
	2	**1**	**2**	**1**
1 C=O	171.90	171.90	174.06	174.09
2 =C	122.58	122.26, 122.53	122.18	122.31, 122.42
3 = C	147.19	147.21, 147.22	148.31	148.39
4 =C	127.30	127.39, 127.41	126.93	127.21, 127.24
5 =CH	97.48	97.43, 97.44	100.98	100.68, 100.70
6 =C	121.79	121.79, 121.81	122.27	122.44, 122.49
7 =C	121.73	121.71, 121.74	124.42	123.94, 123.98
8 =C	122.95	122.64, 122.65	123.72	122.53, 122.56
9 =C	128.80	128.86	131.20	130.89, 130.95
2^1 CH_3	8.04	8.04	8.56	8.50
3^1 CH_2	17.14	17.13	17.93	17.89
3^2 CH_3	14.82	14.82	15.08	14.98
7^1 CH_3	10.02	10.01	10.40	10.37
8^1 CH	29.05	29.43, 29.63	29.83	29.80, 30.56
8^2 CH_2	35.25	28.47, 28.61	35.71	28.50, 29.52
8^{21} CH_3	20.65	20.74, 20.95	20.76	20.92, 21.05
8^3 CH_2	31.93	52.03, 52.16	32.84	53.25, 53.59
8^5 CH_3	14.65	37.99, 38.10	15.52	38.49, 38.70
9^1 CH_3	11.97	11.95, 11.97	12.68	12.55, 12.59

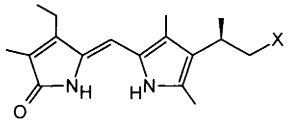
[a] Chemical shifts in δ ppm, downfield from $(CH_3)_4Si$ for 5×10^{-3} M solutions at 25°C. [b] Based on HMQC and HMBC analyses.

It is interesting to note that the ^{13}C chemical shifts of **1** and **2** in a given solvent are nearly identical for all carbons, except those adjacent to the sulfur, viz. C(8^5), C(8^3) and C(8^2). The effect of change from sulfide to sulfoxide is not felt as a long-range effect transmission in the carbon skeleton.

2.3. ^1H NMR analysis and hydrogen bonding

Dipyrrinones are known to be avid participants in hydrogen bonding, generally through in-plane self-association (Fig. 1C),[9] but under the right circumstances association occurs as a π-stacked dimer (Fig. 2).[6,7] In solvents such as dimethylsulfoxide, the dipyrrinone is thought to be associated with the solvent (Fig. 3A).[1] In $CDCl_3$, the NH ^1H NMR chemical shifts are strongly deshielded: generally ~11 ppm for the lactam NH and ~10 ppm for the pyrrole NH, e.g., **10** and **11** of Table 2. In $(CD_3)_2SO$, the lactam NH chemical shift moves upfield to ~10 ppm, while the pyrrole is relatively unchanged (Table 2). In contrast, in the π-stacked dimers, where dipyrrinones engage in hydrogen bonding to carboxylic acids, in nonpolar solvents both the lactam and pyrrole NHs are strongly shielded, as in **12** of Table 2. However, in dimethylsulfoxide the NH chemical shifts of **12** are scarcely different from those of **10** and **11** — suggesting coordination to solvent, as in Fig. 3A.

Table 2
Comparison of lactam and pyrrole NH ^1H NMR chemical shifts in dipyrrinones



Dipyrrinone	Chemical Shift[a] in $(CD_3)_2SO$		Chemical Shift[a] in $CDCl_3$	
X=	lactam	pyrrole	lactam	pyrrole
10 CO_2CH_3	9.78	10.21	11.30	10.30
11 CH_3	9.77	10.18	11.30	10.28
12 CO_2H	9.77	10.20	10.06	8.80
2 CH_2SCH_3	9.76	10.21	11.29	10.29
1 $CH_2S(O)CH_3$	9.76	10.24	11.26	10.31

[a] Chemical shifts in δ ppm downfield from $(CH_3)_4Si$ for 1×10^{-3} M solutions at 25°C.

