Synthesis of Homofascaplysin C and Indolo[2,3-*a*]carbazole from Ditryptophans

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The 2,2′-biindole core of ditryptophan cross-links is prominent in the fascaplysins and the indolocarbazole glycoside natural products. *N*-Acyliminium ions derived from the *C*-terminus of ditryptophan peptides cyclize in one of two modes: *N*-alkylation or *C*-alkylation. The surrounding peptide offers some control over the course of the cyclization and allows the preparation of homofascaplysin C or indolo[2,3-*a*]carbazole. These targets are modest, but they are generated through carbocyclic intermediates rich in stereochemistry, and decidedly non-peptide in character.

I. Introduction

The 2,2′-biindole core of ditryptophan cross-links appears in a variety of natural products that include homofascaplysin C, iheyamine B, and tjipanazole E (Figure 1).[1] This enticing relationship suggests that tryptophan-rich peptides might serve as starting materials for synthesis of these natural products. Although peptides can be expressed in any sequence using recombinant DNA techniques, they have found limited application to natural products synthesis. We have charted a path from ditryptophan-containing peptides to homofascaplysin C and indolo[2,3-*a*]carbazole. This path involves the regioselective cyclization of *N*-acyliminium ions onto the biindole nucleus, and it exemplifies the subtle effects of stereochemistry on the reactivity of 10-membered rings.

Many biindole natural products possess diverse and important biological activities. Indolo[2,3-*a*] carbazole is the heterocyclic core of several natural products including the tjipanazoles (*T. tjipanensis*), rebeccamycin (*S. aerocolonigenes*), and staurosporine (*S. staurosporeus*).[2] Rebeccamycin is an inhibitor of DNA topoisomerase, staurosporine is an inhibitor of protein kinases, and indolocarbazole is an activator of the aromatic hydrocarbon receptor (an orphan nuclear receptor).[3] The striking homology of the fascaplysins with the indolocarbazoles suggests that these separate classes of natural products may arise from common patterns of reactivity. Although the indolocarbazole rebeccamycin is known to be derived from tryptophan, glucose, and *S*-adenosylmethionine, the details of the biosynthesis have not been established.[4] The fascaplysins are less diverse than the indolocarbazole glycosides. Fascaplysin (*F. reticulata*) shows activity against the L-210 mouse leukemia system and is an inhibitor of reverse transcriptase; homofascaplysin C[5,6] has not been tested.[7,8] The iheyamines, recently isolated from the ascidian *Polycitorella* sp., are active against a number of tumor cell lines.[9]

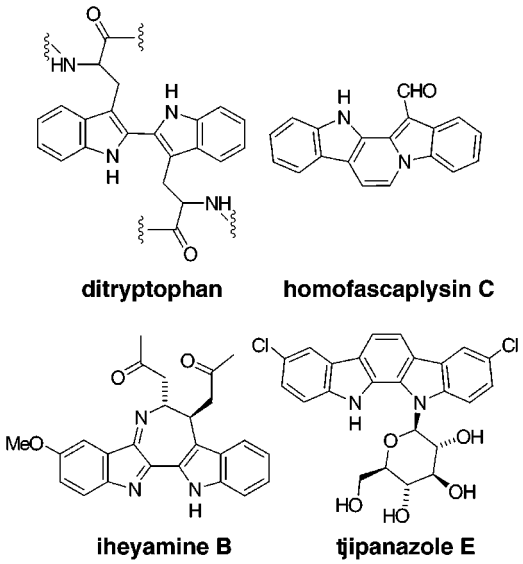

Figure 1. Biindoles in ditryptophan cross-links and natural products.

Indole is an efficient partner for Mannich alkylation, yet the *N*-acyliminium ion derived from decarboxylation of tryptophan is not suited to react with its own side chain because this would lead to a strained three- or four-membered ring. In contrast, a ditryptophan cross-link is well suited to react with an N^{α}-acyliminium ion, but *N*-alkylation of the indole competes with *C*-alkylation of the indole (Scheme 1). The stakes in this competition are target control: *C*-alkylation will lead to the indolocarbazoles, whereas *N*-alkylation will lead to the fascaplysins. As shown in Scheme 1, *C*-alkylation should be favored by a peptide connection between the tryptophan side chains. In fact, *C*-alkylation of the ditryptophan derived from the dipeptide Trp-Trp should benefit from transannular interactions. Conversely, *N*-alkylation might be favored by the steric demands of independent peptide chains.

(1) Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron* **1995**, *51*, 5631.
(2) Gribble, G. W.; Berthel, S. J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers: Dordrecht, 1993; Vol. 12.
(3) Gillner, M.; Bergman, J.; Cambillau, C.; Alexandersson, M.; Fernstrom, B.; Gustafsson, J. A. *Mol. Pharm.* **1993**, *44*, 336.
(4) Pierce, C. J.; Doyle, T. W.; Forenza, S.; Lam, K. S.; Schroeder, D. R. *J. Nat. Prod.* **1988**, *51*, 937.
(5) Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636.
(6) Dubovitskii, S. V. *Tetrahedron Lett.* **1996**, *37*, 5207.
(7) Roll, D. M.; Ireland, C. M.; Lu, H. S. M.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 3276.
(8) Jimenez, C.; Quinoa, E.; Adamczeski, M.; Hunter, L. M.; Crews, P. *J. Org. Chem.* **1991**, *56*, 3403.
(9) Sasaki, T.; Ohtani, I. I.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1999**, *40*, 303.

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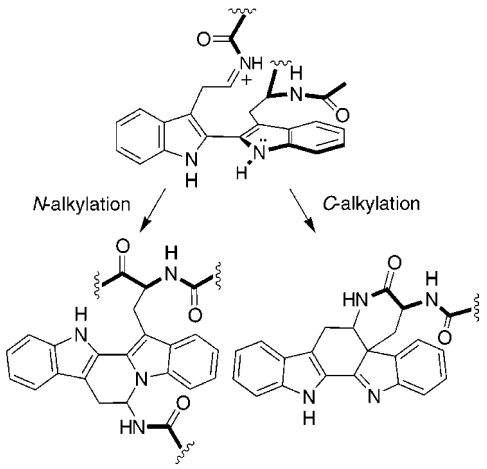
Scheme 1



II. Results and Discussion

Interchain vs Intrachain Ditryptophan. There are two basic topologies for ditryptophan cross-links: interchain and intrachain (Figure 2).[10−12] The reactivity of these two ditryptophans should be distinguished by the conformational effects of the ring. To take advantage of these conformational effects, we set out to first explore the generation of *N*-acyliminium ions from the tryptophan amino acid moiety. Next, we turned to explore the cyclization of *N*-acyliminium ions on an interchain ditryptophan. Finally, we explored the analogous reactions of intrachain ditryptophans.

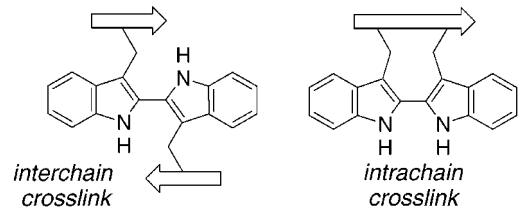
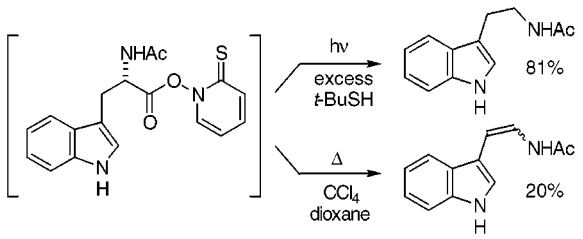


Figure 2. Two types of ditryptophan starting materials.

