Synthesis of the Staurosporine Aglycon

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A short synthesis of the staurosporine aglycon (**6**) is reported, the indolocarbazole skeleton being constructed by an intramolecular Diels–Alder reaction followed by a nitrene-mediated ring closure. The synthesis starts by acylation of ethyl indole-2-acetate with oxalyl chloride. The resulting indole-3-glyoxalyl chloride is quenched with 2-nitrocinnamylamine (**29**) to give the amide (**31**). Hydrolysis of the ester group and cyclodehydration then gives the pyranoindolone (**35**). On heating in bromobenzene, the pyranoindolone **35** undergoes intramolecular Diels–Alder reaction to give, after loss of carbon dioxide and air oxidation, the carbazole **36**, which on treatment with triethyl phosphite cyclizes to the staurosporine aglycon. The overall yield from ethyl indole-2-acetate is 22.6%.

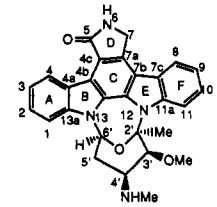
Introduction

The indolocarbazole alkaloids are a structurally rare, but biologically interesting, class of natural products,[1] whose history extends back for about 15 years. In 1977, a natural product with a novel structure was isolated from *Streptomyces staurosporeus*.[2] Initially called AM-2282, but later named staurosporine, the structure of this new alkaloid was not established completely until the X-ray crystal structure of its methanol solvate was obtained.[3,4] Staurosporine (**1**) consists of an unusual indolocarbazole unit linked by two N-glycosidic bonds to a sugar moiety. Preliminary studies on the biosynthesis of staurosporine show that the aglycon moiety is made from two intact units of tryptophan,[5] although the exact metabolic pathway is still under investigation.

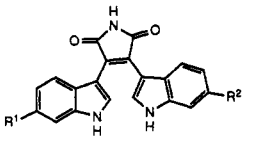
The closely related highly colored pigments arcyriarubins **2** and arcyriaflavins **3–5** were isolated from the fruiting bodies of the slime mould *Arcyria denudata* by Steglich and co-workers in 1980.[6] Steglich showed that it was possible to convert **2b** into **5** by gentle heating in concentrated sulfuric acid, thus suggesting the formation of the 2,2′-indole bond as the final step in the biosynthetic pathway of these systems. This was later used by several groups as the final step in various laboratory syntheses of indolocarbazoles.[7–10]

Somewhat later, several new indolocarbazoles were isolated in succession. The first of these was rebeccamycin, a yellow solid, isolated from *Nocardia aerocoligenes*, in 1985.[11,12] In the same year, Japanese workers reported the isolation and structure elucidation of SF2370 from *Actinomadura*.[13] The same compound was isolated the following year from *Nocardiopsis* sp. K-252 and was called K-252a.[14,15] Another *Nocardiopsis* strain, K-290, produced three other indolocarbazoles, K-252b, K-252c (**6**), and K-252d (**7**),[15,16] and the distinctive UV chromophore of these compounds suggested that they all possessed the same aglycon as staurosporine (**1**), with K-252c (**6**), now sometimes called staurosporinone, being the aglycon itself.

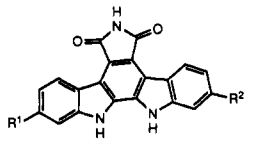
Subsequently, several more indolocarbazoles have been isolated.[17–23] The indolocarbazoles are all biologically active and display properties ranging from antifungal, antimicrobial, and antitumor through to hypertensive effects.[24–31] However, it is the activity as potent inhibitors of protein kinase C (PKC) that has attracted the greatest interest, and much work has been done in this area.[14,16,19,30,32–34]



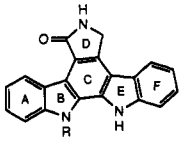
(1) Staurosporine



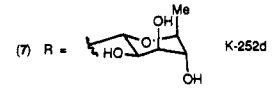
(2a) R^1 = OH, R^2 = H Arcyriarubin B
(2b) R^1 = R^2 = OH Arcyriarubin C



(3) R^1 = R^2 = H Arcyriaflavin A
(4) R^1 = OH, R^2 = H Arcyriaflavin B
(5) R^1 = R^2 = OH Arcyriaflavin C



(6) R = H K-252c (staurosporine aglycone)



(7) R = K-252d

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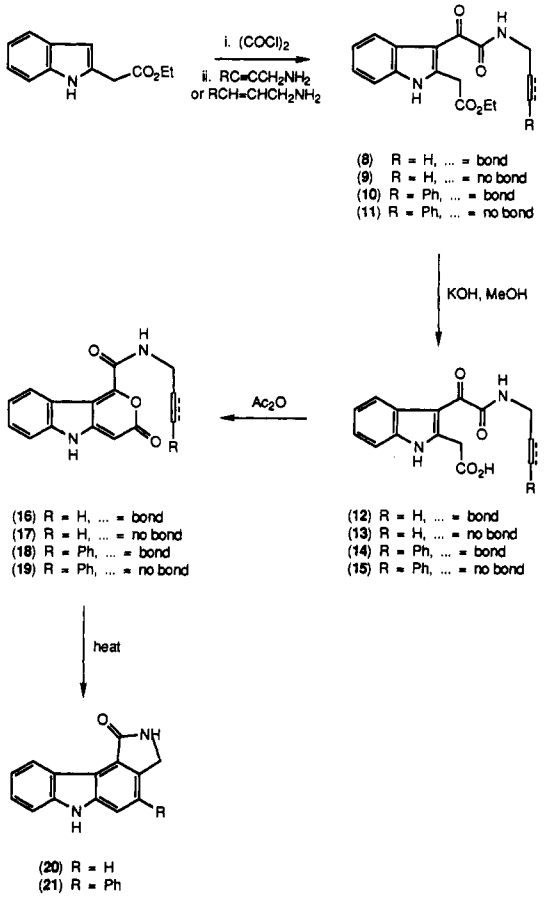
A number of syntheses of indolocarbazoles have been reported in the literature.[7-10,35-39] In considering the hexacyclic structure of the indolocarbazole aglycons, the syntheses, so far, can be divided into two main groups: those which involve formation of the indole B and E rings in the final step[35-37] and those which involve formation of the middle six-membered ring C.[6-10] The exception is Magnus's approach which involves synthesis of the D ring as the final annulation,[38] although the key step is formation of the C ring via an intramolecular indole-2,3-quinodimethane reaction. In the case of staurosporine (1) and related compounds containing the γ-lactam rather than the 5-membered imide, it is worth noting the nonsymmetry of the aglycon. Some workers introduce this nonsymmetry at an early stage of the synthesis, whereas others concentrate on the symmetrical imide structure and only reduce it down to the lactam at a later stage in the synthesis. This is a nontrivial transformation; a variety of methods have been tried ($LiAlH_4$ and related metal hydrides only gave partial reduction, even under forcing conditions) and only Clemmensen reduction appears to give a satisfactory result.[7,36,37] Although rebeccamycin has been synthesized, complete with carbohydrate moiety,[8] methodology has yet to be developed to link the staurosporine sugar via a double N-glycosidic linkage, stereospecifically and regiospecifically, to the aglycon.

Thus, several approaches to the indolocarbazole system have been developed. However, in most cases, the final product is N-protected, or, more commonly, is a derivative of the "symmetrical" imide aglycon such as **3–5**, and so to date only two complete syntheses of the staurosporine aglycon (**6**) have appeared.[9,37] In continuation of our interest in carbazole-containing natural products,[40] we now report the full details of a short new synthesis of the staurosporine aglycon (**6**).[41]

Scheme I



Results and Discussion

Analysis. Our aim was a short synthesis of the staurosporine aglycon (**6**), without the use of protecting groups on the indole or lactam nitrogens. The route is based on an intramolecular Diels–Alder reaction of a pyranoindolone followed by a nitrene-mediated cyclization. We have previously shown that pyrano[3,4-*b*]indol-3-ones, and their [4,3-*b*]-isomers, readily undergo Diels–Alder reaction with alkynes to give, after loss of carbon dioxide, carbazoles in good yield.[42-47] Although, in principle, both isomers of the pyranoindole diene would serve as precursors to the required carbazole, we chose to use the [4,3-*b*]-isomer, since its construction by acylation of an indole-2-acetic acid derivative looked straightforward. In particular, the use of oxalyl chloride as acylating agent seemed particularly attractive since Giua, in 1924, reported that acylation of indoles with oxalyl chloride occurred remarkably easily.[48]

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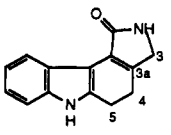
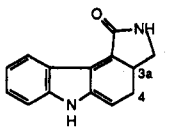
Furthermore, trapping of this indole-3-glyoxalyl chloride with amines, followed by reduction of the carbonyl groups, has been the basis of a variety of substituted tryptamine syntheses.[49]

Model Studies. The reaction of ethyl indole-2-acetate, prepared as previously described,[46] with oxalyl chloride in dry ether proceeded rapidly at room temperature to give the indole-3-glyoxalyl chloride, which was immediately reacted with an amine to give the corresponding amide (Scheme I). Four different amines were used in the model study; propargylamine, allylamine, and the corresponding phenyl-substituted compounds phenylpropargylamine, and cinnamylamine. The first two amines are commercially available, and the latter two were prepared from phenylpropargyl alcohol (by Mitsunobu reaction with phthalimide and cleavage of the phthaloyl group with hydrazine) and cinnamyl chloride (by reaction with potassium phthalimide and hydrazine cleavage), respectively. Thus, the amides **8–11** were readily prepared (29–70% yield). Selective hydrolysis of the ester gave the corresponding acids **12–15** (38–93%) which were cyclodehydrated by treatment with acetic anhydride at room temperature to give the desired pyrano[4,3-*b*]indol-3-ones **16–19**, the substrates for intramolecular Diels–Alder reaction, in 54–79% yield.

The intramolecular Diels–Alder reaction was initially tried by heating the pyranoindolone **16** in boiling chlorobenzene (132 °C). However, after 48 h at reflux only starting material was recovered. However, heating the pyranoindolone **16** neat for 30 s at 250 °C using a Wood's metal bath resulted in rapid evolution of a gas and gave the required carbazole **20** in 74% yield, after chromatography. The reaction was, however, cleaner in solution, and refluxing the pyranoindolone **16** in bromobenzene (156 °C), under nitrogen, for 19 h, gave carbazole (**20**) in 92% yield. In the case of the pyranoindolone **17** with the allyl side chain, Diels–Alder reaction followed by retro-Diels–Alder reaction, to lose carbon dioxide, gives a dihydrocarbazole. Van Doren et al. have referred to the ease of oxidation of these compounds, and it appeared that air oxidation ought to be sufficient to form the carbazole.[50] Thus, pyranoindolone **17** was heated neat for 2 min at 220 °C in the presence of air, and chromatography of the residue gave the required carbazole **20** in only 31% yield. Again the yield was improved by carrying out the reaction in solution; refluxing the pyranoindolone **17** in bromobenzene, with the condenser open to the air, for 20.5 h gave carbazole **20** in 48% yield after chromatography. Interestingly, heating pyranoindolone **17** in refluxing bromobenzene, *under nitrogen*, resulted in the isolation of a different compound, assigned as the 4,5-dihydropyrrolocarbazole (**22**). Presumably, this arises by initial Diels–Alder reaction and loss of carbon dioxide to give the 3a,4-dihydro isomer **23** followed by a [1,5]-hydrogen shift to give the more conjugated product.



