Synthesis of Pyrrolidin-2-ones and of Staurosporine Aglycon (K-252*c*) by Intermolecular Michael Reaction

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Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles were isolated from nature, e.g., from low plants, especially fungi, as structurally rare natural substances. Responsible for naming and also the most important representative of this type is staurosporine (**1**), isolated from *Streptomyces staurosporeus*, and its aglycon (**2**), also known as staurosporinone or K-252*c*. 3,4-Disubstituted pyrrolidin-2-ones, a group of compounds with many interesting biological properties are related to staurosporinone. The most important property is the inhibition of protein kinase C (PKC), so that this antiproliferative agent can interfere with the cell cycle. The synthetic strategy, developed by us, allows the synthesis of pyrrolidin-2-ones by an intermolecular Michael addition, starting from nitroethene derivatives and substituted acetate Michael donors. With this method also enantioselective syntheses can be carried out using chiral auxiliaries. After reduction of the nitro group and subsequent lactamization, the lactam partial structure, which is essential for the biological activity, is obtained. Besides indole substituents, which were used for the synthesis of staurosporinone, substituted indole-, phenyl-, and pyridyl- as well as enantiomerically pure (*S*)-proline derivatives were used. Here, considerably high diastereoselectivity and enantioselectivity ((*S*)-pyrrolidine) could be detected. Just like the total synthesis of staurosporinone within three steps, the easiest and shortest approach reported up to now, with good to moderate yields, this sequence allows highly diastereoselective syntheses, which open the easy access to a new family of compounds.

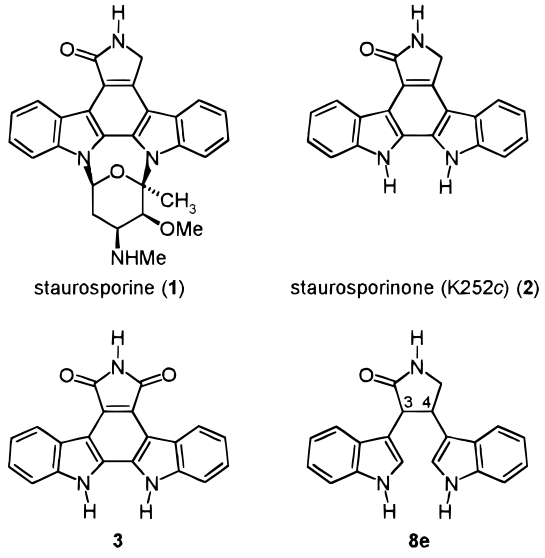
Introduction

Among carbazole alkaloids the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles represent a structurally rare type of natural substance. Compounds showing this heterocyclic skeleton are most common in low plants, especially fungi. The first-isolated and most important example is staurosporine **(1)**, an aminohexose-bound alkaloid isolated from *Streptomyces staurosporeus* in 1977.[1] The lactam-type heterocyclic moiety of **2**, staurosporinone or K-252*c* **(2)**, is also found in a *Nocardiopsis* strain (Scheme 1).[2,3]

Among the widespread biological activities of the foregoing compounds, inhibition of protein kinase C (PKC) is the most important property in some cases.[4,5]

Compounds such as **3** are precursors in most known preparative routes to **2**.[6,7] The major disadvantage of these syntheses is the inability to produce nonsymmetrically substituted staurosporinones, because the isomeric mixtures obtained by reduction of the imides of type **3** could not be separated till now.[8,9] Another limitation of this type of syntheses is the inselectivity of the reduction step, because the reaction could not be stopped at the lactam stage.[10]

Scheme 1



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Other syntheses of **2** including cycloaddition steps, e.g., are too long and low in yield.[11−20] To avoid these disadvantages, a new access to indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazoles is elaborated. An adequate precursor should be a bis-indolo-γ-butyrolactam **8e** (Scheme 1).

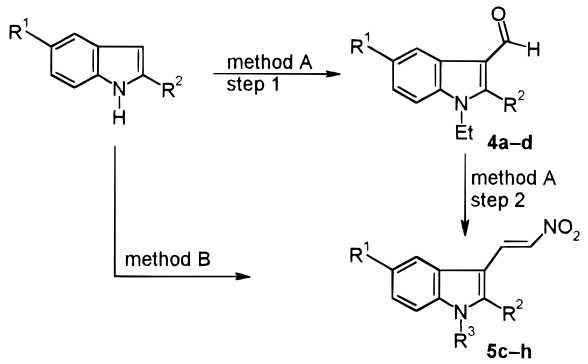
Compounds of the basic structure **8e** are known to be biologically active by themselves, depending on their stereochemistry at C-3 and C-4, but often the reported activity is low, probably because mixtures of diastereomers have been synthesized and tested.[21,22] Nevertheless, these mixtures are part of patent claims.[23]

Synthesis

For the synthesis of the pyrrolidin-2-ones we used a Michael addition route using nitroethene derivatives and substituted acetate Michael donors, which promised a facile way for the introduction of different substituents in the 3 and 4 positions of the desired five-ring lactam. To study different experimental conditions, we first synthesized a couple of model compounds using different substitution patterns. We started with commercially available aryl and heteroaryl aldehydes or heteroaromates, which were converted into the desired nitroethenes by literature methods.[24−27] Additionally, we prepared some 2-phenyl-substituted indoles by known methods and converted them to the corresponding nitroethene derivatives (Scheme 2), which should provide some steric restraint in the γ-lactams (see Scheme 2 and Table 1).

Synthesis of 3,4-Disubstituted Pyrrolidin-2-ones by Michael Reaction. The Michael reaction itself was performed at −78 °C in the presence of freshly prepared LDA in THF (Scheme 3). Formation of diastereomers was observed during every reaction. Therefore we first studied the influence of the temperature on the ratio of diastereomers. For compounds **7b**, **7i**, and **7j** this ratio was examined by ^{1}H NMR analysis. Interestingly, even the sterically more demanding 2-phenyl-substituted indoles show only moderate to low diastereomeric selectivity with only a small influence of different temperatures (Table 3).

Scheme 2[a]

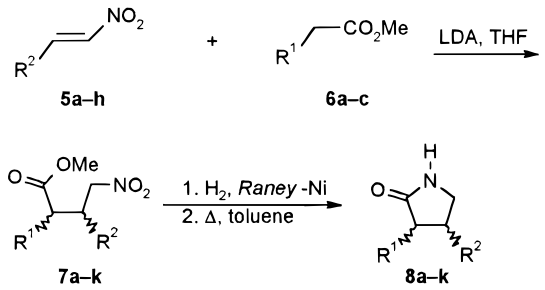


[a] Method A: step 1 (1) NaH/EtI, (2) DMF/$POCl_3$; step 2 CH_3NO_2, NH_4OAc. Method B: *N*,*N*-dimethyl-2-nitroethenamine, TFA (R^1−R^3 see Table 1).

Table 1

cpd	method (step)	R^1	R^2	R^3
4a	A(1)	H	phenyl	
4b	A(1)	H	4-OMe-phenyl	
4c	A(1)	OMe	phenyl	
4d	A(1)	OMe	4-OMe-phenyl	
5c	B	H	H	H
5d	B	OMe	H	H
5e	A(2)	H	phenyl	Et
5f	A(2)	H	4-OMe-phenyl	Et
5g	A(2)	OMe	phenyl	Et
5h	A(2)	OMe	4-OMe-phenyl	Et

Scheme 3[a]



[a] For R^1 and R^2 see Table 2.

