# Homoarcyriaflavin: Synthesis of Ring-Expanded Arcyriaflavin Analogues†

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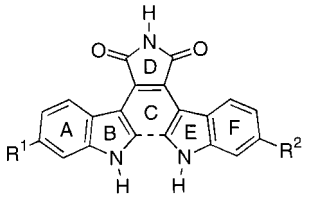
The construction of the ring-expanded carbazole system, forming arcyriaflavin homologues, is efficiently accomplished by the reaction of 2,2′-bridged bis-indoles with 3,4-dibromo-2,5-dihydro-1*H*-2,5-pyrroledione derivatives under Grignard conditions. A ring size of up to nine members in the central ring is achievable. Substitutions either at the indole system or at the imide-N are also possible. The conformation of homoarcyriaflavins as a cross-link between the rigid arcyriaflavins and the flexible arcyriarubins was investigated by NMR, X-ray, and semiempiric quantum chemical calculation methods.

## Introduction

The indole[2,3-*a*]carbazole alkaloid ring system is present in several biologically active molecules, such as the arcyriaflavins and the potent antitumor agent rebeccamycin,[1] isolated from *Nocardia aerocoligenes* in 1985.[2,3] This structurally rare class of compounds represents, together with the closely related arcyriarubins (Figure 1 and Table 1), new lead structures for the synthesis of biologically active substances.

For example, arcyriaflavin derivatives have antimicrobacterial activity against *Bacillus cereus*,[4] antitumor activity against P388 leukemia cells,[4] and inhibit protein kinase A (PKA), protein kinase C (PKC),[4−6] topoisomerases I and II[4] as well as tyrosine and serine kinases.[5] Arcyriaflavin analogues are currently being evaluated in human clinical trials as anticancer drugs.[1]

Arcyriarubins,[7−10] isolated from the fruiting bodies of the slime mould *Arcyria denundata*,[11] and related compounds also show highly potent biological effects. Inhibition of protein kinases A and C and of protein tyrosine kinase (PTK) has been described, and emerging interest




| Compound | $R^1$ | $R^2$ | --- |
|---|---|---|---|
| Arcyriaflavin A (**1a**) | H | H | single bond |
| Arcyriaflavin B (**1b**) | H | OH | single bond |
| Arcyriaflavin C (**1c**) | OH | OH | single bond |
| Arcyriarubin A (**2a**) | H | H | no bond |
| Arcyriarubin B (**2b**) | H | OH | no bond |
| Arcyriarubin C (**2c**) | OH | OH | no bond |

**Figure 1.**

in these compounds can be noted in recent patent literature.[8,12−16] These bis-indolylimides are, in contrast to indolo[2,3-*a*]carbazoles, not bridged at their indole-2-positions. Therefore, they are also named secoindolocarbazoles.[17]

For compounds **1a**−**c** a planar conformation with undistorted indole rings can be assumed. In contrast, computer calculations, NMR-studies and X-ray analysis indicated that arcyriarubin (**2a**−**c**) can adopt three different conformations due to the free rotation around the maleinimide−indole single bond.[12]

Arcyriaflavin and arcyriarubin represent the borderline cases of a completely rigid and a quite flexible arrangement of the indole substituents at the maleinimide ring.

† Dedicated to Prof. W. Wiegrebs on the occasion of his 67th birthday.

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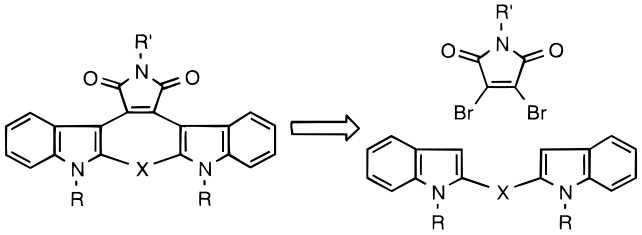
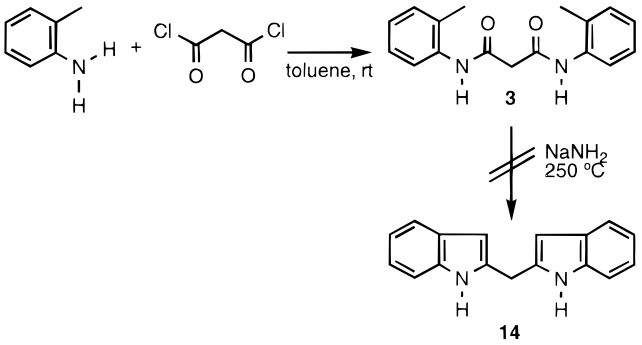


**Figure 2.**

**Scheme 1**



In our group a strategy for synthesizing semirigid, ring-expanded homoarcyriaflavins has been elaborated. New arcyriaflavin derivatives with progressively increasing ring size up to nine ring members are accessible. Due to entropic reasons, larger ring systems could not be synthesized.

## Synthesis

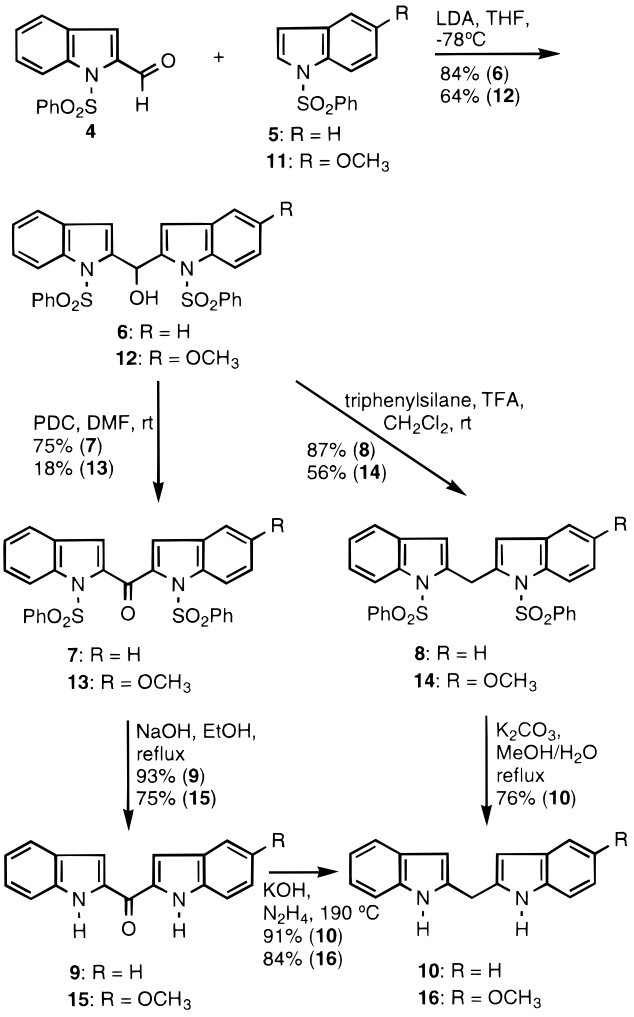
The methods for the synthesis of indolo[2,3-*a*]carbazoles are divided into two categories based on the ring-formation in the last step, i.e., either the rings B and/ or E[18] or the central ring C[18−20] (for the ring description, see Figure 1).

The synthesis of the new class of indole-2,2′-alkyl bridged bis-indolylmaleinimides was designed following a retrosynthetic analysis of the target compounds, which led to two possible synthetic equivalents, the 2,2′-bis-indoles and dibromomaleinimide derivatives (Figure 2).

We intended to synthesize methylene-2,2′-bis-indole (X = $CH_2$) (**10**), the most simple derivative of the 2,2′-bis-indole series, by the Madelung reaction. This method uses the corresponding *N*,*N*′-*o*-toluidine bis-amides, which are cyclized under the influence of strong bases at 200−400 °C. Compound **3** was obtained in moderate yield according to Julia et al.[21] by reacting malonic acid dichloride with *o*-toluidine. However, heating to 250 °C in the presence of $NaNH_2$ afforded no cyclized product (degradation) (Scheme 1).