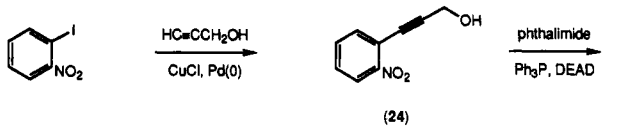
(22)



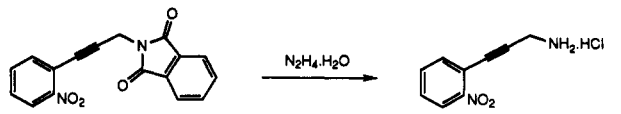
(23)

A similar pattern was observed with the pyranoindolones **18** and **19** containing the phenyl-substituted side chains, in that the alkyne dienophile gave a much better yield of the desired pyrrolocarbazole. Thus, heating the intramolecular Diels–Alder substrate **18** in boiling bromobenzene under nitrogen for 16 h gave carbazole **21** in 86% yield, whereas the same carbazole was formed in only 43% yield by heating the cinnamylamine derived precursor **19** in bromobenzene for 80 h, open to the air. From these model studies, it would appear that the use of an alkyne as the internal dienophile is preferable since the molecule is already at the correct oxidation level, loss of carbon dioxide after the Diels–Alder reaction, leading directly to the aromatic product. Although alkene dienophiles give a dihydrocarbazole which can be aromatized by aerial oxidation, the reaction is considerably less clean.

Scheme II

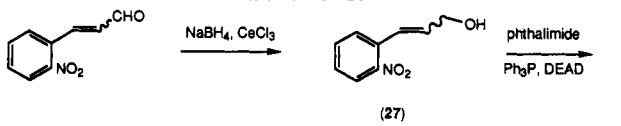


(24)

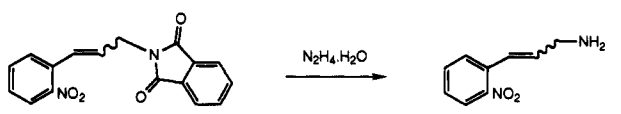


(25) (26)

Scheme III



(27)



(28) (29)

Synthesis of the Staurosporine Aglycon. The intramolecular Diels–Alder substrate required for the synthesis of the staurosporine aglycon has to contain an aromatic-substituted alkyne or alkene with appropriate ortho functionality, which could eventually be converted to a nitrene or a nitrene-type intermediate, to effect the final ring closure. An azide is one possibility, since the decomposition of 2-azidobiphenyls is a well-known route to carbazoles.[51] The alternative to the azide is a nitro group which could be deoxygenated using a phosphorus(III) reagent, again a well-precedented route to carbazoles from 2-nitrobiphenyls.[51,52] The general greater accessibility of nitro compounds over azides led us to choose the *o*-nitro-substituted phenyl dienophile, and hence syntheses of 2-(nitrophenyl)propargylamine (**26**) and the corresponding alkene **29** were required. A literature search revealed that while the amine **26** was not known, 2-(nitrophenyl)propargyl alcohol (**24**) had been prepared by Russian workers using palladium coupling,[53] and although no data on this compound was given, a French patent using the same methodology did report the NMR data.[54] Hence, palladium-catalyzed cross coupling of 2-nitroiodobenzene

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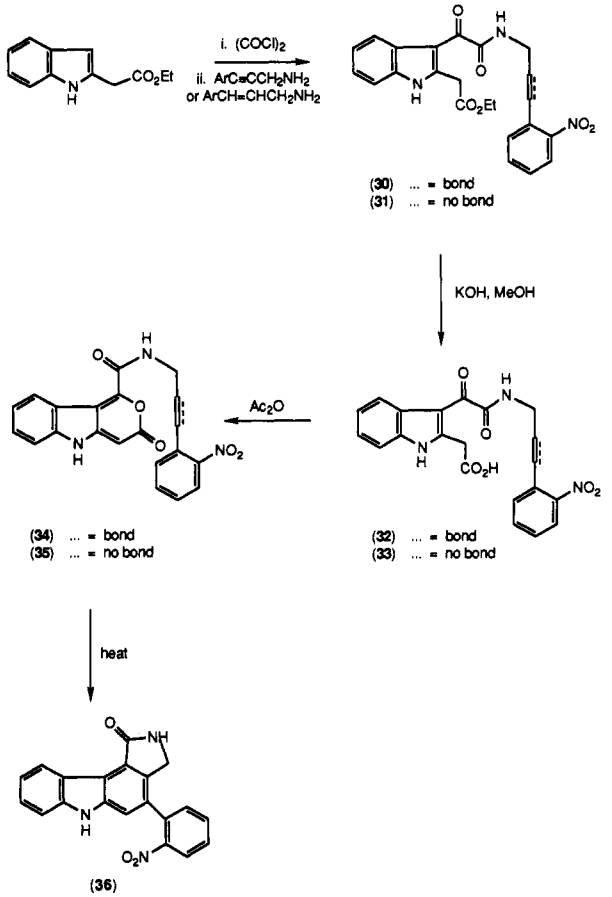
Scheme IV



with propargyl alcohol in the presence of copper(I) chloride, exactly as described,[53] gave the arylpropargyl alcohol **24** in 96% yield. Reaction of the alcohol **24** with phthalimide under Mitsunobu conditions gave the phthalimide **25** (86%), deprotection of which with hydrazine hydrate gave the desired 2-(nitrophenyl)-propargylamine (**26**) in 92% yield (Scheme II).

2-Nitrocinnamylamine was prepared as shown in Scheme III. Reduction of commercially available 2-nitrocinnamaldehyde with sodium borohydride and cerium(III) chloride[55] gave an excellent yield (99%) of 2-nitrocinnamyl alcohol (**27**). Treatment of this with phthalimide, again under standard Mitsunobu conditions, gave the corresponding phthalimide **28** (71%), which was deprotected in the usual fashion with hydrazine hydrate to give 2-nitrocinnamylamine (**29**) in 83% yield.

The amine **26** was then used for the synthesis of the substrate **34** for the key intramolecular Diels–Alder reaction. As before, ethyl indole-2-acetate was acylated with oxalyl chloride and the resulting indole-3-glyoxalyl chloride quenched with the propargylic amine **26**. Surprisingly, this reaction worked rather poorly, and the required amide **30** could only be obtained in ca. 20% yield after chromatography, although the yield was somewhat higher (44%) if the crude product was directly recrystallized from ethanol. Likewise, the hydrolysis of the ester **30** also proceeded in poor yield, and the acid **32** could never be obtained in satisfactory purity and quantity. Nevertheless the crude acid **32** was cyclodehydrated by treatment with acetic anhydride and gave the desired pyranoindolone **34**, although since neither the acid **32** nor the pyrone **34** could be characterized, this route was abandoned.

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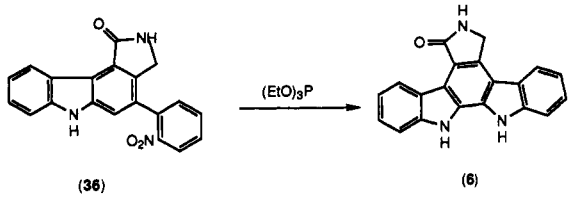
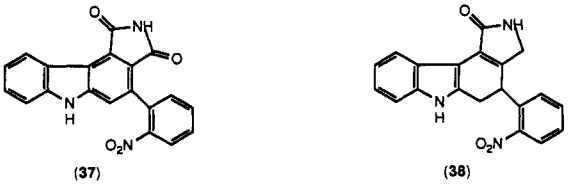
Scheme V



Despite the fact that, in the model studies, the intramolecular Diels–Alder reaction proceeded much better with acetylenic dienophiles, the olefinic substrate **35** was investigated. This was prepared by the usual method from ethyl indole-2-acetate as shown in Scheme IV, but the route did not suffer from the low yields encountered in the acetylenic series described above. Thus the amide **31** was obtained cleanly in 76% yield; hydrolysis to the acid **33** (97%) followed by cyclodehydration (83%) gave the intramolecular Diels–Alder substrate **35**.

Pyranoindolone (**35**) was heated in refluxing bromobenzene, open to the air, to yield the carbazole **36** after only 2 h. The reaction, however, was not clean, and chromatography was required, the major side product being the carbazole **37** in which the lactam had been oxidized to a cyclic imide. However, when the pyranoindolone was refluxed in bromobenzene under nitrogen, a new compound was isolated in a clean reaction. On the basis of its spectroscopic data it was assigned as the dihydrocarbazole **38**, isolated in essentially quantitative yield with no imide products being detected. Several attempts were made to aromatize the dihydrocarbazole **38** using various dehydrogenating agents, but the simple procedure of refluxing it in bromobenzene open to the air proved best. In this way, carrying out the initial Diels–Alder reaction under nitrogen, followed by air oxidation, the carbazole **36** was isolated in 42% yield after chromatography, with no imide being formed.



Although the carbazole **36** could be purified at this stage, it was more convenient to take it directly on to the final cyclization step. Thus, heating the carbazole **36** in triethyl phosphite under reflux for 1.5 h effected the final ring closure in 37% yield from the pyranoindolone (**35**) after chromatography to yield the staurosporine aglycon **6** (Scheme V), whose spectroscopic properties closely matched those described in the literature. A trace of N-ethylation also occurred, but it was possible to purify the staurosporine aglycon by chromatography. Attempts to effect the Diels–Alder reaction and the final ring closure in one pot by heating the pyranoindolone (**35**) in triethyl phosphite first at 110 °C to effect the Diels–Alder reaction and second at reflux to deoxygenate the nitro group resulted in a messy reaction mixture. The use of triphenylphosphine, tributylphosphine, and hexamethylphosphoric triamide as deoxygenating agents was also briefly investigated, but without success.