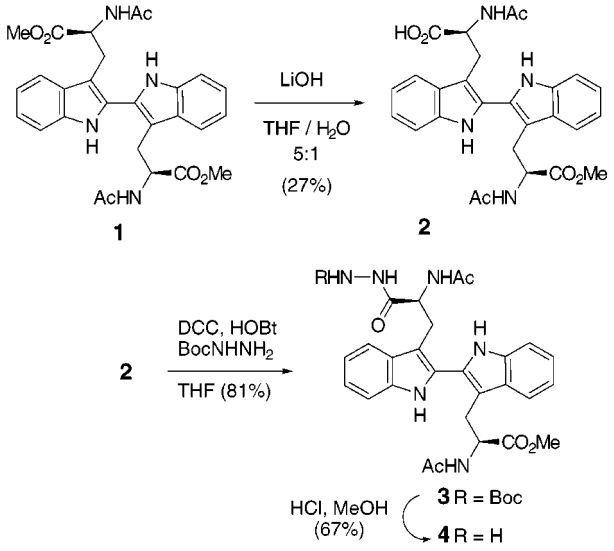
Interchain Ditryptophan Cross-Link. A peptide dimer linked by a ditryptophan has two C-termini. A method was needed for deprotection of just one of these termini. We initially sought to generate the reactive acyliminium ion by a Hunsdiecker approach using radical decarboxylation and oxidation. Despite ample precedent for this transformation on nonnucleophilic amino acids, we were guarded about the prospects for application to tryptophan.[13] Barton−Crich decarboxylation using a *tert*-butylthiol as a hydrogen atom trap gave us confidence that oxidative methods might generate the corresponding *N*-acyl iminium ion in high yield (Scheme 2).[14] Attempts to oxidize the radical and isolate the *N*-acylenamine generated discouraging mixtures. Later attempts to apply these conditions (CCl_4 or cupric ion traps) to biindole analogues were even less rewarding.[15,16]

Scheme 2



Curtius rearrangement offered a more measured approach to the desired *N*-acyliminium intermediate because a stable *N*,*N*-aminal could be isolated, characterized, and subsequently solvolyzed under controlled conditions. We began with ditryptophan **1**, readily obtained from *N*-acetyl tryptophan methyl ester by Mannich dimerization and DDQ oxidation.[11] Two similar strategies were explored: saponification (Scheme 3) and hydrazinolysis (Scheme 4). Surprisingly, even a statistical yield of 50% was difficult to obtain. The low solubility of the diester **1** led to oversaponification. For example, at low conversion, saponification of ditryptophan **1** with 1.5 equiv of lithium hydroxide in 5:1 THF/H_2O afforded monoacid **2**, diacid, and recovered ditryptophan **1** in 27%, 30%, and 23% yield, respectively. At higher conversions, the product distribution was dominated by the unwanted diacid.

Scheme 3

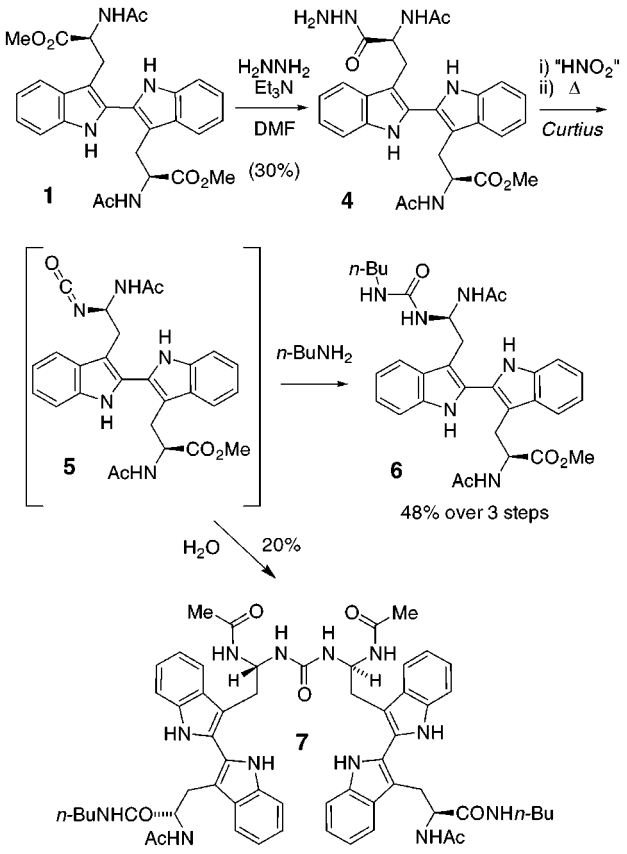


Direct conversion of the monoacid **2** to the isocyanate using diphenylphosphoryl azide gave a complex mixture of products, probably as a result of reaction of the biindole with the reactive phosphoryl azide.[17] As an alternative approach, we sought to form the acyl azide from the corresponding acyl hydrazide. Monoacid **2** was converted to Boc-protected acyl hydrazide **3** in 81% yield using DCC/HOBt. Boc deprotection with methanolic HCl afforded acyl hydrazide **4** in 67% yield.

As an alternative to selective saponification we attempted to directly convert diester **1** into the monohydrazide **4** with 1.5 equiv of hydrazine in DMF. Triethylamine (1.5 equiv) was included to facilitate proton-

(10) Omori, Y.; Matsuda, Y.; Aimoto, S.; Shimonishi, Y.; Yamamoto, M. *Chem. Lett.* **1976**, 805.
(11) Stachel, S. J.; Habeeb, R. L.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 1225.
(12) Carter, D. S.; Van Vranken, D. L. *Tetrahedron Lett.* **1996**, *37*, 5629.
(13) Slates, H. L.; Taub, D.; Kuo, C. H.; Wendler, N. L. *J. Org. Chem.* **1964**, *29*, 1424.
(14) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(15) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979.
(16) Ogibin, Y. N.; Katzin, M. I.; Nikishin, G. I. *Synthesis* **1974**, 889.
(17) Kosugi, Y.; Hamaguchi, H.; Nagasaka, T.; Ozawa, N.; Ohki, S. *Heterocycles* **1980**, *14*, 1245.

Scheme 4

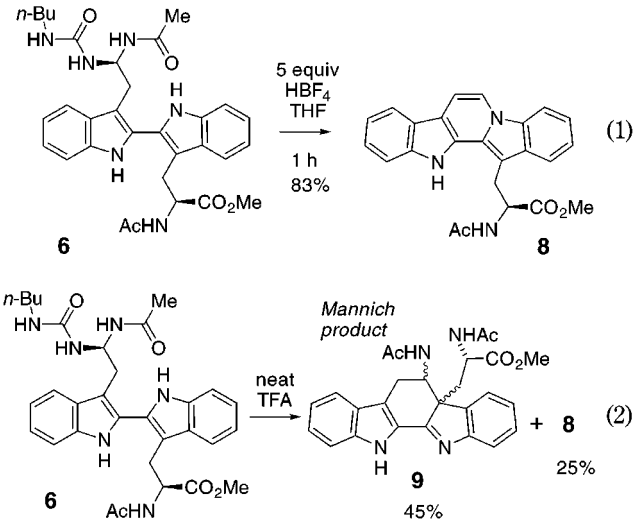


transfer steps in this reaction. On an 11 g scale, the hydrazinolysis afforded a mixture of monoacylhydrazide **4** and the corresponding bisacylhydrazide in 30% and 29% yield, respectively, with 35% recovered starting material. At lower conversion, the yield of monohydrazide **4** is similar (25%), but the ratio of the desired monohydrazide to the bis-hydrazide byproduct was greater than 4:1 (70% based on recovered starting material.)

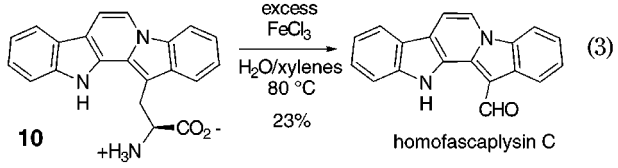
With a reliable route for preparing the monoacylhydrazide we turned our attention to the Curtius rearrangement. Two conditions were used to generate the acyl azide. When aqueous conditions were employed, problems were encountered in the subsequent Curtius rearrangement. The acyl azide product retains water strongly. At the elevated temperature required for rearrangement, residual water hydrolyzes the isocyanate **5** as fast as it forms. The resulting amine (an *N*-acyl aminal) then reacts further with isocyanate leading to the symmetrical dimer, which was transaminated with *n*-butylamine to give **7**. This interesting dimerization reaction is not specific to ditryptophan peptides and has previously been shown to occur in high yields.[18,19] Using more efficient conditions, acyl hydrazide **4** was converted to the acyl azide under biphasic conditions using a 1:1:1:25 mixture of 1 N $NaNO_2$, 1 N HCl, glacial acetic acid, and chloroform.[20] The crude acyl azide was extracted into cold chloroform, carefully dried over $MgSO_4$, filtered, and heated in the presence of powdered 4 Å molecular sieves for 1 h. Isocyanate **5** was then trapped with *n*-butylamine to give the desired urea **6**.

(18) Wieland, T.; Fritz, H. *Chem. Ber.* **1953**, *86*, 1186.
(19) Riniker, B.; Schwyzer, R. *Helv. Chim. Acta* **1964**, *47*, 2375.
(20) Kawasaki, K.; Maeda, M.; Watanabe, J.; Kaneto, H. *Chem. Pharm. Bull.* **1988**, *36*, 1766.