In contrast to these results the formation of unsubstituted bisindolylnitrobutanoates (**7e**) showed high diasteroselectivity and, what is even more important, high sensitivity to just that temperature the reaction mixture was allowed to warm to. Workup at 195 K instead of 293 K converted the ratio of diastereomers from 99:1 (195 K) to 10:90 (293 K).

For the reactions affording **7e** and **7f**, both diastereomers were preparatively separated by column chromatography and, for **7e**, further investigated (see below).

We took a two-way approach in order to examine the influence of chiral substituents on our reaction sequence. At first we replaced the methyl ester function by a chiral isopentyl ester moiety, affording the optically pure compound **10b** prepared from 3-indoleacetic acid **(10a)** (Scheme 4). This ester was then subjected to a Michael addition with the 3-indolylnitroethene **5c** at −78 °C.

The mixture of crude reaction products **9** was analyzed for diastereomeric ratios by HPLC. The diastereomeric

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Table 2. Michael Donors (6a−c) and Michael Acceptors (5a−j) and Products of the Michael Reaction (7a−l) and of the Subsequent Lactamization (8a−l)

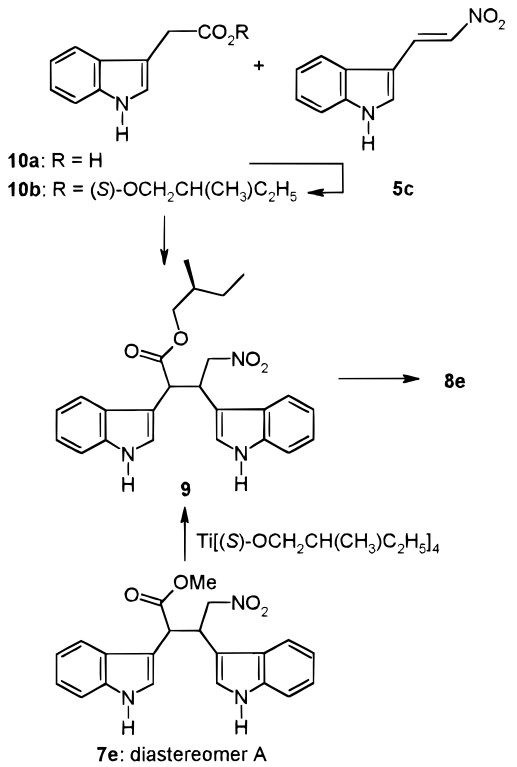
acc	don			R^2	R^1
5a[cf.24]	**6a**	**7a**	**8a**[28]	phenyl	phenyl
5a	**6b**	**7b**	**8b**	phenyl	3-indolyl
5b[cf.24]	**6b**	**7c**	**8c**	3-pyridyl	3-indolyl
5c[cf.24]	**6c**	**7d**	**8d**	3-indolyl	3-pyridyl
5c[cf.25]	**6b**	**7e**	**8e**	3-indolyl	3-indolyl
5d[cf.25]	**6b**	**7f**	**8f**	3-(5-methoxyindolyl)	3-indolyl
5e[cf.26]	**6b**	**7h**	**8h**	3-(2-phenylindolyl)	3-indolyl
5f[cf.26]	**6b**	**7i**	**8i**	3-(1-ethyl-2-(4-methoxyphenyl)indolyl)	3-indolyl
5 g[cf.26]	**6b**	**7j**	**8j**	3-(1-ethyl-5-methoxy-2-phenyl)-indolyl	3-indolyl
5h[cf.26]	**6b**	**7k**	**8k**	3-(1-ethyl-5-methoxy-2-(4-methoxyphenyl))-indolyl	3-indolyl
5j[27]	**6b**	**7l**	**8l**	1-butyloxycarbonyl-2-(2*S*)-pyrrolidinyl	3-indolyl

Table 3. Ratio of Diastereomers during the Michael Reaction

	workup temp (K)	ratio of diastereomers
7b	195	52:48[a]
7b	293	84:16[a]
7e	195	99:1[b]
7e	293	10:90[b]
7i	293	61:39[a]
7i	195	59:41[a]
7j	293	67:33[a]
7j	195	74:26[a]

[a] Assigned by ^{1}H NMR analysis. [b] Assigned by quantitative separation of the diastereomers [erythro:threo].

Scheme 4



excess of this reaction was about 90%. However, the enantiomeric excess was nearly negligible (about 10% for each diastereomer). We explain this minimal chiral induction by the large distance between the localization of the chiral information (ester function) and the reacting center. To obtain more starting material for the growth of a single crystal for X-ray structure analysis, we transesterified the diastereomer A of methyl butanoate **7e**, to assign the stereogenic centers of all diastereomeric nitrobutanoates by this way. This approach, however,

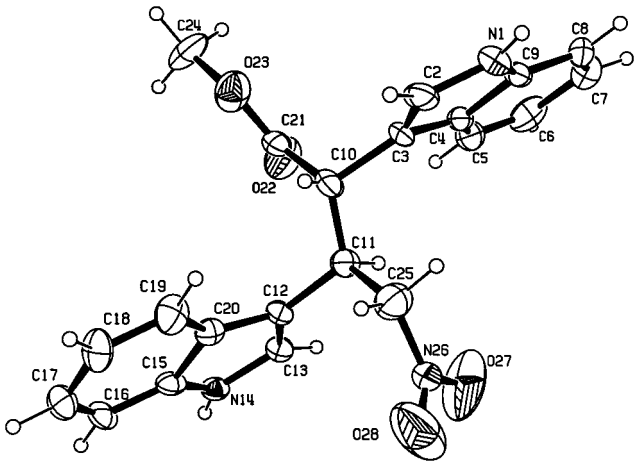


Figure 1. ORTEP plot of **7e**.

failed because no suitable crystals could be obtained. The ratio of enantiomers of this reaction was similar to that stated above.

So we tried to determine the relative configuration of the nitrobutanoate **7e**. We took a suitable crystal from the racemic mixture of diastereomer A of **7e**. This crystal showed a conformation as shown in Figure 1 (ORTEP plot[29] of **7e** diastereomer A with 30% probability for ellipsoids).[30] The two bulky indole substituents adopt an antiperiplanar conformation, so pointing to opposite directions. The erythro configuration was assured. This matches exactly to our results found for the temperature dependence of the Michael reaction, as the erythro form is sterically less demanding and should therefore be the favored product of a kinetically controlled reaction.

The lactam formed from the diastereomer A therefore adopts an s-cis configuration whereas the diastereomer B derived lactam should adopt an s-trans configuration.

Each of the two diastereomers of **7e** and **7f** was submitted to hydrogenation and lactamization separately. Surprisingly, the erythro-diastereomers produced much more cis-lactams (62% **8e**, 56% **8f**) than the threo-diastereomers which only yielded the trans-lactams **8e** and **8f** in 8% and 12% yield, respectively.