Conclusion

The synthesis of the staurosporine aglycon **6** described herein uses a completely different approach to the indolocarbazole skeleton than those previously reported in the literature. The synthesis does not require the use of protecting groups and gives the staurosporine aglycon in

an acceptable yield of 22.6% in six steps from ethyl indole-2-acetate. This compares favorably with the published syntheses of the aglycon; Winterfeldt's route proceeds in seven steps and gives 2.2% overall yield from indole-3-acetyl chloride,[9] whereas the Raphael synthesis gives 11.6% overall from 2-nitrocinnamaldehyde and needs eight steps.[37]

Experimental Section

Commercially available reagents were used throughout without further purification, and solvents were dried by standard methods. Light petroleum refers to the fraction of petroleum ether boiling between 40 and 60 °C, and ether refers to diethyl ether. Column chromatography refers to the flash method and was performed on Merck Kieselgel 60 H, using medium-pressure provided by means of hand-bellows.

Ethyl 3-[(*N*-Propargylamino)glyoxylyl]indole-2-acetate (8). Oxalyl chloride was added to a solution of ethyl indole-2-acetate (2.54 g, 12.5 mmol) in dry ether. This was stirred for 10 min and then concentrated in vacuo. Dry ether was added, and the solution was cooled using an ice/salt bath. Propargylamine (1.71 mL, 25 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 3 h. Water was added, and the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, water, and brine and dried ($MgSO_4$). The solvent was evaporated, and the crude product was recrystallized from hot ethanol to give the title compound 8 (2.65 g, 68%) as a yellow solid, mp 150–153 °C: IR (Nujol) 3320 (alkyne H), 3275 (NH), 1709 (ester C=O), 1657 (ketone C=O), 1631 (amide C=O), 1530 (amide C=O), 1493, 1332, 1249, 1224, and 1184 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 1.22 (3 H, t, J = 7 Hz, ethoxy $-CH_3$), 2.73 (1 H, t, J = 2.5 Hz, acetylene m), 4.14 (2 H, q, J = 7 Hz, ethoxy $-CH_2$), 4.19 (2 H, dd, J = 6 and 2.5 Hz, $CONHCH_2$), 4.28 (2 H, s, CH_2COOEt), 7.15–7.25 (2 H, m, aromatic H), 7.45–7.50 (1 H, m, aromatic H), 8.11–8.15 (1 H, m, indole 4-H), 8.25 (1 H, br, amide NH), and 11.23 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 312 (M^+, 21), 230 (100), 202 (32), 184 (17), and 174 (47). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.2; N, 9.0. Found: C, 65.2; H, 5.1; N, 9.3.

3-[(*N*-Propargylamino)glyoxylyl]indole-2-acetic Acid (12). Ethyl 3-[(*N*-propargylamino]glyoxyl]indole-2-acetate (8) (2.58 g, 8.27 mmol) was dissolved in tetrahydrofuran (55 mL) and methanol (6 mL). Potassium hydroxide solution (2 M, 21 mL) was added and the mixture stirred at room temperature for 2 h. Water (400 mL) was added, and the basic solution was extracted with ether. The organic layer was discarded. The aqueous layer was acidified (pH 1.5) with concentrated hydrochloric acid and then extracted with ethyl acetate (3 × 100 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the title compound 12 (2.19 g, 93%) as a yellow crystalline solid, mp 166 °C dec: IR (Nujol) 3400–2400 (br, COOH), 3309 (alkyne H), 3226 (NH), 2627 (alkyne), 1724 (acid C=O), 1662 (ketone C=O), 1580 (amide C=O), 1547, 1528, 1491, 1264, 1245, and 1185 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 2.72 (1 H, t, J = 2.4 Hz, acetylene H), 4.19 (2 H, dd, J = 5.8 and 2.4 Hz, $CONHCH_2$), 4.29 (2 H, s, CH_2COOH), 7.15–7.25 (2 H, m, aromatic H), 7.47–7.51 (1 H, m, aromatic H), 8.10–8.15 (1 H, m, indole 4-H), 8.25 (1 H, br, amide NH), and 11.26 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 284 (M^+, 0.1), 240 (9), 158 (100), 130 (8), 103 (6), and 77 (8). Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.4; H, 4.25; N, 9.85. Found: C, 63.3; H, 4.0; N, 9.8.

***N*-Propargyl-3-oxopyrano[4,3-*b*]indole-1-carboxamide (16).** Acetic anhydride (100 mL) was added to 3-[(*N*-proparylamino)glyoxylyl]indole-2-acetic acid (12) (1.98 g, 6.97 mmol) and the mixture was stirred for 45 h at room temperature. After 24 h, the acid went into solution, and after a further 21 h, a bright yellow solid precipitated out. This solid was filtered and washed with ether under suction to give the title pyranone 16 (1.46 g, 79%) as a bright yellow solid, mp 229–231 °C dec. IR (Nujol) 3304 (alkyne H), 3259 (NH), 1693 (pyranone C=O), 1652 (amide C=O), 1603, 1538 (amide C=O), 1298, and 1227 cm^{-1}; UV (tetrahydrofuran) 278 (ϵ 47 635), 310 (6697), 339 (4311), and 418 nm (3642); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 2.71 (1 H, t, J = 2.6 Hz, acetylene H), 4.29 (2 H, dd, J = 5.9 and 2.4 Hz, $CONHCH_2$), 5.85 (1 H, s, 4-H), 7.15 (1 H, td, J = 7 and 1 Hz, aromatic H), 7.24 (1 H, dd, J = 7 and 1 Hz, aromatic H), 7.43 (1 H, td, J = 7 and 1 Hz, aromatic H), 8.70 (1 H, br, amide NH), 8.96 (1 H, dd, J = 7 and 1 Hz, 9-H), and 10.4 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 266 (M^+, 25), 222 ($M^+ - CO_2$, 51), 221 (19), 194 (25), 184 (100), 128 (21), and 101 (11). Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.7; H, 3.8; N, 10.5. Found: C, 67.4; H, 3.8; N, 10.3.

2,3-Dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (20) from Diels–Alder Reaction of 16. A. Neat. *N*-Propargyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (16) (86.2 mg, 0.32 mmol) was placed in a Wood's metal bath at 250 °C for 0.5 min. The reaction mixture was chromatographed (ethyl acetate) to give the title carbazole 20 (53.3 mg, 74%) as a yellow solid, mp 244 °C dec: IR (Nujol) 3410 (lactam NH), 3160 (carbazole NH), 1693 (lactam C=O), and 1324 cm^{-1}; UV (methanol) 220 (ϵ 43 590), 249 (24 100), and 312 nm (15 330); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.59 (2 H, s, CH_2), 7.20 (1 H, ~t, J = 8 Hz, aromatic H), 7.42 (1 H, ~t, J = 8 Hz, aromatic H), 7.52 (2 H, m, aromatic H), 7.59 (1 H, br, amide NH), 7.76 (1 H, d, J = 8 Hz, aromatic H), 9.25 (1 H, d, J = 8 Hz, 10-H), and 10.63 (1 H, br, carbazole NH); mass spectrum m/e (relative intensity) 222 (M^+, 100), 221 (36), 194 (42), 193 (22), 166 (17), 139 (10), and 111 (11); HRMS calcd for $C_{14}H_{10}N_2O$ 222.0793, found M^+, 222.0793.

B. In Solution. *N*-Propargyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (16) (37 mg, 0.14 mmol) in bromobenzene (5 mL) was refluxed, under nitrogen, for 19 h. The solution was concentrated under reduced pressure, and the residue was chromatographed (ether + 5% methanol) to yield the title compound (28.5 mg, 92%) as a pale yellow solid.

Ethyl 3-[(*N*-Allylamino)glyoxylyl]indole-2-acetate (9). Oxalyl chloride (2 mL, excess) was added to a solution of ethyl indole-2-acetate (1.06 g, 5.22 mmol) in sodium dry ether (30 mL). This was stirred for 10 min at room temperature and then concentrated in vacuo. Dry ether (50 mL) was added, and the solution was cooled using an ice/salt bath. Allylamine (0.85 mL, 11.3 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 3 h. Dilute hydrochloric acid (30 mL) was added, and the reaction mixture was poured into a separating funnel and extracted with ethyl acetate. The organic extracts were combined and washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, water, and brine and dried ($MgSO_4$). The solvent was evaporated, and the crude product was triturated with ethanol. The solid obtained was filtered and discarded, and the filtrate was concentrated in vacuo and chromatographed to give the title compound 9 (0.69 g, 42%) as a solid, mp 98–100 °C: IR (Nujol) 3317 (NH), 3280 (NH), 1708 (ester C=O), 1658 (ketone C=O), 1631 (amide C=O), 1574, 1531 (amide C=O), 1492, 1331, 1296, 1249, 1221, and 1183 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 1.21 (3 H, t, J = 7 Hz, ethoxy $-CH_3$), 4.01 (2 H, tt, J = 6 and 2 Hz, $CONHCH_2$), 4.12 (2 H, q, J = 7 Hz, ethoxy $-CH_2$), 4.28 (2 H, s, CH_2COOEt), 5.12 (1 H, ddd, J = 10, 3.5, and 1.5 Hz, terminal alkene *H*, cis to H), 5.28 (1 H, ddd, J = 17, 3.5, and 1.5 Hz, terminal alkene *H*, trans to H), 5.96 (1 H, ddt, J = 17, 10, and 5 Hz, CH_2CH), 7.15–7.24 (2 H, m, aromatic H), 7.44–7.50 (1 H, m, aromatic H), 7.98 (1 H, br, amide NH), 8.10–8.16 (1 H, m, indole 4-H), and 11.20 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 314 (M^+, 18), 230 (100), 224 (17), 202 (45), 184 (27), 174 (48), and 128 (16). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 65.0; H, 5.8; N, 8.9. Found: C, 64.8; H, 5.7; N, 8.8.

3-[(*N*-Allylamino)glyoxylyl]indole-2-acetic Acid (13). Ethyl 3-[(*N*-allylamino)glyoxylyl]indole-2-acetate (9) (0.37 g, 1.18 mmol) was dissolved in tetrahydrofuran (9 mL) and methanol (1 mL). Potassium hydroxide solution (2 M, 6 mL) was added and the mixture stirred at room temperature for 2.5 h. Water was added, and the basic solution was extracted with ether. The organic layer was discarded. The aqueous layer was acidified (pH 1.5) with concentrated hydrochloric acid and then extracted with ethyl acetate. These organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the title compound 13 (0.24 g, 71%) as a brown solid. This was recrystallized from ethyl acetate to yield pure acid (0.10 g, 30%), mp 128 °C dec: IR (Nujol) 3328 (NH), 3277 (NH), 2400–3400 (COOH), 1718

(acid C=O), 1645 (ketone C=O), 1613 (amide C=O), 1553, 1529, 1493, 1396, 1296, 1252, 1202, 1181, 1170, and 1148 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.02 (2 H, m, $CONHCH_2$), 4.28 (2 H, s, CH_2COOH), 5.12 (1 H, ddd, J = 10, 3, and 1.5 Hz, terminal H on alkene, cis to H), 5.28 (1 H, ddd, J = 17, 3, and 1.5 Hz, terminal H on alkene, trans to H), 5.96 (1 H, ddt, J = 17, 10, and 5.5 Hz, CH_2CH), 7.14–7.24 (2 H, m, aromatic H), 7.47–7.50 (1 H, m, aromatic H), 8.0 (1 H, br, amide NH), 8.09–8.15 (1 H, m, indole 4-H), and 11.25 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 286 (M^+, 1), 242 (8), 202 (4), 174 (4), 158 (100), 130 (9), and 103 (6). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.9; H, 4.9; N, 9.8. Found: C, 62.8; H, 4.9; N, 9.6.

