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Readily Synthesized Novel Fluorescent Dipyrrinones

Stefan E. Boiadjiev and David A. Lightner*

Chemistry Department, University of Nevada, Reno, Nevada 89557

lightner@scs.unr.edu

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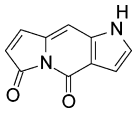

A new, highly fluorescent (ϕ_F up to 0.85) rigid *anti-Z*-dipyrrinone chromophore has been synthesized in high yield in a one-pot reaction by condensing two monopyrroles in the presence of DBU to form the pyrrolo[3,2-*f*]indolizine-4,6-dione nucleus.

Ordinary dipyrrinones, such as those elaborated from the *syn-Z* template of Figure 1A, are typically nonfluorescent because their ~420 nm excited states relax to a new ground state by rapid nonradiative decay involving $Z \rightarrow E$ isomerization of the C(4)−C(5) double bond.[1] When $Z \rightarrow E$ isomerization is prevented by bridging the two nitrogens with short carbon chains, strong dipyrrinone fluorescence (e.g., fluorescence quantum yield, ϕ_F ~0.85) may occur.[1−3] The very few examples of bridged dipyrrinones include the tricyclic ring system 3*H*,5*H*-dipyrrolo-[1,2-*c*:2′,1′-*f*]pyrimidine-3-one (Figure 1B), reported in 1986[2] and prepared from pyrrole-2-aldehyde in 3−4 steps. Analogues with β-substituents were prepared from the parent *syn-Z*-dipyrrinone by inserting a methano up to a 1,3-propano belt.[1,3] More recently we proposed a smoother, higher yield *N*,*N*′-bridging reaction in which a carbonyl group was inserted into the preformed *syn-Z*-dipyrrinone by treatment with 1,1′-carbonyldiimidazole (CDI) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the highly fluorescent 3,5-dione (Figure 1C).[4,5] In the following we describe a novel, high-yield condensation of two pyrroles to give directly the related (but unreported) pyrrolo[3,2-*f*]indolizine-4,6-dione chromophore (Figure 1D), based on the *anti-Z*-dipyrrinone skeleton. Such fluorescent pigments, with suitable polar groups attached, might be useful in fluorescence imaging of hepatic metabolism.

Dipyrrinones are typically synthesized by coupling two pyrrole precursors. Seeking a short, one-pot synthesis of new fluorescent dipyrrinones, we envisaged a reaction

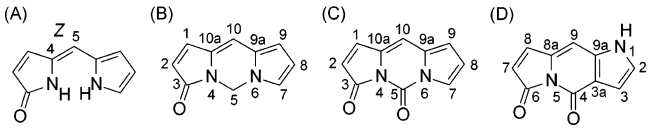

FIGURE 1. The *syn-Z*-dipyrrinone skeleton (A) and its methano-bridge analogue (B), 3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]-pyrimidine-3-one, (C) 3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]pyrimidine-3,5-dione, and (D) pyrrolo[3,2-*f*]indolizine-4,6-dione. The dipyrrinone conformation of (A)−(C) is *syn-Z* and that in (D) is *anti-Z*.