Even though the urea dimer **7** is a potential iminium ion precursor, the simpler *N*-butylurea **6** was chosen for study. Ionization in THF with anhydrous HBF_4 gave no *C*-alkylation product; instead, the *N*-alkylation product **8** was formed in 83% yield. Formation of **8** is interesting because it contains the indolo[1,2-*a*]carbazole ring system of the fascaplysins. In neat trifluoroacetic acid, both *N*-alkylation product **8** and *C*-alkylation products **9** (a mixture of diastereomers) are observed. None of the isolated products retained the *N*-butyl urea group, so it is likely that ionization of the protonated urea is preferred over ionization of the protonated acetamido group. Mannich cyclization to form **9** is reversible under strongly acidic conditions. Attempts to convert **9** into a fully aromatic indolo[2,3-*a*]carbazole with *p*-toluenesulfonic acid in THF led to formation of pyrido[1,2-*a*:3,4-*b*′]-diindole **8** in 81% yield.



Pentacycle **8** contains the complete core of the fascaplysins. To convert the alanyl moiety of **8** into the formyl moiety of homofascaplysin C, the derivative was hydrolyzed to the amino acid **10** under alkaline hydrolysis conditions. This reaction proceeds in a low yield (25%), but it was subsequently found that the corresponding carboxamide hydrolyses under acidic conditions to give **10** in 43% yield. Oxidative cleavage of the amino acid moiety with aqueous ferric chloride[21] gave homofascaplysin C in a single step. The yield for this one-step procedure is low, presumably as a result of overoxidation of the aromatic ring system, but the simplicity of oxidative cleavage offers the possibility that the fascaplysins are formed through similar processes, possibly via ditryptophan intermediates. Ultimately, we conclude that acyclic ditryptophans may be suited for the synthesis of fascaplysins but not of indolo[2,3-*a*]carbazoles.

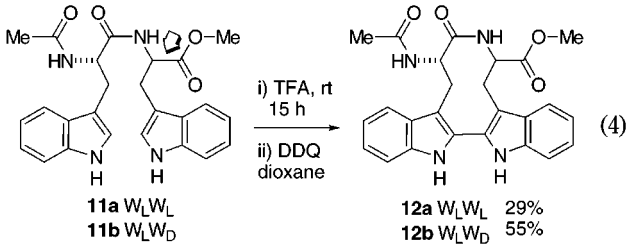


Intrachain Ditryptophan Cross-Link. We next turned to an iminium ion cyclization using an intrachain

(21) Rafelson, M. E.; Ehrensvärd, G.; Bashford, M.; Saluste, E.; Hadén, K. G. *J. Biol. Chem.* **1954**, *211*, 725.

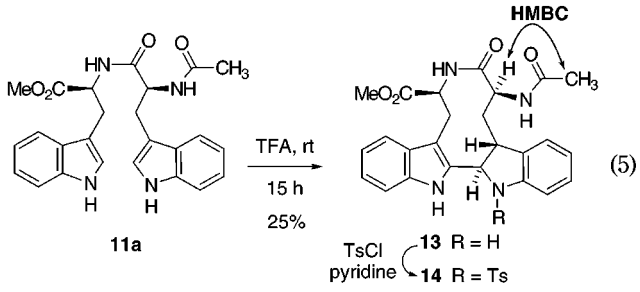
ditryptophan. The primary advantage to this kind of ditryptophan precursor is that it has only one *C*-terminus, so there is no need for desymmetrization. The secondary advantage is that the peptide chain may influence the reactivity of the iminium intermediate. A peptide of the general structure *peptide*-Trp*-*peptide*-Trp*-CO_2H [Trp* = ditryptophan] will allow for decarboxylation to give a reactive iminium ion. We chose to start with a simple dipeptide (AcNH-Trp*-Trp*-CO_2H) containing a ditryptophan cross-link.

Evidence for the controlling influence of the peptide backbone came during the Mannich cyclization of the dipeptides Ac-Trp-Trp-OMe (**11a** and **11b**) in trifluoroacetic acid as reported by Shimonishi. Mannich dimerization of tryptophan side chains is partially reversible in TFA over 24 h,[22] so the ratio of intermolecular to intramolecular cross-links is dependent upon factors such as substrate concentration and ring strain in the cyclic product. Mannich cross-linking of the tryptophan side chains of **11a** and oxidation of dipeptide gives the corresponding intrachain ditryptophan **12a** in about 30% yield.



(4)

Any peptide chain containing two tryptophans could conceivably cyclize to produce a mixture of eight different diastereomeric tryptophan dimers, all of which could convergently oxidize to ditryptophan **12a**. However, the majority of the cyclic product is a single diastereomer (**13**) that can be precipitated from ethyl acetate as an analytically pure compound (eq 5). The remaining products are

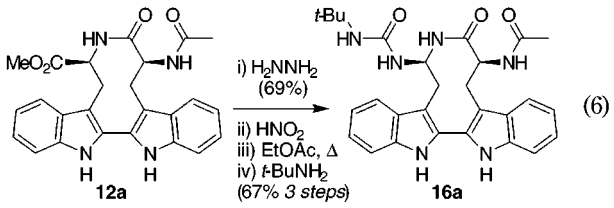


(5)

presumably oligomers rather than diastereomers, because oxidation of the mother liquor does not lead to formation of ditryptophan **12a**. The relative positions of the indole and indoline rings of **13** were unambiguously assigned by ^{1}H NMR analysis of the *N*-tosyl derivative **14**. The indoline spin system was shown to be connected to the acetamido methyl group by using HMBC. The small vicinal coupling (1.5 Hz) between the indoline protons of **14** is most consistent with the 2*R*,3*S* trans isomer (eq 5) with a trans amide in the 10-membered ring. On the basis of molecular mechanics (MM2*), other stereoisomers are expected to show vicinal couplings over 7 Hz.[23] This structure is different from the one originally proposed by Shimonishi, et al.,[24] because the indoline is on the *N*-terminus of the peptide rather than the *C*-terminus. The epimeric dipeptide **11b** also gives primarily one diastereomer upon Mannich cyclization, but the mixture of isomers was convergently oxidized without characterization.

Serendipity provided the impetus to investigate the influence of peptide stereochemistry. During a 50 mmol coupling of N^{α}-Boc-tryptophan with tryptophan methyl ester, the amino acid components precipitated out as a solid mass; addition of DCC to this mass led to kinetic resolution of the Boc-tryptophan, producing the epimeric dipeptide Boc-$_D$Trp-$_L$Trp-CO_2Me in over 60% yield. None of the desired dipeptide, Boc-$_L$Trp-$_L$Trp-CO_2Me, was formed in this reaction. The structure of the epimerized dipeptide was confirmed by synthesis of the enantiomer, Boc-$_L$Trp-$_D$Trp-CO_2Me, from Boc-L-tryptophan and D-tryptophan methyl ester. When the epimeric dipeptide **11b** was subjected to tryptophan cross-linking and oxidation, the cyclic ditryptophan **12b** was formed in 55% yield. Thus, a subtle change in peptide backbone nearly doubles the yield for ditryptophan cross-linking. The improved yield of cyclic vs oligomeric ditryptophan is probably connected with the propensity for alternating L/D peptide sequences to favor β turn structures.[25]

Both of the 10-membered ring cyclic ditryptophans (**12a** and **12b**) exhibit two conformations in d_6-DMSO. These conformations equilibrate with barriers around 16 kcal/mol. Whereas the two conformations of **12a** are nearly equally populated, one conformation of **12b** dominates over the other by a factor of 7:1.



(6)

The cyclic ditryptophans show a distinct advantage in the hydrazinolysis reaction because they possess only one ester group. In contrast to the acyclic ditryptophan **1** with two ester moieties, ditryptophans **12a** and **12b** were readily converted to their corresponding acyl hydrazides **15a** and **15b** without complications. These acyl hydrazides were then taken to their corresponding *N*,*N*-aminals, **16a** and **16b**, respectively, via the Curtius sequence shown in eq 6.

Neither of the *N*,*N*-aminal derivatives **16a** or **16b** undergo Mannich cyclizations using anhydrous HCl in dioxane. However, both **16a** and **16b** form cyclic products in trifluoroacetic acid, and the peptide backbone has a dramatic effect on the course of the reaction. As shown in Scheme 5, when aminal **16a** is ionized in TFA, the endocyclic amide bond ionizes in preference to the exocyclic urea, leading to pyridodiindole **17** as the major product and carbocycle **18** as the minor product. The diastereomeric *N*,*N*-aminal **16b** gives opposite results, favoring ionization of the exocyclic urea over the endocy-

(22) Gilbert, E. J.; Ziller, J. W.; Van Vranken, D. L. *Tetrahedron* **1997**, *53*, 16553.

(23) Macromodel v. 6.5.

(24) Hashizume, K.; Shimonishi, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3806.

