Synthesis of Indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazole Lactam Regioisomers Using Ethyl *cis*-β-Cyanoacrylate as a Dienophile and Lactam Precursor

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Received September 16, 2002

Reported here is the synthesis and characterization of the indenopyrrolocarbazole ring system utilizing a Diels-Alder reaction with 2-indenylindole and maleimide. Clemmensen reduction of imide **10** furnished the 5-oxo (**16**) and 7-oxo (**17**) lactam regioisomers. A new regiospecific route to 5-oxo **16** was developed using ethyl *cis*-β-cyanoacrylate as the dienophile. The regio and stereochemical characterization of the cycloadducts was confirmed by X-ray crystallography.

J. Heterocyclic Chem., **40**, 135 (2003).

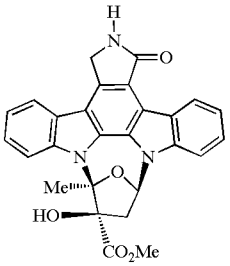
Introduction.

The microbial derived indolocarbazoles continue to attract synthetic interest owing to their remarkable biological profile. (+)K-252a (**1**), originally isolated from the culture broth of *Nocardiopsis sp.* [1], is a potent inhibitor of numerous serine/threonine and tyrosine kinases involved in cell survival, growth and proliferation [2]. The aglycones K-252c (**2a**) and acryriaflavin A (**2b**), natural products from *Nocardiopsis* strain K-290 [3] and *Arcyria denudata* [4], are also biologically active. Our research interests have focused on the synthesis of novel heterocycles related to the indolocarbazoles. Previously we reported the synthesis of fused benzo[*b*]thieno[2,3-*a*]-pyrrolo[3,4-*c*]carbazoles and benzo[*b*]furano[2,3-*a*]-pyrrolo[3,4-*c*]carbazoles *via* a novel oxidative A-E ring closure [5]. An extension of our work exploring the indolocarbazole pharmacophore was to develop a synthesis of the indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazole ring system and a route to each lactam regioisomer. CEP-7055, a first-generation inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinases from 5-oxo-indenopyrrolocarbazole template **16**, has advanced into Phase I clinical trials.

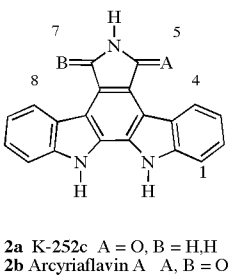
Historically, the [4π + 2π] cycloaddition reaction with 2,2'-biindole and dienophiles such as maleimides or acetylenedicarboxylates to the indolopyrrolocarbazole ring system has not been successful [6]. Diels-Alder reactions with 3-vinylindoles have been widely used for the synthesis of carbazoles [6a, 7 and references therein]. However, few examples of 2-vinylindoles have been reported due to their accessibility and stability [8]. Ethyl β-cyanoacrylate appeared to be an ideal dienophile and lactam precursor, although only one report on the use of a β-cyanoacrylate in a Diels-Alder reaction appears in the literature [9]. The reaction of ethyl *trans*-β-cyanoacrylate and 5-propoxy-oxazoles gave 4-cyano-3-ethoxycarbonyl substituted pyridines in a [4π + 2π] reaction. We report here the synthesis, characterization and structural identification of the indenocarbazole imide (**10**), and the 5-oxo (**16**) and 7-oxo (**17**) lactam regioisomers utilizing a regioselective Diels-Alder reaction with 2-indenylindole and ethyl *cis*-β-cyano-acrylate as a lactam precursor.

Results and Discussion.

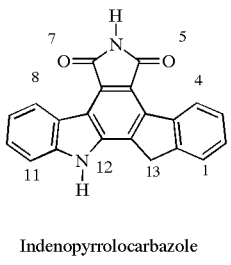
The diene 2-(2-indenyl)indole was prepared by two methods as outlined in Scheme 1. A number of protecting groups were evaluated for the indole nitrogen, subsequent 2-activation and addition to the highly enolizable 2-indanone (CO_2, $PhSO_2$, TBS, BOC, MOM, SEM) (Scheme 1, Method A). The carboxy protecting group was the only N-protecting group successful in the addition to 2-indanone. With the other protecting groups proton transfer from the readily enolizable ketone 2-indanone appeared to be the major pathway, resulting only in starting ketone and