sequence from two pyrrole precursors that would form a dipyrrinone in the first step and then proceed in a second step to form the desired tricyclic product. Thus, to prepare an *N*,*N*′-carbonyl-bridged *syn*-4*Z*-dipyrrinone (Figure 1C) might require a pyrrolinone and the *N*-methoxycarbonyl derivative of an α-formylpyrrole. However, the number of synthetic steps would not be reduced; so we considered an analogous reaction that might lead directly to a new type of fluorescent *Z*-dipyrrinone, rotated into the anti conformation and with the lactam nitrogen linked by a carbonyl group to a pyrrole β-carbon. Condensation−intramolecular cyclization was achieved by a highly successful route (outlined in Figure 2) involving base-catalyzed (ethanolic KOH) coupling of **8**[6] with **10**,[7,8] a readily available pyrrole α-aldehyde possessing a β-carboethoxy group. (Pyrrolinone **8** was obtained from 4-methyl-3-ethyl-2-*p*-toluenesulfonylpyrrole, prepared by a Barton−Zard reaction between *p*-toluenesulfonylmethyl isocyanide and 2-nitropentan-3-ol.[6]) The overall mechanism involves (i) standard formation of the dipyrrinone by aldol condensation followed by (ii) deprotonation of the lactam NH to promote nucleophilic attack on the C(7)−CO_2Et from the anti conformation of the dipyrrinone (Figure 2). From **8** + **10** in ethanolic KOH, a nearly quantitative yield of a very polar product was obtained that was shown to be a 73:27 mixture of the expected bridged dipyrrinone **1** and the unbridged dipyrrinone diacid **14**. Since the C(7) carboethoxy group is difficult to saponify (as with mesitoic acid esters[9]), we suggest that **14** might arise indirectly, from ring opening of **1** under the reaction conditions. Both **1** and **14** were suprisingly insoluble in most organic solvents and thus difficult to work with. Conversion of the mixture to methyl esters (using diazomethane) or isobutyl esters (using *i*-BuI-Cs_2CO_3) led to barely improved solubility, but sufficient for tedious chromatographic separation to give the methyl ester of **1** and its isobutyl analogue.

Interestingly, when the mixture of **1** + **14** was treated under more forcing conditions, with isobutyl iodide−Cs_2CO_3 in hot DMF, only the *N*-isobutyl isobutyl ester (**7**) was obtained. Apparently the C(7) CO_2H of **14** is esteri-

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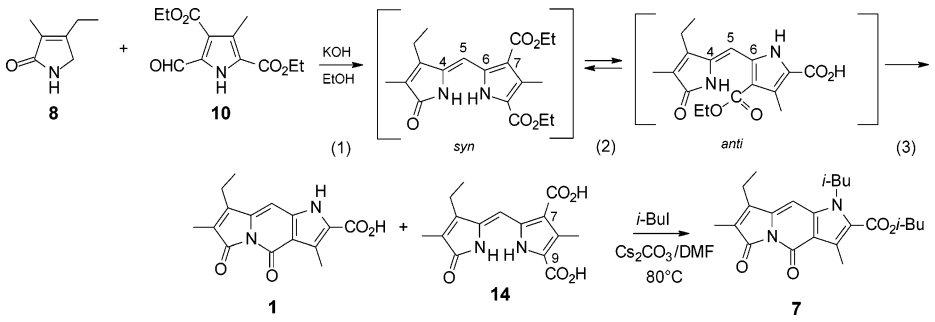
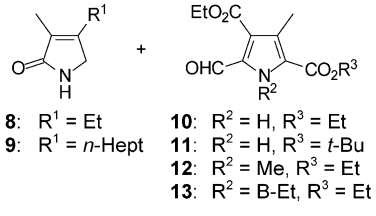
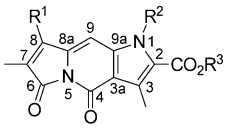


FIGURE 2. Condensation of pyrrolinone **8** and pyrrole aldehyde **10** to give bridged dipyrrinone **1** in three steps. A byproduct (**14**) is formed in the ratio 27:73, **14**:**1**, and the mixture can be converted to **7** as shown.



DBU | EtOH or *t*-BuOH



	R^1	R^2	R^3
2:	Et	H	Et
3:	Et	H	*t*-Bu
4:[a]	*n*-Hept	H	Me
5:[a]	Et	Me	Me
6:	Et	B-Et	Et

n-Hept = *n*-Heptyl
B-Et = $CH_2CH_2CH_2CO_2Et$

[a] Using KOH in place of DBU.

FIGURE 3. General reaction for synthesizing pyrrolo[3,2-*f*]-indolizine-4,6-diones (**2**-**6**) from simple monopyrrole precursors **8**−**13**.

fied, along with the C(9) CO_2H, and the C(7) ester is recycled through the intramolecular cyclization. Compound **7** had much better solubility properties than either the methyl ester of **1** or its isobutyl ester.