***N*-Allyl-3-oxopyrano[4,3-*b*]indole-1-carboxamide (17).** Acetic anhydride (5 mL) was added to 3-[(*N*-allylamino)glyoxylyl]indole-2-acetic acid (13) (93.2 mg, 0.33 mmol), and the mixture was stirred for 98 h at room temperature. The mixture was filtered to yield a bright yellow solid which was washed with ether under suction and then dried under vacuum to yield the title pyranone (52 mg, 60%), mp 219 °C dec: IR (Nujol) 3280 (NH), 3160 (NH), 1697 (pyranone C=O), 1646 (amide C=O), 1593, 1542, 1299, and 1227 cm^{-1}; UV (tetrahydrofuran) 272 (ϵ 84 430), 277 (88 320), 322 (7250), 338 (6540), and 415 nm (8320); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.09 (2 H, dddd, J = 5.5, 5.5, 1.5, and 1.5 Hz, $CONHCH_2$), 5.12 (1 H, ddd, J = 10, 3, and 1.5 Hz, terminal H on alkene, cis to H), 5.27 (1 H, ddd, J = 17, 3, and 1.5 Hz, terminal H on alkene, trans to H), 5.81 (1 H, s, 4-H), 5.99 (1 H, ddt, J = 17, 10, and 5.5 Hz, CH_2CH), 7.12 (1 H, m, aromatic H), 7.23 (1 H, m, aromatic H), 7.42 (1 H, m, aromatic H), 8.60 (1 H, br, amide NH), 8.92 (1 H, ~d, J = 8 Hz, 9-H), and 10.97 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 268 (M^+, 30), 224 ($M^+ - CO_2$, 13), 222 ($M^+ - CO_2 - H_2$, 13), 184 (100), 149 (10), and 128 (16). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.5; N, 10.4. Found: C, 66.9; H, 4.4; N, 10.2.

2,3-Dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (20) from Diels–Alder Reaction of 17. A. Neat. *N*-Allyl 3-oxopyrano-[4,3-*b*]indole-1-carboxamide (17) (22.5 mg, 0.08 mmol) was placed in a Wood's metal bath at 220 °C for 2 min. After cooling, the reaction mixture was chromatographed (ether + 5% methanol) to give the title carbazole **20** (5.8 mg, 31%) as a yellow solid.

B. In Solution. *N*-Allyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (17) (15 mg, 0.06 mmol) was refluxed in bromobenzene (5 mL) for 20.5 h. The solvent was evaporated, and the residue was chromatographed (ethyl acetate) to yield required carbazole **20** (6 mg, 48%).

2,3,4,5-Tetrahydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (22). *N*-Allyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (17) (11.3 mg, 0.04 mmol) was refluxed in bromobenzene (4 mL), under argon, for 6 h. The solution was cooled under argon, and the solvent was evaporated to give a brown solid (9.4 mg, 100%), mp 193–197 °C dec IR (Nujol) 3250 (br, NH), 1665 (lactam C=O), 1459, and 1324 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 2.76 (2 H, t, J = 9 Hz, CH_2), 3.08 (2 H, t, J = 9 Hz, CH_2), 4.06 (2 H, s, $CONHCH_2$), 6.97–7.02 (2 H, m, aromatic H), 7.02 (1 H, br, amide NH), 7.27–7.36 (1 H, m, aromatic H), 8.51 (1 H, m, 10-H), and 10.30 (1 H, br, carbazole NH); mass spectrum m/e (relative intensity) (FAB, matrix NOBA) 225 (MH^+, 17), 224 (M^+, 16), 223 (15), 167 (11), 165 (12), 152 (15), 150 (11), 139 (14), 131 (11), 124 (14), 121 (17), 120 (18), 115 (17), 113 (16), 108 (13), 106 (11), and 105 (14); HRMS calcd for $C_{14}H_{13}N_2O$ 225.1028, found MH^+ 225.1028.

***N*-(Phenylpropargyl)phthalimide.** To a solution of phenylpropargyl alcohol (5.51 g, 41.7 mmol), triphenylphosphine (11.1 g, 42.3 mmol), and phthalimide (6.65 g, 45.2 mmol) in dry THF (40 mL) was added diethyl azodicarboxylate (6.70 mL, 42.3 mmol). The reaction mixture was stirred at room temperature for 24.5 h. HPLC showed the presence of starting material, so 2.0 mL of diethyl azodicarboxylate was added and the mixture was stirred for a further 22 h. The solvent was removed in vacuo to yield a semisolid. This was chromatographed (dichloromethane + 5% light petroleum) to give a pale yellow solid (10.9 g, 100%), mp 157–160 °C (lit.[56] mp 158–160 °C): IR (Nujol) 1773 (imide C=O), 1710 (imide C=O), 1425, 1394, and 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.70 (2 H, s, CH_2), 7.20–7.30 (3 H, m, aromatic H), 7.35–7.45 (2 H, m, aromatic H), 7.70–7.80 (2 H, m, phthalimide H), and 7.85–7.95 (2 H, m, phthalimide H); mass spectrum m/e (relative intensity) 261 (M^+, 100), 232 (46), 204 (29), 178 (11), 165 (10), 115 (14), 114 (11), and 107 (17).

Phenylpropargylamine Hydrochloride. *N*-(Phenylpropargyl)phthalimide (4.32 g, 16.6 mmol) and hydrazine hydrate (0.91 mL, 98%) in methanol (40 mL) were refluxed for 2.5 h. The reaction mixture was cooled, and concentrated HCl (12 mL) was added. The reaction mixture was refluxed for a further 0.5 h. The mixture was recooled and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated and the residue extracted with ethanol (25 mL), refiltered to remove final traces of phthalhydrazide, and concentrated in vacuo. The solid residue was recrystallized from 2-propanol (25 mL) to yield the title compound as white crystals (1.61 g, 58%), mp darkens 208 °C, melts 216–217 °C (lit.[57] 216–217 °C): ^1H NMR (D_2O, 270 MHz) δ 4.77 (2 H, s, CH_2) and 7.39–7.57 (5 H, m, aromatic H).

Ethyl 3-[[*N*-(Phenylpropargyl)amino]glyoxylyl]indole-2-acetate (10). Oxalyl chloride was added to a solution of ethyl indole-2-acetate (0.83 g, 4.09 mmol) in dry ether. This was stirrer for 15 min and then concentrated in vacuo. Dry ether was added, and the solution was cooled using an ice/salt bath. To an aqueous solution of phenylpropargylamine hydrochloride (1.52 g, 9.07 mmol) were added KOH pellets (pH > 10). The solution was extracted with ether. The ethereal extracts were washed with brine and dried (K_2CO_3). The solvent was evaporated to yield phenylpropargylamine as a pale yellow oil (1.18 g, 9.04 mmol). This freshly-made amine was redissolved in ether and was added dropwise to the acylated indole solution. The reaction mixture was stirred at 0 °C for 1 h and was then allowed to warm to room temperature and stirred for a further 2 h. Dilute hydrochloric acid was added, and the reaction mixture was extracted with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate solution, water, and brine, and dried ($MgSO_4$). The solvent was evaporated, and the resultant oil was triturated with ethanol to give the title compound **10** (0.49 g, 31%) as a solid. The filtrate was concentrated and chromatographed (ether) to give a further 0.62 g, thus giving a total yield of 70%, mp 141–144 °C: IR (Nujol) 3317 (NH), 3286 (NH), 1710 (ester C=O), 1659 (ketone C=O), 1629 (amide C=O), 1529, 1492, 1333, 1222, and 1184 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 1.20 (3 H, t, J = 7 Hz, ethoxy $-CH_3$), 4.12 (2 H, q, J = 7 Hz, ethoxy $-CH_2$), 4.30 (2 H, s, CH_2COOEt), 4.42 (2 H, ~d, J = 6 Hz, $CONHCH_2$), 7.13–7.24 (2 H, m, aromatic H), 7.32–7.54 (6 H, m, aromatic H), 8.15 (1 H, d, J = 8 Hz, 4-H indole), 8.35 (1 H, br, amide NH), and 11.25 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 388 (M^+, 6), 230 (100), 202 (30), 174 (34), 130 (19), and 115 (45). Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.1; H, 5.2; N, 7.2. Found: C, 71.1; H, 5.25; N, 7.2.

3-[[*N*-(Phenylpropargyl)amino]glyoxylyl]indole-2-acetic Acid (14). Ethyl 3-[[*N*-(phenylpropargyl)amino]glyoxylyl]-indole-2-acetate (10) (0.39 g, 1.0 mmol) was dissolved in tetrahydrofuran (9 mL) and methanol (1 mL). Potassium hydroxide solution (2 M, 5 mL) was added and the mixture stirred at room temperature for 2 h. Water was added, but the product was not completely soluble in the basic aqueous solution. So the solution was acidified (pH 1) with concentrated hydrochloric acid and then extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield a colored solid. This was recrystallized from ethyl acetate to give the title compound **14** (0.21 g, 58%) as a solid, mp 183–185 °C: IR (Nujol) 3290 (NH), 2400–3400 (COOH), 1736 (acid C=O), 1651 (ketone C=O), 1595 (amide C=O), 1572, 1484, 1241, 1196, and 1117 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.31 (2 H, s, CH_2COOH), 4.43 (2 H, dd, J = 4 and 2 Hz, $CONHCH_2$), 7.10–7.25 (6 H, m, aromatic H), 7.30–7.50 (2 H, m, aromatic H), 8.13 (1 H, dd, J = 8 and 2 Hz, 4-H indole), 8.35 (1 H, br, amide NH), and 11.30 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 316 ($M^+ - CO_2$, 11), 211 (5), 158 (100), 130 (15), and 115 (26). Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 70.0; H, 4.5; N, 7.8. Found: C, 69.9; H, 4.5; N, 7.7.