Given the characteristic NH chemical shift differences in $CDCl_3$ solvent between the two types of dipyrrinone hydrogen-bonded dimers of Fig. 1C and Fig. 2, NMR spectroscopy provided an attractive probe of the structure of the potential dimers of **1**. As expected, the sulfide parent **2** gave the same sets of chemical shifts (in $CDCl_3$ and in $(CD_3)_2SO$) as did **10**–**12**. Sulfoxide **1** gave nearly identical chemical shifts, indicating that its dimer is more like that of Fig. 1C than Fig. 2, that the hydrogen bonding attraction between the sulfoxide oxygen and the dipyrrinone NHs is weaker than that afforded by the lactam to lactam dimer (Fig. 1C).

2.4. Aggregation state by vapor pressure osmometry

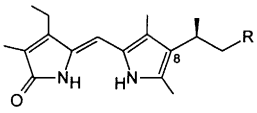
The existence of tightly bound dimers in chloroform solutions of **1** and **2** (at 45°C) was also demonstrated by vapor pressure osmometry measurements in the concentration range $3.0–12.0 \times 10^{-3}$ M. For sulfide **1** an apparent molecular weight of 644±5 vs nominal formula weight of 332.5 was obtained. The sulfoxide **2** showed an apparent molecular weight of 697±8 vs nominal formula weight of 348.5. These values supported the notion of a strong trend toward dimerization in dipyrrinones,[1,4–7] but the

data cannot distinguish between planar (Fig. 1C) and π-stacked (Fig. 2B) dimeric structures in nonpolar solvents. The presence of the latter is detectable, however, by circular dichroism spectroscopy.

2.5. Circular dichroism and dimer stereochemistry

Since dipyrrinones **1** and **2** are optically active, one can expect to observe circular dichroism (CD) associated with their various electronic transitions. Typical of dipyrrinones, both have an intense long wavelength transition (ε_{410}^{max} ~42 000) polarized along the long axis of the chromophore.[6,7] This transition can be expected to exhibit at least a weak CD band due to perturbation of the chromophore by the adjacent stereogenic center. Thus, in CCl_4 a weak CD is seen for the methyl xanthobilirubinate analog **10** and is barely detected in the case of the hydrocarbon chain analog **11** (Table 3). Both are thought to be dimeric in nonpolar solvents, with a planar dimer structure similar to that of Fig. 1C. In contrast, the dipyrrinone acid **12** gives moderately intense bisignate CD Cotton effects.[6,7] Such bisignate Cotton effects find their origin not through dissymmetric vicinal action, but by exciton coupling between two dissymmetrically oriented proximal but not covalently bonded chromophores, as found in the π-stacked dimer in Fig. 2.

Table 3
Comparison of circular dichroism and UV–vis data from optically active dipyrrinones in CCl_4 solvent

	 R	Circular Dichroism[a]			UV-Vis[a]
	R	$\Delta\epsilon^{max}$ (λ)	Δε=0 at λ	$\Delta\epsilon^{max}$ (λ)	ϵ^{max} (λ)
10	CO_2CH_3	+0.29 (400)			35,200 (409)
11	CH_3	(<0.05) Not detectable			43,400 (413)
12	CO_2H	− 25 (425)	411	+ 12 (392)	20,700 (433)^{sh} 28,800 (430)^{sh} 30,400 (415)
1	$CH_2S(O)CH_3$	−0.44 (427)	411	+0.50 (398)	26,500 (431)^{sh} 42,300 (409)
2	CH_2SCH_3	−0.67 (442)	421	+1.20 (404)	28,400 (432)^{sh} 45,000 (411)

[a] Δε and ε in L·mol^{-1} cm^{-1}; λ in nm.