Exploring parameters that influence solubility in common organic solvents we prepared the *N*-methyl analogue (**5**) of **2** and the *n*-heptyl analogue (**4**) and found that the former had better solubility properties than the latter. To avoid the formation of the dipyrrinone diacid (**14**) byproduct, we eschewed ethanolic KOH, replacing it with DBU (Figure 3) to prepare **2** from **8** + **10** directly, smoothly, and in high yield. Similar treatment of **8** + **11** or **8** + **13** afforded the *tert*-butyl ester **3** or diester **6**, respectively.

The structures of **1**−**7** follow logically from their known precursors and their spectroscopic properties. In addition, X-ray quality crystals of **5** (triclinic space group $P\bar{1}$ with cell dimensions a = 8.3584 (17) Å, b = 11.6270 (18) Å, and c = 11.8366 (19) Å) and **7** (triclinic space group $P\bar{1}$ with cell dimensions a = 12.569 (2) Å, b = 14.698 (3) Å, and c = 15.133 (3) Å) were grown from DMSO (**5**) and

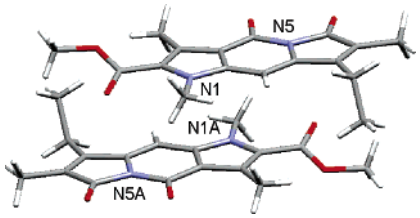


FIGURE 4. Crystal structure drawing of *N*-methyl methyl ester **5** molecules (in the unit cell). One DMSO molecule per molecule of **5** has been deleted for clarity of representation.

ethanol−water (**7**). Their crystal structures were determined, showing that both are planar, with C(3a)−C(9a)−C(9)−C(8a) torsion angles of 0.8° and 0.1°, respectively, and N(5)−C(8a)−C(9)−C(9a) torsion angles of −0.4° and −2.0°, respectively (see Figure 1 for the pyrrolo[3,2-*f*]-indolizine-4,6-dione numbering system). The N(5)−C(4)−C(3a) angles are 112.5° and 114.5°, respectively. The C(8a)−C(9) double bond lengths of **5** and **7** are 1.352 (7) and 1.322 (10) Å, respectively, and the C(9)−C(9a) single bond lengths are 1.415 (7) and 1.400 (11) Å, respectively: bond distances similar to those reported for unbridged dipyrrinones[10] and indicative of bond alternation in the six-membered ring. Crystals of **5** show two molecules in the unit cell in parallel planes (~3.5 Å apart) oriented head to tail (Figure 4) with one molecule of DMSO. The structure of **7** is less refined due to disorder in the isobutyls and significant thermal motion in the *N*-isobutyl. Crystals of **7** show two unique molecules in a 4-molecule unit cell along with one solvent molecule (modeled as EtOH) per pair of dipyrrinones. In contrast to **5**, **7** (with bulkier alkyls) packs not in parallel planes, but in planes inclined at 63° to each other.

As observed previously for *N*,*N*′-carbonyl-bridged *syn*-dipyrrinones, *N*,*C*-carbonyl-bridged *anti*-dipyrrinones **1**−**7** gave pronounced hypochromicity and a bathochromically shifted λ_{max} of long wavelength UV−vis transition (Figure 5) relative to unbridged dipyrrinones, with only a small influence due to changes in solvent type and polarity (Table S-1 of the Supporting Information). Solutions of **1**−**7** were strongly fluorescent to the eye. Excitation of the long wavelength band (392−399 nm) produced intense fluorescence between 435 and 505 nm (Table 1), with a large Stokes shift. The fluorescence quantum yields at room temperature in $CHCl_3$, CH_3OH, and DMSO determined versus 9,10-diphenylantracene stan-

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TABLE 1. Fluorescence Data for Dipyrrinones 3−7[a]

bridged dipyrrinone	*cyclo*-C_6H_{12}			C_6H_6			$CHCl_3$			CH_3OH			$(CH_3)_2SO$		
	λ^{exc}	λ^{em}	ϕ_F	λ^{exc}	λ^{em}	ϕ_F	λ^{exc}	λ^{em}	ϕ_F	λ^{exc}	λ^{em}	ϕ_F	λ^{exc}	λ^{em}	ϕ_F
3	392	443	0.03	396	443	0.16	397	453	0.72	397	505	0.71	397	483	0.86
4	393	448	0.02	395	441	0.10	396	448	0.52	397	500	0.73	397	482	0.83
5	396	435	0.03	397	447	0.18	398	455	0.71	397	501	0.66	397	482	0.80
6	396	434	0.04	397	446	0.20	398	456	0.80	397	499	0.76	397	481	0.86
7	397	437	0.05	397	446	0.22	399	457	0.78	397	498	0.74	397	479	0.84
Kryptoglow[b]	414	474	0.80	421	489	0.71	421	502	0.62	421	533	0.32	421	509	0.63