An alternative strategy led to compound **10** and its 5-methoxy derivative **16** in good overall yields. The 5-methoxy derivatives of these indole alkaloids were synthesized because this substituent increases their biological activity.[12,22,23] *N*-Phenylsulfonylindole (**5**)[24] and the 5-methoxy derivative **11**[25] were coupled with *N*-phenylsulfonylindole-2-carbaldehyde (**4**)[24] in the presence of LDA. The reduction of the hydroxyl group with triphenylsilane and trifluoracetate (TFA) afforded 87% of compound **8** and 56% of compound **14**. Attempts to remove the phenylsulfonyl protecting group of compound **8** with potassium *tert*-butoxide or 10% NaOH in EtOH failed, but hydrolysis with $K_2CO_3$ in MeOH afforded the deprotected product **10**. Alternatively compounds **6** and **12** were oxidized with pyridinium dichromate (PDC), and the sulfonamide moiety was cleft with 10% NaOH in EtOH. The reduction of the keto group of compound **9** and **15** by Wolff−Kishner reaction under Huang−Minlon conditions afforded good yields of the bis-indolyles **10** and **16** (Scheme 2).

**Scheme 2**



The dimethylene- and trimethylene-bridged bis-indoles 1,2-bis(1*H*-2-indolyl)ethane (**17**) and 1,3-bis(1*H*-2-indolyl)-propane (**18**) were prepared according to the method of Smith et al.,[26] reacting *N*-deprotonated *N*-trimethylsilyl-*o*-toluidine with the corresponding diethyl ester. The bis-

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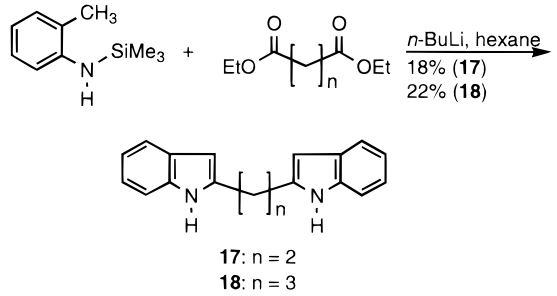
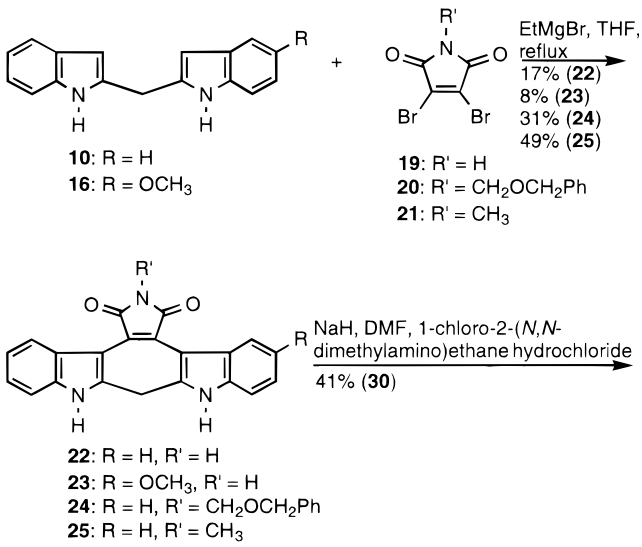
**Scheme 3**




**Scheme 4**



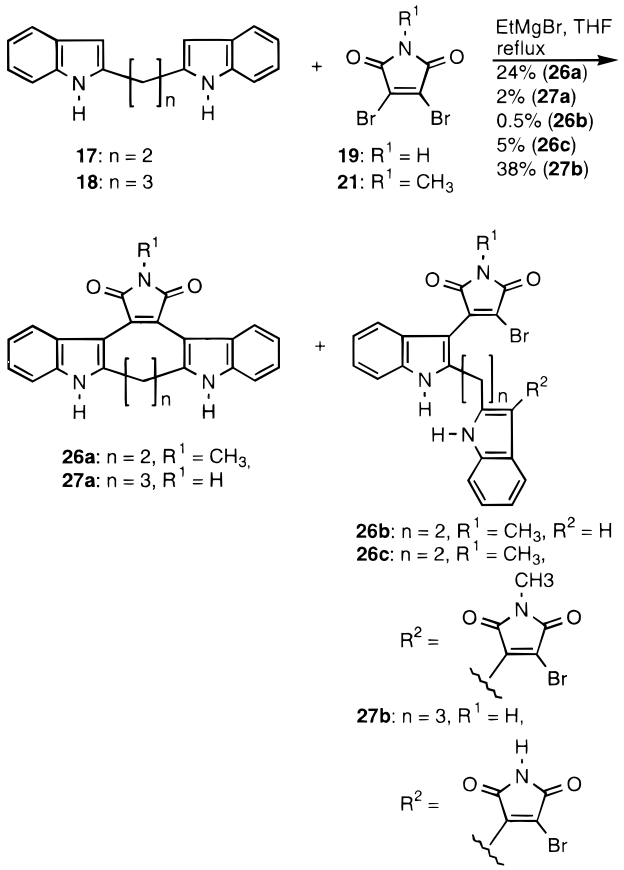

indole derivatives **17** and **18** were obtained in good yields (Scheme 3). The same reaction was carried out for the synthesis of compound **10**, but it was not practicable because the desired product could only be isolated with 1% yield besides a great variety of unidentified products. For the synthesis of the asymmetrically substituted bisindole **16**, this reaction does not seem to be the method of choice because of the low yield mentioned above.

The basic skeleton of the homoarcyriaflavins was formed by reaction of the 2,2′-bis-indoles with ethylmagnesium bromide and the pertinent maleinimide derivatives (Schemes 4 and 5).

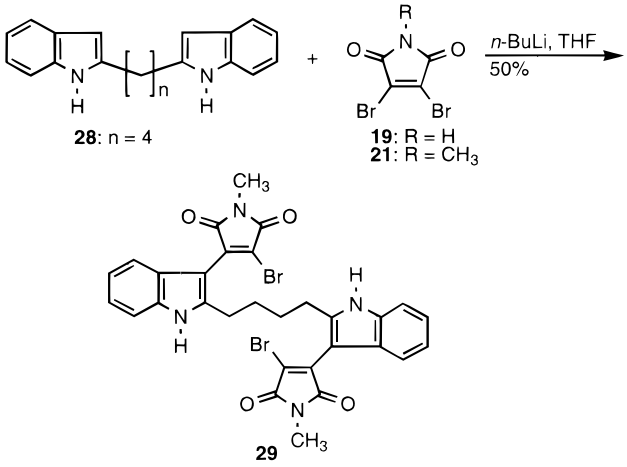
With this approach, the products **22**−**26a** and **27a** could be obtained in low to moderate yields, indicating the wide range of this strategy. In addition, the bisindoles with $n = 2$, 3 led to the noncyclized byproducts **26b**, **26c**, and **27b**.

The reaction of 1,4-bis(1*H*-2-indolyl)butane (**28**),[21] however, with the 3,4-dibromo-2,5-dihydro-1*H*-2,5-pyrroledione **19**[27] and **21**[28] afforded no cyclized products (Scheme 6). For compound **19** no well-defined products could be

**Scheme 5**




**Scheme 6**




isolated. For compound **21** neither the use of EtMgBr nor *n*-BuLi to deprotonate the indole-NH yielded the 10-membered central ring, but produced product **29** consisting of one bisindolylalkane and two maleinimide moieties. Formation of mono- and disubstituted products, already observed for the 8- and 9-membered ring-forming reaction (Scheme 5), here becomes predominant.