(25) Yan, Y.; Tropsha, A.; Hermans, J.; Erickson, B. W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 7898.

clic amide bond. The hexacyclic product **18** is stable in neat TFA. This difference in reactivity might be attributable to transannular interactions between the nucleophilic indole of **16b** and the departing urea moiety.

It is suprising that **16a** and **16b** give the same products but in different ratios. To interpret the difference in reactivity it was necessary to unambiguously establish the structure of the hexacyclic product **18**; four diastereomers were possible. The connectivity of the carbon backbone of **18** was initially established using a combination of HMQC and HMBC. The Trp1 ^{1}H spin system was distinguished from the Trp2 ^{1}H spin system by the coupling between one of the H_β protons and the imine carbon. The presence of the transannular bond was confirmed by the presence of three-bond couplings between protons on *C*-terminal Trp2 fragment and carbons on the *N*-terminal Trp1 fragment (Figure 3). In theory, four diastereomeric configurations are possible, but the 1.5 Hz W-coupling between the Trp1 H_β and Trp2 H_α protons is only possible with diastereomers **18** and **19**. Ultimately, diastereomer **19** was excluded by the presence of a 11.7 Hz vicinal H_α-C-C-H_β coupling in the *N*-terminal Trp1. The large coupling constant is consistent with an equatorial acetamido group and inconsistent with an axial acetamido group that would lead to a small 4 Hz gauche coupling (MM2*).

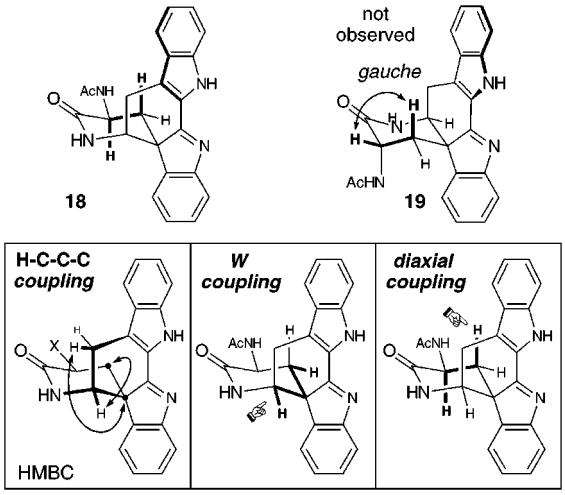
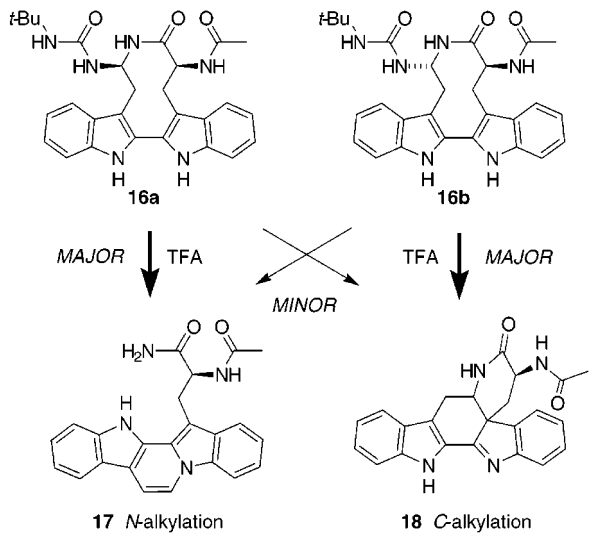


Figure 3. Diagnostic spectroscopic data for assignment of structure **18**.

Mannich substrates **16a** and **16b** cannot readily interconvert, but it is still useful to approximate the forces that contribute to their differential reactivity. A Monte Carlo search was carried out on **16a** and **16b** using the MM2* force field. Similar results were obtained with gas-phase and H_2O parameters. Comparison of the global minima (all conformations within 2 kcal/mol of the global minima) predicts that Mannich substrate **16a** should be less stable than Mannich substrate **16b**, primarily as a result of torsional strain and sterics. This increased strain may be responsible for the tendency of **16a** to open the 10-membered ring as opposed to ionizing the exocyclic urea. The contrasting tendency of **16b** to ionize the exocyclic urea could potentially be ascribed to transannular assistance. Unfortunately, the Monte Carlo results suggest that **16b** does not resemble the observed product **18**; instead, the lowest energy conformations of **16b** resemble the isomer **19** that was never observed (Figure 4). Conformations of **16b** that resemble the observed product **18** force the urea leaving group to point toward the transannular indole ring.

Scheme 5



substrate	**17**	**18**
16a	53%	12%
16b	10%	56%

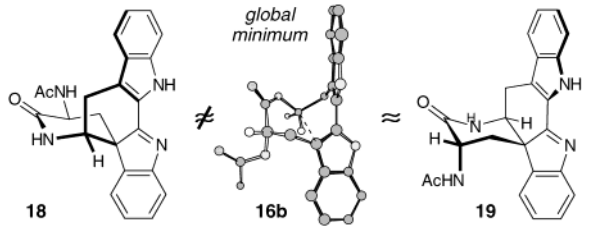


Figure 4. The lowest energy conformations of **16b** resemble **19** but not **18**.

Molecular mechanics (MM2*) predicts that the observed product **18** should be more stable than the isomer **19**. Either **19** is not formed or it isomerizes to the more stable product **18** through a retro-Mannich/Mannich mechanism under the conditions of the reaction. These two possibilities, kinetic and thermodynamic, cannot be distinguished because **19** is unavailable for an equilibration experiment.

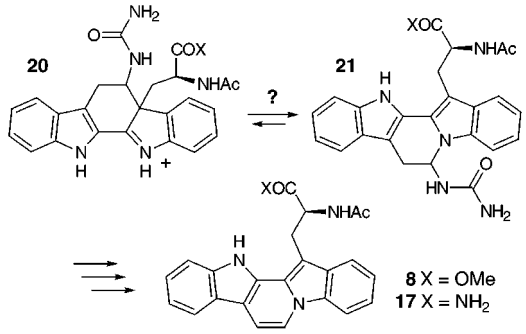
None of the ditryptophan Mannich substrates, cyclic or acyclic, led to Mannich product **20**, with a pendant urea group. It is possible that the potential product **20,** with the pendant urea, is less stable in TFA than the corresponding product **9** with a pendant amide and readily undergoes retro-Mannich cleavage and *N*-alkylation to form the fascaplysin skeleton (Scheme 6).

Mannich product **18** contains the pentacyclic core of the indolo[2,3-*a*]carbazoles. Unfortunately, removal of the vestigial peptide backbone proved to be difficult. Heating this compound in tetralin with catalytic *p*-toluenesulfonic acid readily gave the indolocarbazole **22** (Scheme 7).

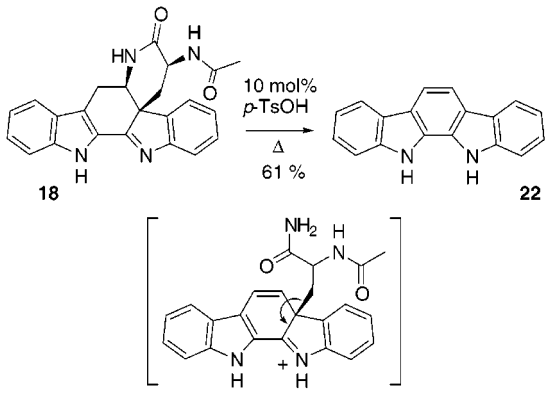
If the Mannich cyclization of dipeptides **12a** and **12b** were followed by a glycosylation reaction with glucose,[26–28]

(26) Suvorov, N. N.; Preobrazhenskaya, M. N. *Zh. Obsch. Khim.* **1961**, *31*, 2839.

Scheme 6



Scheme 7



this could provide a route to the indolocarbazole glycosides. Although the chemistry of tryptophan peptides shows promise, the route from peptide to indolocarbazole is not efficient enough to compete with de novo routes.

This work demonstrates that fascaplysins and indolocarbazoles can be produced from peptides via Mannich dimerization of tryptophan side chains. The targets are modest, but the chemical pathways are rich and informative. The formation of polycyclic aromatics from peptides may have broader implications. Many heterocyclic compounds, including indolo[2, 3-*a*]carbazole, are known to activate the orphan aromatic hydrocarbon receptor.[29,30] Presumed sources for other indolocarbazoles include vegetables and tryptophan photoproducts.[31] It is important to improve our understanding of peptide reactivity (especially with carbohydrates) both for synthetic applications and for its potential health relevance.