[a] λ^{exc} = excitation wavelength in nm, λ^{em} = emission wavelength in nm, ϕ_F = fluorescence quantum yield. [b] Kryptoglow is the *N*,*N*′-carbonyl-bridged derivative of kryptopyrromethenone (Trull, F. R.; Franklin, R. W.; Lightner, D. A. *J. Heterocycl. Chem*. **1987**, *24*, 1573−1579), 1,8-diethyl-2,7,9-trimethyl-3*H*,5*H*-dipyrrolo[1,2-*c*:2′1′-*f*]pyrimidine-3,5-dione.

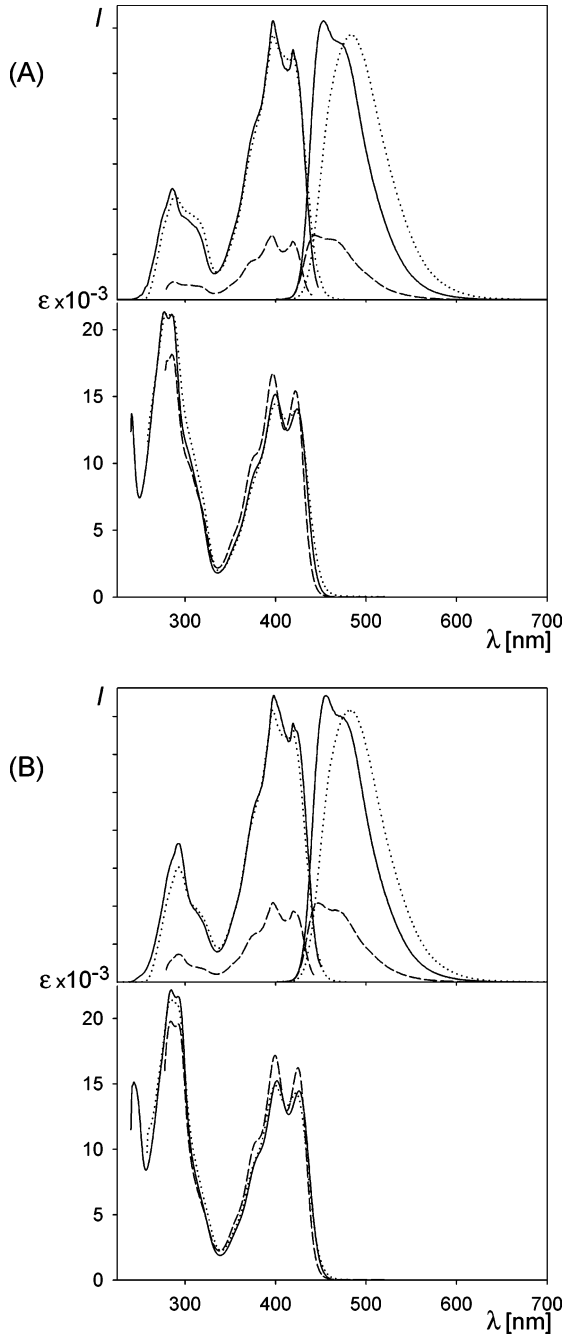

FIGURE 5. Fluorescence (upper part) and UV−vis (lower part) spectra of **3** (A) and **5** (B) in C_6H_6 (- - -), $CHCl_3$ (−), and $(CH_3)_2SO$ (···). Concentrations are ~5 × 10^{-5} M for UV−vis and ~2.5 × 10^{-6} M for fluorescence spectra.

dard, $\phi_F = 0.90 \pm 0.02$,[11] were typically very large ($\phi_F \geq 0.5$), but in cyclohexane and in benzene they were much reduced (ϕ_F 0.02−0.20). The strong fluorescence is consistent with radiative de-excitation being the dominant relaxation pathway for return to the ground state because nonradiative pathways cannot be accessed, e.g., photoisomerization from 4*Z* to 4*E*. The small values of ϕ_F in nonpolar solvents might be attributed to dimer formation in these rather more polar analogues of *N*,*N*′-carbonyldipyrrinones, which exhibited far greater solubility in all solvents and very high ϕ_F values (>0.65) in benzene and in cyclohexane, e.g., for xanthoglow.