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***N*-(Phenylpropargyl)-3-oxopyrano[4,3-*b*]indole-1-carboxamide (18).** Acetic anhydride (5 mL) was added to 3-[[*N*-(phenylpropargyl)amino]glyoxylyl]indole-2-acetic acid (14) (128 mg, 0.36 mmol), and the mixture was stirred for 25 h at room temperature. The mixture was filtered, and the bright yellow solid obtained was washed with ether under suction and then dried to give the title pyranone 18 (95.4 mg, 78%), mp 207–209 °C: IR (Nujol) 3300 (NH), 1693 (pyranone C=O), 1646 (amide C=O), 1599, 1532, 1295, and 1222 cm^{-1}; UV (tetrahydrofuran) 272 (ϵ 88 730), 277 (96 110), 324 (7860), 338 (6880), and 418 (8440); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.49 (2 H, m, CONHCH_2), 5.83 (1 H, s, 4-H), 7.13 (1 H, ~t, J = 8 Hz, aromatic H), 7.22 (1 H, ~d, J = 8 Hz, aromatic H), 7.32–7.47 (6 H, m, aromatic H), 8.93 (1 H, ~d, J = 8 Hz, 9-H), 9.02 (1 H, br, amide NH), and 11.0 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 342 (M^+, 4), 298 ($M^+ - CO_2$, 100), 269 (42), 241 (12), 184 (42), and 128 (12). Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.7; H, 4.1; N, 8.2. Found: C, 73.4; H, 4.1; N, 8.1.

4-Phenyl-2,3-dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (21) from Diels–Alder Reaction of 18. *N*-(Phenylpropargyl)-3-oxopyrano[4,3-*b*]indole-1-carboxamide (18) (42 mg, 0.12 mmol) was refluxed in bromobenzene (15 mL) for 16 h. The solution was concentrated in vacuo to give the title carbazole 21 (31.4 mg, 86%) as a solid, mp 247 °C dec: IR (Nujol) 3233 (br, NH), 1672 (lactam C=O), and 1326 cm^{-1}; UV (methanol) 212 (ϵ 27 560), 262 (24 530), and 322 nm (14 220); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.60 (2 H, s, CH_2), 7.20 (1 H, t, J = 6 Hz, aromatic H), 7.23–7.73 (7 H, m, aromatic H), 7.75 (1 H, s 5-H), 8.05 (1 H, br, amide NH), 9.27 (1 H, d, J = 8 Hz, 10-H), and 11.18 (1 H, br, carbazole NH); mass spectrum m/e (relative intensity) 298 (M^+, 100), 269 (50), 241 (13), and 135 (11); HRMS calcd for $C_{20}H_{14}N_2O$ 298.1106, found M^+ 298.1099.

***N*-Cinnamylphthalimide.** Cinnamyl chloride (15.44 g, 101 mmol), potassium phthalimide (37.48 g, 202 mmol), and potassium iodide (1 spatula full, catalyst) in DMF (75 mL) were heated to 85–90 °C, under nitrogen, for 8 h. The mixture was cooled, diluted with water (1000 mL), and extracted with dichloromethane (4 × 250 mL). The organic extracts were washed with sodium hydroxide solution (3 × 150 mL, 0.2 M), water, and brine and dried ($MgSO_4$). The solvent was evaporated to give a solid (26.56 g, 100%), mp 155–157 °C (lit.[58] mp 156 °C): IR (Nujol) 1771 (imide C=O), 1708 (imide C=O), 1498, 1428, 1397, 1323, and 1108 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.45 (2 H, dd, J = 6.5 and 1.5 Hz, CH_2), 6.26 (1 H, dt, J = 16 and 6 Hz, CHCH$_2$), 6.66 (1 H, d, J = 16 Hz, ArCH), 7.19–7.42 (5 H, m, aromatic H), 7.71–7.76 (2 H, m, phthalimide H), and 7.83–7.90 (2 H, m, phthalimide H); mass spectrum m/e (relative intensity) 263 (M^+, 21), 245 (10), 148 (41), 130 (14), and 116 (100).

Cinnamylamine. *N*-Cinnamylphthalimide (1.22 g, 4.64 mmol) and hydrazine hydrate (0.25 mL, 5.1 mmol) in methanol (20 mL) were refluxed for 1.5 h. The reaction mixture was cooled, and concentrated HCl (3 mL) was added. The reaction mixture was refluxed for a further 0.5 h. The mixture was recooled and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated and the residue dissolved in ethanol. This was refiltered to remove final traces of phthalhydrazide and concentrated under reduced pressure. The residue was dissolved in water, basified with KOH pellets (pH > 10), and extracted with ether. These ethereal extracts were dried (K_2CO_3) and the solvent evaporated to yield a yellow oil (0.57 g, 92%), used without purification: ^1H NMR ($CDCl_3$, 250 MHz) δ 3.5 (2 H, dd, J = 7.5 and 2 Hz, CH_2), 6.3 (1 H, dt, J = 15 and 7.5 Hz, CHCH$_2$), 6.5 (1 H, dd, J = 15 and 2 Hz, ArCH), and 7.2–7.5 (5 H, m, aromatic H).

Ethyl 3-[(*N*-Cinnamylamino)glyoxylyl]indole-2-acetate (11). Oxalyl chloride (1 mL, excess) was added to a solution of ethyl indole-2-acetate (0.54 g, 2.67 mmol) in dry ether (10 mL). This was stirred for 15 min at room temperature and then concentrated in vacuo. Dry ether (10 mL) was added, and the solution was cooled using an ice/salt bath. Freshly-made cinnamylamine (0.72 g, 5.4 mmol) in ether (5 mL) was added dropwise. The solution was allowed to warm to room temperature and stirred for 2 h. Dilute hydrochloric acid was added, and the reaction mixture was extracted with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate solution, water, and brine, and dried ($MgSO_4$). The solvent was evaporated, and the resultant oil was triturated with ethanol to give the title compound 11 (0.30 g, 29%) as a solid, mp 139–141 °C: IR (Nujol) 3398 (NH), 1720 (ester C=O), 1678 (ketone C=O), 1620 (amide C=O), 1524, 1510, and 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.31 (3 H, t, J = 7 Hz, ethoxy $-CH_3$), 4.23 (2 H, td, J = 6 and 1.5 Hz, CONHCH_2), 4.25 (2 H, q, J = 7 Hz, ethoxy $-CH_2$), 4.36 (2 H, s, CH_2COOEt), 6.27 (1 H, dt, J = 16 and 6 Hz, CH_2CH), 6.64 (1 H, d, J = 16 Hz, PhCH), 7.14–7.42 (8 H, m, aromatic H), 7.65 (1 H, br, amide NH), 8.18–8.21 (1 H, m, 4-H indole), and 10.25 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 390 (M^+, 7), 230 (100), 202 (32), 174 (36), 158 (11), 117 (25), and 115 (20). Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.7; N, 7.2. Found: C, 71.0; H, 5.75; N, 7.3.

3-[(*N*-Cinnamylamino)glyoxylyl]indole-2-acetic Acid (15). Ethyl 3-[(*N*-cinnamylamino)glyoxylyl]indole-2-acetate (11) (0.26 g, 0.67 mmol) was dissolved in tetrahydrofuran (9 mL) and methanol (1 mL). Potassium hydroxide solution (2 M, 0.4 mL) was added and the mixture stirred at room temperature for 2 h. Water was added, but the product was not completely soluble in the basic aqueous solution. So the solution was acidified (pH 1) with concentrated hydrochloric acid and then extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield a colored solid. This was recrystallized from ethyl acetate to give the title compound 15 (90.8 mg, 38%) as a solid, mp 184–185 °C: IR (Nujol) 3288 (NH), 2400–3400 (COOH), 1738 (acid C=O), 1646 (ketone C=O), 1594 (amide C=O), 1573, 1483, 1242, and 1192 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.18 (2 H, td, J = 6 and 1.5 Hz, CONHCH_2), 4.31 (2 H, s, CH_2COOH), 6.40 (1 H, dt, J = 16 and 6 Hz, CHCH$_2$), 6.68 (1 H, d, J = 16 Hz, PhCH), 7.10–7.55 (8 H, m, aromatic H), 8.12 (1 H, br, amide NH), 8.14 (1 H, m, 4-H indole), and 11.25 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 318 ($M^+ - CO_2$, 5), 158 (100), 132 (3), 130 (6), and 117 (5). Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.6; H, 5.0; N, 7.7. Found: C, 69.55; H, 5.0; N, 7.7.

***N*-Cinnamyl-3-oxopyrano[4,3-*b*]indole-1-carboxamide (19).** Acetic anhydride (5 mL) was added to 3-[(*N*-cinnamylamino)-glyoxylyl]indole-2-acetic acid (15) (67 mg, 0.19 mmol), and the mixture was stirred for 45 h at room temperature. The mixture was filtered, and the bright yellow solid obtained was washed with ether under suction and then dried to give the title pyranone 19 (34.4 mg, 54%), mp 172 °C dec: IR (Nujol) 3287 (NH), 1650 (br) (pyranone and amide C=O), 1589, 1525, 1297, and 1215 cm^{-1}; UV (tetrahydrofuran) 270 (ϵ 73 900), 277 (83 120), 322 (8350), 338 (6930), and 419 nm (5830); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.27–4.32 (2 H, m, CONHCH_2), 5.84 (1 H, s, 4-H), 6.44 (1 H, dt, J = 16 and 6 Hz, CH_2CH), 6.70 (1 H, d, J = 16 Hz, PhCH), 7.12–7.47 (8 H, m, aromatic H), 8.6 (1 H, br, amide NH), 8.99 (1 H, d, J = 8 Hz, 9-H), and 10.4 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 344 (M^+, 4), 300 ($M^+ - CO_2$, 100), 209 (51), 184 (35), and 158 (75). Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.2; H, 4.7; N, 8.1. Found: C, 73.2; H, 5.0; N, 7.85.

4-Phenyl-2,3-dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (21) from Diels–Alder Reaction of 19. *N*-Cinnamyl-3-oxopyrano[4,3-*b*]indole-1-carboxamide (19) (20.8 mg, 0.06 mmol) was refluxed in bromobenzene (4 mL) for 80 h. The solution was concentrated in vacuo and chromatographed (dichloromethane + 10% methanol) to give the title carbazole 21 (7.8 mg, 43%) as a solid.