As the synthesized imides are scarcely soluble in water, and the corresponding HCl salts are too acidic for pharmacological or medicinal application, we introduced the strongly basic 2-(*N*,*N*-dimethylamino)ethyl group into

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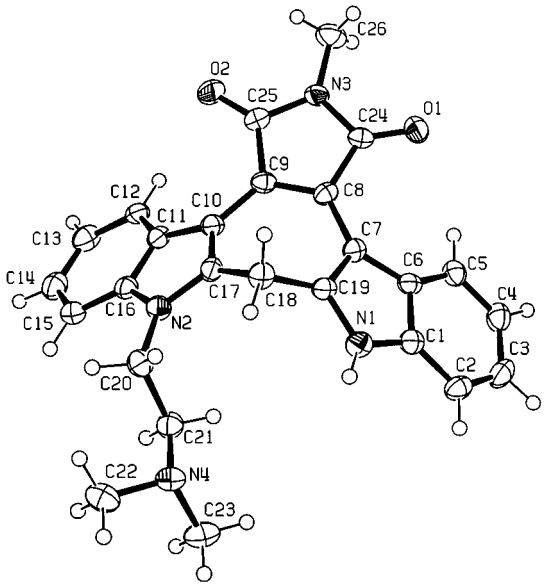


**Figure 3.** X-ray structure of compound **31** showing the crystallographic numbering scheme.

homoarcyriaflavin **22**. As a direct substitution of the indole-NH of **22** was not possible, the imide-*N*-protected derivatives **24** and **25** were used, which were synthesized by reacting the bis-indolylmagnesium bromide of methylene-2,2′-bis-indole (**10**) with the benzyloxymethyl- and methyl-substituted dibromomaleinimides **20** and **21**. Finally the amines **30** and **31** were synthesized. The benzyloxymethyl group of compound **30** was removed hydrogenolytically, followed by ammonolysis[29,30] to complete the deprotection, affording imide **33**. The methyl group of compound **31** was removed by reaction with 5 N KOH in EtOH, yielding the anhydride **32**, and subsequent melting of **32** with $NH_4OAc$ gives **33** (Scheme 4).

## Molecular Structure

Compound **31** nicely crystallized from MeOH so that a X-ray structure analysis could be performed.[31] Figure 3 (ORTEP Plot, thermal ellipsoids for 50% probability[32]) shows the structure of compound **31** (MeOH in the crystal lattice was omitted); the central ring C (Figure 1) adopts a boatlike conformation, and the plane angle between the indole rings amounts to 116.5°.

In contrast to the X-ray analysis, NMR spectroscopy gives information about the average population of conformations in solution. The X-ray analysis shows a different chemical environment for the two methylene protons of the bridge, which should result in different chemical NMR shifts. With $^1$H NMR spectroscopy, however, diastereotopic protons of the bridge could not be distinguished because of their fast interconversion in relation to the NMR time scale.

The singlet of the methylene protons of the bridge between the two indole rings at 4.25 ppm can be attributed to boat inversion. The 7-membered ring of compound **31** adopts, according to the X-ray analysis, a boatlike conformation. Low-temperature $^1$H NMR experiments at 400 MHz with **22** and **27a** as exemplary compounds in THF-$d_8$ as a solvent (solubility at low temperature was sufficient) showed decoalescence at 175 ± 3 K for **22**, but cooling compound **27a** to 175 K did not change its spectrum. Using the Eyring equation the corresponding free energy of activation for **22** amounts to $\Delta G^{\ddagger} = 9.0 \pm 0.2$ kcal mol$^{-1}$.[33,34]

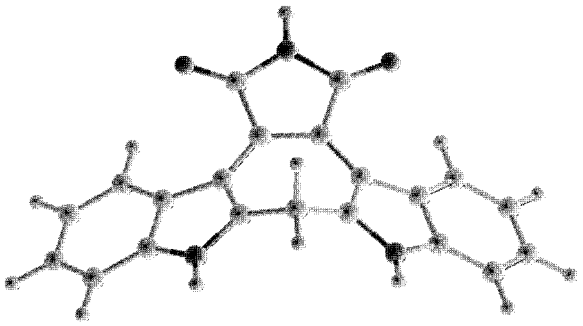

**Figure 4.** Energy minimum conformation of compound **22** ($C_S$ point group) calculated with MOPAC (AM1 Hamiltonian).

This experimental approximation of the barrier to ring inversion of compound **22** has been compared with a semiempirical quantum chemical approach to the activation enthalpy, which additionally should lead to conclusions about the geometry of the transition state. All calculations were performed with the QCPE program MOPAC 6.0 (AM1 Hamiltonian), implemented within the molecular modeling software SYBYL 6.4 (Tripos Assoc.) on a Silicon Graphics Indigo$^2$ Solid Impact workstation.

One of the two global energy minima of **22** with $C_S$ symmetry (see Figure 4, heat of formation 77.16 kcal mol$^{-1}$) essentially corresponds to the X-ray structure of **31**. The angle between the indole planes amounts to 128.2°.

Ring inversion was first simulated by a MOPAC SADDLE approach, starting from both minima. The resulting state was fully planar with an enthalpy of 13.5 kcal mol$^{-1}$ above the minimum. However, the FORCE calculation indicated that this structure represents a third-order transition state. It is therefore likely that the real inversion pathway is neither forced with all possible symmetry relations nor crossing a fully planar conformation. Further work was based on a careful gridsearch with variation of the torsion angles $\tau_1$ (C10−C17−C18−C19; see Figure 3) from −60° to 60° and $\tau_2$ (C19−C7−C8−C24) from 160° to −160°, each with an increment of 5°. All other internal coordinates were optimized without symmetry conditions. Results are illustrated by the isocontour plot in Figure 5. It becomes obvious that the inversion pathway does not proceed along the diagonal of the *xy* plane, but that $\tau_2$ passes 180° *before* $\tau_1$ arrives at 0° and *before* both indole moieties and the C18 atom of the cycloheptatriene ring are nearly coplanar. An inspection of the geometries shows that the pyrroledione oxygens do successively, not jointly, cross the neighboring indole rings without significant repulsion. The highest

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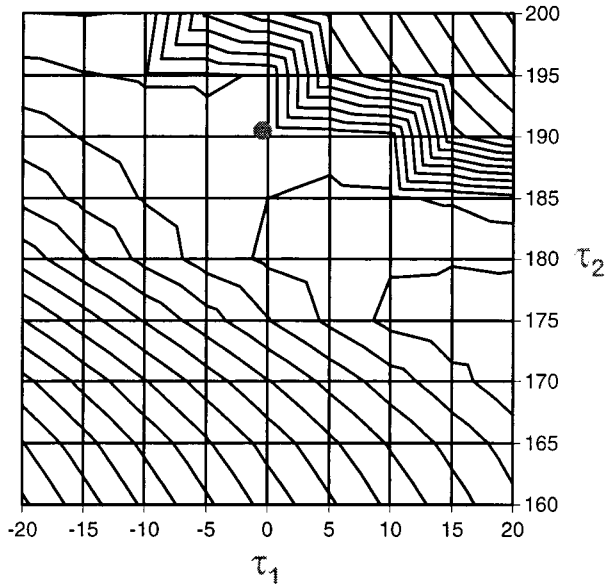


**Figure 5.** Isocontour plot resulting from grid searches of compound **22** (MOPAC, AM1 Hamiltonian). The *x* axis is the torsion angle $\tau_1$ (C10−C17−C18−C19, see Figure 3), and the *y* axis is the torsion angle $\tau_2$ (C19−C7−C8−C24). The isocontour lines are △HF (4.5−11 kcal mol$^{-1}$, interval 0.5 kcal mol$^{-1}$), as the energy difference to the minimum energy conformation. (●): transition state ($\tau_1 = -0.6°$, $\tau_2 = 190.2°$). Two continuous "linewise" approaches (preceding conformation = starting conformation of next grid point) with constant values of $\tau_1$ and $\tau_2$, respectively, and increasing values of the other angle were applied in order to simulate inversion. Both approaches lead to the same result.

energy of the minimum energy pathway results after the first crossing.

