Investigations of the Reaction Mechanisms of 1,2-Indanediones with Amino Acids

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The reaction mechanisms of amino acids with a new class of fluorogenic reagents were investigated. The structures of colored and fluorescent species formed in these reactions were partially confirmed by experimental evidence. Reaction intermediates, C−N−C 1,3-dipoles derived from imines, were trapped with dipolarophiles in 3 + 2 cycloadditions to form spiropyrrolidines.

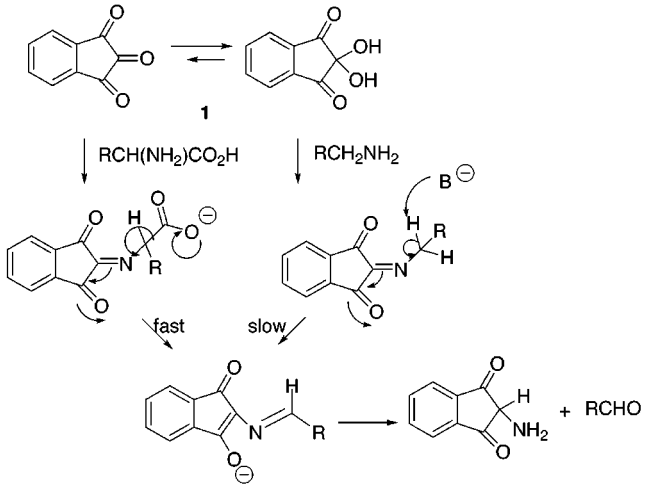
Introduction

The growing need for reagents that allow the identification of latent fingerprints on paper led us to investigate novel reagents for this purpose. Ninhydrin (**1**, Scheme 1) has been the reagent of choice for many years, mainly due to low cost and ease of use.[1] However, chromogenic (colored) imaging has long been considered less sensitive than fluorogenic (fluorescent) imaging for a variety of reasons, and there is a growing demand for fluorogenic reagents.

Fluorogenic reagents such as DFO (1,8-diazafluorenone), NBD-Cl, dansyl chloride, and fluorescein can produce extremely good results. However, the reagent of choice over the past few years has been DFO because of its reasonably long wavelength emission and its ability to differentiate between amines and amino acids. Upon reaction with amino acids, this reagent affords a fluorescent product that offers high quantum yield, good stability, and a reasonable Stokes shift that is beyond the background luminescence of most paper types.[2] We have reported new fluorogenic reagents, 1,2-indanediones, that offer the same desirable properties with the added benefits of being more affordable, more soluble, and easier to use.[3−5]

Modifications of reagents in order to improve the color/fluorescence of the reaction products is best achieved by a complete understanding of the nature of the reaction. While the ninhydrin/amino acid reaction has been well investigated[1] and is still the subject of some reports,[6] the 1,2-indanedione reaction with amines and amino acids has not been elucidated. We now present our attempts to understand the reaction mechanism of 1,2-indanediones and amino acids.

Scheme 1



Background

Amino acids are known to undergo Strecker degradation in the presence of aldehydes and ketones.[7] In the overall transformation, the aldehyde or ketone is reduced to an amine, whereas the amino acid is decarboxylated and converted to an aldehyde. Shoenberg and Moubacher gave a general outline of this reaction.[8,9] The proposed mechanism was consistent with experimental observations that both amino acids and amines with an α-hydrogen can reduce ketones and aldehydes. Later Friedman and co-workers devised mechanisms for the reactions of ninhydrin with amines and amino acids (Scheme 1). The authors accounted for the observed difference in the respective reaction rates.[10−12]

As early as 1970 an alternative mechanistic interpretation of Strecker degradation was offered by Rizzi.[13] This

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(13) Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069−2072.

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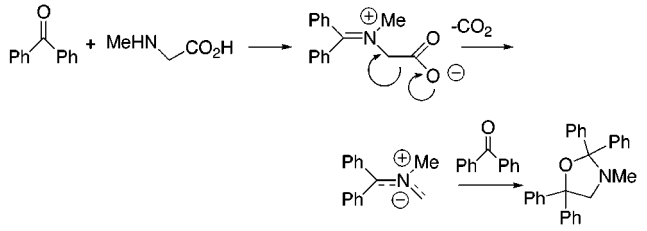
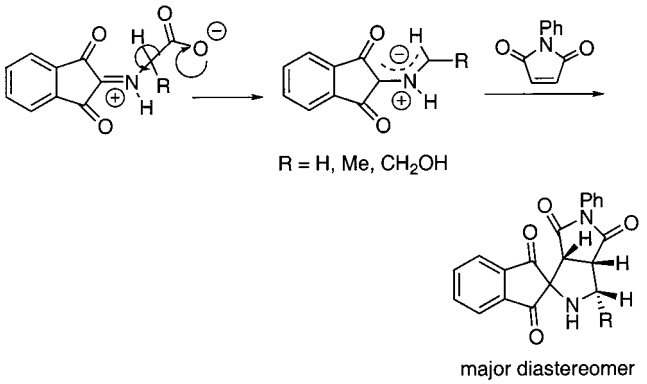
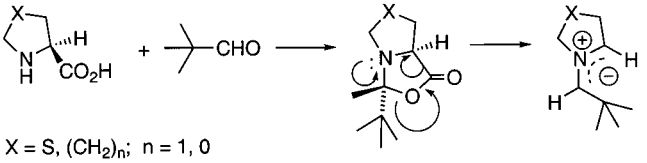
Scheme 2



Scheme 3



Scheme 4



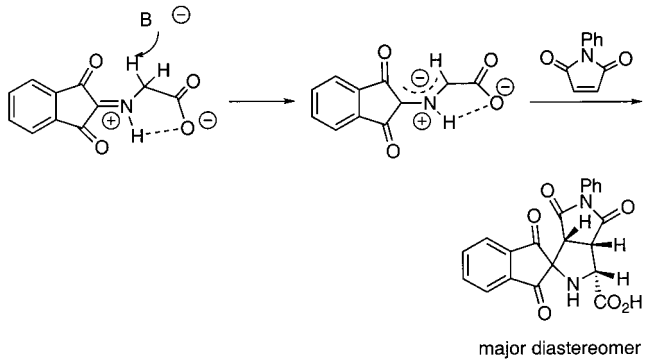
author reported chemical evidence for resonance-stabilized azomethine ylide formation in the reactions of sarcosine with benzophenone or benzaldehyde. The azomethine ylide (a C−N−C 1,3-dipole) is generated by decarboxylation of an iminium zwitterion. It reacts with excess ketone or aldehyde in a 3 + 2 cycloaddition reaction to yield oxazolidines that can be isolated and characterized (Scheme 2).

Later Grigg and co-workers extensively investigated the mechanistic aspects and the scope of C−N−C dipole formation from imines.[14] Decarboxylation of the initial imine formed in the ninhydrin reaction may be the major route to a 1,3-dipole. This dipole was trapped in a 3 + 2 cycloaddition reaction with *N*-phenyl maleimide as dipolarophile (Scheme 3).

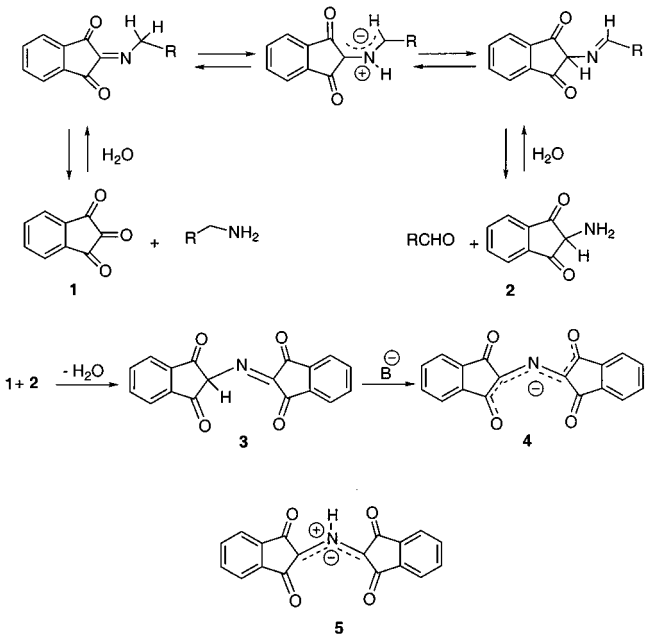
The species that undergoes decarboxylation in the ninhydrin−amino acid reaction may exist not only in an open form, but also in a cyclic, oxazolidinone form. Although oxazolidinones were not detected in ninhydrin reactions, they are known to form in the reactions of other carbonyl compounds with α-amino acids. Several oxazolidinones have been isolated and shown to undergo concerted cycloreversion reactions yielding carbon dioxide and the corresponding 1,3-dipoles upon heating (Scheme 4).[15]