Further studies are currently underway on other isomeric bridged dipyrrinones that can be formed easily in one-pot reactions from two monopyrroles.

Experimental Section

For general procedures, see refs 5 and 12. Fluorescence measurements were carried out from solutions prepared as reported previously.[4,5] Fluorescence quantum yields at 20 °C were determined as reported[5] by relating the quantum yield of the sample to that of a reference standard, 9,10-diphenylanthracene ($\phi_F = 0.90 \pm 0.02$ in cyclohexane[11]). The equation used to relate these quantum yields is given by

$$\phi_s = [(A_r F_s n_s^2)/(A_s F_r n_r^2)]\phi_r$$

where the subscript s refers to the sample and the subscript r refers to the reference standard, ϕ is quantum yield, *A* is the absorbance at the excitation wavelength, *F* is the integrated emission area across the band, and *n* is the index of refraction (at the sodium D line) of the solvent containing the sample and the reference standard.

For the syntheses of **3**−**6**, refer to the Supporting Information. Pyrrolinone **8**[6] (and similarly its *n*-heptyl analogue **9**) and aldehydes **10**[7,8] and **12**[13] were synthesized according to previously published methods.

2-*tert*-Butyl 4-Ethoxycarbonyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate (11). The aldehyde was prepared by CAN oxidation[14] of the corresponding α-methylpyrrole. Thus, to a solution of 2.67 g (10 mmol) of α-methylpyrrole[15] in 70 mL of THF, 70 mL of acetic acid, and 70 mL of H_2O kept at 4 °C was added at once CAN (22.5 g, 41 mmol) and the mixture was stirred for 45 min at ice bath temperature and 20 min more while the temperature rose to ambient. The mixture was diluted

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with 200 mL of H_2O and the product was extracted with $CHCl_3$ (4 × 60 mL). The combined extracts were washed with 5% aq $NaHCO_3$ (50 mL) and H_2O (3 × 50 mL), dried (anhyd $MgSO_4$), and filtered and the solvent was evaporated under vacuum. The residue was purified by radial chromatography and recrystallization from ethanol−water to give 1.64 g (58%) of aldehyde **11**. Mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.2 Hz), 1.58 (9H, s), 2.56 (3H, s), 4.38 (2H, q, J = 7.2 Hz), 9.80 (1H, br s), 10.24 (1H, s) ppm; ^{13}C NMR ($CDCl_3$) δ 11.3, 14.3, 28.3, 60.7, 82.9, 120.8, 125.1, 130.3, 132.9, 159.7, 163.7, 182.6 ppm. Anal. Calcd for $C_{14}H_{19}NO_5$ (281.3): C, 59.77; H, 6.81; N, 4.98. Found: C, 60.10; H, 6.94; N, 5.14.