Therefore, in the transition state the pyrroledione plane should be intersected with the coplanar rest of the molecule ($C_2$ point group). This suggestion was verified by a further SADDLE calculation, starting from grid search conformations closer to the postulated state, but still with $C_S$ symmetry. The resulting saddle geometry was optimized with the TS keyword (eigenvector following routine toward transition states). The final geometry meets all conditions of a transition state: A FORCE calculation yielded one complex eigenvalue of the Hess matrix, and the eigenvalues of the rotational and translational vibrations are sufficiently close to zero. The heat of formation amounts to 87.61 kcal mol$^{-1}$, corresponding to an activation enthalpy of 10.44 kcal mol$^{-1}$. Since entropy contributions to ring inversion are mostly in the range of ±1−2 kcal mol$^{-1}$, this calculated value does well correspond to the measured barrier of ring inversion of **22**. The postulated transition state is drawn in Figure 6. The bisindolylcycloheptatriene and the pyrroledione planes become obvious, which are angled by 21.5°. At room temperature, the molecule flutters such as a hummingbird.

## Conclusion

With the synthesis of the homoarcyriaflavins the successful bridging of the gap between the rigid arcyriaflavins and the flexible arcyriarubins has been achieved. A wide variety of homoarcyriaflavin derivatives can now be synthesized with our method, so that structure−activity relationship (SAR) studies of these bis-indole alkaloids can be performed.

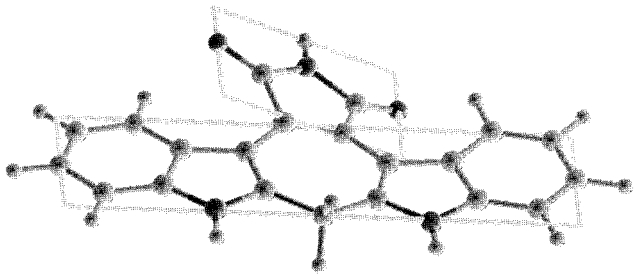

**Figure 6.** Transition state of the inversion of compound **22** ($C_2$ point group) as suggested from MOPAC calculations (AM1 Hamiltonian). Additionally, the bisindolylcycloheptatriene and the pyrroledione planes are drawn.

## Experimental Section

**General Information.** Melting points were recorded on a microscope heating stage and are not corrected. $^1$H and $^{13}$C nuclear magnetic resonance spectra, mass spectra, and microanalyses were performed by Zentrale Analytik, University of Regensburg. IR spectroscopy was performed on a FT-IR spectrometer. Thin-layer chromatography (TLC) was carried out on Al sheets coated with $60F_{245}$ silica. Compounds were detected using sprays of 3% w/v vanillin in 96% ethanol, and 5% w/v $H_2SO_4$ in 96% ethanol, respectively. Column chromatography was carried out using 70−230 mesh ASTM silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures. All reactions were carried out under dried $N_2$ in flame- or oven-dried vessels. A lot of maleimides crystallize with solvents, which could not be removed despite vigorous heating of the ground materials in vacuo. The presence of these solvents was assured by $^1$H NMR spectra.

**Bis(1-phenylsulfonyl-1*H*-2-indolyl)methanol (6).** To a solution of dry diisopropylamine (30.4 mL, 0.22 mol) in dry THF (200 mL) was added *n*-BuLi (125 mL, 0.20 mol, 1.6 M in *n*-hexane) at − 78 °C within 30 min. After stirring at 0 °C for 30 min 1-phenylsulfonyl-1*H*-indole (**5**)[24] (49.1 g, 0.19 mol), dissolved in dry THF (300 mL), was added within 10 min. The resulting mixture was stirred for 30 min at 0 °C and subsequently cooled to − 78 °C. At this temperature, 1-phenylsulfonyl-1*H*-2-indolcarbaldehyde (**4**)[24] (60.0 g, 0.21 mol), dissolved in dry THF (200 mL), was added. The resulting mixture was stirred overnight and allowed to warm to room temperature. A 1% HCl solution (500 mL) was added in one portion. After the addition of diethyl ether (500 mL) the organic layer was separated, and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine and dried over $Na_2SO_4$. The solvent was evaporated. Purification of the residue by column chromatography ($CH_2Cl_2$) yielded the alcohol **6** as colorless crystals (86.5 g, 0.16 mol, 84%): mp 185 °C (MeOH); IR (KBr) 3535, 3180−2950, 1455, 1370, 1175 cm$^{-1}$; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 8.03 (d, $J$ = 7.9 Hz, 6H), 7.58−7.67 (m, 2H), 7.46−7.57 (m, 6H), 7.19−7.38 (m, 5H), 6.76 (d, $J$ = 6.76 Hz, 1H, exchangeable), 6.46 (s, 2H); $^{13}$C NMR (63 MHz, DMSO-$d_6$) $\delta$ 143.39, 137.96, 136.24, 134.32, 129.42, 128.56, 126.62, 124.77, 123.60, 121.38, 114.09, 110.52, 62.26. Anal. Calcd for $C_{29}H_{22}N_2O_5S_2$ (542.62): C, 64.19; H, 4.09; N, 5.16. Found: C, 64.06; H, 4.02; N, 5.08.

**Bis(1-phenylsulfonyl-1*H*-2-indolyl) Ketone (7).** The solution of **6** (20.0 g, 36.9 mmol) in dry DMF (200 mL) was cooled to 0 °C. After the addition of pyridinium dichromate (PDC) (90.4 g) the mixture was stirred for 20 h at room temperature. Then $H_2O$ (700 mL) and $CH_2Cl_2$ (700 mL) were added, the layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 200 mL). The combined organic extracts were washed with $H_2O$ (500 mL) and dried over $Na_2SO_4$, and the solvent was evaporated. After addition of $CH_2Cl_2$ the ketone **7** crystallizes as colorless crystals (15.0 g, 27.7 mmol, 75%): mp 244 °C (MeOH/diethyl ether); IR (KBr) 3100−2950, 1665, 1450, 1375, 1175 cm$^{-1}$; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 8.20−

8.15 (m, 2H), 8.12−8.07 (m, 4H), 7.84−7.57 (m, 12H), 7.45−7.37 (m, 2H). Anal. Calcd for $C_{29}H_{20}N_2O_5S_2$ (540.61): C, 64.43; H, 3.73; N, 5.18. Found: C, 64.14; H, 4.01; N, 5.10.

**Bis(1-phenylsulfonyl-1*H*-2-indolyl)methane (8).** After stirring of a solution of **6** (26.7 g, 49.2 mmol) and triphenylsilane (15.0 g, 57.8 mmol) in dry $CH_2Cl_2$ (400 mL) for 30 min, TFA (22.4 mL) was added. The solution was stirred for 1 h at room temperature, $H_2O$ was added, and the solution was carefully neutralized with solid $Na_2CO_3$ with ice cooling. The organic phase was separated, dried over $Na_2SO_4$, and evaporated. Purification of the residue by column chromatography ($CH_2Cl_2$/hexane 6:4) yielded compound **8** as colorless crystals (22.5 g, 40.0 mmol, 87%): mp 144−145 °C (diethyl ether); IR (KBr) 3150−2900, 1450, 1370, 1175 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 8.08 (d, $J$ = 7.9 Hz, 2H), 7.83−7.92 (m, 4H), 7.60−7.69 (m, 2H), 7.42−7.60 (m, 8H), 7.33 (t, $J$ = 7.1 Hz, 2H), 7.23 (t, $J$ = 6.5 Hz, 2H), 6.46 (s, 2H); $^{13}C$ NMR (63 MHz, DMSO-$d_6$) $\delta$ 138.06, 137.67, 136.30, 134.48, 129.71, 129.09, 126.23, 124.44, 123.73, 120.88, 114.18, 111.36, 28.62. Anal. Calcd for $C_{29}H_{22}N_2O_4S_2$ (526.62): C, 66.14; H, 4.21; N, 5.32. Found: C, 65.99; H, 4.21; N, 5.18.