1 K-252a



2a K-252c A = O, B = H,H
2b Arcyriaflavin A A, B = O



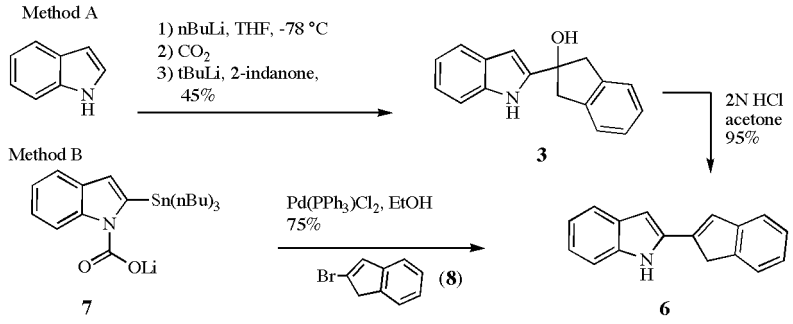
Indenopyrrolocarbazole

Figure 1

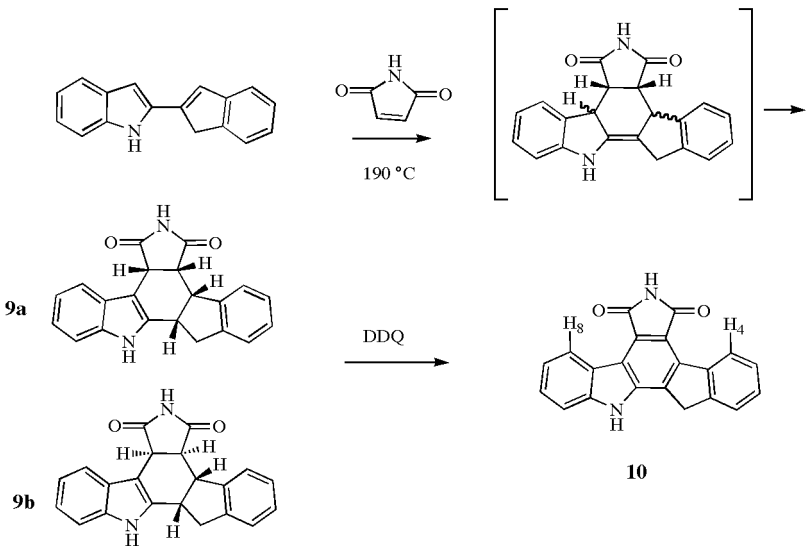
indole. An advantage of the 1-carboxy protecting group for indoles is the ease of removal by decarboxylation in an acidic ammonium chloride workup [10]. Therefore, the alkylation of lithio 2-lithioindole-1-carboxylate [10] (**4**) with 2-indanone (**5**) to alcohol **3**, followed by dehydration (2 *N* HCl, acetone) gave **6** in 40-45% overall yield (Scheme 1, Method A). Alternatively, diene **6** was prepared in 73% yield by coupling 1-carboxy-2-(tributylstannyl)indole (**7**) [11] with 2-bromoindene (**8**) [12] (Scheme 1, Method B).

The favored method which gave good yields of tetrahydrocarbazole **9** (> 80% yield) was using a melt reaction of diene **6** with maleimide at 190 °C (Scheme 2). The reaction is presumed to proceed through a Diels-Alder step to yield the cycloadduct that was stabilized by a spontaneous [1,3]-hydrogen shift to give the tetrahydrocarbazole as a 1:1 mixture of two diastereomers. The isomers were separated by fractional recrystallization and assigned based on 2-D ^{1}H NMR as diastereomers **9a** and **9b**. Observed NOE are

Scheme 1



Scheme 2



The cycloaddition reaction of 2-(2-indenyl)indole **6** and maleimide was studied using solvents such as benzene, toluene and xylene, which gave either low yields of the cycloadduct or no reaction. The use of dichlorobenzene improved the yield but gave bi-products and starting material. A likely by-product in the high temperature solvent reaction was the 2-indenylindole dimer based on mass spectrum analysis [8a,b]. Acid catalysis in toluene or dichloromethane favored the Michael reaction and under stringent conditions produced a rearranged 6-oxo isomer (see Figure 4) *via* a tandem Michael-acid catalyzed condensation sequence [13]. shown in Figure 2. The exo/endo geometry was 1:1 based on the stereochemistry at the tetrahydrocarbazole C-2 position. The Michael adduct was not detected in the reaction under these conditions suggesting a concerted Diels-Alder process predominates. The mixture of isomers **9a**,**b** was dehydrogenated using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene or acetonitrile (room temperature to 60 °C) to give carbazole **10** in 90-95% yield [14].

A characteristic in the proton spectrum of arcyriaflavin A (**2b**) is the deshielding effect of the lactam carbonyls on the C-4 and C-8 aryl protons. The chemical shift of H-4/H-8 on

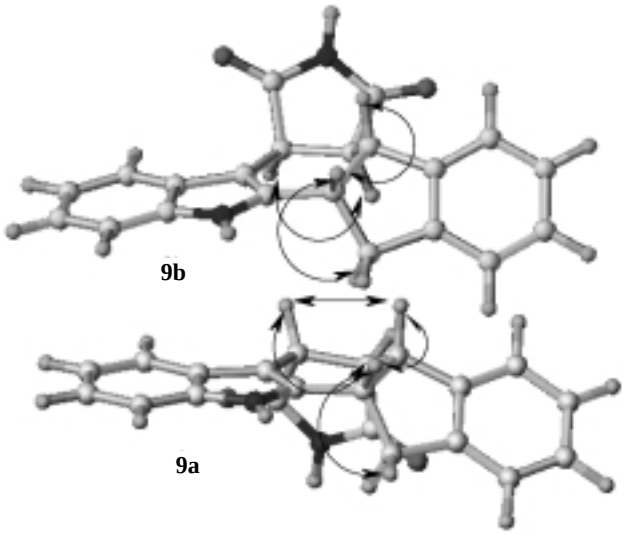
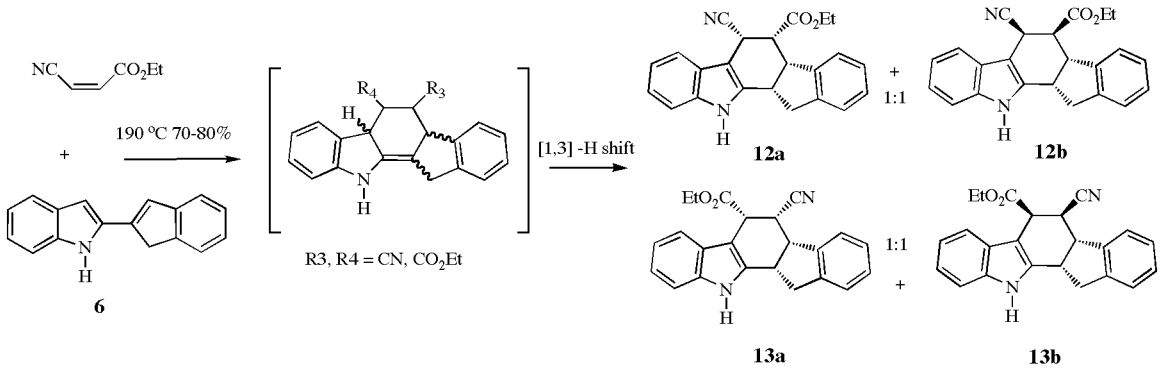