We tried to shift the chiral information nearer to the reacting center, similar to our procedure for the 2-fold

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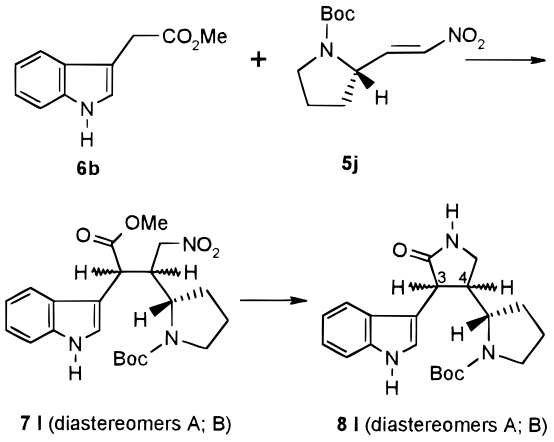
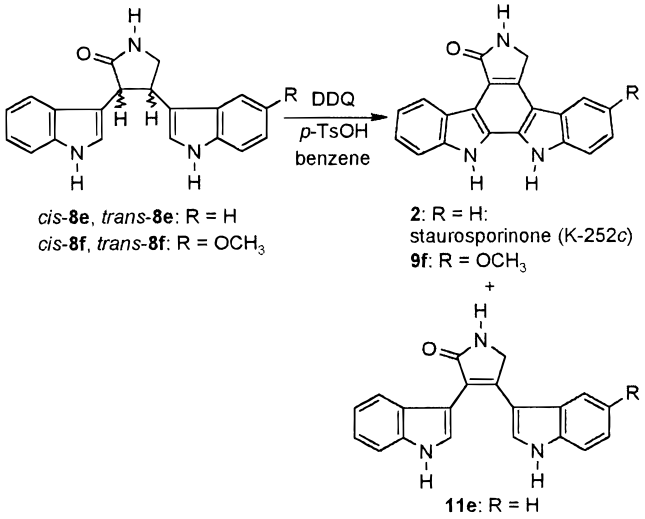
(30) Crystallographic data (excluding structure factors) for the reported structure have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 117005.

Scheme 5



Scheme 6



diastereoselective reaction using two chiral educts in a Michael addition.[27] The reaction between our standard Michael donor **6b** and the chiral nitroethene Michael acceptor **5j**[27] yielded two diastereomers in equal quantities (Scheme 5). The reacting temperature, however, had to be risen to room temperature because otherwise no reaction could be observed.

A more profound investigation of the **7l** diastereomers at the nitrobutanoate level proved to be impracticle due to complicated NMR spectra, even at elevated temperatures. Therefore, the two **7l** diastereomers **7lA** and **7lB** were separated and subjected to reduction and lactamization, affording the diastereomers **8lA** and **8lB** as pure compounds. We examined the two diasteromers at the lactam stage (**8lA** and **8lB**). The protons could be assigned exactly by high-temperature COSY and NOESY experiments, but determination of the relative stereochemistry by the Karplus−Conroy equation was impossible ($J_{H3-H4} = 8.0$ Hz for **8lA** and $J_{H3-H4} = 8.3$ Hz for **8lB** corresponding to a torsion angle of ∼10° or ∼150°). According to NOESY **8lA** shows s-trans configuration for 3-H and 4-H. Nevertheless, the Michael reaction showed a very good diastereoselectivity as only two of the possible four optically active diastereomers have been formed. The assumption that the two diastereomers are epimers could not be verified up to now, because no suitable crystals for X-ray analysis could be obtained till now.

Oxidative Ring Closure of 3,4-Bisarylpyrrolidin-2-ones. Synthesis of Staurosporinone (K-252*c*). To examine whether the lactams **8** are suitable substrates for oxidative ring closure reactions, at first *tert*-butyl hypochlorite in the presence of triethylamine, which is a well-known reactant in carbazole syntheses,[13] was tested using the lactams **8b** and **8e** (both as mixtures of diastereomers). No preparatively useful results could be obtained in any case. For **8b**, e.g., oxidation by DDQ in dry benzene under addition of a catalytic amount of *p*-toluenesulfonic acid[21] also did not yield cyclized products, while in the case of the diastereomeric mixture of **8e**, the cyclization product **2** could be obtained in 60% yield besides 2% of pyrrolinone **11e** isolated only from large scale oxidations, which might be an intermediate in a possible sequence with ring closure being the last step. Separate oxidation trials showed that *cis*- and *trans*-**8e** were both converted to **2**.

For lactam **8f**, the behavior of the separated diastereomers was studied: *cis*-**8f** yielded 15% of the analogous cyclization product **9f** (which until now could only be prepared as a mixture with the 3-methoxy isomer[8,9]). With *trans*-**8f**, the same oxidation conditions led to 12% of **9f**. In both cases the isolation of a byproduct (detectable by thin layer chromatography (TLC)) analogous to **11e** was not possible (Scheme 6).

This synthetic route is presenting the shortest preparation of the staurosporine aglycon (three steps from commercially available or easy obtainable compounds). Until now, other syntheses of staurosporinone comprise more steps.[6,7,11−14]

Conclusion

The reported method is useful for the synthesis of 3,4-disubstituted pyrrolidin-2-ones, with a broad variety of possible substituents. The formation of two new stereogenic centers during the Michael addition key step causes some problems, acquiring stereochemically pure products. The influence of some experimental parameters on the ratio of diastereomers was examined, and with the chiral substituent near the reacting center a good stereoselectivity could be obtained.

Furthermore, the pyrrolidinones were processed to give staurosporinone derivatives. The overall yield and the simplicity of the reaction steps favors our reaction sequence in contrast to the published routes to staurosporinone. With our method, asymmetrically substituted staurosporinone derivatives are *easily* accessible and, what is more important, they can be achieved without separation of complex mixtures of isomers.

Experimental Section

General Information. Melting points were recorded on a microscope heating stage and are not corrected. Proton nuclear magnetic resonance spectra, mass spectra, and microanalyses were performed by Zentrale Analytik, University of Regensburg. FT-IR spectroscopy was performed on a FT-IR spectrometer. All chemical shifts are quoted on the δ-scale. Optical rotations were measured on a polarimeter. Thin-layer chromatography (TLC) was carried out on Al sheets coated with $60F_{245}$ silica. Compounds were detected using a spray of 3% w/v vanillin in 96% ethanol followed by 5% w/v H_2SO_4 in 96% ethanol. Column chromatography was carried out using 70−230 mesh ASTM silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures. All reactions were carried out under dried N_2 in flame- or oven-dried vessels.

X-ray crystal structure analysis of 7e was performed with an Enraf Nonius Turbo-CAD4 equipped with a rotating

anode on a poor quality single crystal with a size of 0.16 × 0.32 × 0.45 mm: orthorhombic space group $Pna2_1$; wavelength used, Cu Kα with graphite monochromator, 1.541 78 Å; T = 298(2) K; unit cell dimensions a = 16.524(3), b = 7.823(1), c = 14.0968(8); V = 1822.1(4) Å^3; Z = 4, d(calc) = 1.376 g/cm^3; absorption μ = 0.8 mm^{-1} (no correction); θ range for data collection, 1.5−75°; index ranges $0 \le h \le 20$, $0 \le k \le 9$, $\le l \le$ 17. No. of reflections collected: 4166 (with Friedel pairs). No. of independent reflections: 3737 [R_σ = 0.045]. The structure was solved by direct methods. Structure refinement was by full-matrix least squares on F^2 with anisotropic temperature factors for all non-hydrogen atoms. Goodness-of-fit on F^2: 1.023. Final R indices [$I > 2\sigma(I)$]: $R1$ = 0.132, $wR2$ = 0.391. The final difference Fourier map showed minimum and maximum values of −0.58 and 1.41 e Å^{-3}. The absolute configuration could not be determined. The Flack absolute structure parameter is 0.2(10).