Experimental Procedures

General experimental procedures may be found in the Supporting Information. Ditryptophans **1** and **12a** were prepared by Mannich dimerization/oxidation according to the method of Stachel, et al.[11]

Acylhydrazide (4) from the *N*-Boc Hydrazide 3. Acetyl chloride (0.090 g, 1.15 mmol) was added dropwise to 5.0 mL of MeOH. After 10 min Boc-acylhydrazide **3** was added in portions. After 20 h the reaction mixture was concentrated in vacuo to yield 0.132 g of crude solid. The resulting solid was purifed via column chromatography (95:5 CH_2Cl_2/MeOH) to afford **4** (0.187 g, 65%) as a pale yellow solid.

Acylhydrazide (4) via Hydrazinolysis of Diester 1. To a solution of ditryptophan **1** (11.45 g, 22.08 mmol) in DMF was added triethylamine (3.25 g, 33.12 mmol) and hydrazine (1.06 g, 33.12 mmol). After 12 h the reaction mixture was concentrated in vacuo (25 mTorr, 60 °C) to yield 15.68 g crude solid. The resulting solid was purified via column chromatography (98:2 to 9:1 CH_2Cl_2/MeOH) to afford **1** (4.02 g, 35%) as a yellow solid, **4** (3.59 g, 30%) as a yellow solid, and dihydrazide (3.35 g, 29%) as a yellow solid. **Data for 4:** mp 178−180 °C; R_f = 0.48 (9:1 CH_2Cl_2/MeOH); IR (KBr) 3288, 3052, 2941, 1739, 1374, 1355, cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 11.05 (s, 1H), 9.23 (bs, 1H), 8.11 (d, J = 4.4 Hz, 1H), 8.09 (d, J = 3.9 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.16 (dd, J = 7.0, 0.8 Hz, 1H), 7.12 (dd, J = 7.8, 1.0 Hz, 1H), 7.06 (dd, J = 6.9, 0.9 Hz, 1H), 7.03 (dd, J = 6.9, 0.9 Hz, 1H), 4.70 (dd, J = 8.4, 8.3 Hz, 1H), 4.41 (dd, J = 7.3, 7.2 Hz, 1H), 4.12 (bs, 2H), 3.33 (s, 3H), 3.31 (s, 2H), 3.29 (d, J = 7.4 Hz, 1H), 3.27 (d, J = 7.7 Hz, 1H), 3.21 (dd, J = 14.2, 6.0 Hz, 1H), 1.75 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.3, 170.4, 169.3, 169.2, 136.4, 136.0, 128.2, 128.1, 127.9, 121.7(br), 119.2, 118.9, 118.8, 118.5, 111.4, 111.3, 109.3, 108.7, 53.0, 52.0, 51.6, 28.3, 26.9, 22.5, 22.2, not all peaks resolved; LRMS (FAB) m/z 518(84); HRMS (FAB) calcd for $C_{27}H_{30}N_6O_5$ 518.2277 $[M]^+$, found 518.2274. Anal. calcd for $C_{27}H_{30}N_6O_5 \cdot H_2O$: C, 60.43; H, 6.01; N, 15.66. Found: C, 60.78; H, 5.87; N, 15.69.

***n*-Butylurea (6).** A solution of 0.522 g (1.01 mmol) of acylhydrazide **4** in 25 mL of $CHCl_3$, 5.0 mL of 1 N HCl, and 5.0 mL of glacial AcOH was cooled to 0 °C via an ice−water bath. $NaNO_2$ (0.069 g, 1.01 mmol) in 1.0 mL of water was added dropwise over 10 min. After 40 min the reaction mixture was poured into cold water. The mixture was extracted with cold $CHCl_3$ (3 × 125 mL). The combined organics were washed successively with cold water, cold saturated $NaHCO_3$, and cold brine. The solution was dried over $MgSO_4$, filtered, and placed in a single-neck round-bottom flask. Powdered 4 Å molecular sieves (1.0 g) were added, and the mixture was warmed to reflux for 1 h. The mixture was cooled to room temperature, and *n*-butylamine (0.368 g, 5.03 mmol) was added. The mixture was allowed to stir for 1 h and filtered through a pad of Celite, and the solvent was removed in vacuo to give 0.345 g of an orange solid. Purification via column chromatography (99:1 to 95:5 CH_2Cl_2/MeOH) gave **6** (0.280 g, 48%) as an orange solid: mp 165−166 °C; R_f = 0.16 (95:5 CH_2Cl_2/MeOH); IR ($CHCl_3$) 3424, 3299, 2959, 2871, 1735, 1657, 1373 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H), 11.07 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.15−7.10 (m, 2H), 7.04 (t, J = 7.7 Hz, 1H), 7.03 (t, J = 7.1 Hz, 1H), 6.02 (d, J = 8.4 Hz, 1H), 5.96 (t, J = 5.5 Hz, 1H), 5.51 (pentet, J = 7.4 Hz, 1H), 4.41 (dd, J = 14.9, 7.6 Hz, 1H), 3.39 (dd, J = 14.3, 6.8 Hz, 1H), 3.34 (s, 3H), 3.23−3.14 (m, 2H), 3.05 (dd, J = 14.4, 7.6 Hz, 1H), 2.93−2.82 (m, 2H), 1.72 (s, 3H), 1.60 (s, 3H), 1.27−1.12 (m, 4H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 169.4, 169.0, 157.0, 136.4, 136.2, 128.3, 128.2, 128.0, 127.8, 121.6, 121.5, 119.4, 118.8, 118.7, 118.5, 111.4, 111.2, 110.0, 108.8, 58.2, 53.0, 51.7, 39.1, 31.8, 31.3, 27.0, 22.7, 22.1, 19.5, 13.6; HRMS (FAB) m/z 575(46); LRMS (FAB) calcd for 575.2982 $[MH]^+$, found 575.2970.

Pyrido[1,2-*a*:3,4-*b*′]diindole Derivative (8). To a solution of *n*-butylurea **6** (0.059 g, 0.10 mmol) in 10 mL of THF was added 7.26 M (ether) HBF_4 (0.07 mL, 0.50 mmol). After 1 h the solvent was removed in vacuo, and saturated $NaHCO_3$ was added. The mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was removed in vacuo. The crude solid was purified via column chromatography to afford **8** (0.033 g, 83%) as an orange solid: mp 242−243 °C; R_f = 0.79 (95:5 CH_2Cl_2/MeOH); IR ($CHCl_3$) 3417, 3232, 2952, 1727, 1657 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 8.66 (d, J = 7.4 Hz, 1H). 8.58 (d, J = 7.3 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.66 (d,

(27) Miniker, T. D.; Mukhanov, V. I.; Chkanikov, N. D.; Yartzeva, I. V.; Preobrazhenskaya, M. N. *Carbohydr. Res.* **1978**, *64*, 17.
(28) Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1995**, *60*, 6672.
(29) Okey, A. B.; Riddick, D. S.; Harper, P. A. *Trends Pharm. Sci.* **1994**, *15*, 226.
(30) Gillner, M.; Bergman, J.; Cambillau, C.; Fernstrom, B.; Gustafsson, J. A. *Mol. Pharm.* **1993**, *28*, 357.
(31) Rannug, U.; Rannug, A.; Sjöberg, U.; Li, H.; Westerholm, R.; Bergman, J. *Curr. Biol.* **1995**, *2*, 841.

J = 8.1 Hz, 1H), 7.38−7.32 (m, 3H), 7.28 (t, J = 7.2 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 4.61 (dd, J = 14.4, 7.6 Hz, 1H), 3.73 (dd, J = 14.7, 6.3 Hz, 1H), 3.67 (dd, J = 14.7, 8.3 Hz, 1H), 3.39 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.8, 170.5, 138.7, 130.2, 128.2, 127.8, 126.1, 123.8, 122.8, 122.0, 119.91, 119.89, 119.3, 118.2, 117.9, 112.1, 111.9, 111.0, 102.5, 97.6, 54.4, 51.9, 27.1, 22.3; HRMS (FAB) *m/z* 399(15); LRMS (FAB) calcd for 399.1582 $[M]^+$, found 399.1581.