**Bis(1*H*-2-indolyl) Ketone (9).** To a solution of **7** (10.0 g, 18.5 mmol) in 99% ethanol (380 mL) was added a 10% solution of NaOH (210 mL), and the mixture was refluxed for 20 h. Then ethanol was evaporated, brine (500 mL) and $CH_2Cl_2$ (500 mL) were added, and the organic phase was separated. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 200 mL), and the combined organic extracts were dried over $Na_2SO_4$ and evaporated. The crude product crystallizes during the evaporation of $CH_2Cl_2$ and was recrystallized from $CH_2Cl_2$, affording yellow crystals (4.50 g, 17.3 mmol, 93%): mp 272−273 °C; IR (KBr) 3335, 3100−2950, 1665, 1445 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.00 (s, 2H), 7.78 (d, $J$ = 7.9 Hz, 2H), 7.60−7.66 (m, 2H), 7.54 (d, $J$ = 7.9 Hz, 2H), 7.33 (t, $J$ = 7.9 Hz, 2H), 7.13 (d, $J$ = 7.9 Hz, 2H); $^{13}C$ NMR (63 MHz, DMSO-$d_6$) $\delta$ 176.75, 137.75, 134.58, 127.29, 125.27, 122.68, 120.32, 112.65, 109.51. Anal. Calcd for $C_{17}H_{12}N_2O$ (260.30): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.22; H, 5.05; N, 10.78.

**Bis(1*H*-2-indolyl)methane (10). Method A.** A solution of **8** (15.0 g, 28.5 mmol) and $K_2CO_3$ (20.0 g) in methanol (800 mL) and $H_2O$ (200 mL) was heated to reflux for 14 d. Then brine (500 mL) and $CH_2Cl_2$ (500 mL) were added, and the organic phase was separated. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 200 mL). After drying of the organic phase over $Na_2SO_4$, the solvent was removed. The crude product was purified by column chromatography ($CH_2Cl_2$/ethyl acetate 1:1), yielding **10** as colorless crystals (5.40 g, 21.9 mmol, 76%): mp 168 °C (diethyl ether/petroleum ether); IR (KBr) 3375, 3150−2950, 1455 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 10.99 (s, 2H), 7.42 (d, $J$ = 7.5 Hz, 2H), 7.30 (d, $J$ = 7.5 Hz, 2H), 6.97−7.05 (m, 2H), 6.89−6.97 (m, 2H), 6.22 (s, 2H), 4.22 (s, 2H); $^{13}C$ NMR (63 MHz, DMSO-$d_6$) $\delta$ 136.98, 136.21, 128.23, 120.29, 119.27, 118.67, 110.81, 99.50, 27.11. Anal. Calcd for $C_{17}H_{14}N_2$ (246.31): C, 82.90; H, 5.73; N, 11.37. Found: C, 82.65; H, 5.81; N, 11.36.

**Method B.** A solution of **9** (5.00 g, 19.2 mmol), KOH (4.80 g), and hydrazine hydrate (3.50 mL) in 2-(2-hydroxyethyloxy)-1-ethanol (50 mL) was slowly heated to 190 °C, and after 2 h the excess hydrazine hydrate and $H_2O$ were removed by distillation. After cooling to room temperature, $H_2O$ (50 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined extracts were dried over $Na_2SO_4$, the solvent was removed, and the crude product was purified by column chromatography (see above), affording **10** (4.30 g, 17.5 mmol, 91%). See method A for characterization data.

**(5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl)methanol (12).** The reaction of 1-phenylsulfonyl-1*H*-2-indolcarbaldehyde (**4**)[24] (2.00 g, 6.98 mmol) with 5-methoxy-1-phenylsulfonyl-1*H*-indole (**11**)[25] (1.82 g, 6.32 mmol) was effected as described for the alcohol **6**. Purification by column chromatography ($CH_2Cl_2$) yielded the alcohol **12** as orange-yellow crystals (2.30 g, 4.03 mmol, 64%): mp 104−105 °C ($CH_2Cl_2$/hexane); IR (KBr) 3550−3240, 3130−2870, 2840, 1620, 1360, 1160 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 7.88−8.09 (m, 6H), 7.58−7.69 (m, 2H), 7.45−7.58 (m, 5H), 7.29−7.39 (m, 1H), 7.17−7.29 (m, 2H), 7.04−7.11 (m, 1H), 6.90−6.99 (m; 1H), 6.69−6.80 (m, 1H, exchangeable), 6.60 (s, 2H), 3.73 (s, 3H); $^{13}C$ NMR (63 MHz, DMSO-$d_6$) $\delta$ 156.21, 143.98, 143.42, 137.97, 137.91, 136.22, 134.31, 134.23, 130.79, 129.72, 129.41, 129.39, 128.55, 126.64, 126.52, 124.76, 123.59, 121.37, 114.99, 114.09, 113.51, 110.86, 110.51, 104.00, 62.29, 55.38. Anal. Calcd for $C_{30}H_{24}N_2O_6S_2$ (572.65): C, 62.92; H, 4.22; N, 4.89. Found: C, 62.81; H, 4.38; N, 4.99.

**(5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl) ketone (13).** Oxidation of alcohol **12** (3.10 g, 5.40 mmol) with PDC (12.2 g) was performed as described for alcohol **6**. The crude product was purified by column chromatography ($CH_2Cl_2$), affording ketone **13** as pale yellow crystals (1.20 g, 2.10 mmol, 39%): mp 205 °C (MeOH); IR (KBr) 3100−2900, 2840, 1650, 1360, 1175 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 7.19−8.19 (m, 19H), 3.80 (s, 3H). Anal. Calcd for $C_{30}H_{22}N_2O_6S_2$ (570.64): C, 63.15; H, 3.89; N, 4.91. Found: C, 62.85; H, 4.16; N, 4.87.

**(5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl)methane (14).** The reduction of alcohol **12** (2.00 g, 3.49 mmol) with triphenylsilane (1.07 g, 4.11 mmol) was effected as described for alcohol **6**. Column chromatography ($CH_2Cl_2$) of the crude product yielded compound **14** as colorless crystals (1.10 g, 1.98 mmol, 56%): mp 98−100 °C ($CH_2Cl_2$/hexane); IR (KBr) 3100−2870, 2840, 1610, 1365, 1175 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 8.02−8.06 (m, 1H), 7.93 (d, $J$ = 9.1 Hz, 1H), 7.84−7.89 (m, 2H), 7.79−7.84 (m, 2H), 7.63−7.70 (m, 2H), 7.51−7.59 (m, 4H), 7.47−7.50 (m, 1H), 7.30−7.35 (m, 1H), 7.21−7.26 (m, 1H), 7.02 (d, $J$ = 2.6 Hz, 1H), 6.92 (dd, $J$ = 9.1, 2.6 Hz, 1H), 6.43 (s, 1H), 6.39 (s, 1H), 4.84 (s, 2H), 3.73 (s, 3H). Anal. Calcd for $C_{30}H_{24}N_2O_5S_2$ (556.66): C, 64.73; H, 4.35; N, 5.03. Found: C, 64.65; H, 4.70; N, 5.09.

**1*H*-2-Indolyl (5-Methoxy-1*H*-2-indolyl) Ketone (15).** The phenylsulfonyl groups of **13** (1.00 g, 1.75 mmol) were removed as described for compound **7**. Column chromatography ($CH_2Cl_2$) afforded yellow crystals (0.38 g, 1.31 mmol, 75%): mp 233−235 °C (MeOH); IR (KBr) 3395, 3100−2900, 2840, 1665, 1440 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 9.30 (br s, 1H), 9.23 (br s, 1H), 7.04−7.56 (m, 9H), 3.88 (s, 3H). Anal. Calcd for $C_{18}H_{14}N_2O_2$ (290.32): C, 74.47; H, 4.86; N, 9.95. Found: C, 74.29; H, 4.90; N, 10.06.

