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Amino-Zinc-Ene-Enolate Cyclization: A Short Access to *cis*-3-Substituted Prolino-homotryptophane Derivatives

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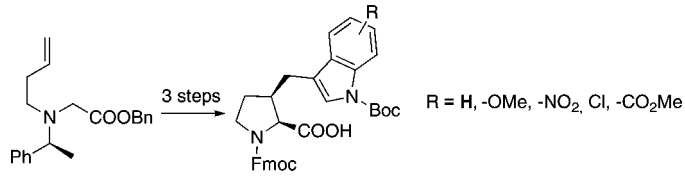
Received May 9, 2008



Proline chimeras are useful tools for medicinal chemistry and/or biological applications. The asymmetric synthesis of *cis*-3-substituted prolines can be easily achieved via amino-zinc-ene-enolate cyclization followed by transmetalation of the cyclic zinc intermediate for further functionalization. Syntheses of prolino-homotryptophane derivatives were achieved through Negishi cross-coupling of the zinc intermediate with indole rings. The use of Pd catalyst derived from Fu's [(*t*-Bu_3)PH]-BF_4 was required to avoid the undesired β-hydride elimination. Optically pure and orthogonally protected compounds were obtained readily usable for peptide synthesis.

Introduction

Proline chimeras are tools combining amino acids side-chain functionalities with conformational rigidity of pyrrolidine ring.[1] One can distinguish between four classes of proline chimeras, depending on the position of the pyrrolidine ring on which the side-chain functionality is introduced. Among these chimeras, 3-substituted prolines are valuable tools for medicinal chemistry first and biological applications. For example, in SAR studies of biologically active peptides, these proline analogues have been used to replace native residues with the aim of probing both the information brought by the side chain and the conformation (around the peptide backbone and the side chain) of the native residue.[2] *cis*-3-Substituted prolines have also been used to build functionalized PPII helices (e.g., polyproline II helix), allowing the development of protein−protein interaction inhibitors.[3] In the same manner, if the insertion of proline in a heterochiral sequence remains the easiest strategy to induce a β-turn,[4] incorporation of *cis*-3-substituted prolines is a pertinent approach to mimic functionalized natural β-turns of types I, II, and II′ found in proteins.[5]

Several useful methods for the synthesis of 3-substituted prolines are reported in the literature,[6] and we have developed a general approach based on the amino-zinc-ene-enolate cyclization (AZEE cyclization).[7,8] We report here the application of this methodology to the preparation of proline-homotryptophane chimeras suitably protected for peptide synthesis.

Results and Discussion

The AZEE cyclization is a straightforward method for the synthesis of *cis*-3-substituted prolines. The versatility of this

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(1) For a review on proline chimeras regarding syntheses, structural features, and biological applications, see: Karoyan, P.; Sagan, S.; Lequin, O.; Quancard, J.; Lavielle, S.; Chassaing, G. *Targets Heterocycl. Syst.* **2004**, *8*, 216.

(2) (a) Sagan, S.; Quancard, J.; Lequin, O.; Karoyan, P.; Chassaing, G.; Lavielle, S. *Chem. Biol.* **2005**, *12*, 5–555. (b) Sugase, K.; Horikawa, M.; Sugiyama, M.; Ishiguro, M. *J. Med. Chem.* **2004**, *47*, 489.

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(4) Chalmers, D. K.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 5927.

(5) Quancard, J.; Karoyan, P.; Lequin, O.; Wenger, E.; Aubry, A.; Lavielle, S.; Chassaing, G. *Tetrahedron Lett.* **2004**, *45*, 623.