1-Ethyl-2-(4-methoxyphenyl)-1*H*-3-indolecarbaldehyde (4b). To a suspension of NaH (60 mmol) (60% suspension in mineral oil) in 100 mL of dry DMF was added a solution of 2-(4-methoxyphenyl)-1*H*-indole (40 mmol) in 85 mL of dry DMF at 0 °C within 15 min, and this mixture was stirred for 30 min at this temperature. Subsequently, ethyl iodide (50 mmol), dissolved in 40 mL of dry DMF, was added dropwise. The resulting solution was allowed to come to room temperature within 1 h. After it recooled to 0 °C, $POCl_3$ (5.50 mL) was added dropwise and the solution was stirred for 30 min at room temperature. Finally the solution was poured into a mixture of 100 mL of 5 N NaOH and 100 mL of ice water, a pH value of approximately 9 was adjusted with 5 N NaOH and 200 mL of ethyl acetate was added. After this mixture stirring was for 30 min, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The organic phase was dried over Na_2SO_4. The solution was allowed to evaporate in the open air overnight, and then the precipitate was filtered off. After the solvent was carefully removed in vacuo, a second fraction crystallized. Purification of the precipitate by column chromatography (CH_2Cl_2) yielded the aldehyde as colorless crystals (8.94 g, 32.0 mmol, 80%): mp 147−148 °C; IR (KBr) 2981, 2838, 1642 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.33 (t, J = 7 Hz, 3H), 3.93 (s, 3H), 4.12 (q, J = 7 Hz, 2H), 6.92−7.14 (m, 3H), 7.33−7.50 (m, 5H), 9.76 (s, 1H). Anal. Calcd for $C_{18}H_{17}NO_2$ (279.34): C, 77.40; H, 6.13; N, 5.01. Found: C, 77.09; H, 6.23; N, 5.01.

1-Ethyl-5-methoxy-2-phenyl-1*H*-3-indolecarbaldehyde (4c). The synthesis of compound **4c** was effected as described for the indole derivative **4b**. Purification of the precipitate by column chromatography (CH_2Cl_2) yielded the aldehyde as colorless crystals (9.07 g, 33.0 mmol, 83%): mp 128−129 °C; IR (KBr) 2979, 2961, 1645 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, J = 7 Hz, 3H), 3.92 (s, 3H), 4.09 (q, J = 7 Hz, 2H), 6.89−7.07 (m, 1H), 7.26−7.36 (m, 1H), 7.53 (m, 5H), 7.96 (d, J = 4 Hz), 9.70 (s, 1H). Anal. Calcd for $C_{18}H_{17}NO_2$ (279.34): C, 77.40; H, 6.13; N, 5.01. Found: C, 77.25; H, 6.21; N, 4.90.

1-Ethyl-2-(4-methoxyphenyl)-3-(2-nitro-(*E*)-1-ethenyl)-1*H*-indole (5f). A solution of compound **4b** (25.1 mmol) and ammonium acetate (2.00 g) in freshly distilled nitromethane (28.0 mL) was heated to reflux for 4 h. The solution was allowed to cool to room temperature overnight, the precipitate was filtered off and was washed with 30 mL of diethyl ether. The mother liquor was concentrated and the residue was purified by column chromatography (CH_2Cl_2), yielding the product as yellow crystals (7.90 g, 25.0 mmol, 98%): mp 183−184 °C (ethyl acetate); IR (KBr) 3129, 2840, 1611 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.31 (t, J = 7 Hz, 3H), 3.93 (s, 3H), 4.13 (q, J = 7 Hz, 2H), 7.00−7.82 (m, 8H), 7.76, 8.03 (AB-system, J_{AB} = 12.6 Hz, 2H). Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.37): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.70; H, 5.63; N, 8.67.

1-Ethyl-5-methoxy-3-(2-nitro-(*E*)-1-ethenyl)-2-phenyl-1*H*-indole (5g). The synthesis of compound **5g** was effected as described for the indole derivative **5f**. Purification of the precipitate by column chromatography (CH_2Cl_2) yielded the product as yellow crystals (7.97 g, 25.0 mmol, 98%): mp 162−164 °C (ethyl acetate); IR (KBr) 3141, 2834, 1605 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H), 3.94 (s, 3H), 4.09 (q, J = 7 Hz, 2H), 6.98−7.67 (m, 9H), 7.62, 7.99 (AB-system, J_{AB} = 15 Hz, 2H). Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.37): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.62; H, 5.63; N, 8.69.

General Procedure for the Michael Addition of Acetic Acid Derivatives to Nitroethenyl Compounds. Method A. To a solution of dry diisopropylamide (2.39 mL, 17.0 mmol) in dry THF (7 mL) in a three-necked flask, equipped with a deep-temperature thermometer and a septum, was added *n*-BuLi (10.4 mL, 17.0 mmol) at −78 °C within 30 min. After the solution was stirred at 0 °C for 30 min and recooled to −78 °C, the acetic ester derivative (8.21 mmol), dissolved in dry THF (50 mL), was added by a syringe within 30 min. The mixture was stirred at −78 °C for 30 min, and subsequently the nitroethenyl derivative (9.03 mmol), dissolved in dry THF (20 mL), was added by syringe. The mixture was vigorously stirred for 3 h at −78 °C, then saturated NH_4Cl solution was added, and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with ethyl acetate, the organic extract was washed with water and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by column chromatography.

Method B. This method is similar to method A, but after the addition of the nitroethenyl compound the reaction mixture was stirred for 3 h at −78 °C and then it was allowed to warm to room temperature overnight.

Methyl 4-Nitro-2,3-diphenylbutanoate (7a). Method B. Column chromatography (CH_2Cl_2) yielded the product as colorless crystals (56%): melting range 100−136 °C (mixture of diastereomers); IR (KBr) 3000, 2954, 1740, 1553 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.25−3.31 (m, 1.5H), 3.61−3.67 (m, 1.5H), 3.95−4.33 (m, 2.5H), 4.73−4.86 (m, 0.5H), 4.95−5.02 (m, 1H), 7.02−7.58 (m, 10H); MS m/z (%) 299 (6) [M$^{+\bullet}$], 252 (10), 193 (18), 121 (100), 77 (32). Anal. Calcd for $C_{17}H_{17}NO_4$ (299.33): C, 68.21; H, 5.72; N, 4.68. Found: C, 68.04; H, 5.66; N, 4.86.

Methyl 2-(3-1*H*-Indolyl)-4-nitro-3-phenylbutanoate (7b). Method A. Column chromatography (CH_2Cl_2) yielded the product as colorless crystals (58%): melting range 162−168 °C (mixture of diastereomers); IR (KBr) 3415, 1730, 1555 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.40 (s, 1.5 H), 3.67 (s, 1.5 H), 4.28−4.53 (m, 4H), 7.16−7.38 (m, 10H), 8.15 (br s, 0.5 H) 8.40 (br s, 0.5 H).

Method B. Column chromatography (CH_2Cl_2) yielded the product as colorless crystals (55%): melting range 155−157 °C (mixture of diastereomers); IR (KBr) 3413, 1733, 1553 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.40 (s, 2.5 H), 3.67 (s, 0.5 H), 4.28−4.53 (m, 4H), 7.16−7.38 (m, 10H), 8.15 (br s, 0.85 H) 8.40 (br s, 0.15 H); MS m/z (%) 338 (9) [M$^{+\bullet}$], 188 (100), 160 (23). Anal. Calcd for $C_{19}H_{18}N_2O_4$ (338.36): C, 67.45; H, 5.36; N, 8.27. Found: C, 66.76; H, 5.20; N, 8.22.

Methyl 2-(3-1*H*-Indolyl)-4-nitro-3-(3-pyridyl)butanoate (7c). Method B. Column chromatography (CH_2Cl_2/ethyl acetate 1:1) yielded the product as colorless crystals (21%); mp 203−205 °C; IR (KBr) 3413, 1721, 1551 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.15 (s, 3H), 4.03−4.92 (m, 4H), 6.90−7.38 (m, 5H), 7.64−7.93 (m, 2H), 8.31−8.55 (m, 2H), 11.13 (s, 1H); MS m/z (%) 339 (12) [M$^{+\bullet}$], 293 (3), 188 (100). Anal. Calcd for $C_{18}H_{17}N_3O_4$ (339.35): C, 63.71; H, 5.05; N, 12.38. Found: C, 63.85; H, 5.09; N, 12.43.