**1*H*-2-Indolyl-(5-methoxy-1*H*-2-indolyl)methane (16).** Compound **16** was obtained from ketone **15** (0.35 g, 1.21 mmol) using method B (cf. reduction of ketone **9**). The crude product was purified by column chromatography ($CH_2Cl_2$), yielding **16** as colorless crystals (0.28 g, 1.01 mmol, 84%): mp 112 °C (MeOH); IR (KBr) 3400, 3150−2950, 2840, 1620, 1450 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 7.68 (br s, 2H, exchangeable), 6.50−7.27 (m, 7H), 6.36 (s, 1H), 6.32 (s, 1H), 4.17 (s, 2H), 3.80 (s, 3H). Anal. Calcd for $C_{18}H_{16}N_2O$ (276.34): C, 74.47; H, 4.86; N, 9.95. Found: C, 74.37; H, 4.95; N, 9.77.

**1,2-Bis(1*H*-2-indolyl)ethane (17).** To a solution of *N*-trimethylsilyl-*o*-toluidine (2.00 g, 11.2 mmol) in dry hexane (100 mL) was added *n*-BuLi (14.0 mL, 22.4 mmol, 1.6 M in *n*-hexane) drop by drop at room temperature. The mixture was refluxed overnight and then cooled to − 78 °C. At this temperature diethyl succinate (0.97 g, 5.57 mmol), dissolved in THF (40 mL), was added slowly. Then the mixture was warmed to room temperature and poured into ice water (100 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over $Na_2SO_4$, the solvent was evaporated, and the residue was purified by column chromatography ($CH_2Cl_2$/hexane 4:1), yielding the bis-indole **17** as colorless crystals (0.26 g, 0.99 mmol, 18%): mp 264−267 °C; IR (KBr) 3394, 3048, 2911 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.00 (s, 2H), 7.40 (d, $J$ = 7.6 Hz, 2H), 7.29 (d, $J$ = 7.4 Hz, 2H), 6.91−6.99 (m, 4H), 6.19 (s, 2H), 3.16 (s, 4H); MS $m/z$ (%) 260 (42) [$M^{+\bullet}$]. Anal. Calcd for $C_{18}H_{16}N_2$ (260.34): C, 83.04; H, 6.19; N, 10.76. Found: C, 82.77; H, 6.31; N, 10.67.

**1,3-Bis(1*H*-2-indolyl)propane (18).** Compound **18** was prepared as described for the bis-indole **17** with diethyl pentandioate (20.5 mL, 0.11 mol) and *N*-trimethylsilyl-*o*-toluidine (38.0 g, 0.21 mol). The residue was purified by column

chromatography ($CH_2Cl_2$/hexane 1:1), yielding the bis-indole **18** as colorless crystals (6.55 g, 23.9 mmol, 22%): mp 143−145 °C (ethanol); IR (KBr) 3388, 3053, 2941, 2916, 2863, 1542, 1457 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 10.91 (br s, 2H), 7.37−7.43 (m, 2H), 7.24−7.31 (m, 2H), 6.87−7.03 (m, 4H), 6.18 (d, $J$ = 1.6 Hz, 2H), 2.78 (t, $J$ = 7.3 Hz, 4H), 2.12 (quint, $J$ = 7.3 Hz, 2H). Anal. Calcd for $C_{19}H_{18}N_2$ (274.37): C, 83.18; H, 6.61; N, 10.21. Found: C, 82.94; H, 6.87; N, 10.21.

**1,2,3,8,9,10-Hexahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cyclohepta[*b*]indole-1,3-dione (22).** Mg shavings (0.24 g, 9.75 mmol) and ethyl bromide (0.37 mL, 4.88 mmol) were added to dry THF (6 mL). When the reaction has started, further ethyl bromide (0.37 mL, 4.88 mmol) was added dropwise so that the solution was refluxing gently. Then the solution was heated to reflux until all Mg has dissolved (ca. 30 min). After cooling to room temperature compound **10** (1.00 g, 4.06 mmol), dissolved in a mixture of dry toluene (25 mL) and THF (1 mL), was added slowly, and the mixture was stirred for 45 min at 45 °C. After the mixture has cooled to room temperature, a solution of 3,4-dibromo-2,5-dihydro-1*H*-2,5-pyrroledione (**19**)[27] (1.04 g, 4.06 mmol) in dry toluene (50 mL) and THF (2 mL) was added drop by drop during 1 h, and the resulting dark solution was heated to reflux overnight. Then ice (100 g) and 20% citric acid (50 mL) were added, the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with $H_2O$ and dried over $Na_2SO_4$, and the solvent was evaporated. The crude product was separated from remaining starting material and byproducts by column chromatography (1, $CH_2Cl_2$/ethyl acetate 4:1; 2, $CH_2Cl_2$/ethyl acetate 7:1), affording product **22** as red crystals (0.29 g, 0.68 mmol, 17%): mp >350 °C (ethyl acetate); IR (KBr) 3385, 3100−2900, 1750, 1455 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.92 (br s, 2H), 10.79 (br s, 1H), 8.03 (d, $J$ = 7.5 Hz, 2H), 7.41 (d, $J$ = 7.5 Hz, 2H), 7.03−7.16 (m, 4H), 4.27 (s, 2H); MS $m/z$ (%) 339 (84) [$M^{+\bullet}$], 338 (100) [$M - H]^+$; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 475 (3.94), 384 (3.69), 274 (4.21), 219 nm (4.65). Anal. Calcd for $C_{21}H_{13}N_3O_2$ (339.35): C, 74.24; H, 3.86; N, 12.38. Found: C, 74.12; H, 3.63; N, 12.45.

**5-Methoxy-1,2,3,8,9,10-hexahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cyclohepta[*b*]indole-1,3-dione (23).** Compound 2**3** was obtained from the bis-indole **16** (0.27 g, 0.98 mmol) and compound **19** (0.25 g, 0.98 mmol) as described for compound **22**. The crude product was purified by column chromatography ($CH_2Cl_2$/ethyl acetate 4:1) affording the product as red crystals (35.0 mg, 0.08 mmol, 8%): mp >350 °C (EtOH); IR (KBr) 3380, 3100−2950, 2840, 1705, 1450 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.89 (br s, 1H), 11.78 (br s, 1H), 10.79 (br s, 1H), 8.04 (d, $J$ = 7.5 Hz, 1H), 7.61 (d, $J$ = 7.5 Hz, 1H), 6.68−7.46 (m, 5H), 4.24 (s, 2H), 3.75 (s, 3H); MS $m/z$ (%) 369 (97) [$M^{+\bullet}$], 368 (100) $[M - H]^+$. Anal. Calcd for $C_{22}H_{15}N_3O_3$ (369.38): C, 72.12; H, 4.09; N, 11.38. Found: C, 72.31; H, 3.95; N, 11.52.

**2-Benzyloxymethyl-1,2,3,8,9,10-hexahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cyclohepta[*b*]indole-1,3-dione (24).** Compound **24** was obtained from the indole derivative **10** (4.00 g, 16.2 mmol) and 1-benzyloxymethyl-3,4-dibromo-2,5-dihydro-1*H*-2,5-pyrroledione **(20)**[29] (6.12 g, 16.3 mmol) as described for compound **22**. The crude product was purified by column chromatography ($CH_2Cl_2$/ethyl acetate 9:1), affording **24** as dark red crystals (2.30 g, 5.00 mmol, 31%): mp 288−290 °C ($CH_2Cl_2$/hexane); IR (KBr) 3385, 3100−2900, 1740, 1705, 1455 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.00 (br s, 2H), 8.09 (d, $J$ = 7.4 Hz, 2H), 7.07−7.56 (m, 11H), 5.15 (s, 2H), 4.69 (s, 2H), 4.29 (s, 2H); MS $m/z$ (%) 459 (10) [$M^{+\bullet}$]; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 481 (3.52), 339 (3.49), 277 (3.84), 223 (4.26), 208 nm (4.32). Anal. Calcd for $C_{29}H_{21}N_3O_3$ (459.50): C, 75.80; H, 4.61; N, 9.14. Found: C, 75.86; H, 4.76; N, 8.91.