Diethyl 1-(3-Ethoxycarbonylpropyl)-5-formyl-3-methyl-1*H*-pyrrole-2,4-dicarboxylate (13). To a solution of 2.53 g (10 mmol) of pyrrolealdehyde **10**[7,8] in 20 mL of anhydrous $(CH_3)_2SO$ under N_2 was added *t*-BuOK (1.23 g, 11 mmol) and the mixture was stirred for 1 h. Ethyl 4-bromobutyrate (2.93 g, 15 mmol) was added and the mixture was stirred for 2 h at 60 °C. After cooling, the mixture was diluted with 150 mL of $CHCl_3$ and washed with 1% aq HCl (100 mL) followed by H_2O (3 × 50 mL). The solution was dried (anhyd $MgSO_4$) and filtered and the solvent was evaporated under vacuum. The residue was purified by radial chromatography to afford 3.09 g (84%) of *N*-alkylated aldehyde **13** as a colorless mobile oil. ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7.1 Hz), 1.35 (3H, t, J = 7.2 Hz), 1.37 (3H, t, J = 7.2 Hz), 1.98−2.04 (2H, m), 2.30 (2H, t, J = 7.6 Hz), 2.44 (3H, s), 4.08 (2H, q, J = 7.1 Hz), 4.33 (2H, q, J = 7.2 Hz), 4.34 (2H, q, J = 7.2 Hz), 4.72 (2H, t, J = 7.5 Hz), 10.30 (1H, s) ppm; ^{13}C NMR ($CDCl_3$) δ 12.1, 14.1, 14.1, 14.2, 26.6, 31.2, 46.4, 60.3, 60.9, 61.1, 123.4, 126.5, 129.7, 132.9, 161.1, 163.8, 172.5, 183.7 ppm. Anal. Calcd for $C_{18}H_{25}NO_7$ (367.4): C, 58.84; H, 6.86; N, 3.81. Found: C, 58.58; H, 6.74; N, 3.73.

General Procedure for Condensation−Cyclization with KOH Leading to 1, 4, and 5. A mixture of 6 mmol of pyrrolinone and 5 mmol of the corresponding aldehyde in 12.5 mL of ethanol and 25 mL of 20% aq KOH was heated at vigorous reflux for 5−6 h. Almost all of the ethanol solvent was distilled, then the aqueous residue was cooled in an ice bath and acidified with 10% aq HCl. The precipitated product was collected by filtration, washed with H_2O until neutral ,and dried overnight under vacuum (P_2O_5) to afford near quantitative recovery of bright yellow tricyclic acid. A portion of the acid was suspended in $CH_3OH-CHCl_3$ (1 mmol in 8−30 mL) and treated with an excess of ethereal diazomethane for 20 min. After being quenched with acetic acid, the mixture was diluted with CH_2Cl_2 and washed with H_2O. The solution was dried over anhyd Na_2SO_4 and filtered, and the solvent was evaporated under vacuum. The residue was purified by radial chromatography followed by recrystallization.

3,7-Dimethyl-8-ethylpyrrolo[3,2-*f*]indolizine-4,6-dione-2-carboxylic Acid (1). A 98% yield of **1** + **14** was obtained, with **1** comprising 73% of the mixture. The following spectroscopic data were obtained from an ∼95% pure sample of **1** that had been recovered following an unsuccessful attempt to convert the crude mixture into the *t*-Bu ester of **1**: ^{1}H NMR ($(CD_3)_2SO$) δ 1.11 (3H, t, J = 7.6 Hz), 1.82 (3H, s), 2.50 (2H, q, J = 7.6 Hz), 2.55 (3H, s), 6.49 (1H, s), 12.19 (1H, s), 12.96 (1H, br s) ppm; ^{13}C NMR ($(CD_3)_2SO$) δ 8.0, 10.9, 13.4, 17.3, 95.4, 115.4, 123.2, 127.1, 127.7, 137.1, 139.7, 146.8, 156.5, 162.2, 168.2 ppm; HRMS (FAB, 3-NBA + Li^+) calcd for $C_{15}H_{14}N_2O_4{\cdot}Li^+$ 293.1114, found 293.1118 (Δ = −0.4 mDa, error −1.4 ppm). The presence of **14** in the 73:27 mixture of **1**:**14** was deduced from the lower intensity NMR set of signals (found after subtracting those from **1**). ^{1}H NMR ($(CD_3)_2SO$) δ 1.10 (3H, t, J = 7.6 Hz), 1.79 (3H, s), 2.45 (2H, q, J = 7.6 Hz), 2.47 (3H, s), 6.85 (1H, s), 10.45 (1H, s), 11.39 (1H, s), 12.77 (2H, br s) ppm; ^{13}C NMR ($(CD_3)_2SO$) δ 8.1, 11.9, 14.3, 17.4, 96.5, 116.1, 121.9, 126.9, 129.5, 133.5, 136.2, 147.6, 162.1, 166.0, 172.9 ppm.