Sulfoxide **1**, unlike acid **12**, exhibits only a very weak bisignate CD in CCl_4 (Table 3). This evidence suggests the presence of some π-stacking, possibly involving sulfoxide to dipyrrinone intermolecular hydrogen bonding. However, the sulfide **2** also exhibits a weak bisignate CD of the same order of magnitude found in **1**. Since **2** is probably incapable of intermolecular hydrogen bonding involving S and NHs, π-stacking, if it exists in **2**, probably also occurs in **1** for the same reason — without the assistance of any S→O···H–N hydrogen bonding.

Alternatively, the bisignate CD of **1** may be weak because the pigment is a mixture of diastereomers with opposite exciton chirality.[25] Since the mixture could not be separated, this possibility could not be examined. However, the ^{1}H NMR chemical shifts of the dipyrrinone NHs suggest that π-stacking is probably minimal.

3. Concluding comments

Optically active dipyrrinones with sulfoxide **1** and sulfide **2** fragments exhibit weak bisignate CD Cotton effects in nonpolar solvents such as CCl_4. While these data suggest the presence of π-stacked dimers, ^{1}H NMR evidence suggests that the presence of such dimers is probably small.

4. Experimental

4.1. General

Nuclear magnetic resonance spectra were obtained on GE GN-300 or Varian Unity Plus spectrometers operating at ^{1}H frequency of 300 or 500 MHz, respectively. $CDCl_3$ solvent (unless otherwise specified) was used throughout and chemical shifts are reported in δ ppm referenced to residual $CHCl_3$ ^{1}H signal at 7.26 ppm and $CDCl_3$ ^{13}C signal at 77.00 ppm. *J*-modulated spin–echo experiment (Attached Proton Test) was used to obtain the ^{13}C NMR assignments. Optical rotations were measured on a Perkin–Elmer model 141 polarimeter and circular dichroism (CD) spectra were recorded on a JASCO J-600 instrument. All ultraviolet–visible spectra were recorded on a Perkin–Elmer Lambda-12 spectrophotometer. Vapor pressure osmometry measurements were performed on an OSMOMAT 070-SA instrument (Gonotec GmbH, Berlin, Germany) in chloroform at 45°C. Gas chromatography–mass spectrometry analyses were carried out on a Hewlett–Packard 5890A capillary gas chromatograph (30 m DB-1 column) equipped with a Hewlett–Packard 5970 mass selective detector. Analytical thin-layer chromatography was carried out on J. T. Baker silica gel IB-F plates (125 μm layer). Radial chromatography was carried out on Merck Silica gel PF_{254} with $CaSO_4$ binder preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2 or 4 mm thick rotors. Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. The spectral data were obtained in spectral grade solvents (Aldrich or Fischer). HPLC grade solvents were dried and purified following standard procedures.[26]

The starting compounds (+)-(*S*)-3-(2,4-dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)butanoic acid **9**,[23] 5-bromomethylene-4-ethyl-3-methyl-2-oxo-1*H*-pyrrole **8**,[22] and (+)-(*S*)-3-(2,4-dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)butyl iodide **7**[6] were synthesized as described previously.

4.2. (+)-(S)-3-(2,4-Dimethyl-5-ethoxycarbonyl-1H-pyrrol-3-yl)butyl methylsulfide 4

Sodium (1.38 g, 60 mg atoms) was added slowly under nitrogen to 75 mL of anhydrous ethanol over 30 min. After all the sodium had reacted, the solution was cooled with ice bath and methanethiol (**Caution!** Highly toxic, stench) was slowly bubbled through the mixture at 0°C for 30 min (until a yellow precipitate appeared in the 15 cm long trap filled with saturated aqueous $Pb(OAc)_2$ and attached to the condenser effluent end). A solution of 6.98 g (20 mmol) of iodide **7** in 100 mL of dry ethanol was added dropwise over 20 min and the mixture was stirred at room temperature for 3 h. The mixture was concentrated under vacuum to ~40 mL, diluted with 200 mL of $CHCl_3$ and washed with water till neutral (4×200 mL). The organic extract was dried over anh. Na_2SO_4 and filtered, and the solvent was evaporated under vacuum. The residue was purified by radial chromatography on silica gel and recrystallization (EtOAc/hexane) to afford 5.17 g (96%) of sulfide **4**. It had an mp of 75–76°C (racemate mp 81–82°C); $[\alpha]_D^{20}$ +40.0 (*c* 1.0, EtOH); ^{1}H NMR: δ 1.24 (3H, d, *J*=7.2 Hz), 1.34 (3H, t, *J*=7.1 Hz), 1.87 (2H, m), 2.06 (3H, s), 2.24 (3H, s), 2.32 (3H, s), 2.36 (2H, m), 2.86 (1H, m), 4.28 (2H, q, *J*=7.1 Hz), 8.58 (1H, br.s) ppm; ^{13}C