Figure 2. Energy minimized structures and observed NOE for **9a**, **9b**.

Lactam formation by reduction of the imide was not satisfactory for obtaining larger quantities of each pure isomer; in addition, a selective route to **16** was desired. As a result, an alternate method was developed using ethyl *cis*-β-cyanoacrylate as a dienophile precursor to the lactam. Ethyl *cis*-β-cyanoacrylate was prepared from maleamic acid using the literature procedure [16]. The cycloaddition reaction of 2-(2-indenyl)indole (**6**) with ethyl *cis*-β-cyanoacrylate (**11**) in a melt at 190 °C yielded four 1,2,3,4-tetrahydrocarbazole products: two nitrile-ester regioisomers **12** (4-CN, 3-CO_2Et) and **13** (4-CO_2Et, 3-CN) in a ratio of approximately 2:1, as a mixture of two diastereomers, each in a ratio of about 1:1 (Scheme 3).

The cycloaddition step was stabilized by a spontaneous [1,3]-hydrogen shift to the tetrahydrocarbazole. The regiochemistry was assigned from the ^{1}H NMR spectra. The tetrahydrocarbazole C-4 proton on **12a** and **12b** appears at δ 4.58 and δ 4.60, respectively. The C-4 protons on **13a** and **13b** are located at δ 4.27, further downfield due

Scheme 3



symmetrical **2b** is δ 9.00. The chemical shifts of H-4 and H-8 on **10** are found at δ 9.10 and δ 8.96, respectively. The indene methylene hydrogens are at δ 4.30 (s, 2H). Imide **10** was subjected to a Clemmensen reduction [15] (Zn•Hg amalgam, HCl(g), ethanol reflux) to give a 4:1 mixture of the 5-oxo (**16**) to 7-oxo (**17**) lactam isomers. A pure sample of each regioisomer was obtained by HPLC and assigned by comparative ^{1}H NMR chemical shifts with the natural products **1** and **2a**. The regioisomers could be distinguished from the ^{1}H chemical shifts of the H-4/H-8 protons. The C-4 aryl proton on **2a** appears at δ 9.22 (d, J = 7.9 Hz) as opposed to H-8, which is at δ 8.05 (d, J = 7.4 Hz). The chemical shifts of H-4 and H-8 on **16** are δ 9.40 and δ 8.00, while the ^{1}H NMR of isomer **17** shows H-4 and H-8 to be at δ 7.71 and δ 9.13, respectively. The H-8 proton of **16** appears in the expected region for the indole ring proton, while the corresponding indene H-4 proton appears up field. The selectivity ratio favors the 5-oxo isomer **16**, since the carbonyl is vinylogous with the indole N-H and protonated under the acidic reaction conditions.

to the electron withdrawing effect of the ester compared to the nitrile. The four isomers were separated by fractional crystallization and the stereochemistry of each diastereomer was assigned from 2-D ^{1}H NMR experiments. The diastereomers were assigned as the *cis-cis-cis* (**12a**, **13a**) and the *cis-trans-cis* (**12b**, **13b**) configurations of each regioisomer. The exo/endo transition state geometry of 1:1 was anticipated for the thermal Diels-Alder reaction. The structures of diastereomers **12a** and **12b** were confirmed by X-ray crystallography (Figure 3) verifying the C-4 substituted nitrile and the *cis* configuration of the hydrogen in **12a** and *cis-trans-cis* in **12b**. The *cis-cis-cis* ring fusion renders **12a** a dish-like shape.

The Diels-Alder reaction run in xylene or chlorobenzene produced similar results. Aluminum and tin Lewis acids were also examined which generally gave messy reactions or numerous products. The use of trifluoroacetic acid in the reaction favored the Michael products and at high temperatures produced the tandem Michael-acid condensation rearranged 6-oxo product (Figure 4) [13].