A less common pathway of C−N−C dipole formation in the ninhydrin−amino acid reaction is via deprotonation of parent imines, without decarboxylation. Grigg et

Scheme 5



Scheme 6

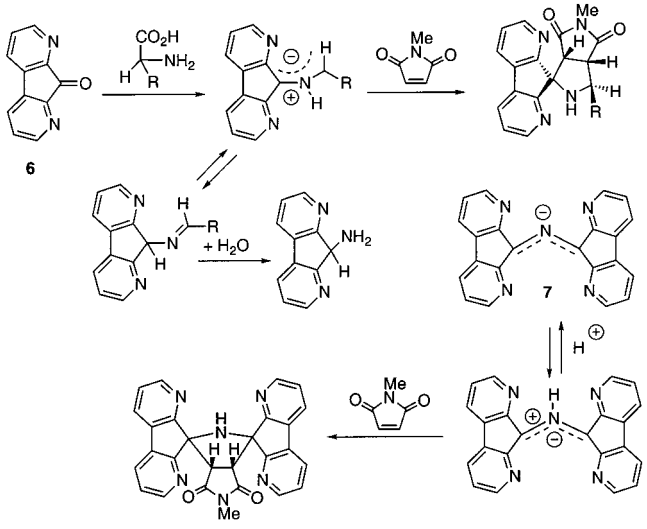


al. have observed glycine to form dipoles via deprotonation (Scheme 5). The observation involved direct deprotonation of a zwitterion with an external base, but the initial intramolecular deprotonation of imines in the ninhydrin reaction is a possibility.[16] This deprotonation can be also described as a 1,5-shift. The concept of a 1,5-shift facilitating dipole formation was applied not only to amino acid reactions, but to reactions of primary and secondary amines as well.[17] The carbonyl compound in this case contains a O=C−C=X moiety, where the C=X group can be a part of an aldehyde, ketone, amide, ester, or a heterocycle, such as pyridine or thiazole. The role of the C=X group is 2-fold: it enables the proton transfer and increases the partial positive charge on the reactive carbonyl.

Once formed, a 1,3-dipole can undergo an internal or solvent-assisted 1,2-proton shift to yield either the parent imine or its regioisomer. These imines can then undergo hydrolysis resulting in either regeneration of the initial ketone or in its reduction to the corresponding amine. When ninhydrin (**1**) plays the role of the initial ketone, it is reduced to 2-amino-1,3-indanedione (**2**, Scheme 6).

(14) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, pp 161−204.
(15) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390−5398.
(16) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thiapatangul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602−604.
(17) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89−121.

Scheme 7



2-Amino-1,3-indanedione (**2**) reacts with excess ninhydrin to yield an imine (**3**), which in turn can undergo fast deprotonation to form the anionic chromophore Ruhemann's purple (**4**), a highly stabilized aza-allylic anion with a high molar extinction coefficient (Scheme 6). It is the formation of Ruhemann's purple that allows one to visually detect patterns of amino acid distribution on surfaces, thus ensuring applications of ninhydrin in forensic science for latent fingerprint detection.

Imine **3** is not a stable form of protonated Ruhemann's purple. Experiments conducted by Grigg and co-workers demonstrated that the protonated form of Ruhemann's purple exists as a 1,3-dipole (**5**, Scheme 6) and displays the corresponding reactivity.[18]

1,8-Diazafluoren-9-one (**6**, DFO, Scheme 7), a reagent developed by Pounds and co-workers,[2] is structurally similar to ninhydrin. Its carbonyl is activated by two flanking electron-withdrawing moieties. Upon reaction with amino acids it forms a chromophore (**7**, Scheme 8) which is not unlike Ruhemann's purple. The structures of dipolar intermediates shown in Scheme 7 were confirmed by trapping the 1,3-dipoles with *N*-methyl maleimide as a dipolarophile.

Unlike ninhydrin, which produces nonfluorescent dark purple traces in the amino acid reactions, 1,8-diaza-9-fluorenone (**6**) produces somewhat faint pink traces. The advantage of **6** lies in the intense fluorescence of developed amino acid stains; it is one of the most sensitive fluorogenic reagents currently employed for latent fingerprint detection.[19,20] The nature of the fluorophore has not been ascertained.

Results and Discussion

1,2-Indanedione (**8**), which has a carbonyl group activated toward nucleophilic attack, is similar to both ninhydrin and DFO in this respect. The C-2 keto group of **8** is the more reactive of the two: carbon nucleophiles such as malonic acid dinitrile attack 1,2-indanediones at the C-2 carbonyl.[21]

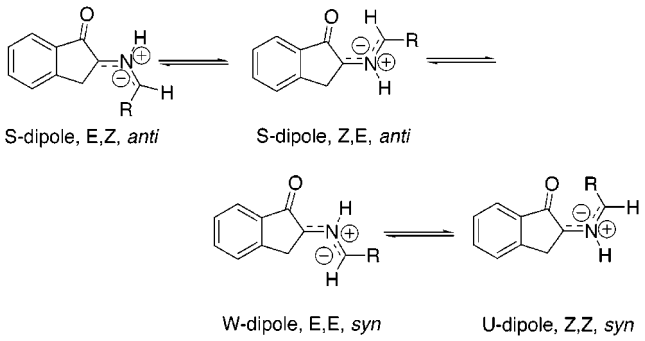


Figure 1. Geometric Isomers of −C−N−C− 1,3-Dipoles.

It has been suggested in the literature that oxygen nucleophiles (alcohols) may display the same type of reactivity with 1,2-indanediones, but no hemiketals were isolated. We have obtained 2,2-dimethoxy-1-indanone (**9**) by treating **8** with methanol at reflux, in the presence of a catalytic amount of acetic acid (Scheme 8). The structural assignment was confirmed by the presence of NOE between the methyl protons of the ketal and the methylene protons at C-3.

2-Thiosemicarbazones and 2-oximes are known to form in the reactions of 1,2-indanediones with thiosemicarbazides[22] and hydroxylamine.[23] Similarly, the reaction of 4,5-methylenedioxy-1,2-indanedione with 2-(3-hydroxy-4-methoxyphenyl)ethylamine generated the 2-imine.[24,25] The reaction of 1,2-indanedione with 3,5-dimethoxyaniline in benzene afforded several products. The initial mode of addition occurred through attack of nitrogen at the C-2 position of the 1,2-indanedione generating an enamine which underwent subsequent reactions.[26] The only known example of a 1,2-indanedione reaction with an amino acid is its reaction with 3,4-dehydroproline (Scheme 8) to form an *N*-substituted pyrrole.[27]

We have observed the formation of fluorescent species when 1,2-indanediones were reacted with α-amino acids both in solutions and on paper surfaces. The fluorescence intensity was affected by substitution on the aromatic ring. We have synthesized a series of 10 1,2-indanediones (**8**, **10a**−**i**, Scheme 9), of which 5,6-dimethoxyindane-1,2-dione (**10b**) showed the highest fluorogenic activity in the reactions with α-amino acids.

To elucidate the mechanisms involved in the reactions of 1,2-indanedione with amino acids, we first investigated the possibility of C−N−C 1,3-dipole formation. The C−N−C dipoles (azomethine ylides) can exist as several geometric isomers (Figure 1) that differ in their relative stability. *Z*,*Z*, syn dipoles (U dipoles) are the least favored due to intramolecular steric interactions. The nature of R substituents as well as changes in solvent polarity may affect the relative stabilization of S and W dipoles, since

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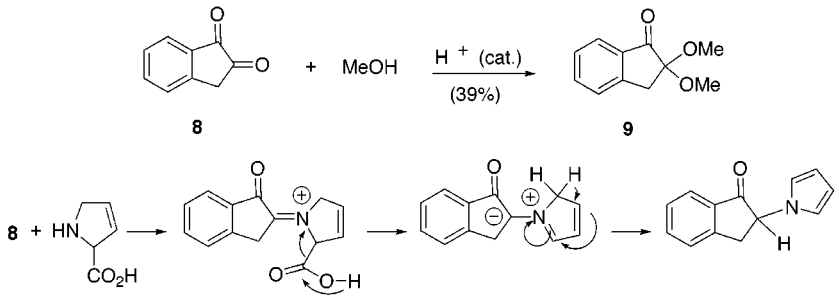
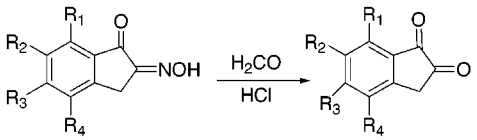
(27) Hudson, C. B.; Robertson, A. V. *Aust. J. Chem.* **1967**, *20*, 1511−1520.