NMR: δ 11.12, 12.50, 14.50, 15.38, 20.56, 29.52, 32.66, 35.46, 59.55, 116.67, 124.52, 126.65, 129.41, 161.86 ppm. MS *m/z* (rel. abund.): 269 ($M^{+\cdot}$, 22%), 224 (7%), 194 (61%), 180 (10%), 148 (100%), 61 (33%) amu. Anal. calcd for $C_{14}H_{23}NO_2S$ (269.4): C, 62.41; H, 8.61; N, 5.20. Found: C, 62.62; H, 8.53; N, 5.18.

4.3. (+)-(S)-3-(2,4-Dimethyl-5-ethoxycarbonyl-1H-pyrrol-3-yl)butyl methylsulfoxide ***5***

To a solution of 539 mg (2 mmol) of sulfide **4** in 7 mL of ethanol was added 4 mL of 30% hydrogen peroxide over 15 min. After stirring for 15 min, the mixture was diluted with 50 mL of CH_2Cl_2 and washed with water (4×20 mL). It was dried (anh. Na_2SO_4) and filtered, and the solvent was evaporated under vacuum. The residue was purified by radial chromatography on silica gel and recrystallization from benzene/hexane to afford 524 mg (92%) of sulfoxide **5**, as a mixture of *S,R*- and *S,S*-diastereomers. It had an mp of 130–132°C (diastereomeric racemate mp 130–131°C); $[\alpha]_D^{20}$ +29.8 (*c* 1.2, EtOH); ^{1}H NMR: δ 1.30, 1.31 (2×1.5H, 2×d, *J*=7.1 Hz), 1.35 (3H, t, *J*=7.1 Hz), 2.06 (2H, m), 2.23, 2.24 (2×1.5H, 2×s), 2.30, 2.31 (2×1.5H, 2×s), 2.48 (1H, m), 2.49, 2.51 (2×1.5H, 2×s), 2.59 (1H, m), 2.83, 2.91 (2×0.5H, 2×m), 4.29 (2H, q, *J*=7.1 Hz), 8.57 (1H, br.s) ppm; ^{1}H NMR (DMSO-d_6): δ 1.18, 1.19 (2×1.5H, 2×d, *J*=7.1 Hz), 1.25 (3H, t, *J*=7.1 Hz), 1.87 (2H, m), 2.14, 2.15 (2×1.5H, 2×s), 2.20, 2.21 (2×1.5H, 2×s), 2.39 (1H, m), 2.45, 2.47 (2×1.5H, 2×s), 2.56 (1H, m), 2.76 (1H, m), 4.17 (2H, q, *J*=7.1 Hz), 11.04 (1H, br.s) ppm; ^{13}C NMR: 11.08, 11.10, 12.55, 14.51, 20.75, 20.89, 28.46, 29.28, 29.64, 30.31, 38.50, 38.65, 53.20, 53.46, 59.63, 117.01, 117.02, 123.27, 123.48, 126.41, 126.47, 129.20, 161.64 ppm; ^{13}C NMR (DMSO-d_6): δ 10.94, 11.95, 14.58, 20.66, 20.88, 28.38, 28.55, 29.25, 29.48, 38.01, 38.10, 51.99, 52.09, 58.73, 115.86, 115.89, 123.00, 123.28, 125.54, 129.92, 160.82 ppm; MS *m/z* (rel. abund.): 222 (3%), 221 (44%), 206 (78%), 181 (9%), 160 (100%), 148 (20%), 132 (20%) amu. Anal. calcd for $C_{14}H_{23}NO_3S$ (285.4): C, 58.91; H, 8.12; N, 4.91. Found: C, 58.75; H, 8.06; N, 4.81.