Ethyl 3-(3-1*H*-Indolyl)-4-nitro-2-(3-pyridyl)butanoate (7d). Method B. Column chromatography (CH_2Cl_2/ethyl acetate/hexane 5:2:1) yielded the product as yellowish crystals (19%): mp 161−163 °C; IR (KBr) 3413, 1715, 1546 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16 (t, J = 6 Hz, 3H), 4.15 (q, J = 6 Hz, 2H), 4.39−4.73 (m, 2H), 5.01−5.13 (m, 2H), 6.93−7.48 (m, 6H), 7.59−8.79 (m, 2H), 8.19−8.49 (m, 2H); MS m/z (%) 353 (15) [M$^{+\bullet}$], 307 (1), 165 (70), 143 (100). Anal. Calcd for $C_{19}H_{19}N_3O_4$ (353.38): C, 64.58; H, 5.42; N, 11.89. Found: C, 64.27; H, 5.42; N, 11.92.

Methyl 2,3-Bis(3-1*H*-indolyl)-4-nitrobutanoate (7e). Method A. Column chromatography (CH_2Cl_2−CH_2Cl_2/ethyl acetate 19:1) yielded the two diastereomers of **7e**.

Diastereomer A: colorless crystals (10%); mp 192−194 °C (MeOH); IR (KBr) 3450, 1742, 1560 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.25 (s, 3H), 4.45 (dd, 1H, J = 11.7, 4.0 Hz), 4.48 (d, 1H, J = 11.5 Hz), 4.60 (m, 1H), 4.77 (dd, 1H, J = 11.7, 9.6 Hz), 6.99−7.87 (m, 10H), 11.03 (s, 1H), 11.23 (s, 1H); EI-MS m/z (%) 377 (10) [$M^{+\bullet}$], 188 (100).

Diastereomer B: pale brown crystals (0.1%); mp 132 °C (MeOH); IR (KBr) 3411, 1732, 1549 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.20 (s, 3H), 4.20−4.88 (m, 4H), 6.79−7.90 (m, 10H), 11.00 (s, 1H), 11.30 (s, 1H); EI-MS m/z (%) 377 (6) [$M^{+\bullet}$], 188 (100).

Method B. Distereomer A: yield 1%.

Distereomer B: yield 10%.

Methyl 2-(3-1*H*-Indolyl)-3-(5-methoxy-1*H*-indol-3-yl)-4-nitrobutanoate (7f). Method B. Column chromatography (CH_2Cl_2/ethyl acetate 19:1) yielded the two diastereomers of **7f**.

Diastereomer A: brownish oil (12%); IR (neat) 3440, 1710, 1550 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.29 (s, 3H), 3.80 (s, 3H), 4.46−4.61 (m, 3H), 4.71−4.80 (m, 1H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 7.05−7.19 (m, 3H), 7.23 (d, J = 8.8 Hz, 1H), 7.38−7.43 (m, 2H), 7.48 (d, J = 2.5 Hz, 1H), 7.84 (d, J = 7.1 Hz, 1H), 10.87 (d, J = 2.1 Hz, 1H), 11.22 (d, J = 1.8 Hz, 1H); EI-MS m/z (%) 407 (9) [$M^{+\bullet}$], 376 (1), 361 (3), 219 (23), 218 (23), 188 (100), 173 (83), 160 (20), 130 (29).

Diastereomer B: pale brown oil (24%); IR (neat) 3450, 1715, 1545 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.50 (s, 3H), 3.80 (s, 3H), 4.28−4.70 (m, 4H), 6.58−7.85 (m, 9H), 10.85 (d, J = 2.2 Hz, 1H), 11.10 (d, J = 2.5 Hz, 1H); EI-MS m/z (%) 407 (5) [$M^{+\bullet}$], 361 (3), 219 (1), 218 (4), 188 (100), 173 (94), 160 (35), 130 (56).

Methyl 2-(2-1*H*-Indolyl)-4-nitro-3-(2-phenylindol-3-yl)-butanoate (7h). Method B. Recrystallization from ethanol yielded the product as colorless crystals (59%): mp 221−223 °C; IR (KBr) 3406, 1721, 1553 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.08 (s, 3H), 11.73 (s, 1H), 4.11−4.14 (m, 1H), 4.73 (m, 2H), 5.07 (br s, 1H), 6.61 (m, 1H), 6.88−7.71 (m, 12H), 7.92 (m, 1H), 11.35 (s, 1H); MS m/z (%) 453 (11) [$M^{+\bullet}$], 265 (22), 219 (100). Anal. Calcd for $C_{27}H_{23}N_3O_4$ (453.50): C, 71.51; H, 5.11; N, 9.27. Found: C, 71.52; H, 5.22; N, 9.77.

Methyl 3-(1-Ethyl-2-(4-methoxyphenyl)-1*H*-3-indolyl)-2-(1*H*-3-indolyl)-4-nitrobutanoate (7i). Method A. Column chromatography (CH_2Cl_2) yielded the product as colorless crystals (44%).

Method B. Column chromatography (CH_2Cl_2) yielded the product as colorless crystals (41%): melting range 98−106 °C; IR (KBr) 3411, 2952, 1737, 1553 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.99−1.18 (m, 3H), 3.31−3.60 (m, 3H), 3.70−3.98 (m, 5H), 4.21−5.40 (m, 4H), 6.70−6.89 (m, 1H), 7.11−7.37 (m, 4H), 7.16−7.25 (m, 3H), 7.26−7.34 (m, 2H), 7.39−7.60 (m, 2H), 7.66−7.84 (m, 1H), 7.88−8.19 (m, 1H); MS m/z (%) 511 (5) [$M^{+\bullet}$], 596 (1), 450 (1), 323 (28), 277 (100), 188 (7). Anal. Calcd for $C_{30}H_{29}N_3O_5$ (511.58): C, 70.44; H, 5.71; N, 8.21. Found: C, 70.23; H, 5.81; N, 8.07.

Methyl 3-(1-Ethyl-5-methoxy-2-phenyl-1*H*-3-indolyl)-2-(1*H*-3-indolyl)-4-nitrobutanoate (7j). Method A. Column chromatography (CH_2Cl_2) yielded the product as off white crystals (44%).

Method B. Column chromatography (CH_2Cl_2) yielded the product as off white crystals (46%): melting range 99−103 °C; IR (KBr) 3413, 2952, 1734, 1553 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.99−1.17 (m, 3H), 3.35−3.80 (m, 4H), 3.82−3.97 (m, 4H), 4.18−5.39 (m, 4H), 6.68−6.95 (m, 2H), 7.03−7.25 (m, 5H), 7.27−7.65 (m, 6H), 7.91−8.19 (m, 1H); MS m/z (%) 511 (7) [$M^{+\bullet}$], 596 (1), 450 (2), 323 (42), 277 (100), 188 (41). Anal. Calcd for $C_{30}H_{29}N_3O_5$ (511.58): C, 70.44; H, 5.71; N, 8.21. Found: C, 70.59; H, 5.85; N, 7.95.