Scheme 8

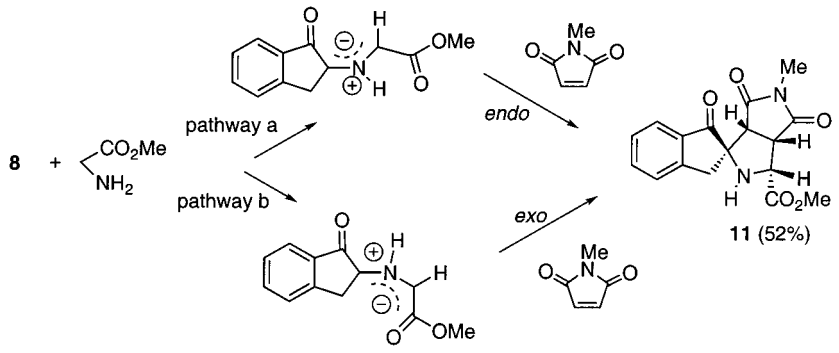


Scheme 9



8 $R_1 = R_2 = R_3 = R_4 = H$ (85%)
10 a $R_1 = R_3 = R_4 = H$, $R_2 = NO_2$ (94%)
10 b $R_1 = R_4 = H$, $R_2 = R_3 = OMe$ (92%)
10 c $R_1 = R_2 = R_4 = H$, $R_3 = Cl$ (84%)
10 d $R_1 = R_3 = R_4 = H$, $R_2 = Br$ (92%)
10 e $R_1 = R_4 = H$, $R_2 = R_3 = -O-CH_2-O-$ (98%)
10 f $R_1 = H$, $R_2 = R_3 = R_4 = OMe$ (95%)
10 g $R_1 = R_2 = R_3 = OMe$, $R_4 = H$ (85%)
10 h $R_1 = R_2 = R_4 = H$ $R_3 = F$ (68%)
10 i $R_1 = R_3 = R_4 = H$ $R_2 = SMe$ (66%)

Scheme 10



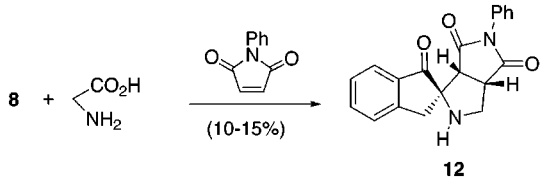
they differ in the magnitude of their dipole moments. Assuming that the 1,3-dipolar cycloaddition to these species occurs in a concerted fashion, one may deduce dipole geometry from the structure of cycloaddition products.

Dipole formation via 1,2-proton shift was the first pathway to be studied. Glycine methyl ester, a compound that could not undergo decarboxylation, was reacted with 1,2-indanedione. Addition of *N*-methylmaleimide (NMM) to the reaction mixture resulted in formation of a spiro indene pyrrolo[3,4-*c*]pyrrole **11** (Scheme 10) as a single diastereomer in a 52% yield. The stereochemistry of this product, as well as of other cycloadducts in this study, was confirmed by X-ray crystallography. Compound **11** can be obtained via *endo*-addition to a *Z*,*E*, anti 1,3-dipole (Scheme 10, pathway a). Alternatively, the same diastereomer can be obtained via *exo*-addition to *E*,*Z*, anti 1,3-dipole (pathway b). The *endo* pathway is a more likely one: the *Z*,*E*, anti 1,3-dipole is more stabilized than its isomer, and *endo* addition allows for the more favorable alignment of the dipole moments.

Formation of compound **12** (Scheme 11) in the reaction of 1,2-indanedione with glycine confirmed the decarboxylation pathway to C−N−C 1,3-dipoles.

Reactions of 1,2-indanedione with amino acids such as L-phenylalanine (Scheme 12) illustrate the impact of

Scheme 11

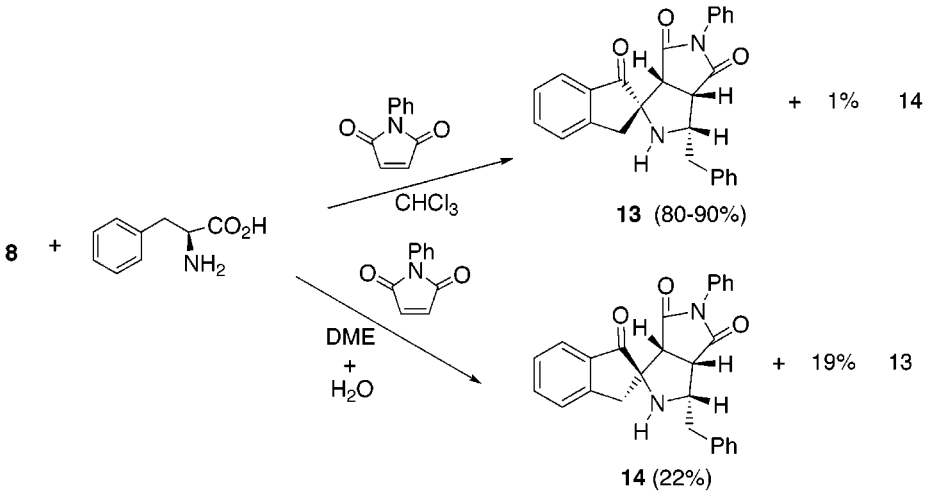


solvent on the diastereomeric ratio of products and overall yields. L-Phenylalanine-derived product **13** was obtained in 80−90% yields when the reaction was carried out in chloroform. The cycloaddition product (**13**) is predominantly derived from the W-dipole; no more than 1% of the other isomer (**14**) was observed. The same reaction in aqueous dimethoxyethane resulted in an approximately equal ratio of W- and S-derived cycloaddition products; the overall yield decreased substantially.

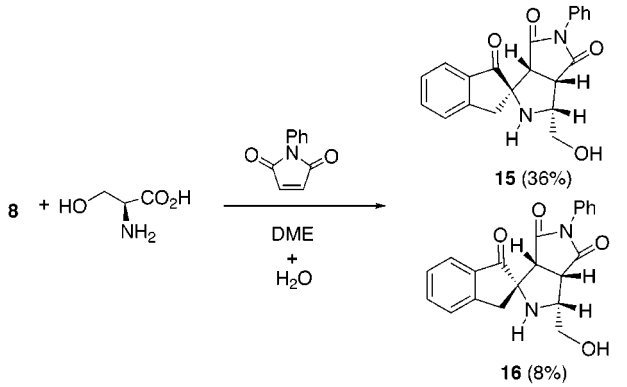
L-Serine gave a 36% yield of S-derived cycloaddition product (**15**) in aqueous dimethoxyethane (Scheme 13). A side product presumed to be a W-derived cycloaddition product (**16**) was also isolated.

Amino acids with a secondary amino group (L-proline and L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) were shown to generate 1,3-dipolar intermediates as well. Two electron-deficient dipolarophiles were utilized to trap the proline-dione adduct to give the diastereomerically

Scheme 12



Scheme 13



pure cycloadducts **17** and **18** (Scheme 14) in comparable yields. The *Z*,*E*, anti dipole shown in Scheme 14 is the major intermediate in the proline reaction.

L-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid generated a 1,3-dipole of the same geometry as the proline-derived dipole (Scheme 15). Dipole generation proceeded via decarboxylation. Cycloadducts generated via carbonyl-assisted 1,5-H shift were not identified in the reaction mixture. The yield of the cycloadduct (**19**, 11%) was much lower than in the proline reaction. This can be explained by the lower nucleophilicity of the tetrahydroisoquinoline nitrogen as compared to the proline nitrogen.

Having established the presence of C−N−C 1,3-dipoles in the 1,2-indanedione/α-amino acid reaction mixtures, we attempted to identify the presence of Ruhemann's purple analogues in these systems. Reaction of glycine with excess 1,2-indanedione, followed by subsequent addition of *N*-methylmaleimide, did not yield the desired product. Since we were interested in evaluating the properties of this compound, we explored a stepwise approach to Ruhemann's purple analogue formation (**21**, Scheme 16).

Using L-phenylalanine as the starting material,[28,29] we first synthesized 2-amino-1-indanone hydrochloride **20** (Scheme 16) in 50% yield. This compound displayed interesting properties. Addition of inorganic base to the solutions of compound **20** resulted in a dramatic color change from a colorless solution with negligible absorption above 400 nm to a purple solution with absorption maxima at 518 and 550 nm (solvent: dimethoxyethane/water, 1:1). Excitation at the long-wave absorption maxima did not induce any luminescence. Short-wave excitation (383 nm) resulted in the appearance of a strong and broad emission band with a 418 nm maximum. The emission band extended into the visible range (up to 520 nm). These observations suggested that the chromophore and the fluorophore generated upon addition of base to 2-amino-1-indanone hydrochloride solutions are different species.