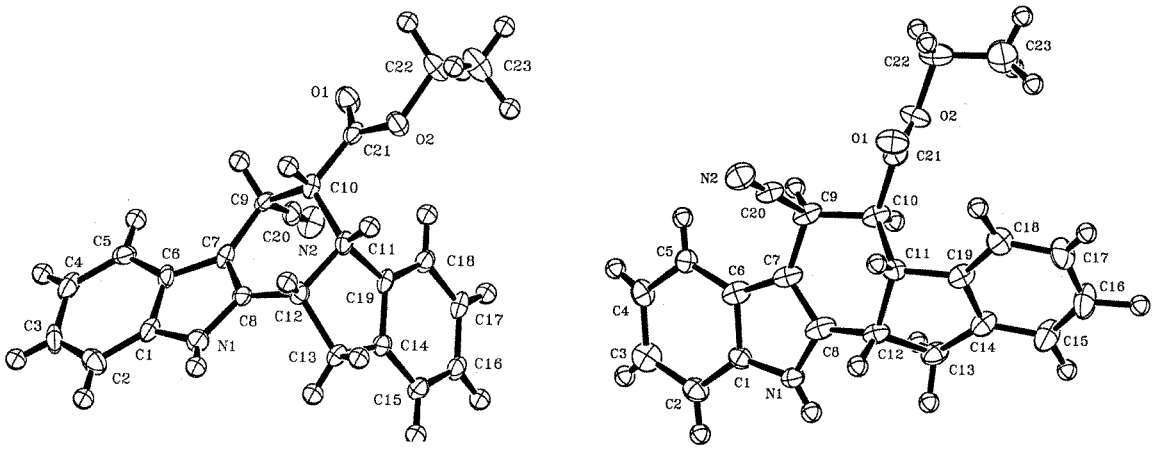
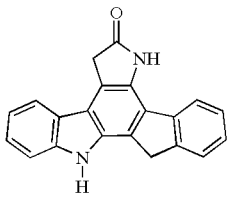


Figure 3. ORTEP drawings of **12a** (left) and **12b** (right). The C, N, and O atoms are represented as 50% ellipsoids and the H atoms as spheres with B = 1.5 Å.



6-oxo isomer

Figure 4. Structure of the 6-oxo indenopyrrolocarbazole isomer

Diels-Alder reactions of 2-vinylindoles based on Frontier Molecular Orbital (FMO) theory follows a normal electron demand process controlled by the HOMO (diene)-LUMO (dienophile) interaction. Molecular orbital calculations performed on 2-indenylindole and ethyl *cis*-β-cyanoacrylate predict regio-preference for the 4-cyano isomer (Figure 5). The electron density of the indole C-3 carbon is 4.1042 and the indene C-1 carbon is 4.0057. The coefficients for the diene (E_{HOMO} = -7.9917 eV) are -0.4328 for the C-3 indole carbon and 0.3491 for the indene C-1 carbon. The coefficients for the β-cyanoacrylate dienophile (E_{LUMO} = -6.2125 eV) are 0.0171 for the C-3 and 0.0074 for the C-2 carbon. The electron density of β-cyanoacrylate C-3 carbon is 3.8693 and C-2 carbon is 4.1500.

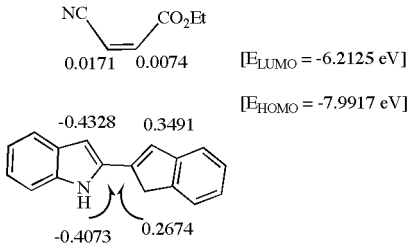


Figure 5. MNDO calculated HOMO LUMO energy and coefficients.

With verification of the correct assignments of the lactam isomers, the next step was aromatization of the center C-ring followed by formation of the lactam ring. Dehydrogenation of the C-ring of *cis-cis-cis* isomers **12a** or **13a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in toluene or acetonitrile quantitatively formed the corresponding carbazole, while the *cis-trans-cis* isomers **12b** or **13b** oxidized to the carbazole in only about 50% yield, with numerous by-products observed. The *cis*-hydride transfer mechanism of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone dehydrogenation [14] would favor the dish shape of the *cis*-isomer compared to the more hindered *cis-trans-cis*. Dehydrogenation with palladium on carbon produced similar results as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The lactam regioisomers **16** and **17** were formed in high yield by reductive cyclization (H_2, RaNi, methanol, DMF, > 95%) of cyano-esters **14** and **15** (Scheme 4).

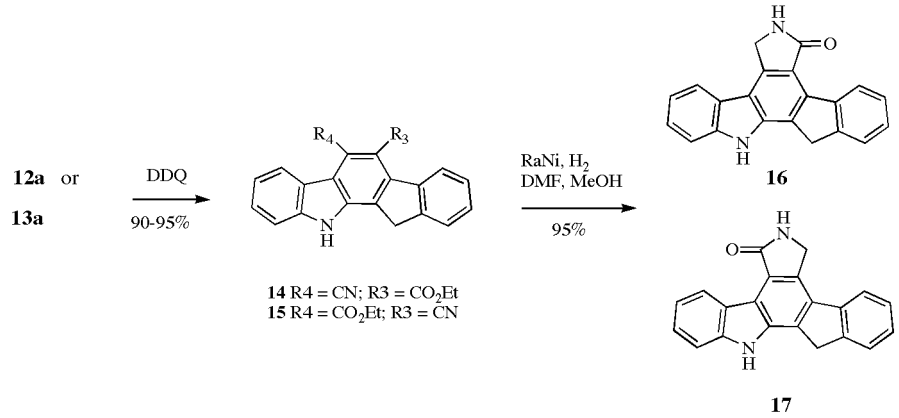
In conclusion, we report the first synthesis of the indenopyrrolocarbazole ring system, an important kinase inhibitor template, utilizing a Diels-Alder reaction with 2-indenylindole and maleimide. Clemmensen reduction of imide **10** furnished the 5-oxo (**16**) and 7-oxo (**17**) lactam regioisomers. A regiospecific route to the 5-oxo isomer was developed using ethyl *cis*-β-cynaoacrylate as the dienophile. The regio- and stereochemistry of the tetrahydrocarbazole Diels-Alder adducts **12a** and **12b** was confirmed using X-ray crystallography.