**2-Methyl-1,2,3,8,9,10-hexahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cyclohepta[*b*]indole-1,3-dione (25).** Compound **25** was obtained from the indole derivative **10** (10.0 g, 28.3 mmol) and 3,4-dibromo-1-methyl-2,5-dihydro-1*H*-2,5-pyrroledione **(21)**[28] (10.98 g, 40.8 mmol) as described for compound **22**. The crude product was purified by column chromatography ($CH_2Cl_2$/ethyl acetate 9:1), affording **25** as red crystals (4.50 g, 11.3 mmol, 40%): mp >350 °C (EtOH); IR (KBr) 3400, 3100−2900, 1760, 1615, 1455 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.59 (br s, 2H), 8.07 (d, $J$ = 7.6 Hz, 2H), 7.42 (d, $J$ = 7.6 Hz, 2H), 7.04−7.36 (m, 4H), 4.28 (s, 2H), 3.10 (s, 3H); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 486 (3.70), 385 (3.50), 276 (4.08), 220 (4.44), 209 nm (4.46). Anal. Calcd for $C_{22}H_{15}N_3O_2$ (353.38): C, 74.77; H, 4.28; N, 11.89. Found: C, 74.68; H, 4.39; N, 11.82.

**2-Methyl-2,3,8,9,10,11-hexahydro-1*H*-indolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cycloocta[*b*]indole-1,3-dione (26a). 3-Bromo-4-(2-(2-(1*H*-2-indolyl)ethyl)-1*H*-3-indolyl)-1-methyl-2,5-dihydro-1*H*-2,5-pyrroledione (26b) and 3-Bromo-4-(2-(2-(3-(4-bromo-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-3-pyrrolyl)-1*H*-2-indolyl)ethyl)-1*H*-3-indolyl)-1-methyl-2,5-dihydro-1*H*-2,5-pyrroledione (26c).** Compounds **26a**−**c** were obtained when 3,4-dibromo-1-methyl-2,5-dihydro-1*H*-2,5-pyrroledione (**21**)[28] (0.26 g, 0.96 mmol) was reacted with compound **17** (0.25 g, 0.96 mmol) under the conditions used for compound **22**. The mixture of products was separated ($CH_2Cl_2$/ethyl acetate 9:1) and further purified by column chromatography (**26a**, $CH_2Cl_2$/ethyl acetate 9:1; **26b**, **26c**, diethyl ether).

**26a**: red crystals (83.0 mg, 0.23 mmol, 24%): mp >350 °C; IR (KBr) 3410, 3349, 2931, 1692, 1626 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.61 (s, 2H), 7.48 (d, $J$ = 7.8 Hz, 2H), 7.30 (d, $J$ = 7.9 Hz, 2H), 6.84−7.16 (m, 4H), 3.24 (br s, 4H), 3.09 (s, 3H); MS $m/z$ (%) 367 (100) [$M^{+\bullet}$]. Anal. Calcd for $C_{23}H_{17}N_3O_2$ (367.41) C, 75.19; H, 4.66; N, 11.44. Found: C, 75.38; H, 4.53; N, 11.35.

**26b**: orange crystals (2.0 mg, 0.005 mmol, 0.5%): mp 169 °C (dec); IR (KBr) 3391, 2933, 1709, 1623 $cm^{-1}$; FD-MS $m/z$ 447; 449 [$M^{+\bullet}$]. Anal. Calcd for $C_{23}H_{18}BrN_3O_2$ (448.32) C, 61.62; H, 4.05; N, 9.37. Found: C, 61.78; H, 4.17; N, 9.42.

**26c**: orange crystals (30.0 mg, 0.05 mmol, 5%): mp 179 °C (dec); IR (KBr) 3387, 2938, 1710, 1625 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.77 (br s, 2H), 7.31−7.49 (m, 4H), 6.97−7.20 (m, 4H), 3.16 (br s, 4H), 3.00 (s, 6H); FD-MS $m/z$ 634; 636; 638 [$M^{+\bullet}$]. Anal. Calcd for $C_{28}H_{20}Br_2N_4O_4$ (636.30) C, 52.85; H, 3.17; N, 8.81. Found: C, 52.80; H, 3.23; N, 8.63.

**1,2,3,8,9,10,11,12-Octahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]-cyclonona[*b*]indole-1,3-dione (27a) and 3-Bromo-4-(2-(3-(3-(4-bromo-2,5-dioxo-2,5-dihydro-1*H*-3-pyrrolyl)-1*H*-2-indolyl)propyl)-1*H*-3-indolyl)-2,5-dihydro-1*H*-pyrrol-2,5-dione (27b).** Compounds **27a** and **27b** were obtained from compounds **18** (11.0 g, 0.04 mol) and **19** (5.70 g, 0.02 mol), according to the procedure used for compound **22**. The mixture of products was separated and purified by column chromatography ($CH_2Cl_2$/ethyl acetate 2:1).

**27a**: red powder (0.21 g, 0.54 mmol, 2%): mp >350 °C; IR (KBr) 3400, 3188, 3064, 2929, 2854, 1702 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.25 (s, 2H), 11.00 (s, 1H), 7.15−7.27 (m, 4H), 6.82−7.03 (m, 4H), 2.73−2.92 (br m, 4H), 1.95−2.10 (br m, 2H); MS $m/z$ (%) 367 (100) [$M^{+\bullet}$]. Anal. Calcd for $C_{23}H_{17}N_3O_2$ (367.41): C, 75.19; H, 4.66; N, 11.44. Found: C, 75.33; H, 4.82; N, 11.20.

**27b**: orange powder (4.80 g, 7.72 mmol, 38%): mp >350 °C; IR (KBr) 3217, 3056, 2929, 1719 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.68 (s, 2H), 11.36 (s, 2H), 7.29−7.42 (m, 2H), 6.74−7.25 (m, 6H), 2.70−2.90 (br m, 4H), 1.99−2.17 (br m, 2H). Anal. Calcd for $C_{27}H_{18}Br_2N_4O_4$ (622.28): C, 52.12; H, 2.92; N, 9.00. Found: C, 51.89; H, 3.11; N, 8.87.

**3-Bromo-4-(2-(4-(3-(4-bromo-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-3-pyrrolyl)-1*H*-2-indolyl)butyl)-1*H*-3-indolyl)-1-methyl-2,5-dihydro-1*H*-2,5-pyrroledione (29).** A solution of 1,2-bis(1*H*-2-indolyl)butane (**28**)[21] (8.05 g, 28.0 mmol) in dry THF (100 mL) was cooled to 0 °C, and *n*-BuLi (42.0 mL, 67.2 mmol, 1.6 M in *n*-hexane) was added drop by drop. The solution was stirred for 1 h at this temperature, then 3,4-dibromo-1-methyl-2,5-dihydro-1*H*-2,5-pyrroledione (**21**)[28] in THF (100 mL) was added. The mixture was stirred at room temperature overnight, then 2 N HCl (250 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over $Na_2SO_4$, the solvent was evaporated, and the residue was purified by column chromatography ($CH_2Cl_2$/ethyl acetate 9:1), yielding compound **29** as a red powder (9.37 g, 14.1 mmol, 50%): mp 190 °C (dec); IR (KBr) 3398, 1769, 1709 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.70 (s, 2H), 6.99−7.38 (m, 8H), 3.00 (s,

6H), 2.66−2.82 (m, 4H), 1.68−1.83 (m, 4H); MS *m*/*z* (%) 504 (20) $[M - 2\ Br]^{+\bullet}$, 156 (100). Anal. Calcd for $C_{30}H_{24}Br_2N_4O_4$ (664.4): C, 54.24; H, 3.64; N, 8.43. Found: C, 54.34; H, 3.76; N, 8.39.