Methyl 3-(1-Ethyl-5-methoxy-2-(4-methoxyphenyl)-1*H*-3-indolyl)-2-(1*H*-3-indolyl)-4-nitrobutanoate (7k). Method B. Column chromatography (CH_2Cl_2) yielded the product as off white crystals (60%): melting range 100−104 °C; IR (KBr) 3409, 2952, 1737, 1551 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.99−1.16 (m, 3H), 3.34−3.76 (m, 3H), 3.87−3.95 (s, 8H), 4.21−5.39 (m, 4H), 6.75−6.88 (m, 1H), 6.91 (m, 1H), 7.11−7.37 (m, 4H), 7.14−7.17 (m, 1H), 7.17−7.25 (m, 2H), 7.30−7.55 (m, 3H), 7.91−8.20 (m, 1H); MS m/z (%) 541 (4) [$M^{+\bullet}$], 526 (2), 480 (1), 353 (24), 307 (100), 188 (42). Anal. Calcd for $C_{31}H_{31}N_3O_6$ (541.60): C, 68.75; H, 5.77; N, 7.76. Found: C, 68.98; H, 5.99; N, 7.49.

Methyl 2-(1*H*-3-Indolyl)-4-nitro-3-((2*S*)-*N*-*tert*-butyloxycarbonylpyrrolidin-2-yl)butanoate (7l). Method B. Column chromatography (CH_2Cl_2/ethyl acetate 9.5:0.5) yielded the product as two diastereomers:

Diastereomer A: colorless foam (27%); mp 79−82 °C; $[\alpha]_D^{20} = -55.4°$ (c = 1.02, MeOH); IR (KBr) 3401, 2977, 1734, 1686, 1553 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35−1.63 (m, 9H), 1.66−2.19 (m, 4H), 2.89−3.58 (m, 3H), 3.65, 3.74 (2s, 3H), 3.92−4.17 (m, 1H), 4.18−4.84 (m, 2H), 4.90−5.14 (m, 1H), 7.05−7.43 (m, 4H), 7.49−7.67 (m, 1H), 8.19, 8.58 (2 br s, 1H); MS m/z 432 [M + H]$^{+\bullet}$, 863 [2M + H]$^{+\bullet}$. Anal. Calcd for $C_{22}H_{29}N_3O_6$ (431.49): C, 61.24; H, 6.77; N, 9.74. Found: C, 60.85; H, 6.88; N, 9.55.

Diastereomer B: off white foam (26%); mp 121−123 °C; IR (KBr) 3411, 2977, 1735, 1679, 1553 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.34−1.61 (m, 9H), 1.79−2.11 (m, 4H), 2.92−3.59 (m, 3H), 3.63−3.74 (m, 3H), 3.92−5.12 (m, 4H), 7.12−7.25 (m, 2H), 7.27−7.30 (m, 1H), 7.35−7.41 (m, 1H), 7.61−7.70 (m, 1H), 8.28 (br s, 1H); MS m/z 432 [M + H]$^{+\bullet}$, 863 [2M + H]$^{+\bullet}$. Anal. Calcd for $C_{22}H_{29}N_3O_6$ (431.49): C, 61.24; H, 6.77; N, 9.74. Found: C, 60.81; H, 6.79; N, 9.53.

General Procedure for the Reduction of Nitrobutanoates and Subsequent Lactamization. A solution of the nitrobutanoates **7a**−**k** (0.23 mmol) in dry diethyl ether (1 mL) and dry ethanol (1 mL) was hydrogenated over *Raney*-Ni (0.5 g) with 12 bar of H_2. After 48 h the autoclave was flushed with nitrogen, the reaction mixture was filtered through Celite, and the Celite pad was washed with warm ethanol. The solvent was evaporated under reduced pressure, the residue was dissolved in toluene (5 mL), NaH (10 mg, 80% suspension in mineral oil) was added, and the mixture was refluxed for 2 days. Toluene was removed in vacuo and the residue purified by column chromatography.

3,4-Diphenyl-2-pyrrolidinone (8a). Recrystallization from diethyl ether yielded the product as colorless crystals (80%): mp 170−172 °C; IR (KBr) 3212, 2909, 1694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.85−3.40 (m, 4H), 7.68−7.05 (m, 11H); MS m/z 237 (87) [$M^{+\bullet}$], 194 (11), 180 (100). Anal. Calcd for $C_{16}H_{15}NO$ (237.30): C, 80.98; H, 6.37; N, 5.95. Found: C, 79.30; H, 6.35; N, 5.88.

3-(3-1*H*-Indolyl)-4-phenyl-2-pyrrolidinone (8b). Recrystallization from CH_2Cl_2/hexane yielded the product as colorless crystals (18%): mp 199−212 °C; IR (KBr) 3255, 2884−3060, 1667 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.32−4.04 (m, 4H), 6.61−7.46 (m, 10H), 7.78−7.97 (m, 2H); MS m/z 276 (100) [$M^{+\bullet}$], 232 (6), 218 (20), 157 (55), 130 (46). Anal. Calcd for $C_{18}H_{16}N_2O$ (276.34): C, 78.24; H, 5.84; N, 10.14. Found: C, 77.98; H, 5.79; N, 10.23.

3-(3-1*H*-Indolyl)-4-(3-pyridyl)-2-pyrrolidinone (8c). Column chromatography (ethyl acetate/MeOH 5:2) yielded the product as colorless crystals (34%): melting range 138−164 °C (mixture of diastereomers); IR (KBr) 3247, 2877−3058, 1690 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.03−3.78 (m, 4H), 6.60−7.21 (m, 6H), 7.52−7.77 (m, 2H), 8.12−8.28 (m, 2H), 10.63 (br s, 1H); MS m/z 277 (100) [$M^{+\bullet}$], 233 (11), 219 (27), 157 (62), 130 (69). Anal. Calcd for $C_{17}H_{15}N_3O$ (277.33): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.29; H, 5.32; N, 14.84.

4-(3-1*H*-Indolyl)-3-(3-pyridyl)-2-pyrrolidinone (8d). Recrystallization from acetone yielded the product as colorless crystals (77%): mp 200−205 °C; IR (KBr) 3330, 3238−2898, 1692 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) δ 3.56−4.02 (m, 4H), 7.83−7.42 (m, 6H), 7.63−7.76 (m, 1H), 8.32−8.47 (m, 2H); MS m/z 277 (100) [$M^{+\bullet}$], 233 (24). Anal. Calcd for $C_{17}H_{15}N_3O$ (277.33): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.97; H, 5.47; N, 14.91.

3,4-Bis-(3-1*H*-indolyl)-2-pyrrolidinone (8e). Diastereomer A. According to the general procedure for the reduction of nitrobutanoates and subsequent lactamization, the crude product was obtained from **7e** (diastereomer A). Column chromatography (CH_2Cl_2/ethyl acetate 1:1) yielded the product

as colorless crystals (87%): mp 233−237 °C (dec); IR (KBr) 3270, 1685, 1460 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.30−3.40 (m, 1H), 3.66−3.72 (m, 0.5H), 3.77−3.85 (m, 0.5H), 4.00−4.09 (m, 1H), 4.15−4.28 (m, 1H), 6.70−7.58 (m, 10H), 7.91 (s, 0.5H), 8.00 (s, 0.5H), 10.52 (s, 0.5H), 10.64 (s, 0.5H), 10.83 (s, 0.5H), 10.86 (s, 0.5H); MS *m*/*z* 315 (62) [$M^{+\bullet}$], 258 (11), 158 (100), 157 (65).