General Procedure for Condensation−Cyclization with DBU Leading to 2, 3, and 6. A mixture of 2.5 mmol of pyrrolinone **8**, 2.0 mmol of the corresponding aldehyde, 10 mL of anhyd ethanol (or *tert*-butyl alcohol in the case of **3**) and 1.5 mL (10 mmol) of DBU was heated under N_2 at reflux for 16 h. After cooling, the mixture was acidified with 1.5 mL of acetic acid and diluted with 2 mL of H_2O. After cooling from 0 to −20 °C, the precipitated product was collected by filtration, washed with cold 75% ethanol, dried, and purified by radial chromatography followed by recrystallization.

Ethyl 3,7-Dimethyl-8-ethylpyrrolo[3,2-*f*]indolizine-4,6-dione-2-carboxylate (2). This tricycle was synthesized in 75% yield. Mp 301−303 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.12 (3H, t, J = 7.6 Hz), 1.31 (3H, t, J = 7.1 Hz), 1.83 (3H, s), 2.51 (2H, q, J = 7.6 Hz), 2.56 (3H, s), 4.28 (2H, q, J = 7.1 Hz), 6.51 (1H, s), 12.27 (1H, s) ppm; ^{13}C NMR ($(CD_3)_2SO$) δ 8.0, 10.9, 13.4, 14.3, 17.3, 60.2, 95.4, 115.4, 122.3, 127.2, 128.2, 137.5, 140.0, 146.8, 156.4, 160.6, 168.1 ppm. Anal. Calcd for $C_{17}H_{18}N_2O_4$ (314.3): C, 64.95; H, 5.77; N, 8.91. Found: C, 64.84; H, 5.74; N, 8.78.

2-Methylpropyl 3,7-Dimethyl-8-ethyl-1-(2-methylpropyl)pyrrolo[3,2-*f*]indolizine-4,6-dione-2-carboxylate (7). A mixture of 286 mg (1 mmol) of crude acid **1** (containing 27% of noncyclic diacid), 489 mg (1.5 mmol) of Cs_2CO_3, 0.7 mL (6 mmol) of isobutyl iodide, and 9 mL of anhyd DMF was heated under N_2 at 80 °C for 18 h. After cooling, the mixture was diluted with $CHCl_3-CH_2Cl_2$ (200 mL) and washed with H_2O (3 × 50 mL). The solution was dried (anhyd Na_2SO_4), the solvent was evaporated under vacuum, and the residue was purified by radial chromatography followed by recrystallization from EtOH−H_2O to give 284 mg (85%) of diisobutyl derivative **7**. Mp 124−125 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, d, J = 6.6 Hz), 1.02 (6H, d, J = 6.7 Hz), 1.22 (3H, t, J = 7.7 Hz), 1.95 (3H, s), 2.03−2.12 (2H, m), 2.54 (2H, q, J = 7.7 Hz), 2.76 (3H, s), 4.08 (2H, d, J = 6.5 Hz), 4.22 (2H, d, J = 7.2 Hz), 6.29 (1H, s) ppm; ^{13}C NMR ($CDCl_3$) δ 8.4, 12.2, 13.7, 17.9, 19.3, 20.0, 27.8, 30.4, 52.7, 70.9, 93.1, 115.1, 123.7, 128.5, 131.9, 139.6, 140.3, 146.4, 157.3, 162.0, 168.7 ppm. Anal. Calcd for $C_{23}H_{30}N_2O_4$ (398.5): C, 69.32; H, 7.59; N, 7.03. Found: C, 69.38; H, 7.47; N, 7.01.

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Supporting Information Available: The syntheses of **3**−**6** are described; UV−visible spectral data for **2**−**7** are available in Table S-1; X-ray crystal data for **5** and **7** are reported. This material is available free of charge via the Internet at http://pubs.acs.org. Crystal structure coordinates of **5** and **7**, tables of bond lengths, bond angles and torsion angles are also available from the Cambridge Structural Data File (CCDC No. 235 487 (**5**) and CCDC No. 235 488 (**7**)).

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