**2-Benzyloxymethyl-8-(2-(*N*,*N*-dimethylamino)ethyl)-1,2,3,8,9,10-hexahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cyclohepta[*b*]indole-1,3-dione (30).** NaH (80% in paraffin oil) (0.42 g, 3.92 mmol) was suspended in dry DMF (15 mL), compound **24** (0.60 g, 1.31 mmol) was added, and the resulting mixture was stirred for 30 min at room temperature. Then a solution of 1-chloro-2-(*N*,*N*-dimethylamino)ethane (80.7 mg, 0.75 mmol) (freshly prepared from 1-chloro-2-(*N*,*N*-dimethylamino)ethane hydrochloride[35]) in DMF (5 mL) was added drop by drop, and the mixture was stirred for 4.5 h at 40 °C. After 2 and 4 h, further 1-chloro-2-(*N*,*N*-dimethylamino)ethane (each time 30.0 mg, 0.28 mmol, see above) was added. This addition in portions increases the yield of compound **30**. Then saturated $NaHCO_3$ solution (15 mL) was added, and the resulting mixture was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phases were washed with $H_2O$ (100 mL) and dried over $Na_2SO_4$, and the solvent was evaporated. The crude product was purified by column chromatography (toluene/isopropylamine 4:1), affording pure **30** as red crystals (0.30 g, 0.53 mmol, 41%): mp 164−165 °C (MeOH); IR (KBr) 3560, 2939, 1698, 1459 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.88 (br s, 1H), 8.05 (d, $J$ = 8.9 Hz, 1H), 8.01 (d, $J$ = 8.2 Hz, 1H), 7.55 (d, $J$ = 8.1 Hz, 1H), 7.47 (d, $J$ = 7.3 Hz, 1H), 7.07−7.41 (m, 9H), 5.16 (s, 2H), 4.69 (s, 2H), 4.50 (t, $J$ = 6.5 Hz, 2H), 4.26 (s, 2H), 2.57 (t, $J$ = 6.5 Hz, 2H), 2.26 (s, 6H); MS *m*/*z* (%) 530 (6) $[M^{+\bullet}]$; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 483 (3.65), 388 (3.49), 277 (3.95), 207 nm (4.49). Anal. Calcd for $C_{33}H_{30}N_4O_3$·MeOH (562.67): C, 72.58; H, 6.09; N, 9.96. Found: C, 72.19; H, 6.17; N, 9.97.

**8-(2-(*N*,*N*-Dimethylamino)ethyl)-2-methyl-1,2,3,8,9,10-hexahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cyclohepta[*b*]-indole-1,3-dione (31).** Compound **31** was obtained from compound **25** (2.00 g, 5.66 mmol) as described for compound **30**, affording the product as red crystals (1.30 g, 2.95 mmol, 52%): mp 185 °C (MeOH); IR (KBr) 3390, 3100−2900, 1750, 1610, 1460 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.84 (br s, 1H), 8.06 (d, $J$ = 7.7 Hz, 1H), 8.02 (d, $J$ = 7.8 Hz, 1H), 7.53 (d, $J$ = 7.6 Hz, 1H), 7.46 (d, $J$ = 7.6 Hz, 1H), 7.01−7.24 (m, 4H), 4.48 (t, $J$ = 6.8 Hz, 2H), 4.25 (s, 2H), 3.11 (s, 3H), 2.62 (t, $J$ = 6.8 Hz, 2H), 2.26 (s, 6H); MS *m*/*z* (%) 424 (4) $[M^{+\bullet}]$; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 486 (3.68), 358 (3.49), 277 (4.05), 207 nm (4.51). Anal. Calcd for $C_{26}H_{24}N_4O_2$·MeOH (440.52): C, 72.25; H, 5.95; N, 12.72. Found: C, 72.60; H, 6.08; N, 12.68.

**8-(2-(*N*,*N*-Dimethylamino)ethyl)-3,8,9,10-tetrahydro-1*H*-indolo[3′,2′:5,6]furo[3′,4′:3,4]-cyclohepta[*b*]indole-1,3-dione (32).** A solution of **31** (1.00 g, 2.36 mmol) in EtOH (340 mL) and 5 N KOH (60 mL) was stirred overnight at room temperature. After acidifying the solution with 2 N HCl to pH = 7, the mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic phases were dried over $Na_2SO_4$, and the solvent was evaporated. The crude product was purified by column chromatography ($CH_2Cl_2$/MeOH 9:1), affording **32** as red crystals (0.90 g, 2.10 mmol, 89%): mp >350 °C (MeOH); IR (KBr) 3430, 3100−2900, 1850, 1750, 1440, 1040 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.80 (br s, 1H), 8.00−8.05 (m, 2H), 7.82 (d, $J$ = 8.1 Hz, 1H), 7.48 (d, $J$ = 7.1 Hz, 1H), 7.11−7.33 (m, 4H), 4.93 (t, $J$ = 7.7 Hz, 2H), 4.50 (s, 2H), 3.51 (t, $J$ = 7.8 Hz, 2H), 2.51 (s, 6H); MS *m*/*z* (%) 411 (8) $[M^{+\bullet}]$; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 477 (4.44), 386 (3.26), 351 (3.49), 286 (3.70), 260 (3.54), 223 (4.07), 207 nm (4.05). Anal. Calcd for $C_{25}H_{21}N_3O_3$·$H_2O$ (429.48): C, 69.92; H, 5.40; N, 9.78. Found: C, 69.56; H, 5.68; N, 9.37.

**8-(2-(*N*,*N*-Dimethylamino)ethyl)-1,2,3,8,9,10-hexahydroindolo[3′,2′:5,6]pyrrolo[3′,4′:3,4]cyclohepta[*b*]indole-1,3-dione (33). Method A.** A suspension of compound **30** (0.30 g, 0.57 mmol) and 5% Pd/C (0.60 g) in dry ethanol (200 mL) was stirred for 7 d at a $H_2$ pressure of 20 bar. When the reaction was complete (TLC control) the catalyst was filtered off through Celite, the filter was washed with $CH_2Cl_2$ (100 mL), and the solvent was removed. The crude product was dissolved in THF (40 mL), the solution was cooled to 0 °C, and $NH_3$ was bubbled through the solution[29,30] for 10 min. After stirring for 2 h at room temperature, the solvent was removed, and the residual oil was purified by column chromatography (toluene/ethyl acetate 4:1), yielding **33** as red crystals (9.0 mg, 0.02 mmol, 3%): mp 213−214 °C (EtOH); IR (KBr) 3203, 2964, 1750, 1699, 1463 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 11.84 (br s, 1H), 11.82 (br s, 1H), 8.04 (d, $J$ = 7.5 Hz, 1H), 8.01 (d, $J$ = 7.7 Hz, 1H), 7.52 (d, $J$ = 8.1 Hz, 1H), 7.44 (d, $J$ = 8.1 Hz, 1H), 7.04−7.23 (m, 4H), 4.50 (t, $J$ = 6.7 Hz, 2H), 4.24 (s, 2H), 2.61 (t, $J$ = 6.7 Hz, 2H), 2.22 (s, 6H); MS *m*/*z* (%) 410 (6) $[M^{+\bullet}]$; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 474 (3.69), 385 (3.49), 285 (3.98), 277 (3.97), 223 (4.44), 208 nm (4.46). Anal. Calcd for $C_{25}H_{22}N_4O_2$·EtOH (456.54): C, 71.03; H, 6.18; N, 12.27. Found: C, 71.38; H, 5.86; N, 12.40.

**Method B.** A mixture of **32** (0.90 g, 2.19 mmol) and ammonium acetate (30.0 g) was melted and stirred at 140 °C for 1 h. After cooling of the mixture to room temperature, saturated $NaHCO_3$ solution (50 mL) and $CH_2Cl_2$ (50 mL) were added, the phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined extracts were dried over $Na_2SO_4$, the solvent was removed, and the crude product was purified as described above, affording **33** (0.10 g, 0.22 mmol, 10%).

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**Supporting Information Available:** Crystallographic data for **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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