Diastereomer B. According to the general procedure for the reduction of nitrobutanoates and subsequent lactamization the crude product was obtained from **7e** (diastereomer B). Column chromatography (CH_2Cl_2/ethyl acetate/methanol 4:4:1) yielded the product as colorless crystals (8%): mp 169−173 °C; IR (KBr) 3419, 2876, 1707, 1460 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.40−4.10 (m, 4H), 6.85−7.50 (m, 10H), 10.78 (s, 1H), 10.82 (s, 1H). EI-MS *m*/*z* (%) 315 (83) [$M^{+\bullet}$], 257 (16), 158 (100), 157 (59), 130 (49). Anal. Calcd for $C_{20}H_{17}N_3O$ (315.37): C, 76.17; H, 5.43; N, 13.32. Found: C, 75.95; H, 5.54; N, 13.06.

3-(2-1*H*-Indolyl)-3-(5-methoxy-1*H*-indol-3-yl)-2-pyrrolidinone (8f).

Diastereomer A (Derived from 7f, Diastereomer A). Column chromatography (CH_2Cl_2/ethyl acetate/methanol 4:4:1) yielded the product as pale brown crystals (56%): mp 226−229 °C (methanol/hexane); IR (KBr) 3265, 1680, 1460 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.37−4.07 (m, 4H), 3.48 (s, 3H), 6.80−7.34 (m, 9H), 7.92 (s, 1H), 10.69 (d, J = 2.0 Hz, 1H), 10.82 (d, J = 1.5 Hz, 1H); MS *m*/*z* 345 (98) [$M^{+\bullet}$], 188 (100), 157 (27). Anal. Calcd for $C_{21}H_{19}N_3O_2$ (345.40): C, 73.03; H, 5.54; N, 12.17. Found: C, 73.39; H, 5.21; N, 11.90.

Diastereomer B (Derived from 7f, Diastereomer B). Column chromatography (CH_2Cl_2/ethyl acetate/methanol 4:4:1) yielded the product as colorless crystals (12%): mp 163−165 °C (methanol/hexane); IR (KBr), 3270, 1685, 1465 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.63 (s, 3H), 3.66−4.22 (m, 4H), 6.53−7.54 (m, 9H), 7.99 (s, 1H), 10.36 (d, J = 1.6 Hz, 1H), 10.82 (d, J = 1.3 Hz, 1H); MS *m*/*z* 345 (86) [$M^{+\bullet}$], 188 (100), 157 (30). Anal. Calcd for $C_{21}H_{19}N_3O_2$ (345.40): C, 73.03; H, 5.54; N, 12.17. Found: C, 73.25; H, 5.33; N, 12.01.

3-(2-1*H*-Indolyl)-4-(2-phenyl-1*H*-indol-3-yl)-2-pyrrolidinone (8h). Recrystallization from methanol yielded the product as colorless crystals (93%): mp 200−203 °C (dec); IR (KBr) 3251−3394, 2875−3054, 1690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.53 (m, 1H), 3.81 (m, 1H), 4.29−4.37 (m, 2H), 6.97−7.36 (m, 12H), 7.72 (m, 1H), 7.72 (s, 1H), 11.00 (s, 1H), 11.45 (s, 1H); MS *m*/*z* 391 (42) [$M^{+\bullet}$], 333 (8), 234 (92), 193 (100). Anal. Calcd for $C_{26}H_{21}N_3O$ (391.47): C, 79.77; H, 5.41; N, 10.73. Found: C, 79.74; H, 5.81; N, 10.72.

4-(1-Ethyl-2-(4-methoxyphenyl)-1*H*-3-indolyl)-3-(1*H*-3-indolyl)-2-pyrrolidinone (8i). Column chromatography (ethyl acetate) yielded the product as a colorless powder (23%): melting range 220−225 °C (ethyl acetate, mixture of diastereomers); IR (KBr) 3404, 3276, 2973, 1692 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 0.92−1.08 (m, 3H), 3.54−3.60 (m, 1H), 3.65−4.17 (m, 7H), 4.19−4.33 (m, 1H), 6.70−7.34 (m, 10H), 7.40−7.55 (m, 1H), 7.71−7.94 (m, 2H), 10.67−10.87 (m, 1H), lactam-NH not observed; MS *m*/*z* 449 (100) [$M^{+\bullet}$], 419 (1), 292 (72), 264 (35), 157 (20). Anal. Calcd for $C_{29}H_{27}N_3O_2 \times 1$ ethyl acetate (493.61): C, 75.43; H, 6.33; N, 8.51. Found: C, 75.21; H, 6.04; N, 8.97.

4-(1-Ethyl-5-methoxy-2-phenyl-1*H*-3-indolyl)-3-(1*H*-3-indolyl)-2-pyrrolidinone (8j). Column chromatography (ethyl acetate) yielded the product as a colorless powder (32%): mp 273−275 °C (ethyl acetate); IR (KBr) 3413, 3226, 2975, 1677 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 0.92−1.05 (m, 3H), 3.52−3.58 (m, 1H), 3.60−3.95 (m, 7H), 4.16−4.35 (m, 1H), 6.70−6.99 (m, 4H), 7.01−7.07 (m, 1H), 7.10−7.15 (m, 1H), 7.20−7.28 (m, 1H), 7.29−7.52 (m, 5H), 7.76−7.85 (m, 1H), 10.73−10.87 (m, 1H), lactam-NH not observed; MS *m*/*z* 449 (100) [$M^{+\bullet}$], 419 (1), 292 (54), 264 (23), 157 (4). Anal. Calcd for $C_{29}H_{27}N_3O_2 \times 1$ ethyl acetate (537.66): C, 73.72; H, 6.56; N, 7.81. Found: C, 73.82; H, 6.81; N, 7.80.

4-(1-Ethyl-5-methoxy-2-(4-methoxyphenyl)-1*H*-3-indolyl)-3-(1*H*-3-indolyl)-2-pyrrolidinone (8k). Column chromatography (ethyl acetate) yielded the product as a colorless powder (38%): mp 261 °C (dec) (ethyl acetate); IR (KBr) 3218, 2935, 1694 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 0.93−1.06 (m, 3H), 3.59−3.84 (m, 6H), 3.86−3.98 (m, 4H), 4.03−4.11 (m, 1H), 4.15−4.33 (m, 1H), 6.67−6.63 (m, 1H), 6.75−7.08 (m, 6H), 7.08−7.32 (m, 4H), 7.37−7.84 (m, 1H), 10.76−10.91 (m, 1H), lactam-NH not observed; MS *m*/*z* 479 (100) [$M^{+\bullet}$], 449 (4), 322 (81), 294 (35), 157 (5). Anal. Calcd for $C_{30}H_{29}N_3O_3$ (479.58): C, 75.13; H, 6.09; N, 8.76. Found: C, 74.86; H, 5.94; N, 8.85.

3-(1*H*-3-Indolyl)-4-((2*S*)-*N*-tert.-butyloxycarbonylpyrrolidin-2-yl)-2-pyrrolidinone (8l). Diastereomer A. Column chromatography (CH_2Cl_2/methanol 9.5:0.5) yielded the product as colorless crystals (41%): mp 121−123 °C; $[\alpha]_D^{20}$ = −5.8° (*c* = 0.99, MeOH); IR (KBr) 3284, 2975, 1692 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2, 253 K) δ 1.31 (s, 3H), 1.41 (s, 6H), 1.64−1.98 (m, 4H), 3.12−3.33 (m, 3H), 3.39 (m, 2H), 3.79 (d, J = 8.3 Hz, 1H), 3.87 (dd, J = 10.1, 10.1 Hz, 1H), 6.65 (m, 1H), 6.85−6.95 (m, 1H), 7.04−7.18 (m, 2H), 7.32−7.39 (m, 1H), 7.55−7.59 (m, 1H), 9.31, 9.46 (2s, 1H); FAB-MS *m*/*z* 370 [M + H]$^+$. Anal. Calcd for $C_{21}H_{27}N_3O_3$ (369.47): C, 68.27; H, 7.37; N, 11.37. Found: C, 67.95; H, 7.29; N, 11.47.