Compound **20** was reacted with 1,2-indanedione (**8**) in an attempt to promote formation of Ruhemann's purple protonated analogue **21** (Scheme 16). Upon heating in methanol, the yellow reaction solution became dark red (a broad absorption band with $\lambda_{max} = 516$ nm was observed) and fluorescent. Upon addition of *N*-methylmaleimide, a precipitate was formed. On the basis of NMR, MS, and elemental analysis data, it was assigned structure **22** (11% yield). Due to difficulties in crystallizing this compound, which showed a poor solubility in most solvents, we could not obtain its X-ray crystal structure, and we do not have direct proof of the relative stereochemistry of this *meso*-compound. However, we obtained an X-ray crystal structure of **23 (**Scheme 16**)**, a dimethoxy analogue of **22**, and extrapolated the result to assign the stereochemistry of **22**. A single diastereomer **24** was also obtained in the reaction of 2-amino-1-indanone with ninhydrin (**1**) and *N*-phenylmaleimide (Scheme 16).

It is of interest to note that addition of excess *N*-methylmaleimide to 1,2-indanedione/amino acid reaction mixtures as well as to 1,2-indanedione/2-amino-1-indanone reaction mixtures would invariably result in an observed decrease of fluorescence both in solution and on porous surfaces (paper). On the other hand, addition of excess *N*-methylmaleimide to 2-amino-1-indanone would not visibly affect the fluorescence.

The nature of the fluorophore(s) in the 2-amino-1-indanone reaction is still elusive. It could be the result of a reaction sequence initiated by tautomerization and subsequent condensation reactions. A short-wave fluorophore that is the product of the self-condensation and oxidation of **20** was identified, and its structure was confirmed by X-ray crystallography. This product (**25**)

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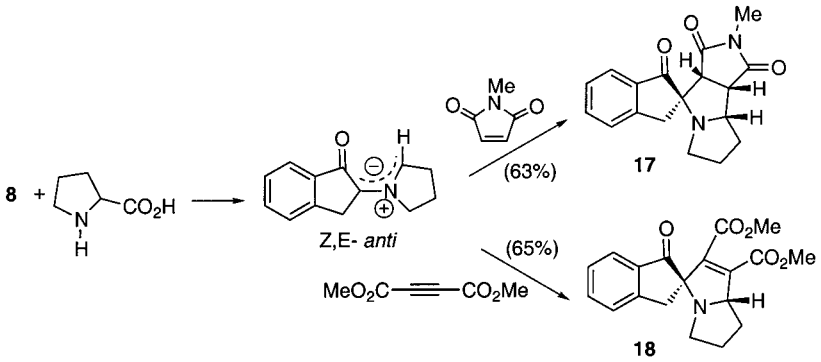
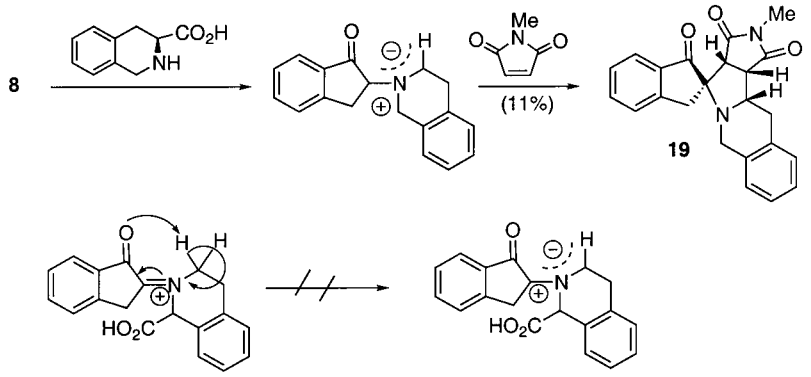
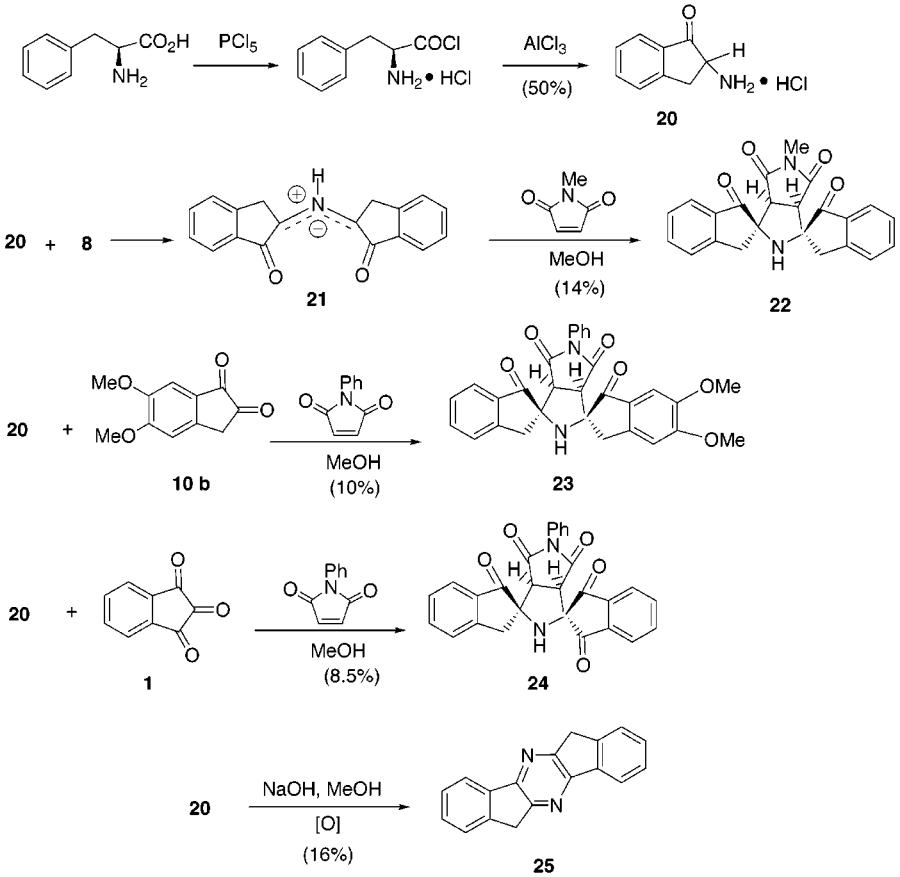
Scheme 14