EXPERIMENTAL

General Methods

All reagents and solvents were obtained from commercial sources and used as received. The NMR spectra were recorded at 400 MHz (proton) and 100 MHz (carbon) in the solvent indicated

Scheme 4



with tetramethylsilane as an internal standard. Coupling constants (*J*) are given in Hertz (Hz). Preparative HPLC was carried out on Zorbax RX8, 4 x 25 cm eluted with a mixture of acetonitrile and water containing 0.1% trifluroacetic acid. Analytical HPLC was carried out on a Zorbax RX8, 5 x 150 mm eluted with a mixture of acetonitrile and water containing 0.1% trifluoroacetic acid with a gradient of 10-100%. Column chromatography was performed on silica gel 60 (230-400 mesh). M-Scan Inc., West Chester, PA, performed high-resolution mass spectra (FAB). Quantitative Technologies Inc., performed elemental analyses.

2-(2-Hydroxyindanyl)indole (**3**).

To a solution of indole (12.0 g, 102.4 mmol) in dry tetrahydrofuran (400 mL) at -78 °C under a nitrogen atmosphere was added butyllithium (107.5 mmol, 43 mL of 2.5 *M* solution in hexanes) dropwise. The solution was stirred for 0.5 hours, then dry carbon dioxide(g) was passed *via* a double tip syringe below the surface of the solution for 10 minutes. The dry ice bath was removed, the flask fitted with a side condenser for distillation and the tetrahydrofuran removed to about half volume under reduced pressure. Tetrahydrofuran was added (200 mL) to the solution, cooled to -78 °C, and *t*-butyllithium (102 mmol, 60 mL of 1.7 *M* solution in hexanes) was added slowly drop wise. The resulting yellowish solution was stirred for 2 hours, then 2-indanone (15.0 g, 112.6 mmol) in tetrahydrofuran (100 mL) was added drop wise. After stirring for 2 hours the reaction was quenched by addition of water (5 mL) and poured into saturated NH_4Cl solution (250 mL). The layers were separated and the aqueous layer washed with ether (1 x 200 mL). The combined ether and tetrahydrofuran layer was dried ($MgSO_4$) and concentrated at reduced pressure to give a semi-solid. Ether (*ca*. 50 mL) was added followed by hexanes to complete precipitation of a tan product, which was collected to give 10.5 g. The ether-hexanes solution was concentrated and the residue chromatographed on silica gel using ethyl acetate:hexanes (2:1) to give an additional 1 g of product (total yield 11.5 g, 45%). mp 244-245 °C (dec). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.22 (d, *J* = 16.2 Hz, 2H), 3.43 (d, *J* = 16.2 Hz, 2H), 5.54 (s, 1H), 6.31 (d, *J* = 1.5 Hz, 1H), 6.91-7.04 (m, 2H), 7.15-7.19 (m, 2H), 7.23-7.27 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 11.06 (s, 1H). ^{13}C nmr (dimethyl sulfoxide-d_6): δ 48.4, 78.9, 97.6, 111.6, 119.1, 120.1, 121.0, 125.0, 126.8, 136.7, 142.0, 145.9. MS (ES^+) m/z 250 (M + 1).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.16; H, 6.03; N, 5.58.

2-(2-Indenyl)indole(**6**).

Method A.

To a stirred solution of **3** (4.0 g, 16.1 mmol) in acetone (30 mL) was added 2 *N* HCl (5 mL). The mixture was stirred at room temperature for 1 hour, water (*ca*. 10 mL) was added and the precipitate collected by filtration and dried to give 3.6 g (98%) of a white solid; mp 273-274 °C (MeOH). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.87 (s, 2H), 6.68 (s, 1H), 7.00 (t, *J* = 7.5Hz, 1H), 7.10-7.19 (m, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.35-7.53 (m, 5H), 11.47 (s, 1H). ^{13}C nmr (dimethyl sulfoxide-d_6): δ 101.2, 111.5, 119.8, 120.6, 121.3, 122.5, 124.2, 125.1, 125.9, 127.1, 129.0, 135.4, 137.8, 139.4, 143.0, 145.4. MS (ES^+) m/z 232 (M + 1).

Anal. Calcd. for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.11; H, 5.60; N, 5.98.

Method B.

A mixture of 2-bromoindene **8** (3.0 g, 15.4 mmol), 1-carboxy-2-tributylstannylindole **7** (10.0 g, 23.1 mmol) and $Pd(PPh_3)_2Cl_2$ (810 mg, 1.2 mmol) in ethanol (50 mL) was maintained at reflux under a nitrogen atmosphere for 24 hours. The solution was cooled to room temperature, filtered through Celite and the solvent concentrated at reduced pressure. The resulting solid was purified by column chromatography (silica gel, toluene: THF; 9:1 to 6:4) to give 2.6 g (73%). This material displayed identical physical and spectral characteristics to the product prepared by Method A.

4c,7a,7b,12a-Tetrahydro-6*H*,12*H*,13*H*-indeno[2,1-*a*]pyrrolo-[3,4-*c*]carbazole-5,7-(5*H*,7*H*)-dione (**9**).