Diastereomer B. Column chromatography (CH_2Cl_2/methanol 9.5:0.5) yielded the product as colorless crystals (44%): mp 149−151 °C; IR (KBr) 3290, 2975, 1690 cm^{-1}; $[\alpha]_D^{20}$ = −105.1° (*c* = 0.77, MeOH); ^1H NMR (400 MHz, $C_2D_2Cl_4$, 323 K) δ 1.36 (s, 9H), 1.65−1.90 (m, 4H), 2.99 (dddd, J = 6.9, 7.2, 8.0, 8.1 Hz, 1H), 3.11−3.19 (m, 1H), 3.40 (dd, J = 6.9, 10.0 Hz, 1H), 3.43−3.47 (m, 1H), 3.50 (dd, J = 8.1, 10.0 Hz, 1H), 3.64 (d, J = 8.0 Hz, 1H), 4.10 (dd, J = 2.7, 7.2 Hz, 1H), 5.55 (br s, 1H), 7.05 (s, 1H), 7.07 (ddd, J = 1.0, 7.0, 8.0 Hz, 1H), 7.15 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 7.31 (dd, J = 0.9, 8.1 Hz, 1H), 7.55 (dd, J = 1.0, 7.9 Hz, 1H), 8.00 (br s, 1H); FAB-MS *m*/*z* 370 [M + H]$^+$. Anal. Calcd for $C_{21}H_{27}N_3O_3$ (369.47): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.11; H, 7.38; N, 11.55.

(−)-*S*-2-Methyl-1-butyl 2,3-Bis(3-1*H*-indolyl)-4-nitrobutanoate (9). Method A. The mixture of diastereomer A of **7e** (0.1 g, 0.26 mmol) and titanium tetrakis((−)-*S*-2-methyl-1-butoxide) (0.2 mL, 0.59 mmol) in (−)-*S*-2-methyl-1-butanol (2 mL) was refluxed for 20 h (TLC control). The mixture was cooled, and excess alcohol was removed under reduced pressure. The residue was dissolved in diethyl ether, and 2 drops of 1 N HCl was added. The etheral phase was washed with water, dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography ((1) hexane/ethyl acetate 1:10, (2) hexane/ethyl acetate 1:3), affording the product as colorless crystals (62 mg, 0.14 mmol, 55%): mp 79 °C (diisopropyl ether); IR (KBr) 3420, 3120−2930, 1719, 1551 cm^{-1}; $[\alpha]_D^{20}$ = −15.8° (*c* = 0.01, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.52 (t, 3H, J = 7.3 Hz), 0.63 (d, 3H, J = 6.6 Hz), 1.00 (m, 2H), 1.32 (m, 1H), 3.56 (m, 2H), 4.56−4.82 (m, 4H), 7.10−7.90 (m, 10H), 8.10 (s, 1H), 8.26 (s, 1H); MS *m*/*z* 433 (9) [$M^{+\bullet}$], 244 (100), 189 (2), 174 (13), 143 (74). Anal. Calcd for $C_{25}H_{27}N_3O_4$ (433.51): C, 69.27; H, 6.28; N, 9.69. Found: C, 69.19; H, 6.23; N, 9.65.

Method B. According to the general procedure for the Michael addition of acetic acid derivatives with nitroethenyl compounds, **10b** and **5c** were reacted to yield compound **9** as colorless crystals (61%).

(−)-*S*-2-Methyl-1-butyl 3-1*H*-Indolyl Acetate (10b). A mixture of (−)-*S*-2-methyl-1-butanol (5.00 mL, 80.0 mmol), (3-1*H*-indolyl)acetic acid (**10a**) (14.0 g, 80.0 mmol), and concentrated H_2SO_4 (5 drops) in toluene (150 mL) was refluxed for 1.5 h, cooled, poured into ice water, and extracted with diethyl ether. The etheral layer was washed with saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2), affording the product as a colorless oil (16 g, 81%): IR (neat) 3415, 3123−2934, 1740, 1458 cm^{-1}; $[\alpha]_D^{20}$ = +12.2° (*c* = 0.01, $CHCl_3$); ^1H NMR (250 MHz, DMSO-d_6) δ 0.81−0.84 (m, 6H), 1.30 (m, 2H), 1.62 (m, 1H), 3.74 (s, 2H), 3.83 (m, 2H), 6.94−7.50 (m, 5H), 10.92 (s, 1H). Anal. Calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.34; H, 7.81; N, 5.71. Found: C, 73.11; H, 7.71; N, 5.59.

6,7,12,13-Tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5(6*H*)-one (2). (Staurosporin Aglycon (K-252c)). 8e (mixture of diastereomers A and B) (0.20 g, 0.63 mmol) was

suspended in dry benzene (105 mL) and DDQ (0.30 g, 1.33 mmol), and *p*-toluenesulfonic acid monohydrate (15.0 mg, 0.08 mmol)) was added. The mixture was stirred for 24 h at ambient temperature and then the solvent was evaporated below 25 °C. The residue was dissolved in ethyl acetate (150 mL), washed with saturated $NaHSO_3$ solution (2 × 50 mL) and brine (2 × 50 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (CH_2Cl_2/ethyl acetate/methanol 20:3:0.5) affording the product as pale yellow crystals (0.12 g, 0.38 mmol, 60%): mp 310 °C (ethanol/diethyl ether, dec; cf.[11] 313 °C); IR (KBr) 3440, 3315, 1645, 1560, 1455 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.97 (s, 2H), 7.21−7.25 (m, 1H), 7.29−7.33 (m, 1H), 7.41−7.45 (m, 1H), 7.46−0.50 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 8.50 (s, 1H), 9.26 (d, J = 7.9 Hz, 1H), 11.33 (s, 1H), 11.50 (s, 1H); MS *m*/*z* 311 (83) [$M^{+\bullet}$], 282 (100), 255 (58), 227 (22), 201 (13).

3,4-Bis(3-1*H*-indolyl)-2,5-dihydro-1*H*-2-pyrrolone (11e). Isolated as a byproduct from the column chromatography of **2** as colorless crystals (8 mg, 0.03 mmol, 2%): mp 101 °C (diethyl ether, dec); IR (KBr) 3420, 1655, 1540 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 4.54 (s, 2H), 6.71−7.47 (m, 10H), 8.19 (s, 1H), 11.24 (d, J = 1.5 Hz, 1H), 11.36 (d, J = 1.3 Hz, 1H); MS *m*/*z* 313 (100) [$M^{+\bullet}$], 130 (44).

6,7,12,13-Tetrahydro-9-methoxy-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5(6*H*)-one (9f). Prepared analogous to **2** as colorless crystals from the following substrates: **8f** (diastereomer A) 32 mg, 0.09 mmol, 15%; **8f** (diastereomer B) 26 mg, 0.08 mmol, 12%. Data: mp >350 °C (methanol); IR (KBr) 3435, 3320, 1645, 1555 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.91 (s, 3H), 4.98 (s, 2H), 7.09−9.29 (m, 7H), 8.48 (s, 1H), 11.28 (s, 1H), 11.40 (s, 1H); MS *m*/*z* 341 (100) [$M^{+\bullet}$]. Anal. Calcd for $C_{21}H_{15}N_3O_2$ (341.37): C, 73.89; H, 4.43; N, 12.31. Found: C, 74.24; H, 4.68; N, 11.95.

Supporting Information Available: X-ray structural data for compound **7e**, including tables of atomic coordinates, bond lengths, and bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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