(2′-Nitrophenyl)propargyl Alcohol (24). 1-Iodo-2-nitrobenzene (2.18 g, 8.76 mmol), triethylamine (2.44 mL, 17.5 mmol), propargyl alcohol (0.61 mL, 10.5 mmol), tetrabutylammonium bromide (0.30 g, 0.93 mmol), copper(I) chloride (0.12 g, 1.21 mmol), and bis(triphenylphosphine)palladium dichloride (64 mg, 0.09 mmol) were heated in sodium dry benzene (20 mL), under argon, for 20 min at 60–70 °C. The reaction mixture was cooled, and the solvent was evaporated. The residue was dissolved in acetone and filtered through Celite. The filtrate was concentrated in vacuo, preadsorbed, and chromatographed (ether) to yield the title compound as a solid (1.48 g, 96%), mp 66–67.5 °C (lit.[53] not reported): IR (Nujol) 2500–3500 (br, OH), 1609, 1567, 1523 (NO_2), 1464, 1346 (NO_2), 1303, 1262, 1148, 1084, and 1035 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.46 (2 H, s, CH_2), 7.59–7.76 (3 H, m,

(58) Bergmann, E. *J. Chem. Soc.* **1935**, 1361.

aromatic H), and 8.04 (1 H, d, J = 7 Hz, aromatic H ortho to NO_2); mass spectrum m/e (relative intensity) 177 (M^+, 26), 148 (39), 132 (50), 104 (45), and 77 (100).

***N*-[(2′-Nitrophenyl)propargyl]phthalimide (25).** To a solution of (2′-nitrophenyl)propargyl alcohol (**24**) (1.48 g, 8.36 mmol), triphenylphosphine (2.21 g, 8.44 mmol), and phthalimide (1.27 g, 8.64 mmol) in dry tetrahydrofuran (40 mL) was added diethyl azodicarboxylate (1.32 mL, 8.34 mmol). The reaction mixture was stirred at room temperature for 26 h. The solvent was removed in vacuo to yield a semisolid. This was chromatographed (dichloromethane) to give a yellow solid **25** (2.20 g, 86%), mp 170–172.5 °C: IR (Nujol) 1778 (imide C=O), 1769 (imide C=O), 1724 (imide C=O), 1611, 1568, 1520 (NO_2), 1415, 1392 (NO_2), 1344, 1319, 1310, 1192, 1116, 1087, and 938 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.75 (2 H, s, CH_2), 7.41–7.62 (3 H, m, aromatic H), 7.72–7.79 (2 H, m, phthalimide H), 7.88–7.94 (2 H, m, phthalimide H), and 8.02 (1 H, dd, J = 8 and 1.5 Hz, aromatic H ortho to NO_2); mass spectrum m/e (relative intensity) 306 (M^+, 0.6), 289 (100), 261 (17), 233 (11), 160 (68), 149 (27), 130 (40), 104 (88), and 76 (53). Anal. Calcd for $C_{17}H_{10}N_2O_4$: C, 66.7; H, 3.3; N, 9.15. Found: C, 66.6; H, 3.2; N, 9.15.

[(2′-Nitrophenyl)propargyl]amine (26). *N*-[(2′-Nitrophenyl)propargyl]phthalimide (**25**) (0.64 g, 2.09 mmol) and hydrazine hydrate (0.11 mL, 98%) in methanol (15 mL) were refluxed for 1.5 h. The reaction mixture was cooled, and concentrated HCl (3 mL) was added. The reaction mixture was refluxed for a further 10 min. The mixture was cooled and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated to yield the amine hydrochloride (0.41 g, 92%). A small portion of the amine hydrochloride was dissolved in water, and KOH pellets were added (pH > 10). The resulting oil was extracted with ether, dried (K_2CO_3), and concentrated in vacuo to yield the free amine as a pale yellow solid **26** which darkened (to red) on standing and was used without purification: IR (Nujol) 3363 (NH), 3286 (NH), 1608, 1568, 1519 (NO_2), 1346 (NO_2), 1305, and 1246 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 2.8 (2 H, br, NH_2), 4.29 (2 H, s, CH_2), 7.57–7.74 (3 H, m, aromatic H), and 8.02 (1 H, d, J = 8 Hz, aromatic H ortho to NO_2).

Ethyl 3-[[*N*-[(2′-Nitrophenyl)propargyl]amino]glyoxylyl]indole-2-acetate (30). Oxalyl chloride (1 mL, excess) was added to a solution of ethyl indole-2-acetate (0.16 g, 0.8 mmol) in sodium dry ether (15 mL). This was stirred for 10 min and then concentrated in vacuo. Dry ether (20 mL) was re-added, and the solution was cooled using an ice/salt bath. Meanwhile, to an aqueous solution of (2′-nitrophenyl)propargylamine hydrochloride (0.41 g, 1.9 mmol) were added KOH pellets (pH > 10). The solution was extracted with ether. The ethereal extracts were dried (K_2CO_3), and the solvent was evaporated to yield (2′-nitrophenyl)propargylamine. This was added to the cooled acylated indole solution. The solution was stirred at 0 °C for 1 h and then was allowed to warm to room temperature and stirred for a further 17 h. Concentrated hydrochloric acid (5 mL) was added, and the mixture was poured into water and extracted with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate solution, water, and brine and dried ($MgSO_4$). The solvent was evaporated, and the resultant solid was recrystallized from ethanol to give the title compound **30** (0.15 g, 44%) as a pale yellow solid, mp 190–192 °C dec: IR (Nujol) 3276 (NH), 1707 (ester C=O), 1661 (ketone C=O), 1628 (amide C=O), 1609, 1567 (amide C=O), 1522 (NO_2), 1493, and 1340 (NO_2) cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 1.18 (3 H, t, J = 7 Hz, ethoxy $-CH_3$), 4.11 (2 H, q, J = 7 Hz, ethoxy $-CH_2$), 4.29 (2 H, s, CH_2COOEt), 4.49 (2 H, m, $CONHCH_2$), 7.13–7.24 (2 H, m, aromatic H), 7.48 (1 H, dd, J = 7 and 2 Hz, aromatic H), 7.61–7.68 (1 H, m, aromatic H), 7.74–7.77 (2 H, m, aromatic H), 8.08 (1 H, d, J = 8 Hz, aromatic H), 8.15 (1 H, dd, J = 6 and 1.5 Hz, aromatic H), 8.42 (1 H, br, amide NH), and 11.25 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 433 (M^+, 3), 415 (19), 381 (10), 360 (39), 342 (19), 339 (24), 335 (18), 326 (13), 310 (20), 294 (10), 284 (12), 270 (16), 256 (15), 230 (74), 202 (37), 184 (28), 174 (45), 160 (29), 145 (59), 130 (36), 119 (26), and 104 (45). Anal. Calcd for $C_{23}H_{19}N_3O_6$: C, 63.7; H, 4.4; N. 9.7. Found: C, 63.9; H, 4.5; N, 9.6.

2-Nitrocinnamyl Alcohol (27). To a suspension of 2-nitrocinnamaldehyde (925 mg, 5.22 mmol) and cerium trichloride heptahydrate (2.04 g, 5.48 mmol) in methanol (13 mL) was added sodium borohydride (0.80 g, 21.1 mmol). Violent effervescence was observed. The mixture was stirred at room temperature for 26 h. Dilute hydrochloric acid was added to work up the reaction. The methanol was removed on the rotary evaporator, and the residue was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield a solid **27** (0.93 g, 99%), mp 54–56 °C: IR (Nujol) 3312 (br, OH), 1516 (aromatic NO_2), 1352 (aromatic NO_2), 1085, 1025, and 954 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.78 (1 H, s, br, OH), 4.38 (2 H, dd, J = 5.4 and 1.5 Hz, CH_2), 6.34 (1 H, dt, J = 15.6, 5.4 and 5.4 Hz, $CHCH_2$), 7.08 (1 H, dd, J = 15.6 and 1.5 Hz, ArC*H*), 7.39 (1 H, m, aromatic H), 7.53–7.62 (2 H, m, aromatic H), and 7.92 (1 H, d, J = 8.8 Hz, aromatic H ortho to NO_2); mass spectrum m/e (relative intensity) 179 (M^+, 18), 149 (27), 148 (28), 134 (34), 132 (44), 120 (43), 104 (49), 92 (61), and 77 (100). Anal. Calcd for $C_9H_9NO_3$: 60.3; H, 5.1; N, 7.8. Found: C, 60.2; H, 4.9; N, 7.75.

***N*-(2-Nitrocinnamyl)phthalimide (28).** To a solution of 2-nitrocinnamyl alcohol **27** (0.51 g, 2.85 mmol), triphenylphosphine (0.78 g, 2.98 mmol), and phthalimide (0.49 g, 3.33 mmol) in dry tetrahydrofuran (15 mL) was added diethyl azodicarboxylate (0.48 mL, 3.03 mmol). The reaction mixture was stirred at room temperature for 26 h. The solvent was removed in vacuo to yield a semisolid. This was chromatographed (dichloromethane) to give a solid **28** (0.62 g, 71%), mp 162–163 °C: IR ($CHBr_3$) 1770 (imide C=O), 1713 (imide C=O), 1523 (NO_2), 1393 (NO_2), and 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.50 (2 H, dd, J = 6 and 1 Hz, CH_2), 6.24 (1 H, dt, J = 15, 6, and 6 Hz, $CHCH_2$), 7.13 (1 H, d, J = 15 Hz, ArC*H*), 7.35–7.42 (1 H, m, aromatic H), 7.50–7.57 (2 H, m, aromatic H), 7.70–7.77 (2 H, m, phthalimide H), 7.85–7.90 (2 H, m, phthalimide H), and 7.93 (1 H, d, J = 8 Hz, aromatic H ortho to NO_2); mass spectrum m/e (relative intensity) 291 (M^+ – OH, 3), 279 (2), 276 (6), 263 (3), 160 (100), and 120 (24); HRMS calcd for $C_{17}H_{12}N_2O_4$ 308.0797 and $C_{17}H_{11}N_2O_3$ 291.0770, found M^+ 308.0797 and M^+ – OH 291.0765.

(2-Nitrocinnamyl)amine (29). *N*-(2-Nitrocinnamyl)-phthalimide (**28**) (3.76 g, 12.2 mmol) and hydrazine hydrate (0.67 mL, 98%) in methanol (40 mL) were refluxed for 21.5 h. The reaction mixture was cooled, and concentrated HCl (10 mL) was added. The reaction mixture was refluxed for a further 0.5 h. The mixture was recooled (0 °C) and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated and the residue dissolved in ethanol. This was refiltered to remove final traces of phthalhydrazide, and the filtrate was concentrated in vacuo. The solid residue was dissolved in water and KOH pellets were added (pH > 10). The resulting oil was extracted with ether and concentrated in vacuo to yield a yellow oil **29** (1.80 g, 83%), used without further purification: ^1H NMR ($CDCl_3$, 250 MHz) δ 3.55 (2 H, d, J = 7 Hz, CH_2), 6.33 (1 H, dt, J = 15, 7, and 7 Hz, $CHCH_2$), 6.97 (1 H, d, J = 15 Hz, ArC*H*), 7.30–7.43 (1 H, m, aromatic H), 7.50–7.65 (2 H, m, aromatic H), and 7.90 (1 H, d, J = 8 Hz, aromatic H ortho to NO_2); 178 (M^+, 0.7), 176 (8), 161 (13), 145 (28), 129 (10), 104 (30), 103 (17), 90 (15), 89 (12), 86 (23), and 84 (34).