4.4. (+)-(S)-3-(2,4-Dimethyl-5-ethoxycarbonyl-1H-pyrrol-3-yl)butyl methylsulfone ***6***

It had an mp of 99–100°C (racemate mp 109–110°C); $[\alpha]_D^{20}$ +11.4 (*c* 1.2, EtOH); ^{1}H NMR: δ 1.31 (3H, d, *J*=7.1 Hz), 1.35 (3H, t, *J*=7.1 Hz), 2.14 (2H, m), 2.24 (3H, s), 2.31 (3H, s), 2.83 (2H, m), 2.85 (3H, s), 2.87 (1H, m), 4.29 (2H, q, *J*=7.1 Hz), 8.55 (1H, br.s) ppm; ^{13}C NMR: δ 11.06, 12.57, 14.54, 20.78, 28.43, 29.78, 40.53, 53.59, 59.74, 117.21, 122.85, 126.38, 129.11, 161.56 ppm; MS *m/z* (rel. abund.): 301 ($M^{+\cdot}$, 28%), 256 (8%), 206 (8%), 194 (100%), 148 (92%) amu. Anal. calcd for $C_{14}H_{23}NO_4S$ (301.4): C, 55.79; H, 7.69; N, 4.65. Found: C, 55.52; H, 7.73; N, 4.65.

4.5. (+)-(S)-3-(3-Ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydro-11H-dipyrrin-8-yl)butyl methylsulfide ***2***

A mixture of 1.08 g (4 mmol) of sulfide **4**, 1.28 g (32 mmol) of sodium hydroxide, 15 mL of ethanol, and 3 mL of water was vigorously refluxed for 3.5 h. After cooling with an ice bath, it was carefully acidified with conc. HNO_3. Bromomethylene pyrrolinone **8** (864 mg, 4 mmol) was added, and the mixture was heated at reflux for 5 h. Then it was chilled overnight at −20°C. The precipitated solid was filtered and washed with cold methanol. The crude product was dissolved in $CHCl_3$ (100 mL), washed with H_2O (2×100 mL), and dried (anh. Na_2SO_4). It was filtered and the solvent was evaporated under vacuum. Purification by radial chromatography on silica gel and recrystallization from dichloromethane/methanol afforded 724 mg (54%) of bright yellow dipyrrinone **2**. It had an mp of 161–162°C (racemate mp 178–179°C); $[\alpha]_D^{20}$ +36.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR: δ 1.17 (3H, t, *J*=7.6 Hz), 1.27 (3H, d, *J*=7.1 Hz), 1.86 (2H, m), 1.95 (3H, s), 2.07 (3H, s), 2.17 (3H, s), 2.39 (2H, m), 2.45 (3H, s), 2.55 (2H, q, *J*=7.6

Hz), 2.89 (1H, m), 6.14 (1H, s), 10.29 (1H, br.s), 11.29 (1H, 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), 1.76 (2H, m), 1.77 (3H, s), 1.99 (3H, s), 2.05 (3H, s), 2.20 (3H, s), 2.30 (2H, t, J=7.5 Hz), 2.49 (2H, q, J=7.5 Hz), 2.79 (1H, m), 5.92 (1H, s), 9.76 (1H, s), 10.21 (1H, s) ppm; ^{13}C NMR: δ 8.56, 10.40, 12.68, 15.08, 15.52, 17.93, 20.76, 29.83, 32.84, 35.71, 100.98, 122.18, 122.27, 123.72, 124.42, 126.93, 131.20 148.31, 174.06 ppm; ^{13}C NMR (DMSO-d_6): δ 8.04, 10.02, 11.97, 14.65, 14.82, 17.14, 20.65, 29.05, 31.93, 35.25, 97.48, 121.73, 121.79, 122.58, 122.95, 127.30, 128.80, 147.19, 171.90 ppm. Anal. calcd for $C_{19}H_{28}N_2OS$ (332.5): C, 68.63; H, 8.49; N, 8.43. Found: C, 68.59; H, 8.67; N, 8.35.