Scheme 15



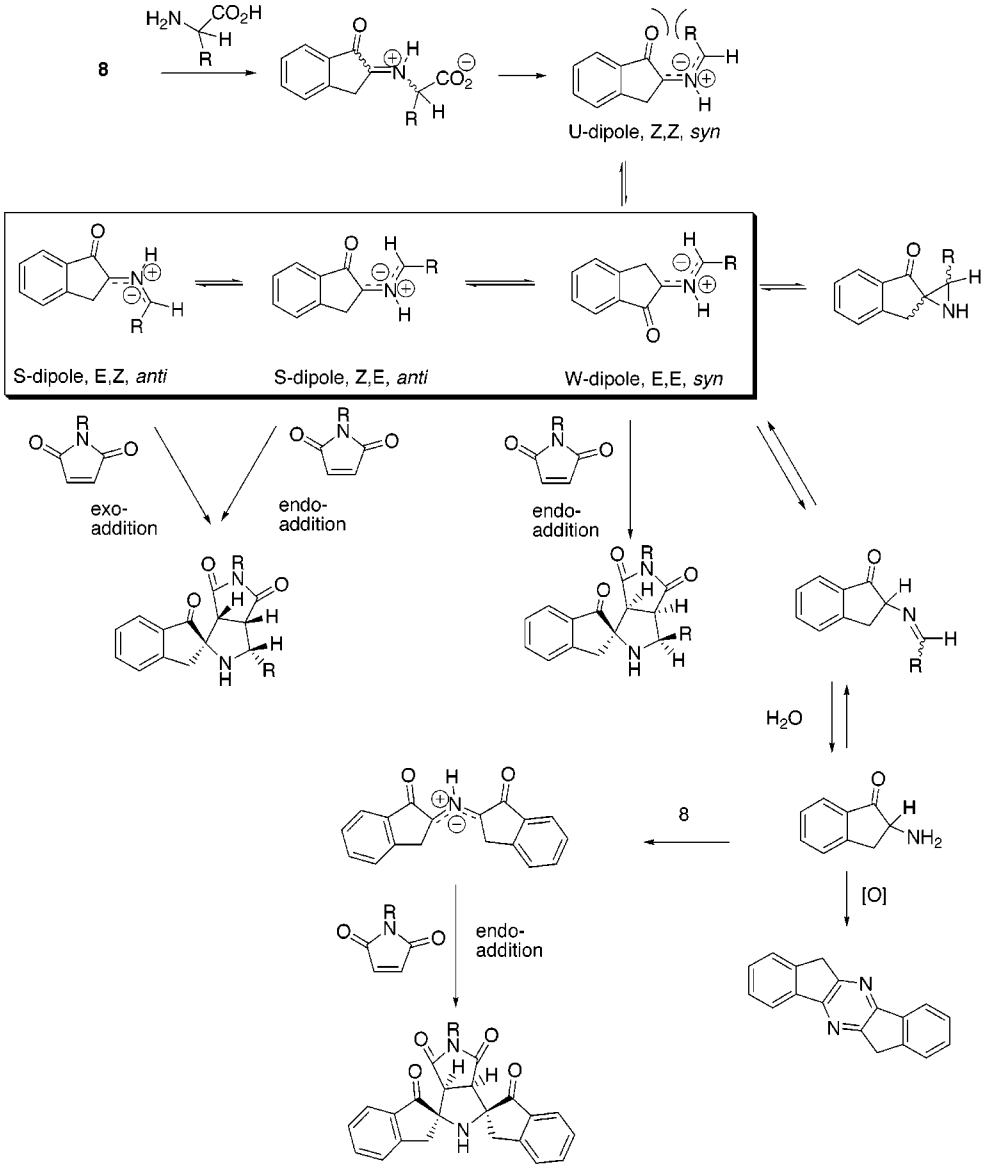
Scheme 16



displayed intense short-wave fluorescence when its solutions were irradiated (λ_{ex} = 366 nm). This fluorescence was perceived as blue and corresponds to higher-energy transitions than the yellow fluorescence noted above.

Scheme 17 represents a summary of general reaction pathways in the system under study. A plausible first step in the reaction of 1,2-indanedione with an α-amino acid is imine formation, followed by decarboxylation to

Scheme 17



form 1,3-dipolar species of various geometries. These dipoles can be trapped as cycloaddition products. Collapse of the resulting dipoles to aziridines is a possibility. Equilibria between azomethine ylides and aziridines have been documented,[30] and although we did not observe aziridines in our experiments, we cannot rule out their existence. Another possible pathway for the C−N−C 1,3-dipolar species is the Strecker degradation. This reaction would afford 2-amino-1-indanone, which could react further with an excess of 1,2-indanedione to form a "Ruhemann's purple"-like dipole.

Experimental Section

General Procedures. All solvents were reagent grade and distilled from the appropriate drying agents. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker Ac-250 (250 MHz) or a Bruker AMX-500 (500 MHz) spectrometer in the solvents indicated. Infrared spectra (IR) were obtained on a Perkin-Elmer 1600 FT-IR spectrometer. High-resolution mass spectra (HRMS) were obtained on either a VG 70−70HS or VG ZAB-E mass spectrometer, using either Chemical Ionization (CI), fast atom bombardment (FAB) using a cesium (Cs) ion gun, or electron spray ionization (ESI). The mass spectrometers were interfaced with a VG/DEC 11−73 data system. Elemental Analyses (EA) were performed at the Analytical Facility of the Department of Chemistry at the University of Pennsylvania. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60F-254) plates (0.25 mm), precoated with a fluorescent indicator. Visualization was effected with ultraviolet light. Flash column chromatography was carried out on E. Merck silica gel 60 (240−400 mesh) using the solvent systems indicated in the individual experiments.

General Method for the Preparation of 1,2-Indanediones. 5,6-Dimethoxy-1,2-indanedione (10b). To a solution of concentrated aqueous formaldehyde (36%, 1 mL) and concentrated aqueous HCl (37%, 2 mL) at room temperature was added 5,6-dimethoxy-1,2-indanedione 2-oxime (663 mg, 3.0 mmol). The reaction mixture turned from a light yellow suspension to a dark yellow suspension within 5 min of the addition. The reaction was allowed to stir overnight at room temperature. The precipitate was collected by filtration, washed with water (3 × 2 mL), and allowed to dry at ambient

(30) Trozzolo, A. M.; Leslie, T. M.; Sarpotdar, A. S.; Small, R. D.; Ferraudi, G. J. *Pure Appl. Chem.* **1979**, *51*, 261−270.

temperature to yield 566 mg (91.6%) of **10b** as a yellow solid. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.48 (s, 2H), 3.83 (s, 3H), 3.92 (s, 3H), 7.19 (s, 1H), 7.24 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.9, 56.3, 56.6, 105.9, 107.9, 131.4, 143.3, 150.1, 157.9, 185.0, 199.9. IR (KBr) 1756, 1704 cm^{-1}. HRMS calcd for $C_{11}H_{10}O_4N$ $(M + NH_4)^+$: *m/z* 224.0923, found 224.0930. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89. Found: C, 63.81; H, 4.94.

1,2-Indanedione (8): 3.36 g, 85.2%, mp 114−115 °C; R_f 0.71 (EtOAc/petroleum ether, 40:60). ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.58 (s, 2H), 7.46−7.53 (m, 1H), 7.60−7.7.63 (m, 1H), 7.75−7.81 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.6, 125.7, 127.5, 128.7, 136.7, 137.6, 146.5, 187.1, 199.7. IR (KBr) 1763, 1707 cm^{-1}. HRMS (FAB) calcd for $C_9H_{10}O_2N$ $(M + NH_4)^+$: *m/z* 164.0711, found 164.0709. Anal. Calcd for $C_9H_6O_2$: C, 73.97; H, 4.14. Found: C, 73.59; H, 4.09.

6-Nitro-1,2-indanedione (10a). Compound **10a** exists in equilibrium with its enol form in DMSO (ketone:enol = 2:0.9). 1.27 g, 93.6%. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.67 (s, 2H), 5.45 (s, 0.9 H), 7.10 (d, J = 8.1 Hz, 0.9 H), 7.79 (d, J = 1.6 Hz, 0.9 H), 7.88 (d, J = 8.5 Hz, 1H), 8.22 (dd, J = 8.0 Hz, J = 2.2 Hz, 0.9 H), 8.40 (d, J = 2.3 Hz, 1H), 8.55 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.9, 120.7, 129.0, 131.2, 136.8, 151.6 (note: signal for one aromatic carbon was not detected) 185.7, 196.9. IR (KBr) 1767, 1726 cm^{-1}. HRMS calcd for $C_9H_9O_4N_2$ $(M + NH_4)^+$: *m/z* 209.0562, found 209.0569.

5-Chloro-1,2-indanedione (10c): 455 mg, 84%, mp 144−145 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.56 (s, 2H), 7.55 (dd, J = 8.2 Hz, J = 1.7 Hz, 1H), 7.73−7.80 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.4, 127.0, 127.7, 129.6, 135.1, 144.1, 147.8, 185.7, 198.5. IR (KBr) 1766, 1719 cm^{-1}. HRMS calcd for $C_9H_9O_2ClN$ $(M + NH_4)^+$: *m/z* 198.0322, found 198.0328. Anal. Calcd for $C_9H_5O_2Cl$: C, 59.86; H, 2.79. Found: C, 59.80; H, 2.75.

6-Bromo-1,2-indanedione (10d): 0.43 g, 91.8%. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.51 (s, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.91−7.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 122.9, 128.5, 129.1, 137.8, 140.4, 144.9, 185.8, 198.4. IR (KBr) 1766, 1715 cm^{-1}. HRMS calcd for $C_9H_9O_2NBr$ $(M + NH_4)^+$: *m/z* 241.9817, found 241.9825. Anal. Calcd for $C_9H_5O_2Br$: C, 48.04; H, 2.24. Found: C, 48.42; H, 2.22.

Indano[5,6-d][1,3]dioxole-5,6-dione (10e): 1.0 g, 98%. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.47 (s, 2H), 6.22 (s, 2H), 7.16 (s, 1H), 7.23 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.5, 102.6, 104.1, 106.4, 133.0, 145.5, 148.8, 156.0, 184.6, 199.2. IR (KBr) 1757, 1690 cm^{-1}. HRMS calcd for $C_{10}H_7O_4$ $(M + H^+)$: *m/z* 191.0344, found 191.0343. Anal. Calcd for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 63.09; H, 3.06.

4,5,6-Trimethoxy-1,2-indanedione (10f): 434 mg, 95%. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.47 (s, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 7.16 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.1, 56.4, 60.9, 61.3, 102.7, 132.4, 134.6, 150.0, 150.4, 154.7, 185.6, 199.4. IR (KBr) 1758, 1720 cm^{-1}. HRMS calcd for $C_{12}H_{13}O_5$ $(M + H^+)$: *m/z* 237.0763, found 237.0776. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.70; H, 5.15.

5,6,7-Trimethoxy-1,2-indanedione (10g): 264 mg, 85%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.48 (s, 2H), 3.85 (s, 3H), 3.98 (s, 3H), 4.10 (s, 3H), 6.70 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 56.7, 61.5, 62.1, 104.1, 125.0, 140.4, 144.4, 153.7, 162.3, 182.3, 199.7. IR (KBr) 1752, 1697 cm^{-1}. HRMS calcd for $C_{12}H_{16}O_5N$ $(M + NH_4)^+$: *m/z* 254.1029, found 254.1036. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.62; H, 4.93.