A mixture of **6** (1.0 g, 4.3 mmol) and maleimide (525 mg, 5.41 mmol) in a 10 cm sealed reaction vial was heated in an oil bath at 180-190 °C, with stirring for 1 h. While cooling to room temperature methanol (5-7 mL) was added slowly to the syrupy material. The product was triturated to a solid and collected to give 1.25 g (88%) of a white solid. ^{1}H nmr showed an equal mixture of two isomers. Triturating with MeOH-ether isolated isomer **9a**. The methanol-ether solution was reduced, additional ether added and cooled at –30 °C to collect additional **9a**. Total yield obtained was 600 mg (43%); **9a**: mp (methanol-ether) 246-248°C. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.07-3.27 (m, 2H), 3.72-3.77 (m, 2H), 3.91 (t, *J* = 6.34 Hz, 1H), 4.31 (d, *J* = 6.4 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 7.08-7.12 (m, 2H), 7.18-7.28 (m, 3H), 7.70 (d, *J* = 7.8 Hz, 1H), 11.12 (s, 1H), 11.19 (s, 1H). MS (ES^-)

m/z 327 (M - 1). ^{13}C nmr (dimethyl sulfoxide-d_6): δ 37.2, 38.2, 41.1, 43.3, 44.1, 103.6, 111.2, 119.1, 120.6, 121.5, 124.7, 125.3, 126.6, 126.9, 127.2, 136.7, 136.9, 142.5, 143.7, 178.5, 179.6.

Diastereomer **9b** was precipitated from the ether solution by addition of hexanes. Recrystallization from ether-hexanes gave pure isomer **9b** as a white solid (575 mg, 41%), **9b**: mp 309-310.5 °C. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.30 (bs, 2H), 3.68 (m, 1H), 3.92 (d, *J* = 7.7 Hz, 1H), 4.08 (d, *J* = 5.3 Hz, 1H), 4.31 (d,d J = 5.7, 1.5, 1H), 6.90 (t, *J* = 6.8 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 7.06-7.16 7 (m, 3H), 7.22 (d, J = 7.9 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.65 (d, J = 7.8, 1H), 11.08 (s, 1H), 11.12 (s, 1H). MS (ES$^-$) m/z 327 (M - H). ^{13}C nmr (dimethyl sulfoxide-d_6): δ 36.1, 37.7, 40.7, 41.8, 42.1, 104.3, 111.2, 119.1, 120.2, 121.6, 122.9, 125.2, 126.4, 126.8, 127.4, 136.1, 136.5, 141.9, 143.7, 178.7, 180.4.

6*H*,12*H*,13*H*-Indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazole-5,7(5*H*,7*H*)-dione (**10**).

To a mixture of isomers **9a** and **9b** (800 mg, 2.44 mmol) in toluene (60 mL) was added solid 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.4 g, 6.1 mmol) in one portion. The solution was maintained at 60-65 °C for 6 hours, cooled on an ice bath and the solids collected by filtration. The solid was suspended in methanol (20 mL) and stirred 1 hour to remove DDQ and by-products. The product was collected and recrystallization (acetone-methanol) gave 710 mg (90%) of **10** as a yellow solid, mp > 330 °C. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.30 (s, 2H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.46-7.65 (m, 4H), 7.75 (d, *J* = 7.0 Hz, 1H), 8.95 (d, *J* = 7.9 Hz, 1H), 9.10 (d, *J* = 7.5 Hz, 1H), 11.21 (s, 1H), 12.25 (s, 1H). MS (FAB) m/z 325 (M + 1).

Anal. Calcd. for $C_{21}H_{12}N_2O_2$•0.75H_2O: C, 74.65; H, 4.03; N, 8.29. Found: C, 74.40; H, 3.75; N, 8.26.

Diels-Alder Reaction of 2-(2-Indenyl)indole with Ethyl *cis*-β-Cyanoacrylate.

4-Cyano-3-ethoxycarbonyl-1,2,3,4-tetrahydro-[1*H*]indeno[2,1-*a*]-9*H*-carbazole (**12**) and 3-Cyano-4-ethoxycarbonyl-1,2,3,4-tetrahydro-[1*H*]indeno[2,1-*a*]-9*H*-carbazole (**13**).

A 100 mL round bottom flask equipped with a reflux condenser and nitrogen inlet was charged with **6** (10 g, 43.3 mmol) and ethyl *cis*-β-cyanoacrylate (**11**) (10.8 g, 86.6 mmol) then heated at 190 °C with stirring for 1.5 h. The mixture was allowed to cool to below 60 °C when methanol (20 mL) was slowly added through the top of the reflux condenser. Isomer **12a** separated as the mixture cooled to room temperature and collected to give 4.2 g (27%) as a white solid. Isomer **12a**: mp 267-268 °C (acetonitrile). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.28 (t, *J* = 7.1, 3H), 3.16-3.36 (m, 2H), 3.66-3.71 (m, 1H), 3.86-3.90 (m, 1H), 4.29-4.36 (m, 3H), 4.58 (d, *J* = 5.6 Hz, 1H), 6.93-7.17 (m, 6H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.7, 1H), 11.25 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 14.6, 23.2, 37.5, 38.4, 42.6, 44.6, 61.6, 103.2, 111.6, 117.8, 119.6, 120.1, 121.9, 125.4, 125.5, 126.1, 126.2, 127.6, 136.7, 138.1, 140.0, 143.1, 171.9. IR (potassium bromide): cm^{-1} 2210 (CN) 1690 (C=O). MS(ES$^+$) m/z 357 (M + 1). HPLC Rt = 13.04 min.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.77; H, 5.39; N, 7.71.