Indolenines (9a, 9b). *n*-Butylurea **6** (0.156 g, 0.27 mmol) was dissolved in 27 mL of TFA, and the solution was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. After the organic layer was dried over Na_2SO_4, solvent was removed in vacuo to give 0.150 g of solid. Purification via preparative TLC (alumina; 95:5 CH_2Cl_2/MeOH) gave **8** (0.014 g, 13%) as an orange solid, **9a** (0.027 g, 22%) as a yellow solid, and **9b** (0.028 g, 23%) as a yellow solid. **Data for 9a** (two diastereomers): mp 184−185 °C; R_f = 0.36 (95:5 CH_2Cl_2/MeOH; alumina); IR ($CHCl_3$) 3668, 3424, 2996, 1742, 1672 cm^{-1}. The ^{1}H and ^{13}C NMR spectra of **9a** show a 3:1 mixture of diastereomers: ^{1}H NMR major diastereomer (500 MHz, DMSO-d_6) δ 11.84 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H, overlapping), 7.47 (d, J = 7.6 Hz, 1H, overlapping), 7.46−7.41 (m, 2H), 7.30 (td, J = 7.6, 1.2 Hz, 1H, overlapping), 7.26 (ddd, J = 8.2, 7.0, 1.0 Hz, 1H, overlapping), 7.12 (td, J = 7.4, 0.9 Hz, 1H, overlapping), 7.07 (ddd, J = 7.9, 7.0 0.9 Hz, 1H, overlapping), 5.27 (dd, J = 9.5, 4.0 Hz, 1H), 3.99 (dd, J = 8.4, 4.3 Hz, 1H), 3.60 (dd, J = 17.5, 4.9 Hz, 1H, overlapping), 3.39 (s, 3H), 2.90 (d, J = 16.4 Hz, 1H, overlapping), 2.30 (dd, J = 14.4, 8.5 Hz, 1H), 1.93 (dd, J = 14.3, 4.3 Hz, 1H, overlapping), 1.71 (s, 3H), 1.33 (s, 3H, overlapping); ^{13}C NMR major diastereomer (125 MHz, DMSO-d_6) δ 172.5, 171.8, 168.8, 168.4, 156.8, 138.7, 138.0, 128.2, 127.6, 126.4, 124.5, 124.2, 124.0, 119.9, 119.7, 119.2, 118.2, 112.1, 61.5, 51.9, 50.8, 48.9, 37.3, 26.5, 22.2, 22.0; HRMS (FAB) 459(76), 400(80), 269(68), 256(42), 220(10); LRMS (FAB) calcd for 458.1954 $[M]^+$, found 458.1953. **Data for 9b** (two diastereomers): mp 197−198 °C; R_f = 0.31 (95:5 CH_2Cl_2/MeOH; alumina); IR ($CHCl_3$) 3650, 2996, 1742, 1676, 1370, 1330 cm^{-1}. The ^{1}H and ^{13}C NMR spectra of **9b** show a 3:1 mixture of diastereomers: ^{1}H NMR major diastereomer (500 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.68 (d, J = 9.7 Hz, 1H, overlapping), 7.72 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H, overlapping), 7.51 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H, overlapping), 7.36 (d, J = 7.6 Hz, 1H, overlapping), 7.34 (td, J = 7.6, 1.1 Hz, 1H), 7.26 (td, J = 8.1, 0.9 Hz, 1H, overlapping), 7.17 (td, J = 6.7, 0.8 Hz, 1H), 7.11−7.06 (m, 1H, overlapping), 4.15−4.10 (m, 1H), 3.51 (dd, J = 14.8, 7.0 Hz, 1H), 3.38 (s, 3H), 3.11−3.00 (m, 3H, overlapping), 2.57 (dd, J = 14.4, 6.5, 1H), 2.41 (dd, J = 14.0, 7.6 Hz, 1H), 2.00 (s, 3H, overlapping), 1.50 (s, 3H); ^{13}C NMR major diastereomer (125 MHz, DMSO-d_6) δ 172.8, 171.6, 168.8, 168.1, 156.6, 138.8, 138.6, 128.4, 128.3, 125.7, 124.7, 124.5, 124.2, 119.8, 119.5, 118.7, 112.2, 58.8, 53.5, 51.7, 48.2, 31.9, 26.7, 22.7, 22.0, not all peaks resolved; LRMS (FAB) *m/z* 459(79); HRMS (FAB) calcd for 458.1954 $[M]^+$, found 458.1957.

Pyrido[1,2-*a*:3,4-*b*′]diindole Derivative (10). Pyridodiindole **17** (0.134 g, 0.35 mmol) was dissolved in 5 mL of 6 N HCl and warmed to 110 °C in a bomb. After 12 h the solvent was removed in vacuo. The residue was purified by reverse-phase HPLC (3:2 0.1% TFA/acetonitrile; isocratic). The solvent was removed by lyophilization to give **10** (0.069 g, 43%) as a tan solid (trifluroacetic acid salt): mp 159−160 °C; R_f = 0.75 (85:15:5 butanol/formic acid/water); IR (KBr) 3425, 3085, 2954, 2915, 1743, 1664, 1335 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.63 (bs, 3H), 8.25 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.41−7.34 (m, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 4.15 (dd, J = 15.5, 7.0 Hz, 1H), 4.02 (dd, J = 15.0, 8.0 Hz, 1H), 3.88 (dd, J = 15.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.5, 158.5, (J = 34 Hz), 138.8, 130.5, 128.2, 127.5, 126.7, 123.9, 122.7, 122.3, 120.1, 119.3, 118.8, 117.8, 116.1 (J = 293 Hz), 112.6, 112.2, 111.1, 102.7, 95.4; LRMS (FAB) *m/z* 344, 285, 269, 256; HRMS (FAB) calcd for $C_{21}H_{17}N_3O_2$ $[M]^+$ 343.1321, found 343.1326.

Pyrido[1,2-*a*:3,4-*b*′]diindole Derivative (10). Pyridodiindole **8** (0.060 g, 0.15 mmol) was dissolved in 8 mL of 20% aqueous NaOH and heated at reflux for 20 h. The mixture was cooled to 5 °C and acidified to pH 1 with 12 N HCl. The mixture was concentrated in vacuo. The remaining solids were extracted with acetonitrile, and the extract was concentrated in vacuo to give 0.5 g of crude product mixed with sodium chloride. The crude product was purified by reverse-phase HPLC (3:2 0.1% TFA/acetonitrile; isocratic). The solvent was removed by lyophilization to give **10** (0.017 g, 25%) as a tan solid (trifluroacetic acid salt).

Homofascaplysin C. Amino acid **10** (0.030 g, 0.07 mmol) was dissolved in 30 mL of water and warmed to 80 °C. To this solution was added 10 mL of 5% (w/v) aqueous $FeCl_3$ solution via syringe pump over 3 h. During the same period, 500 mL of xylenes was added via cannula to the rapidly stirring aqueous mixture through a glass tube such that it continually passed though the aqueous solution and was removed by another cannula into a collection flask. This procedure allows the product to be removed as it is formed. The collected xylenes were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo to give 0.012 g of brown solid. Purification via preparative thin-layer chromatography (85:15 hexanes/ethyl acetate) gave homofascaplysin C (0.004 g, 23%) as a yellow solid.

Tryptophan Dimer (13). N^{α}-Ac-$_L$Trp-$_L$Trp-OMe (7.75 g, 17.40 mmol) **11a** was dissolved in 87.0 mL of trifluroacetic acid. After 15 h trifluroacetic acid was removed in vacuo to yield a thick syrup, which was suspended in 200 mL of ethyl acetate. The rapidly stirred solution was adjusted to pH 14 by the slow addition of 2 N NaOH solution. The precipitate was filtered, washed twice with 2 N NaOH solution, washed with water, and dried in vacuo for 15 h at 50 °C (25 mTorr) to yield **13** (1.97 g, 25%) as a white solid: mp 320−322 °C (dec); R_f = 0.25 (3:1 hexanes/ethyl acetate); IR (KBr) 3303, 3052, 2932, 1733 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, rt) δ 10.22 (s, 1H), 8.74 (d, J = 6.7 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.0−6.8 (m, 3H), 6.92 (t, J = 7.0 Hz, 1H), 6.56 (t, J = 10.0 Hz, 1H), 6.47 (d, J = 7.7 Hz, 1H), 6.06 (s, 1H), 4.45 (s, 1H), 4.36 (m, 1H), 3.63 (s, 3H), 3.4−3.3 (m, 3H), 3.20 (d, J = 5.0 Hz, 1H), 1.94−1.82 (m, 2H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 170.7, 168.8, 150.5, 140.7, 136.3, 130.8, 127.8, 126.8, 124.1, 120.9, 118.3, 117.5, 116.8, 111.6, 107.6, 106.1, 57.5, 54.2, 52.1, 51.7, 47.6, 42.2, 22.5, 21.8; LRMS (FAB) *m/z* 447(87); HRMS (FAB) calcd for $[MH]^+$ $C_{25}H_{27}N_4O_4$, 447.2032, found 447.2029. Anal. calcd for $C_{25}H_{26}N_4O_4$: C, 67.25; H, 5.87; N, 12.55. Found: C, 66.99; H, 5.89; N, 12.44.