5-Fluoro-1,2-indanedione (10h): 281 mg, 68%, mp 100−103 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 3.71 (s, 2H), 7.28−7.33 (m, 1H), 7.45 (dt, J = 1.01, 8.83 Hz, 1H), 7.91 (dd, J = 5.52, 8.45 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 37.4, 115.1, 117.1, 128.7, 134.7, 151.8, 167.3, 186.5, 199.5. IR (KBr) 1763, 1718 cm^{-1}.

6-(Methylthio)-1,2-indanedione (10i). The crude solid was recrystallized from 10% EtOAc/Et_2O to afford **10i** (0.338 g) as golden needles in 66% yield. ^{1}H NMR (500 MHz, acetone-d_6) δ 2.59 (s, 3H), 3.62 (s, 2H), 7.61−7.62 (m, 2H), 7.70 (dd, J = 1.91, 8.19 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 15.31, 36.81, 121.27, 128.87, 135.87, 138.15, 140.83, 145.11, 187.77, 200.21. IR (KBr) 1760, 1705 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{12}NO_2S$ $(M + NH_4)^+$: *m/z* 210.0589, found 210.0591. Anal. Calcd for $C_{10}H_8O_2S$: C, 62.48; H, 4.19. Found C, 62.83; H, 4.30.

2,2-Dimethoxy-1-indanone (9). To a solution of **8** (292 mg, 2 mmol) in methanol (10 mL) was added acetic acid (1 drop). The reaction was heated at reflux for 24 h. The reaction was cooled, and the solvent was removed under reduced pressure. The crude yellow oil was purified by column chromatography (20% Et_2O/petroleum ether) to provide **9** (150 mg, 39%) as a colorless oil, which solidified upon prolonged storage at 4 °C. R_f 0.31 (Et_2O/petroleum ether, 20:80). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.25 (s, 2H), 3.43 (s, 6H), 7.34−7.40 (m, 2H), 7.56−7.63 (m, 1H), 7.77 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.5, 50.6, 101.9, 125.0, 126.6, 127.7, 133.8, 135.8, 149.4, 197.3. IR (KBr) 1727, 1048 cm^{-1}. HRMS calcd for $C_{11}H_{16}O_3N$ $(M + NH_4)^+$: *m/z* 210.1130, found 210.1128. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.42; H, 6.35.

1′*R*,3′*R*-(3′*β*,3′a*β*,6′a*β*)-3′a,6′a-Dihydro-5′-methylspiro (2*H*-indene-2,1′(2′*H*)-pyrrolo(3,4-*c*)pyrrole)1,4′,6′(3′*H*,5′*H*)-trione 3′-Carboxylic Acid Methyl Ester (11). To a yellow solution of **8** (730 mg, 3.0 mmol) and *N*-methylmaleimide (333 mg, 5.0 mmol) in methanol (35 mL) was added glycine methyl ester hydrochloride (377 mg, 3.0 mmol) with stirring. A solution of KOH (170 mg, 3.0 mmol) in methanol (5 mL) was added, and the reaction mixture was heated at reflux overnight. The brown reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude solid was treated with boiling methanol to yield 511 mg (52%) of **11** as a white solid: mp 197.5−198 °C; R_f 0.46 (acetone/petroleum ether, 40:60). ^{1}H NMR (250 MHz, acetone-d_6) δ 2.88 (s, 3H), 3.04 (d, J = 17.9 Hz, 1H), 3.43 (d, J = 7.7 Hz, 1H), 3.71 (s, 3H), 3.84 (dd, J = 7.9 Hz, J = 7.9 Hz, 1H), 4.06 (d, J = 17.9 Hz, 1H), 4.44 (d, J = 8.1 Hz, 1H), 7.41−7.47 (m, 1H), 7.54 (d, J = 7.5, 1H), 7.66−7.72 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 35.1, 48.6, 49.9, 52.5, 60.0, 71.5, 125.2, 126.4, 128.0, 132.6, 135.8, 151.9, 170.6, 175.9, 176.1, 203.5. IR (KBr) 3284, 2952, 1774, 1742, 1698, 1607 cm^{-1}. HRMS calcd for $C_{17}H_{16}N_2O_5Na$ $(M + Na)^+$: *m/z* 351.0957, found 351.0967. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.51; H, 4.87; N, 8.54.

1′*R*-(3′a*β*,6′a*β*)-3′a,6′a-Dihydro-5′-phenylspiro(2*H*-indene-2,1′(2′*H*)-pyrrolo(3,4-*c*)pyrrole)-1,4′,6′(3′*H*,5′*H*)-trione (12). A solution of **8** (200 mg, 1.37 mmol), glycine (300 mg, 4.1 mmol), and *N*-phenylmaleimide (1.0 g, 5.78 mmol) in $CHCl_3$ (100 mL, anhydrous) was heated at reflux for 48 h. The reaction mixture was cooled to room temperature and filtered to collect the precipitate. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (30% acetone/hexanes). The product with R_f 0.24 was recrystallized from acetone/hexanes, to provide **12** as colorless needles (63 mg, 14%): mp 125 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (br, 1H), 2.81 (d, J = 17.44 Hz, 1H), 3.39 (d, J = 7.86 Hz, 1H), 3.48 (d, J = 10.35 Hz, 1H), 3.59−3.62 (m, 2H), 4.05 (d, J = 17.42 Hz, 1H), 7.26 (d, J = 7.76 Hz, 2H), 7.34−7.44 (m, 5H), 7.55 (dd, J = 7.31, 4.82 Hz, 1H), 7.70 (d, J = 7.66 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9, 46.9, 47.5, 47.8, 72.1, 125.1, 126.43, 126.45, 128.0, 128.8, 129.2, 131.9, 132.9, 134.3, 135.7, 136.2, 152.0, 176.3, 178.2, 203.3. IR (KBr) 3317, 2921, 2850, 1707 cm^{-1}. HRMS calcd for $C_{20}H_{17}N_2O_3$ $(M + H)^+$: *m/z* 333.1239, found 333.1239.

1′*S*,3′*S*-(3′*β*,3′a*β*,6′a*β*)-3′a,6′a-Dihydro-3′-benzyl-5′-phenylspiro(2*H*-indene-2,1′(2′*H*)-pyrrolo(3,4-*c*)pyrrole)1,4′,6′-(3′*H*,5′*H*)-trione (13). A solution of **8** (200 mg, 1.37 mmol), L-phenylalanine (670 mg, 4.11 mmol), and *N*-phenylmaleimide (1.0 g, 5.78 mmol) in $CHCl_3$ (150 mL, anhydrous) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and separated by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (30% acetone/hexanes) to produce **13** as a white solid. Recrystallization from acetone/hexanes afforded **13** as colorless needles in 80% yield: mp 141−145 °C; R_f 0.28 (30% acetone/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 (br, 1H), 2.93 (dd, J = 14.20, 8.06 Hz, 1H), 3.14 (d, J = 16.58 Hz, 1H), 3.29 (d, J = 6.77 Hz, 1H), 3.33 (d, J = 15.51 Hz, 1H), 3.45−3.55 (m, 2H), 3.68−3.78 (m, 1H), 7.21−7.49 (m,

12H), 7.62 (dd, J = 7.75, 7.70 Hz, 1H), 7.81 (d, J = 7.54 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.1, 45.2, 50.7, 58.3, 64.3, 74.9, 124.8, 126.4, 126.5, 126.6, 128.3, 128.5, 128.7, 128.9, 129.1, 131.7, 135.3, 136.1, 139.2, 150.3, 174.5, 174.8, 203.3. IR (KBr) 3320, 3062, 3028, 2922, 1708, 1606, 1497, 1384, 1191 cm-1. HRMS calcd for $C_{27}H_{23}N_2O_3$ $(M + H)^+$: m/z 422.1630, found 423.1699. Anal. Calcd for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63. Found: C, 76.71; H, 5.32; N, 6.60.

The other isomer (**14**) (R_f 0.37, 30% acetone/hexanes) was observed as a minor product (<1%), and correctly characterized from the next experiment.