Isomer **13a** was isolated by addition of ether to give 1.9 g (12%) as a white solid. Isomer **13a**: mp 232-233 °C (acetone-ethyl acetate). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.25 (t, *J* = 7.1 Hz, 3H), 3.13-3.23 (m, 1H), 3.41-3.50 (m,1H), 3.82 (q, *J* = 8.9 Hz, 2H), 3.90-3.94 (m, 1H), 4.02 (t, *J* = 4.3 Hz, 1H), 4.21-4.27 (m, 3H), 6.97 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.22-7.38 (m, 5H), 7.55 (m, 1H), 11.33 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 14.6, 34.8, 36.1, 38.0, 42.3, 46.4, 61.4, 103.7, 111.6, 119.1, 119.4, 119.8, 121.3, 125.5, 125.9, 127.3, 128.4, 136.9, 137.4, 142.5, 143.5, 171.3. MS (ES$^+$) m/z 357 (M + 1). HPLC Rt = 13.45 min.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.61; H, 5.49; N, 7.81.

The solvents were removed at reduced pressure to leave a viscous oil, and the excess ethyl *cis*-β-cyanoacrylate was removed by Kugelrohr distillation (oven temperature 80-85 °C, 0.5 mm). The remaining residue was dissolved in methanol and ether added, followed by excess hexanes to precipitate **12b** and **13b**. Isomer **12b** was obtained by triturating with ether to leave a white solid, which was collected to give 4.0 g (26%). An analytically pure sample was obtained by recrystallization from acetone-ethyl acetate. Isomer **12b**: mp 235-236 °C (acetone-ethyl acetate). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.21 (t, *J* = 7.1, 3H), 2.96-3.03 (m, 1H), 3.28-3.41 (m, 2H), 3.85-3.95 (m, 2H), 4.29-4.36 (m, 3H), 4.18 (q, *J* = 5.8 Hz, 2H), 4.60 (d, *J* = 4.7 Hz, 1H), 7.00-7.37 (m, 7H), 7.58 (d, *J* = 7.7, 1H), 11.35 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 14.5, 26.6, 37.4, 37.8, 44.3, 44.6, 61.2, 101.8, 111.7, 118.1, 119.6, 121.85, 121.90, 125.28, 125.34, 125.5, 127.0, 128.1, 136.6, 137.2, 143.0, 143.1, 171.6. MS (ES$^+$) m/z 357 (M + 1). HPLC Rt = 13.86.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.65; H, 5.60; N, 7.67.

Isomer **13b** was precipitated from the ether solution by addition of hexanes to give a white solid (1.8 g, 12%). An analytically pure sample was obtained by recrystallization from acetonitrile. Isomer **13b**: mp 230-231 °C (acetonitrile), ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.18 (t, *J* = 7.1 Hz, 3H), 2.85-2.94 (dd, *J* = 10 Hz, 10Hz, 1H), 3.32-3.44 (m, 2H), 3.79-3.88 (m, 1H), 4.05-4.16 (m, 3H), 4.27 (d, *J* = 4.8 Hz, 1H), 6.96-7.08 (m, 2H), 7.23-7.33 (m, 4H), 7.46-7.52 (m, 2H), 11.25 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 14.6, 32.0, 37.4, 37.7, 44.3, 49.1, 61.3, 103.2, 111.6, 118.8, 119.4, 121.1, 121.7, 125.5, 125.8, 126.0, 127.0, 128.4, 136.6, 137.3, 142.9, 143.3, 171.6. MS (ES$^+$) m/z 357 (M + 1H). Rt = 13.34 min.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.72; H, 5.58; N, 7.68.

4-Cyano-3-ethoxycarbonyl[1*H*]indeno[2,1-*a*]9*H*-carbazole (**14**).

To a stirred solution of diastereomer **12a** (1.1 g, 3.1 mmol) in dry toluene (70 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.75 g, 7.7 mmol) in one portion. The solution was stirred at 60-65 °C for 6 hours. After cooling on an ice bath the precipitate was collected, suspended and stirred in methanol (20 mL) 1 hour, collected and washed with cold methanol (10 mL) to yield 975 mg (89%) of a light green solid. Crystallization from acetone produced white needles, mp 260-263 °C (acetone). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.41 (t, J = 7.1 Hz, 3H), 4.26 (s, 2H), 4.58 (q, J = 6.7 Hz, 2H), 7.33-7.42 (m, 3H), 7.57 (t, J = 8.2 Hz, 1H), 7.65-7.73 (m, 3H), 8.42 (d, J = 8.0 Hz, 1H), 12.32 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 14.4, 35.4, 62.8, 100.5, 112.6, 117.6, 120.8, 120.9, 121.1, 121.6, 122.4, 122.9, 126.0, 127.6, 128.2, 128.5, 131.8, 136.2, 137.4, 139.2, 142.1, 143.8, 167.4. IR (potassium bromide): cm^{-1} 2210 (CN); 1710 (C=O). MS (FAB) m/z 353 (M + 1).

Anal. Calcd. for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.77; H, 4.39; N, 7.71.

6*H*,7*H*,12*H*,13*H*-Indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazole-5(5*H*)one (**16**).