Ethyl 3-[[*N*-(2′-Nitrocinnamyl)amino]glyoxylyl]indole-2-acetate (31). Oxalyl chloride (2 mL, excess) was added to a solution of ethyl indole-2-acetate (1.00 g, 4.93 mmol) in sodium dry ether (20 mL). This was stirred for 10 min and then concentrated in vacuo. Dry ether (60 mL) was re-added, and the solution was cooled using an ice/salt bath. Freshly-made (2-nitrocinnamyl)amine (**29**) (1.80 g, 10.1 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h, and then was allowed to warm to room temperature and stirred for a further 19.5 h. Concentrated hydrochloric acid (5 mL) was added, and the reaction mixture was poured into water and extracted with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate solution, water, and brine, and dried ($MgSO_4$). The solvent was evaporated to give the title compound **31** (1.64 g, 76%) as a solid, mp 81–83 °C: IR (Nujol) 3372 (br, NH), 3215 (br, NH), 1739 (ester C=O), 1635 (ketone C=O), 1598 (amide C=O), 1574 (aromatic NO_2), 1523 (amide C=O), 1485 (aromatic NO_2), 1248, 1220, and 1188 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 250 MHz) δ 1.18 (3 H, t, J = 7 Hz, ethoxy $-CH_3$), 4.10 (2 H, q, J = 7 Hz, ethoxy $-CH_2$), 4.23 (2 H, ddd, J = 6, 6, and 2 Hz, $CONHCH_2$) 4.29 (2 H, s, CH_2COOEt), 6.48 (1 H, dt, J = 16 and

6 Hz, CH_2CH), 7.04 (1 H, d, J = 16 Hz, ArC*H*), 7.15–7.24 (2 H, m, aromatic H), 7.46–7.56 (2 H, m, aromatic H), 7.70 (1 H, t, J = 8 Hz, aromatic H), 7.82 (1 H, d, J = 8 Hz, aromatic H), 7.93 (1 H, d, J = 8 Hz, aromatic H), 8.13–8.25 (2 H, m, indole 4-H and amide NH), and 11.23 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 435 (M^+, 3), 403 (3), 230 (100), 202 (32), 184 (16), 174 (40), 145 (12), and 130 (16); HRMS calcd for $C_{23}H_{21}N_3O_6$ 435.1430, found M^+ 435.1442.

3-[[*N*-(2′-Nitrocinnamyl)amino]glyoxylyl]indole-2-acetic Acid (33). Ethyl 3-[[*N*-(2′-nitrocinnamyl)amino]glyoxylyl]-indole-2-acetate (**31**) (0.45 g, 1.03 mmol) was dissolved in tetrahydrofuran (9 mL) and methanol (1 mL). Potassium hydroxide solution (2 M, 5 mL) was added and the mixture stirred at room temperature for 4 h. Water (150 mL) was added, and the mixture was extracted with ether. These ethereal extracts were discarded. The basic aqueous solution was then acidified with concentrated hydrochloric acid (pH 1) and saturated with solid sodium chloride. It was then extracted with ethyl acetate (3 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield a yellow solid **33** (0.41 g, 97%), mp 181–183 °C: IR (Nujol) 3300 (br, NH), 3270 (br, NH), 2400–3700 (COOH), 1719 (acid C=O), 1660 (ketone C=O), 1592 (amide C=O), 1519, 1490 (aromatic NO_2), 1342, 1245, and 1185 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 250 MHz) δ 4.20–4.30 (4 H, m, $CONHCH_2$ and CH_2COOH), 6.50 (1 H, dt, J = 16 and 6 Hz, $CHCH_2$), 7.05 (1 H, d, J = 16 Hz, ArC*H*), 7.10–7.25 (2 H, m, aromatic H), 7.45 (1 H, dd, J = 8 and 2 Hz, aromatic H), 7.55 (1 H, d, J = 8 Hz, aromatic H), 7.70 (1 H, t, J = 8 Hz, aromatic H), 7.85 (1 H, d, J = 8 Hz, aromatic H), 7.95 (1 H, d, J = 8 Hz, aromatic H), 8.15 (1 H, dd, J + 8 and 2 Hz, indole 4-H), 8.40 (1 H, br, amide NH), and 11.65 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 407 (M^+, 0.3), 363 ($M^+ - CO_2$, 5), 202 (4), 158 (100), 149 (26), and 130 (7). Anal. Calcd for $C_{21}H_{17}N_3O_6$: C, 61.9; H, 4.2; N, 10.3. Found: C, 61.9; H, 4.3; N, 10.0.

***N*-(2′-Nitrocinnamyl)-3-oxopyrano[4,3-*b*]indole-1-carboxamide (35).** Acetic anhydride (1 mL) was added to a solution of 3-[[*N*-(2′-nitrocinnamyl)amino]glyoxylyl]indole-2-acetic acid (**33**) (300 mg, 0.74 mmol) in tetrahydrofuran (50 mL), and the solution was stirred for 120 h at room temperature. The reaction mixture was concentrated in vacuo, triturated with ether, and filtered to yield a bright yellow solid **35** (184 mg, 64%). The filtrate was concentrated in vacuo and chromatographed (ether + 1% methanol) to yield a further 55 mg of the title pyranone, thus making a total yield of 83%, mp 195 °C dec: IR (Nujol) 3438 (NH), 1673 (pyranone C=O), 1646 (amide C=O), 1590, 1569, 1508 (aromatic NO_2), 1340, 1299, and 1217 cm^{-1}; UV (tetrahydrofuran) 277 (ϵ 48510), 323 (6190), 338 (5260), and 416 nm (3540); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.30 (2 H, ddd, J = 6, 6, and 2 Hz, $CONHCH_2$), 5.83 (1 H, s, 4-H), 6.51 (1 H, dt, J = 16 and 6 Hz, CH_2CH), 7.03 (1 H, d, J = 16 Hz, ArC*H*), 7.12 (1 H, t, J = 8 Hz, aromatic H), 7.23 (1 H, d, J = 8 Hz, aromatic H), 7.41 (1 H, td, J = 8 and 1.5 Hz, aromatic H), 7.51 (1 H, td, J = 8 and 1.5 Hz, aromatic H), 7.68 (1 H, td, J = 8 and 1.5 Hz, aromatic H), 7.83 (1 H, dd, J = 8 and 1.5 Hz, aromatic H), 7.91 (1 H, dd, J = 8 and 1 Hz, aromatic H), 8.90 (1 H, br, amide NH), 8.93 (1 H, d, J = 9 Hz, 9-H), and 11.13 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 389 (M^+, 1), 313 (38), 311 (42), 310 (39), 309 (67), 284 (21), 269 (30), 268 (27), 255 (24), and 184 (39); HRMS calcd for $C_{21}H_{15}N_3O_5$ 389.1012, found M^+ 389.1012.

4-(2′-Nitrophenyl)-2,3-dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (36). *N*-(2′-Nitrocinnamyl)-3-oxopyrano[4,3-*b*]-indole-1-carboxamide (**35**) (58.7 mg, 0.15 mmol) was refluxed in bromobenzene (20 mL), under nitrogen, for 4 h. The solution was then cooled, the nitrogen inlet was removed, and the solution refluxed in air for 4 h. The solution was concentrated in vacuo and chromatographed (ether + 1% methanol) to give the title carbazole **36** (21.6 mg, 42%) as an oil: IR (Nujol) 3253 (NH), 1682 (amide C=O), 1609, 1524, 1459, 1349, and 1329 cm^{-1}; UV (methanol) 220 (ϵ 45770), 252 (29940), and 317 nm (17230); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 4.35 (2 H, s, CH_2), 7.24 (1 H, ~t, J = 8 Hz, aromatic H), 7.46 (1 H, ~t, J = 8 Hz, aromatic H), 7.58 (1 H, d, J = 8 Hz, aromatic H), 7.62 (1 H, s, 5-H), 7.71–7.78 (2 H, m, aromatic H), 7.86 (1 H, ~t, J = 8 Hz, aromatic H), 8.11 (1 H, ~d, J = 8 Hz, aromatic H), 9.28 (1 H, ~d, J = 8 Hz, 10-H), and 10.7 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 343 (M^+, 22), 310 (30), 309 (100), 293 (37), 268 (33), and 254 (18); HRMS calcd for $C_{20}H_{13}N_3O_3$ 343.0957, found M^+ 343.0957.

4-(2′-Nitrophenyl)-2,3-dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (36) and 4-(2′-Nitrophenyl)-2,3-dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (37). *N*-(2′-Nitrocinnamyl)-3-oxopyrano[4,3-*b*]indole-1-carboxamide (**35**) (40.7 mg, 0.1 mmol) was refluxed in bromobenzene (11 mL) for 2 h. The solution was concentrated in vacuo and chromatographed (ether + 5% methanol) to give **36** as an oil (26 mg, 72%) and **37** as a yellow solid (6 mg, 16%). **36** was purified further by HPLC to give a solid (4.7 mg, 13%), mp 168 °C dec. **37** did not require further purification, mp > 300 °C: IR (Nujol) 3360 (NH), 3200 (NH), 1758 (imide C=O), 1699, 1611, 1523, 1350, 1314, 1208, and 1147 cm^{-1}; UV (methanol) 230 (ϵ 24600), 274 (13700), and 307 nm (13500); ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 7.3–7.9 (7 H, m, aromatic H), 8.2 (1 H, ~d, J = 8 Hz, aromatic H), 9.0 (1 H, ~d, J = 8 Hz, 10-H), 9.9 (1 H, br, imide NH), and 11.2 (1 H, br, indole NH); mass spectrum m/e (relative intensity) 357 (M^+, 9), 325 (44), 311 (42), and 309 (100); HRMS calcd for $C_{20}H_{11}N_3O_4$ 357.0750, found M^+ 357.0750.