***N*-Tosylindoline (14).** To a solution of cyclic tryptophan dimer **13** (0.170 g, 0.38 mmol) in pyridine (5.0 mL) was added 0.080 g (0.42 mmol) of *p*-tolunesulfonyl chloride. After 2 h the reaction mixture was concentrated in vacuo and combined with water. The crude mixture was extracted with ethyl acetate, washed with 2 N HCl and brine, and dried over $MgSO_4$. The solvent was filtered and removed in vacuo to yield a pink solid. Purification via column chromatography afforded **14** (0.123 g, 54%) as a white solid: mp 304−305 °C; R_f = 0.19 (ethyl acetate); IR (KBr) 3045, 2947, 1736, 1653, 1356; ^{1}H NMR (500 MHz, DMSO-d_6, rt) δ 10.35 (s, 1H), 8.91 (d, J = 6.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H) 7.60−7.53 (m, 4H), 7.37−7.31 (m, 3H), 7.36 (d, J = 8.5 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 9.3 Hz, 1H), 7.07 (t, J = 9.3 Hz, 1H), 6.99 (t, J = 8.9 Hz, 1H), 5.21 (d, J = 1.5 Hz, 1H), 4.32 (ddd, J = 11.7, 7.8, 5.2 Hz, 1H), 3.75 (ddd, J = 11.6, 5.1, 3.6 Hz, 1H), 3.71 (s, 3H), 3.59 (t, J = 12.4 Hz, 1H), 3.32 (dd, J = 11.1, 3.3 Hz, 1H), 3.24 (d, J = 11.6 Hz, 1H), 2.30 (s, 3H), 1.81 (s, 3H), 1.62 (dd, J = 12.7, 4.7 Hz, 1H), 0.75 (dd, J = 24.3, 11.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.7, 170.2, 168.5, 144.3, 140.2, 137.5, 136.5, 134.9, 133.6, 129.9, 128.3, 127.1, 126.3, 125.4, 124.7, 121.5, 118.7, 118.1, 115.3, 111.6, 107.6, 61.5, 54.3, 51.9, 51.7, 45.7, 41.8, 22.4, 21.5, 20.9; LRMS (FAB) *m/z* 601(100); HRMS (FAB) calcd for $C_{32}H_{32}N_4O_6$ $[M]^+$ 600.2042, found 600.2040. Anal. calcd for $C_{32}H_{32}N_4O_6$: 63.99; H, 5.37; N, 9.23. Found: C, 63.76; H, 5.53; N, 9.23.

Ditryptophan (12b). N^{α}-Ac-$_L$Trp-$_D$Trp-OMe **11b** (0.448 g, 1.00 mmol) was dissolved in 5.0 mL of trifluoroacetic acid. After 15 h the solvent was removed in vacuo, resulting in a thick syrup, which was neutralized by the addition of saturated $NaHCO_3$. Water was added, and the crude mixture was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. The solvent was filtered and removed in vacuo to yield 0.431 g of crude solid. The solid was dissolved in 5 mL of 1,4-dioxane. In portions, DDQ was added (0.227 g, 1.00 mmol) over 5 min. After 2 h, the reaction mixture was filtered through a pad of Celite. The solvent was evaporated in vacuo to yield a solid, which was dissolved in ethyl acetate. The solution was washed with 1:1 saturated $NaHCO_3/H_2O$ until the washes remained colorless. The solvent was dried over $MgSO_4$, filtered, and evaporated in vacuo to yield 0.319 g of yellow sold. Purification via flash chromatography (1:1 to 2:1 hexanes/ethyl acetate) afforded **12b** (0.249 g, 55%) as a pale yellow solid: mp 240−241 °C (dec); R_f = 0.55 (3:1 hexanes/ethyl acetate); IR (KBr) 3384, 3061, 2930, 1732, 1649 cm^{-1}. The ^1H and ^{13}C NMR spectra of **12b** show two sets of signals. The signals coalesce at 87 °C in the ^1H NMR spectrum: ^1H NMR major isomer (500 MHz, DMSO-d_6, rt) δ 11.25 (s, 1H), 11.18 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 10.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.20−7.03 (m, 4H), 4.51 (m, 1H), 4.14 (ddd, J = 11.3, 8.0, 2.6 Hz, 1H), 3.60 (s, 3H), 3.32 (dd, J = 13.9, 2.0 Hz, 1H), 3.31 (s, 1H), 3.03 (dd, J = 13.5, 3.2 Hz, 1H), 2.75−2.65 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 90 °C) δ 170.7, 169.3, 168.0, 135.7, 135.6, 128.6, 128.2, 127.5, 126.7, 121.1, 121.0, 118.3, 118.2, 117.9, 117.3, 118.8, 111.5, 110.9, 110.8, 53.5, 52.4, 51.3, 29.0, 26.9, 22.3; LRMS (FAB) m/z 445(100); HRMS (FAB) calcd for $C_{25}H_{26}N_4O_4$ $[MH]^+$ 445.1876, found 445.1872. Anal. calcd for $C_{25}H_{25}N_4O_4 \cdot {}^1/_2H_2O$: C, 66.21; H, 5.56; N, 12.35. Found: C, 66.49; H, 5.56; N, 12.29.

Acylhydrazide (15a). Ditryptophan ester **12a** (0.969 g, 2.16 mmol) was dissolved in 40 mL of THF. Hydrazine (0.68 g, 21.56 mmol) was added. After 4 h the reaction mixture was concentrated in vacuo to yield 1.035 g of yellow solid. Purification via flash chromatography afforded **15a** (0.713 g, 69%) as a white solid: mp 284−286(dec)°C; R_f = 0.26 (9:1 CH_2Cl_2/MeOH); IR (KBr) 3329, 3067, 2927, 1654 cm^{-1}. The ^1H and ^{13}C NMR spectra show two isomers (1:0.43) that coalesce above 67 °C: ^1H NMR major isomer (500 MHz, DMSO-d_6, rt) δ 11.35 (s, 1H), 11.27 (s, 0.43H), 11.07 (m, overlapping, 1.43H), 9.35 (s, 0.43H), 9.25 (s, 1H), 8.23 (d, J = 8.0 Hz, 0.43H), 7.62 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 0.43H), 7.54−7.44 (m, overlapping, 1.86H), 7.39−7.27 (m, overlapping, 4.86 H), 7.18−7.03 (m, overlapping, 5.29H), 6.99 (t, J = 7.3 Hz, 0.43H), 6.92 (d, J = 8.4 Hz, 0.43H), 4.46−4.16 (m, overlapping, 5.72H), 3.31 (s, 4H), 3.17−3.03 (m, overlapping, 2.86H), 2.98−2.88 (m, overlapping, 1.86H) 1.78 (t, J = 10.6 Hz, 1H), 1.78 (s, 0.43H), 1.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 80 °C) δ 169.3, 168.8, 135.7, 135.5, 127.9, 121.0, 118.40, 118.1, 117.8, 110.9, 110.6, 54.6(br), 27.9(br), 21.4, not all peaks resolved; LRMS (FAB) m/z 444(52); HRMS (FAB) calcd for $C_{24}H_{24}N_6O_3$ $[M]^+$ 444.1909, found 444.1910. Anal. calcd for $C_{24}H_{24}N_6O_3 \cdot 2H_2O$: C, 59.64; H, 5.56; N, 17.51. Found: C, 59.99; H, 5.87; N, 17.50.

Acylhydrazide (15b). Using the same hydrazinolysis procedure that was used to prepare ditryptophan **12a**, ditryptophan ester **12b** (0.458 g, 1.02 mmol) and hydrazine were combined to give 0.445 g ofyellow solid. Purification via flash chromatography (9:1 $CHCl_3$/MeOH) afforded **15b** (0.375 g, 83%) as a white solid: mp 294−296 °C (dec); R_f = 0.19 (9:1 $CHCl_3$/MeOH); IR (KBr) 3390, 3302, 3049, 2929, 1648, 1336 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.44 (s, 1H), 11.30 (s, 1H), 9.18 (s, 1H), 7.92 (d, J = 7.4 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.24−7.04 (m, 4H), 6.59 (d, J = 10.0 Hz, 1H), 4.46−4.34 (m, 1H), 4.26−4.12 (m, 3H), 3.31 (s, 1H), 2.70 (t, J = 12.6 Hz, 1H), 2.59 (t, J = 12.7 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.8, 169.7, 168.7, 135.9, 135.8, 129.2, 128.2, 127.7, 127.2, 121.7, 121.6, 118.9, 118.6, 118.5, 118.2, 112.1, 112.0, 111.4, 111.2, 54.0, 53.4, 29.9, 28.9, 22.6; LRMS (FAB) m/z 444(48); HRMS (FAB) calcd for $[M]^+$ $C_{24}H_{24}N_6O_3$, 444.1910, found 444.1911. Anal. calcd for $C_{24}H_{24}N_6O_3 \cdot {}^1/_2H_2O$: C, 63.56; H, 5.56; N, 18.53. Found: C, 63.42; H, 5.54; N, 18.53.