A mixture of **14** (750 mg; 2.1 mmol) and Raney Nickel catalyst (*ca*. 2 g) in DMF-methanol (40 mL; 9:1) was hydrogenated on a Parr Apparatus until tlc analysis (silica gel; ethyl acetate:hexane; 2:1, Rf = 0.3) showed the reaction complete. The solution was filtered through celite and the solvent was concentrated at reduced pressure. The product was triturated with methanol to leave a white solid, which was dried at 80 °C under vacuum for 24 h to give 610 mg (94%). The product is > 95% pure by HPLC. An analytical sample was obtained by column chromatography (silica gel, ethyl acetate: methanol; 95:5, R_f = 0.6). Recrystallization from tetrahydrofuran-methanol produced an off white powder, mp > 320 °C. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.17 (s, 2H), 4.93 (s, 2H), 7.25-7.50 (m, 4H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 6.8 Hz, 1H), 8.00 (d, *J* = 7.4 Hz, 1H), 8.55 (s, 1H), 9.40 (d, *J* = 7.3 Hz, 1H), 11.93 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 35.3, 45.5, 111.9, 116.2, 119.7, 120.2, 122.4, 125.1, 125.8, 126.3, 126.8, 127.0, 1137.0, 138.7, 140.1, 141.1, 142.1, 143.8, 172.4. MS(FAB) m/z 311 (M + 1).

Anal. Calcd. for $C_{21}H_{14}N_2O$•$0.4H_2O$: C, 79.42; H, 4.65; N, 8.82. Found: C, 79.61; H, 4.56; N, 8.63.

3-Cyano-4-ethoxycarbonyl[1*H*]indeno[2,1-*a*]-9*H*-carbazole (**15**).

This compound was prepared by the same general procedure as **14** using **13a** (400 mg, 1.12 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (640 mg, 2.8 mmol). Recrystallization from acetone gave white needles yielding 355 mg (90%), mp 292-293 °C (acetone). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.47 (t, *J* = 7.1 Hz, 3H), 4.23 (s, 2H), 4.65 (q, *J* = 7.1 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.49-7.58 (m, 3H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 7.1 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 7.5 Hz, 1H), 12.43 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 14.4, 35.0, 62.9, 92.8, 112.4, 118.1, 119.0, 120.9, 121.4, 122.6, 124.0, 126.2, 127.8, 128.2, 128.6, 128.7, 130.4, 139.4, 139.5, 142.0, 144.3, 166.9. Ir (potassium bromide): cm^{-1} 1 2210 (CN); 1710 (C=O). MS (FAB) m/z 353 (M + 1).

Anal. Calcd. for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.61; H, 4.28; N, 7.75.

5*H*,6*H*,12*H*,13*H*-Indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazole-7(7*H*)one (**17**).

A mixture of **15** (300 mg; 0.85 mmol) and Raney Nickel catalyst (*ca*. 1 g) in DMF-methanol (20 mL; 9:1) was hydrogenated on a Parr Apparatus until tlc analysis (silica gel; ethyl acetate:hexanes; 2:1, Rf = 0.3) showed the reaction complete. The solution was filtered through celite and the solvent concentrated at reduced pressure. The product was triturated with methanol to a white solid and dried at 80 °C under vacuum for 24 hours to give 250 mg (96%) of an off white solid. The product is > 95% pure by HPLC. A sample was obtained by column chromatography (silica gel, ethyl acetate:hexanes; 95:5, R_f = 0.6) mp > 320 °C. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.21 (s, 2H), 4.84 (s, 2H), 7.2 (t, J = 7.6 Hz, 1H), 7.33-7.43 (m, 3H), 7.54 (d, J = 8.1 Hz, 1H), 7.71 (t, J = 7.9 Hz, 1H), 8.72 (s, 1H), 9.13 (d, J = 7.9 Hz, 1H), 11.76 (s, 1H). ^{13}H nmr (dimethyl sulfoxide-d_6): δ 35.6, 45.7, 111.4, 117.8, 119.3, 122.2, 122.5, 125.8, 126.2, 126.5, 126.7, 126.9, 127.6, 129.1, 131.2, 133.7, 136.9, 141.1, 141.4, 143.6, 172.1. MS(FAB) m/z 311 (M + 1).

Anal. Calcd. for $C_{21}H_{14}N_2O$•$0.4H_2O$: C, 79.42; H, 4.65; N, 8.82. Found: C, 79.54; H, 4.60; N, 8.70.

Synthesis of **16** and **17** by Clemmensen reduction of Imide **10**.

To a stirred suspension of zinc dust (5 g) and mercuric chloride (1 g) in water (10 mL) was added concentrated HCl (2 mL) dropwise. After 10 min, the aqueous layer was decanted off and the zinc amalgam obtained was first washed with water, then washed with ethanol. The zinc amalgam was suspended in ethanol (75 mL), and then **10** (500 mg, 1.5 mmol) added in one portion. HCl(g) was passed through as the mixture was maintained at reflux for 2 h. After cooling to room temperature, the solution was concentrated at reduced pressure to an oil. Tetrahydrofuran-ethyl acetate (200 mL, 1:1) was added and the mixture was extracted with saturated $NaHCO_3$ solution (3 x 100 mL), saturated NaCl solution (3 x 100 mL), and then dried ($MgSO_4$). The solvent was concentrated at reduced pressure to give a crude solid. Column chromatography (silica gel, 95:5, ethyl acetate:methanol) yielded 240 mg (50 %) of a 4:1 mixture of **16**:**17**. A pure sample of each product was obtained by reverse phase HPLC (column RX-8, 4 x 25 cm, acetonitrile-water). Isomers **16** and **17** prepared from **10** showed identical physical and spectral characteristics to those prepared from **14** and **15**.

Acknowledgements.

The authors thank John Mallamo for a critical reading of the manuscript and many helpful scientific discussions.

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