4.6. (+)-(S)-3-(3-Ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydro-11H-dipyrrin-8-yl)butyl methylsulfoxide ***1***

To a cooled (−30°C) solution of 665 mg (2 mmol) of sulfide **2** in 60 mL of anhydrous CH_2Cl_2 was added a solution of 432 mg (2 mmol) of *m*-CPBA in 35 mL of CH_2Cl_2 over 2 min. After 5 min stirring at −30°C, the mixture was diluted with 200 mL of $CHCl_3$ and washed with 2% aq. $NaHCO_3$ (100 mL) and water (2×100 mL). The organic phase was dried over anh. Na_2SO_4 and filtered, and the solvent was removed under vacuum. The residue was purified by radial chromatography on silica gel and recrystallization from EtOAc/Et_2O to afford 610 mg (88%) of bright yellow sulfoxide **1**, which is a mixture of *S*,*R*- and *S*,*S*-diastereomers. It had an mp of 190–200°C (diastereomeric racemate mp 194–203°C); $[\alpha]_D^{20}$ +36.1 (*c* 0.4, $CHCl_3$); ^{1}H NMR: δ 1.18 (3H, t, J=7.6 Hz), 1.32, 1.33 (2×1.5H, 2×d, J=7.2 Hz), 1.95 (3H, s), 2.10 (2H, m), 2.15, 2.16 (2×1.5H, 2×s), 2.44, 2.45 (2×1.5H, 2×s), 2.50, 2.52 (2×1.5H, 2×s), 2.53 (1H, m), 2.56 (2H, q, J=7.6 Hz), 2.62 (1H, m), 2.85, 2.95 (2×0.5H, 2×m), 6.13 (1H, s), 10.31 (1H, br.s), 11.26 (1H, br.s) ppm; ^{1}H NMR (DMSO-d_6): δ 1.07 (3H, t, J=7.6 Hz), 1.20 (3H, t, J=7.1 Hz), 1.77 (3H, s), 1.88 (2H, m), 2.050, 2.054 (2×1.5H, 2×s), 2.196, 2.204 (2×1.5H, 2×s), 2.41 (1H, m), 2.46, 2.47 (2×1.5H, 2×s), 2.48 (2H, q, J=7.6 Hz), 2.59 (1H, m), 2.77 (1H, m), 5.93 (1H, s), 9.76 (1H, s), 10.24 (1H, s) ppm; ^{13}C NMR: δ 8.50, 10.37, 12.55, 12.59, 14.98, 17.89, 20.92, 21.05, 28.50, 29.52, 29.80, 30.56, 38.49, 38.70, 53.25, 53.59, 100.68, 100.70, 122.31, 122.42, 122.44, 122.49, 122.53, 122.56, 123.94, 123.98, 127.21, 127.24, 130.89, 130.95, 148.39, 174.09 ppm; ^{13}C NMR (DMSO-d_6): δ 8.04, 10.01, 11.95, 11.97, 14.82, 17.13, 20.74, 20.95, 28.47, 28.61, 29.43, 29.63, 37.99, 38.10, 52.03, 52.16, 97.43, 97.44, 121.71, 121.74, 121.79, 121.81, 122.26, 122.53, 122.64, 122.65, 127.39, 127.41, 128.86, 147.21, 147.22, 171.90 ppm. Anal. calcd for $C_{19}H_{28}N_2O_2S$ (348.5): C, 65.48; H, 8.10; N, 8.04. Found: C, 65.66; H, 8.21; H, 8.00.

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