1′*R*,3′*S*-(3′α,3′a*β*,6′a*β*)-3′a,6′a-Dihydro-3′-benzyl-5′-phenylspiro (2*H*-indene-2,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole)1,4′,6′-(3′*H*,5′*H*)-trione (14). A solution of **8** (200 mg, 1.37 mmol) and L-phenylalanine (670 mg, 4.11 mmol) in 5% aqueous dimethoxyethane (20 mL) was heated at reflux for 10 min. The solution turned pink/red; no **8** was detected by TLC analysis. To the red solution was added *N*-phenylmaleimide (1.0 g, 5.78 mmol). The reaction was heated at reflux for 12 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (30% acetone/hexanes) to provide **13** (0.11 g, 19% yield), and **14** (0.138 g, 22% yield). R_f 0.37 (30% acetone/hexanes); mp 182−183 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.83 (br, 1H), 2.52 (dd, J = 13.60, 10.50 Hz, 1H), 2.89 (d, J = 17.90 Hz, 1H), 3.41 (dd, J = 13.83, 3.45 Hz, 1H), 3.43 (d, J = 7.83 Hz, 1H), 3.75 (dd, J = 8.05, 8.06 Hz, 1H), 4.23 (d, J = 17.70 Hz, 1H), 7.15−7.18 (m, 1H), 7.21−7.26 (m, 4H), 7.34−7.44 (m, 5H), 7.52 (dd, J = 7.68, J = 7.82 Hz, 2H), 7.58 (dd, J = 7.43, J = 7.55 Hz, 1H), 7.69 (d, J = 7.83 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.8, 38.3, 47.8, 48.2, 58.1, 70.6, 125.1, 126.4, 126.6, 127.9, 128.6, 128.8, 128.9, 129.19, 131.91, 132.94, 134.2, 135.7, 139.2, 152.4, 175.6, 176.1, 204.1. IR (KBr) 1707, 1607, 1497, 1384, 1195 cm^{-1}. HRMS calcd for $C_{27}H_{23}N_2O_3(M + H)^+$: m/z 422.1630, found 422.1723. Anal. Calcd for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N 6.63. Found: C, 76.91; H, 5.22; N, 6.63.

3′-(1′*R*,3′*R*-(3′*β*,3′a*β*,6′a*β*)-3′a,6′a-Dihydro-5′-phenylspiro-(2*H*-indene-2,1′(2′*H*)-pyrrolo(3,4-*c*)pyrrole)-1,4′,6′-(3′*H*,5′*H*)-trione)methanol (15). A solution of **8** (200 mg, 1.37 mmol), L-serine (200 mg, 1.9 mmol), and *N*-phenylmaleimide (1.0 g, 5.78 mmol) in 5% aqueous DME (20 mL) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude solid was purified by column chromatography (50% acetone/hexanes) to afford **15** (180 mg) as a white solid in a 36% yield. R_f 0.43 (50% acetone/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.93 (d, J = 17.73 Hz, 1H), 3.44 (d, J = 8.10 Hz, 1H), 3.76−3.80 (m, 2H), 3.94 (dd, J = 11.70, 3.64 Hz, 1H), 4.10−4.13 (m, 1H), 4.30 (d, J = 17.73 Hz, 1H), 7.31 (dd, J = 2.72, 0.95 Hz, 2H), 7.39−7.59 (m, 5H), 7.61 (dd, J = 7.33, 7.42 Hz, 1H), 7.76 (d, J = 7.66 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.4, 47.3, 48.6, 59.1, 61.0, 71.6, 125.2, 126.5, 128.0, 128.8, 129.2, 131.8, 132.9, 135.8, 152.2, 175.8, 177.0, 203.9. IR (KBr) 3465, 3309, 1701, 1597, 1494, 1376, 1178 cm^{-1}. HRMS calcd for $C_{21}H_{19}N_2O_4$ 363.1345 $(M + H)^+$, found 363.1344. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.40; H, 4.88; N, 7.68. The minor product was isolated as an oil (R_f 0.20, 50% acetone/hexanes) and is presumed to be **16** (35 mg, 8%). HRMS calcd for $C_{21}H_{19}N_2O_4$ $(M + H)^+$: m/z 363.1345, found 363.1343.

1′*R*,5′a*S*-(5′a*β*,5′b*β*,8′a*β*)-Hexahydro-7-methylspiro(2*H*-indene-2,1′(2′*H*)-pyrrolo[3,4-*a*]pyrrolizine-1,6′,8′-(5′a*H*,7′*H*)-trione (17). A solution of **8** (186 mg, 1.27 mmol) and L-proline (146 mg, 1.27 mmol) in MeOH (20 mL) was stirred at ambient temperature until the reaction mixture turned brown. *N*-Methylmaleimide (141 mg, 1.27 mmol) was added, and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude solid was purified by column chromatography (30% acetone:petroleum ether) to yield 249 mg (63.3%) of **17** as a white solid: mp 166.5 °C; R_f 0.38 (30% acetone/petroleum ether). ^{1}H NMR (250 MHz, acetone-d_6) δ 1.63−1.90 (m, 2H), 1.96−2.23 (m, 2H), 2.38 (dd, J = 17.3 Hz, J = 9.9 Hz, 1H), 2.72−2.82 (m, 1H), 2.95 (s, 3H), 3.18 (d, J = 17.8 Hz, 1H), 3.35 (d, J = 8.0 Hz, 1H), 3.51 (dd, J =8 0.2 Hz, 1H), 4.16−4.23 (m, 2H), 7.34−7.46 (m, 2H), 7.57−7.63 (m, 1H), 7.71−7.74 (d, J = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 24.6, 25.1, 32.5, 48.0, 48.3, 50.8, 64.7, 74.4, 124.9, 126.1, 127.9, 133.6, 135.5, 151.6, 177.6, 177.8, 203.0; IR (KBr) 2962, 1768, 1696, 1607 cm^{-1}. HRMS calcd for $C_{18}H_{19}O_3N_2$ $(M + H)^+$: m/z 311.1396, found 311.1393. Anal. Calcd for $C_{18}H_{18}O_3N_2$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.35; H, 5.97; N, 8.88.

1′*R*,5′*R*-(5′a*β*)-3′,4′,5′,5′a-Tetrahydrospiro(2*H*-indene-2,1′(1′*H*)-pyrrolizine)-1-one-6′,7′-dicarboxylic Acid Dimethyl Ester (18). Compound **8** (584 mg, 4.0 mmol) and L-proline (1.38 g, 12 mmol) were placed in a solution of Et_2O (10 mL) and $CHCl_3$ (10 mL). The reaction mixture was heated at reflux for 1 h. Dimethyl ester of acetylenedicarboxylic acid (852 mg, 6.0 mmol) was added, and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, and solvents were removed under reduced pressure. The crude oil was purified by column chromatography (30% acetone/petroleum ether) to afford 888 mg (65%) of **18** as a clear oil that solidified on standing: mp 89−90 °C; R_f 0.29 (30% acetone/petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77−1.86 (m, 3H), 2.22−2.26 (m, 1H), 2.64−2.70 (m, 1H), 2.99−3.04 (m, 1H), 3.47 (s, 3H), 3.52 (s, 2H), 3.78 (s, 3H), 4.88 (dd, J = 8.0 Hz, J = 5.9 Hz, 1H), 7.34−7.43 (m, 2H), 7.55−7.62 (m, 1H), 7.76 (d, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 29.5, 33.1, 51.0, 52.1, 52.2, 70.7, 81.2, 125.2, 126.0, 127.9, 134.2, 135.3, 139.4, 142.0, 151.1, 164.1, 164.2, 201.9. IR (KBr) 2952, 1721, 1650, 1606 cm-1. HRMS calcd for $C_{19}H_{19}NO_5Na$ $(M + Na)^+$: m/z 364.1161, found 364.1168. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.48; H, 5.67; N, 4.05.

1′,3′,8′,8′a*β*,8′b*β*,10′,11′,11′a*β*-Octahydro-2-methylspiro-(2*H*-indene-2,1′ (1′H)pyrrolo(3′,4′:3,4)pyrrolo(1,2-*b*)isoquinoline-1,9′,11′-trione (19). 1,2-Indanedione **8** (438 mg, 3.0 mmol) and L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (532 mg, 3.0 mmol) were placed in 30 mL of DME. The reaction mixture was refluxed for 1 h. The color of the reaction mixture gradually turned to dark brown. *N*-Methylmaleimide (333 mg, 3.0 mmol) was added, and the reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure, and the resulting solids were separated on a column (40% acetone/petroleum ether, 40:60) to yield 124 mg (11%) of **19** as a yellow solid. (A single diastereomer was obtained, one enantiomer is shown): mp 230−231 °C; R_f 0.63 (40% acetone/petroleum ether). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.58−2.69 (m, 1H), 3.01 (s, 3H), 3.07 (d, J = 18.8 Hz, 1H), 3.13 (dd, J = 5.9 Hz, J = 3.3 Hz, 1H), 3.21 (d, J = 7.6 Hz, 1H), 3.42 (d, J = 14.2 Hz, 1H), 3.71 (d, J = 14.3 Hz, 1H), 3.82 (dd, J = 9.2 Hz, J = 7.7 Hz, 1H), 3.81−3.95 (m, 1H), 4.52 (d, J = 18.8 Hz, 1H), 6.80 (d, J = 6.2 Hz, 1H), 7.01−7.06 (m, 1H), 7.09−7.11 (m, 2H), 7.42 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.67−7.73 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 32.5, 33.1, 47.0, 48.3, 49.0, 57.1, 73.8, 123.5, 126.0, 126.4, 126.5, 126.6, 128.0, 129.2, 133.4, 134.2, 134.9, 136.3, 153.0, 176.5, 176.7, 203.0. IR (KBr) 3020, 2934, 1772, 1698, 1607 cm^{-1}. HRMS calcd for $C_{23}H_{20}N_2O_3Na$ $(M + Na)^+$: m/z 395.1372, found 395.1359. Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.51. Found: C, 74.20; H, 5.52; N, 7.51.