2,3,4,5-Tetrahydro-4-(2′-nitrophenyl)pyrrolo[3,4-*c*]carbazol-1-one (38). *N*-(2′-Nitrocinnamyl)-3-oxopyrano[4,3-*b*]-indole-1-carboxamide (**35**) (23.7 mg, 0.06 mmol) was refluxed in bromobenzene (5 mL), under argon, for 1 h. The solution was cooled under argon, and the solvent was evaporated to give a brown solid (21 mg, 100%), mp darkness ~200 °C: IR (Nujol) 3200 (NH), 1673 (amide C=O), 1525 (NO_2), and 1348 (NO_2) cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 270 MHz) δ 3.28 (1 H, dd, J = 17 and 7 Hz, 5-H), 3.69 (1 H, dd, J = 17 and 10 Hz, 5-H), 3.92 (2 H, AB quartet, $CONHCH_2$), 4.72 (1 H, dd, J = 10 and 7 Hz, 4-H), 7.01–7.07 (2 H, m, aromatic H), 7.18 (1 H, br, amide NH), 7.29–7.38 (1 H, m, aromatic H), 7.49–7.68 (3 H, m, aromatic H), 7.95 (1 H, ~d, J = 8 Hz, aromatic H), 8.59 (1 H, m, 10-H), and 10.35 (1 H, br, indole NH); mass spectrum m/e (relative intensity) (FAB, matrix MNBA(+)) 346(MH^+, 11), 345 (M^+, 9), and 307 (9); HRMS calcd for $C_{20}H_{16}N_3O_3$ 346.1192, found MH^+ 346.1192.

K252-c (Staurosporine Alycon) (6). A. Triethyl phosphite (10 mL) was added to 4-(2′-Nitrophenyl)-2,3-dihydro-2*H*,6*H*-pyrrolo[3,4-*c*]carbazol-1-one (**36**) (21.6 mg, 0.06 mmol), and the mixture was refluxed for 1.5 h. The solution was concentrated in vacuo and chromatographed (ether + 3% methanol) to yield the title compound (10.6 mg, 54%) as a yellow solid, mp > 300 °C (lit.[9] mp 323–326 °C dec): IR (Nujol) 3437 (NH), 3315 (NH), 1650 (amide C=O), 1615, 1582, 1490, 1456, 1393, 1330, 1263, 1109, 1031, 939, and 736 cm^{-1}; UV (methanol) 229 (ϵ 18110), 289 (32090), 324 (8960), 333 (7940), 344 (6350), and 359 nm (4450); ^1H NMR ($(CD_3)_2CO$, 500 MHz) δ 4.95 (2 H, s, CH_2), 7.22 (1 H, t, J = 8 Hz, aromatic H), 7.30 (1 H, t, J = 8 Hz, aromatic H), 7.42 (1 H, t, J = 8 Hz, aromatic H), 7.46 (1 H, t, J = 8 Hz, aromatic H), 7.71 (1 H, d, J = 8 Hz, aromatic H), 7.78 (1 H, d, J = 8 Hz, aromatic H), 8.03 (1 H, d, J = 8 Hz, aromatic H), 8.48 (1 H, s, amide NH), 9.21 (1 H, d, J = 8 Hz, 4-H), 11.35 (1 H, s, carbazole NH) and 11.52 (1 H, s, carbazole NH); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 45.3 (CH_2), 111.3, 111.9, 114.1, 115.6, 118.9, 119.9 (2 carbons), 121.1, 122.6, 122.8, 125.0 (2 carbons), 125.2, 125.4, 127.9, 132.9, 139.1, 139.2, and 172.4 (C=O) (cf. ref 15); mass spectrum m/e (relative intensity) 311 (M^+, 67), 309 (17), 282 (32), 255 (16), 155 (52), and 127 (61).

B. *N*-(2′-Nitrocinnamyl)-3-oxopyrano[4,3-*b*]indole-1-carboxamide (**35**) (173 mg, 0.44 mmol) was refluxed in bromobenzene (25 mL), under nitrogen, for 1.5 h. The solution was then cooled, the nitrogen inlet was removed, and the solution refluxed in air for 3.5 h. The bromobenzene was removed on the rotary evaporator to yield the carbazole **36** as a solid (170 mg). Triethyl phosphite (25 mL) was added to this solid (114.6 mg), and the mixture was refluxed under nitrogen for 2 h. The solvent was evaporated, and the residue was chromatographed (ether + 3% methanol) to yield the staurosporine aglycon (**6**) (35 mg, 37% over two steps).

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Registry No. **6**, 85753-43-1; **8**, 138955-91-6; **9**, 138955-92-7;

10, 138955-93-8; 11, 138955-94-9; 12, 138955-95-0; 13, 138955-96-1; 14, 138955-97-2; 15, 138955-98-3; 16, 138955-99-4; 17, 138956-00-0; 18, 138956-01-1; 19, 138956-02-2; 20, 138956-03-3; 21, 138956-04-4; 22, 138956-05-5; 24, 80151-24-2; 25, 138956-06-6; 26, 138956-13-5; 26 free base, 138956-07-7; 27, 1504-65-0; 28, 75059-03-9; 29, 75059-00-6; 30, 138956-08-8; 31, 138956-09-9; 33, 138956-10-2; 35, 138956-11-3; 36, 132148-42-6; 37, 128287-91-2; 38, 138956-12-4; $HC{\equiv}CCH_2NH_2$, 2450-71-7; $H_2C{=}CHCH_2NH_2$, 107-11-9; $PhC{\equiv}CCH_2OH$, 1504-58-1; $PhC{\equiv}CCH_2NH_2{\cdot}HCl$, 30011-36-0; $PhCH{=}CHCH_2Cl$, 2687-12-9; $PhCH{=}CHCH_2NH_2$, 4360-51-4; $HC{\equiv}CCH_2OH$, 107-19-7; ethyl indole-2-acetate, 33588-64-6; *N*-(phenylpropargyl)phthalimide, 4656-94-4; *N*-cinnamylphthalimide, 56866-32-1; 1-iodo-2-nitrobenzene, 609-73-4; 2-nitrocinnamaldehyde, 1466-88-2.

An Asymmetric Ammonia Synthon for Michael Additions[1]

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The highly diastereoselective 1,4-addition of lithiated chiral amine 1 to α,β-unsaturated esters, followed by hydrogenolysis of the benzylic-type C–N bonds of the 1,4-adducts, provides an asymmetric ammonia synthon for Michael additions. Under optimized conditions, lithiated 1 adds to α,β-unsaturated *tert*-butyl esters in dimethoxyethane at –63 °C in high yield with very high diastereoselectivity. Small, large, functionalized, and chiral β-ester substituents are amenable, with (*S*)-1 consistently adding to (*E*)-3 from the top as drawn in Table II. Hydrogenolysis liberates the β-amino esters with typically 95–99% ee.

The direct control of stereochemistry at nitrogen-bearing stereocenters is not nearly as well developed as the control of stereochemistry at oxygen-bearing centers. Our approach to the stereoselective formation of carbon–nitrogen bonds involves the diastereoselective 1,4-addition of a chiral lithium amide to an α,β-unsaturated ester followed by cleavage of the chiral auxiliary on nitrogen providing an asymmetric ammonia synthon (eq 1).[2,3] For this process, the structure of the lithium amide must both promote diastereoselectivity and allow auxiliary cleavage. In this paper, we report the 1,4-addition of the lithium amide of 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine (1) to a variety of esters with high diastereoselectivity and the hydrogenolysis of the benzylic-type C–N bonds of the resulting adducts yielding β-amino esters with high enantiomeric and diastereomeric excesses. These materials are important as peptide components[4,5] and β-lactam precursors.[6]

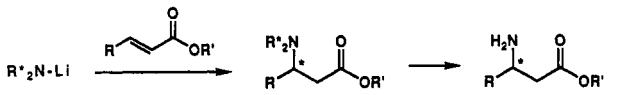
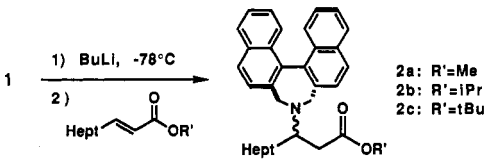


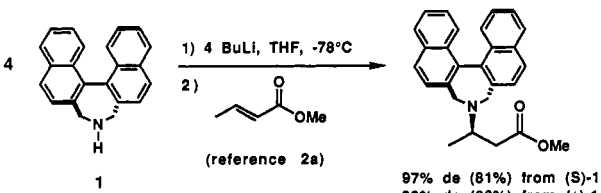
Table I. Optimization with Respect to Solvent, Ester Substituent, and Stoichiometry



entry	R′	solvent	equiv R_2NLi	diastereomer ratio (yield, %)
1	Me	THF	4.0[a]	20:1 (44)
2	Me	THF	1.0[a]	20:1 (25)
3	Me	THF/HMPA (4:1)	1.0[a]	3:1 (18)
4	Me	THF/20 equiv TMEDA	4.0[a]	12:1 (28)
5	Me	toluene	1.0[a]	3:1 (6)
6	Me	THF/4 equiv 12-crown-4[c]	4.0[a]	44:1 (60)
7	Me	THF/4 equiv 12-crown-4[d]	4.0[a]	24:1 (42)
8	iPr	THF/8 equiv 12-crown-4[c]	4.0[b]	17:1 (65)
9	tBu	THF/4 equiv 12-crown-4[c]	4.0[b]	37:1 (88)
10	tBu	THF/1 equiv 12-crown-4[c]	1.0[b]	16:1 (43)
11	tBu	DME[e]	1.5[b]	53:1 (80)
12	tBu	DME[e]	1.1[b]	66:1 (70)
13	tBu	DME[e]	1.0[b]	62:1 (66)
14	iPr	DME[e]	1.5[b]	30:1 (63)
15	Me	DME[e]	2.0[a]	22:1 (32)

[a] Reaction with (±)-1. [b] Reaction with (*S*)-1. [c] BuLi added to 1 plus 12-crown-4. [d] 12-Crown-4 added to 1 plus BuLi. [e] Reaction at –63 °C.

Our previously reported conditions for the diastereoselective addition of lithiated 1 to methyl crotonate (eq 2)[2a,7] worked poorly with methyl decenoate (Table I, entry 1).



1,2-Addition and/or γ-deprotonation appeared to lower

(1) Presented by T.A.L. at the 200th National Meeting of the American Chemical Society, Washington, DC, August 29, 1990.

(2) For other asymmetric 1,4-additions of nitrogen nucleophiles, see: (a) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820. (b) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (c) Davies, S. G.; Dordor-Hedgecock, I. M.; Sutton, K. H.; Walker, J. C. *Tetrahedron Lett.* **1986**, *27*, 3787. (d) Baldwin, S. W.; Aube, J. *Tetrahedron Lett.* **1987**, *28*, 179. (e) de Lange, B.; van Bolhuis, F.; Feringa, B. L. *Tetrahedron* **1989**, *45*, 6799. (f) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.

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(5) For lead references on bestatin and amastatin, see: Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1990**, *55*, 2232.

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(7) A computational study of this reaction and the corresponding 1,4-addition of nonlithiated 1 rationalized the observed selectivities: Rudolf, K.; Hawkins, J. M.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 3879.

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