***tert*-Butylurea (16a).** Sodium nitrite (0.113 g, 1.63 mmol) was added to a solution of 6.5 mL of 1,4-dioxane and 1.3 mL of 2 N HCl. Acylhydrazide **15a** (0.618 g, 1.29 mmol) was added in portions. After 30 min the solution was poured into cold water and extracted with cold ethyl acetate (3 × 130 mL). The combine organics were washed with saturated $NaHCO_3$, brine, and water. The crude extracts were carefully filtered, placed in a round-bottom flask equipped with reflux condenser, and warmed to reflux for 1 h. The solvent was removed *in vacuo* to give an orange solid. In another round-bottom flask equipped with reflux condenser, the isolated solid was dissolved in 20 mL of *tert*-butylamine. The solution was warmed to reflux. After 15 h the solvent was removed in vacuo to yield a crude solid. Purification via flash chromatography (98:2 to 95:5 CH_2Cl_2/MeOH) afforded **16a** (0.430 g, 67%) as pale yellow solid: mp 249−250 °C (dec), R_f = 0.52 (9:1 CH_2Cl_2/MeOH); IR (KBr) 3396, 3060, 2968, 1652, 1334 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, 1H), 11.13 (s, 1H), 8.45 (vbs, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.29−7.20 (m, 2H), 7.20−7.01 (m, 5H), 6.42−6.31 (m, 1H), 6.24 (bs, 1H), 5.11−4.95 (m, 1H), 4.50−4.42 (m, 1H), 3.19 (dd, J = 14.3, 3.3 Hz, 2H), 2.97−2.83 (m, 2H), 1.94 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.5, 168.6, 156.0, 135.8, 135.7, 128.4, 128.1, 127.9, 127.0, 121.9, 121.6, 119.3, 118.8, 118.7, 118.3, 113.5, 111.6, 111.2, 111.1, 58.6, 53.0, 49.1, 29.3, 28.8, 28.6, 23.0; LRMS (FAB) m/z 500(41); HRMS (FAB) calcd for $C_{28}H_{32}N_6O_3$ $[M]^+$ 500.2636, found 500.2636. Anal. calcd for $C_{28}H_{32}N_6O_3$: C, 67.18; H, 6.44; N, 16.79. Found: C, 67.06; H, 6.40; N, 16.70.

***tert*-Butylurea (16b).** Sodium nitrite (0.083 g, 1.21 mmol) was added to a solution of 5.5 mL of 1,4-dioxane and 1.1 mL of 2 N HCl. Acylhydrazide **15b** (0.456 g, 1.10 mmol) was added in portions. After 30 min the solution was poured into cold water and extracted with cold ethyl acetate (3 × 110 mL). The combined organics were washed with cold saturated $NaHCO_3$, brine, and water. The crude extracts were carefully filtered, placed in a round-bottom flask equipped with reflux condenser, and warmed to reflux for 1 h. The solvent was removed in vacuo to give an orange solid. In another round-bottom flask equipped with reflux condenser, the isolated solid was dissolved in 16.5 mL of *tert*-butylamine. The solution was warmed to reflux. After 15 h the solvent was removed in vacuo to yield 0.450 g of orange solid. Purification via flash chromatography (98:2 to 95:5 $CHCl_3$/MeOH) afforded **16b** (0.225 g, 42%) as a pale yellow solid: mp 228−230 °C (dec); R_f = 0.46 (9:1 $CHCl_3$/MeOH); IR (KBr) 3401, 2973, 1648, 1334 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.26 (s, 1H), 11.14 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.70−7.62 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.25−7.03 (m, 5H), 5.90 (s, 1H), 5.84 (d, J = 8.4 Hz, 1H), 5.42−5.30 (m, 1H), 4.12−3.99 (m, 1H), 3.31 (s, 1.5H), 3.00 (d, J = 13.1 Hz, 2H), 2.70 (t, J = 11.3 Hz, 2H), 1.81 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.1, 168.5, 155.8, 135.8, 129.0, 127.8, 127.62, 127.56 121.52, 121.47, 118.7, 118.5, 118.2 (br), 112.2, 111.7, 111.4, 111.1, 57.8, 54.2, 49.1, 31.3, 29.3, 29.0, 22.6, not all peaks resolved; LRMS (FAB) m/z 500(69); HRMS (FAB) calcd for $C_{28}H_{32}N_6O_3$ $[M]^+$ 500.2537, found 500.2540. Anal. calcd for $C_{28}H_{32}N_6O_3 \cdot {}^3/_2H_2O$: C, 63.74; H, 6.69; N, 15.93. Found: C, 63.98; H, 6.41; N, 15.91.

Hexacycle (18) and Pyridodiindole (17). Urea **16a** (0.094 g, 0.19 mmol) was dissolved in 19 mL of TFA. After 15 h the reaction mixture was concentrated in vacuo, and the residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. After the organic layer was dried over Na_2SO_4, solvent was removed in vacuo to give 0.114 g of an orange solid. Purification via flash chromatography (gradient 300 mL; 1:1 ethyl acetate/hexanes; 2:1 ethyl acetate/hexanes; ethyl acetate; 95:5 ethyl acetate/CH_3OH) afforded **17** (0.038 g, 53%) as an orange solid and **18** (0.009 g, 12%) as a pale yellow solid. **Data for 17:** mp = 269−271 °C (dec); R_f = 0.40 (95:5 CH_2Cl_2/MeOH); IR ($CHCl_3$) 3684, 3506, 3392, 3214, 2985, 1689, 1648 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.70 (d, J = 7.1 Hz, 1H), 8.55 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.42−7.19

(m, 6H), 7.07 (bs, 1H), 4.58−4.48 (m, 1H), 3.63 (dd, J = 14.7, 9.4 Hz, 1H), 3.51 (dd, J = 14.1, 4.1 Hz, 1H),3.31 (s, 2H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.4, 171.3, 138.8, 130.0, 128.4, 128.3, 126.6, 123.6, 122.9, 121.8, 119.8, 119.6, 119.3, 118.5, 118.0, 111.7, 111.6, 110.8, 102.5, 98.5, 55.7, 27.6, 22.5; LRMS (FAB) *m*/*z* 384(87); HRMS (FAB) calcd for $C_{23}H_{20}N_4O_2$ $[M]^+$ 384.1578, found 384.1586. Anal. calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 71.60; H, 5.39; N, 14.32. **Data for 18:** $[\alpha]_D$ = +151.2 (*c* 1.02, MeOH), mp 241−242 °C (dec), R_f = 0.17 (95:5 EtOAc/MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.67 (d J = 8.0 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.48−7.41 (m, 3H), 7.30−7.26 (m, 2H), 7.10 (t, J = 7.2 Hz, 1H), 4.30 (dt, J = 11.7, 5.9 Hz, 1H), 3.70 (ddd, J = 7.9, 4.4, 1.4 Hz, 1H), 3.46 (d, J = 8.0 Hz, 2H), 3.31 (s, 2H), 2.58 (t, J = 12.4 Hz, 1H), 1.76 (s, 3H), 1.35 (ddd, J = 12.9, 7.3, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 169.2, 169.0, 155.7, 140.7, 139.1, 128.8, 127.1, 125.6, 124.7, 123.2, 120.5, 120.2, 119.9, 119.6, 112.3, 55.4 (doubled peak height suggests overlapping resonances), 47.3, 32.9, 30.6, 22.5; LRMS (FAB) *m*/*z* 385(100), 363(5), 298(6), 270(16), 256(28); HRMS (FAB) calcd for $C_{23}H_{21}N_4O_2$ $[MH]^+$ 385.1664, found 385.1664. Anal. calcd for $C_{23}H_{20}N_4O_2 \cdot H_2O$: C, 68.64; H, 5.51; N, 13.92. Found: C, 68.41; H, 5.79; N, 14.05.

Indolo[2,3-*a*]carbazole. To hexacycle **18** (0.052 g, 0.14 mmol) in 5.0 mL of tetralin was added *p*-TsOH (0.003 g, 0.01 mmol). The mixture was warmed to reflux. After 1 h the tetralin was removed via Kugelrhor distillation (50 °C, 25 mTorr) to give a dark solid. Purification via chromatography (9:1 to 7:3 hexane/ethyl acetate) gave indolo[2,3-*a*]carbazole (0.022 g, 61%) as a tan solid. This product was identical with authentic material.[32]

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Supporting Information Available: Procedures and characterization data for the dipeptides and compounds **2**, **3**, **11b**, **7**, **10**; results of Monte Carlo calculations; ^{1}H NMR spectra for compounds **6**, **8**, **9a**, **9b**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Gilbert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500.