2-Amino-1-indanone Hydrochloride (20). A solution of L-phenylalanine (11 g, 66.67 mmol) and phosphorus pentachloride (15 g, 72 mmol) in CCl_4 (200 mL, anhydrous) was stirred for 10 h in a flame-dried, round-bottomed flask equipped with a $CaCl_2$ drying tube. The flask was transferred into a glovebag filled with nitrogen. A solid was collected by filtration and washed with CCl_4 (3 × 30 mL, anhydrous) to remove the traces of $POCl_3$. The solid showed a single IR band in the carbonyl region (1787 cm^{-1}, KBr pellet). The solid was placed in a flame-dried flask, equipped with a condenser and a $CaCl_2$ drying tube. Anhydrous $AlCl_3$ (17.6 g, 132 mmol) and CS_2 (200 mL, anhydrous) were added. The reaction mixture was stirred at 50 °C for 4 h. The flask was then placed in an ice−salt bath, and the reaction mixture was cooled to 0 °C and slowly quenched by addition of a mixture of ice (200 g), water (100

g), and concentrated aqueous HCl (20 mL). The aqueous phase was then separated and concentrated on a rotary evaporator at 40 °C (bath temperature). Concentrated HCl (80 mL) was added, and the resulting slurry was separated by filtration. The filtrate was concentrated to yield a beige solid, which was recrystallized from methanol to yield 6.09 g (49.8%) of **20**. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.14 (dd, J = 16.9 Hz, J = 5.2 Hz, 1H), 3.35 (dd, J = 16.9 Hz, J = 8.3 Hz, 1H), 4.28 (dd, J = 8.2 Hz, J = 5.3 Hz, 1H), 7.47−7.53 (m, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.72−7.80 (m, 2H), 8.65 (s, <2H, exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.3, 53.2, 123.7, 127.0, 128.2, 134.1, 136.1, 151.5, 200.4. IR (KBr) 2927, 1720, 1610, 1465, 1300, 1218 987, 746 cm^{-1}. HRMS calcd for $C_9H_{10}NO$ (M-Cl): m/z 148.0762, found 148.0762.

1′*R*,3′*S*-(3′a*β*,6′a*β*)-3′a,6′a-Dihydro-5′-methylspiro((2*H*-indene-2,1′)(2″*H*-indene-2″,3′)(2′*H*)-pyrrolo(3,4-*c*)pyrrole)-1,1″,4′,6′ (3′*H*,5′*H*)-tetrone (22). A solution of **8** (438 mg, 3 mmol), **20** (643 mg, 3.5 mmol), and *N*-methylmaleimide (333 mg, 3 mmol) in MeOH (60 mL) was brought to reflux. Upon heating, the yellow solution became pink with green fluorescence. In approximately 40 min precipitate formation was observed and fluorescence disappeared. The reaction mixture was cooled to room temperature. The precipitate was collected by filtration and washed with MeOH (3 × 1 mL) to yield 160 mg (13.7%) of **22** as a pale yellow solid insoluble in most solvents with the exception of DMSO: mp > 320 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.74 (s, 3H), 3.24 (d, J = 16.4 Hz, 2H), 3.57 (s, 2H), 3.72 (d, J = 16.5 Hz, 2H), 7.51−7.57 (m, 2H), 7.64 (d, J = 7.5 Hz, 2H), 7.76−7.83 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.6, 44.3, 59.5, 75.8, 124.0, 127.2, 128.3, 134.8, 136.2, 150.5, 174.8, 202.7. IR (KBr) 3458, 3264, 2953, 1779, 1716, 1697, 1608 cm^{-1}. HRMS calcd for $C_{23}H_{18}N_2O_4$ (M + H)$^+$: m/z 387.1345, found 387.1342. Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.33; H, 4.63; N, 7.09.

1′*R*,3′*S*-(3′a*β*,6′a*β*)-3′a,6′a-Dihydro-5,6-dimethoxy-5′-phenylspiro((2*H*-indene-2,1′)(2″*H*-indene-2″,3′)(2′*H*)-pyrrolo-(3,4-*c*)pyrrole)-1,1″,4′,6′ (3′*H*,5′*H*)-tetrone (23). A solution of **10b** (206 mg, 1.00 mmol), **20** (185 mg, 1.00 mmol), and *N*-phenylmaleimide (1.0 g, 6.25 mmol) in MeOH (22 mL, anhydrous) was stirred for 48 h. A white precipitate was formed after several hours. The mixture was diluted with ether (50 mL) and filtered to provide **23** (43 mg) as a white solid in a 8.5% yield: mp > 310 °C (dec). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.39 (s, 2H), 3.44 (d, J = 8.54 Hz, 2H), 3.53 (s, 2H), 3.91 (s, 3H), 3.99 (s, 3H), 6.89 (s, 1H), 7.30 (s, 1H), 7.33−7.35 (m, 3H), 7.41−7.49 (m, 4H), 7.66 (dd, J = 6.6, 6.5 Hz, 1H), 7.89 (d, J = 8.77 Hz, 1H). HRMS calcd for $C_{30}H_{25}N_2O_6$ (M + H)$^+$: m/z 509.1712, found 509.1703. Due to the insoluble nature of this compound a ^{13}C NMR could not be performed.

1′*R*-(3′a*β*,6′a*β*)-3′a,6′a-Dihydro-5′-phenylspiro((2*H*-indene-2,1′)(2″*H*-indene-2″,3′)(2′*H*)-pyrrolo(3,4-*c*)pyrrole)-1,1″,3″,4′,6′ (3′*H*,5′*H*)-pentone (24). A solution of **1** (260 mg, 1.47 mmol), **20** (250 mg, 1.35 mmol), and *N*-phenylmaleimide (1.0 g, 6.25 mmol) in MeOH (50 mL, anhydrous) was stirred for 48 h. A white precipitate formed after several hours. The mixture was diluted with Et_2O (50 mL). The precipitate was collected by filtration to afford **24** (58 mg) as a white solid in 10% yield: mp 295 °C (dec). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.53 (d, J = 15.24 Hz, 1H), 3.69 (d, J = 8.55 Hz, 1H), 3.74 (d, J = 15.25 Hz, 1H), 3.84 (d, J = 7.88 Hz, 1H), 7.34−7.56 (m, 7H), 7.69−7.71 (m, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.96−8.00 (m, 2H), 8.09−8.12 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.0, 54.6, 60.4, 74.6, 77.8, 124.4, 124.5, 125.0, 126.67, 126.71, 128.4, 128.9, 129.2, 131.4, 132.5, 135.1, 136.2, 136.9, 137.0, 140.0, 141.7, 150.3, 173.4, 176.9, 198.6, 202.0. HRMS calcd for $C_{28}H_{18}N_2O_5$ (M + H)$^+$: m/z 463.1293, found 463.1215.

Diindano[1,2-*b*;1′,2′-*e*]pyrazine (25). To a solution of **20** (0.92 g, 5 mmol) in MeOH (8 mL) was added aqueous NaOH (5 mL, 2M) dropwise, with stirring at ambient temperature. The clear solution instantly turned red, and gradual precipitate formation was observed. The reaction mixture was stirred overnight at room temperature. The precipitate was collected by filtration, washed with MeOH (2 × 1 mL), and purified by column chromatography (20% EtOAc/CH_2Cl_2) to provide **25** as a light yellow solid (0.10 g) in a 15.6% yield: mp 273−274 °C; R_f 0.67 (20% EtOAc/CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.05 (s, 4H), 7.44−7.49 (m, 4H), 7.62 (d, J = 6.4 Hz, 2H), 8.11 (d, J = 7.6 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 36.1, 121.1, 125.5, 127.7, 129.1, 138.9, 142.2, 151.7, 157.3. IR (KBr) 3045, 2885, 1390, 1361 cm^{-1}. HRMS calcd for $C_{18}H_{13}N_2$ (M + H)$^+$: m/z 257.1078, found 257.1072. Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.06; H, 4.84; N, 10.57.

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Supporting Information Available: General procedures and X-ray data for compounds **11**, **13**−**15**, **17**−**19**, **23**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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