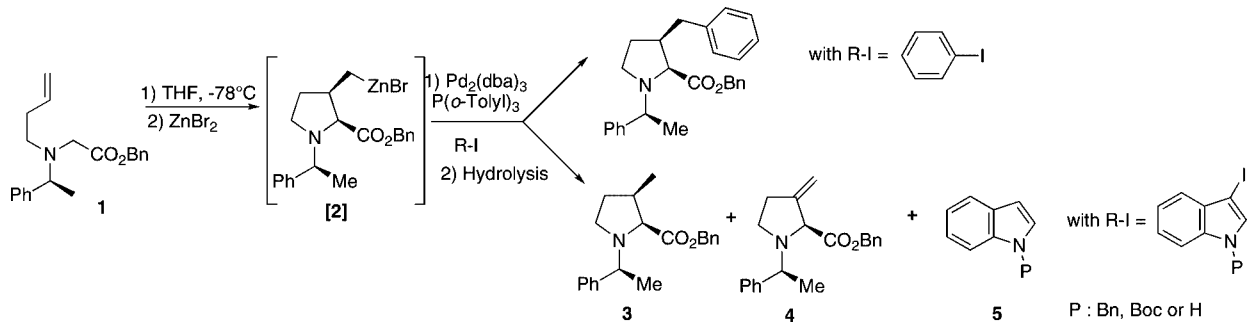
(6) (a) Kumar, S.; Wang, Q.; Sasaki, N. A. *Tetrahedron* **2007**, *63*, 2084. (b) Angle, S. R.; Belanger, D. S. *J. Org. Chem.* **2004**, *69*, 4361, and references therein.

(7) For the synthesis of 3-substituted prolines through amino-zinc-ene-enolate cyclization, see: Quancard, J.; Labonne, A.; Jacquot, Y.; Chassaing, G.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2004**, *69*, 7940, and references therein.

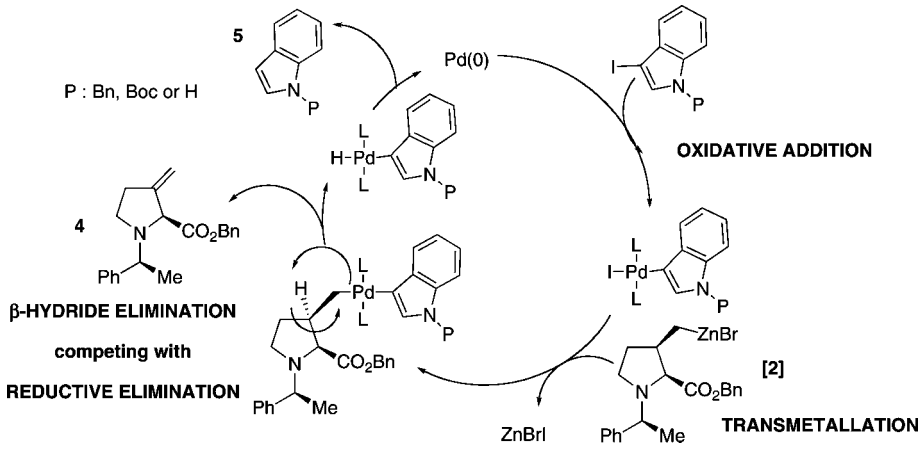
(8) For a review on carbometalation of unactivated alkenes by zinc enolate derivatives, see: Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *New.J. Chem.* **2008**, *32*, 594, and references therein.

10.1021/jo801006a CCC: $40.75
Published on Web 07/26/2008

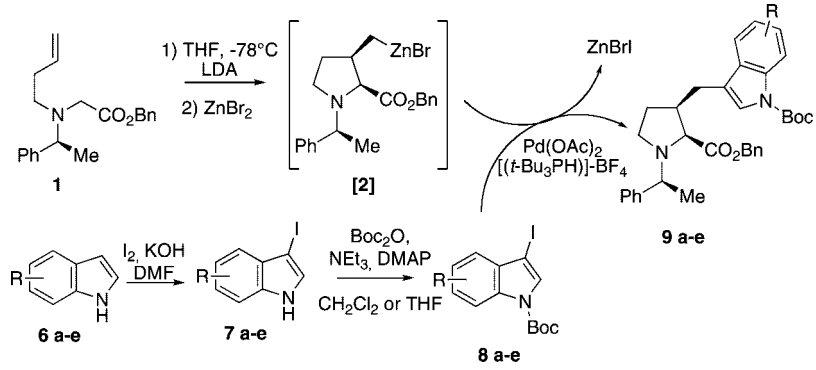
SCHEME 1. Negishi Cross-Coupling Reaction with $Pd_2(dba)_3$/P(*o*-Tolyl)$_3$



SCHEME 2. *β*-Hydride Elimination



SCHEME 3. Iodation and Boc Protection of Indol Rings Followed by Negishi Coupling



strategy is linked to the relative stability of zinc intermediate that can be transmetalated into a variety of new organometallic species, allowing reaction pathways not available for the zinc derivative.[9] We recently took advantage of this characteristic to achieve Pd(0) Negishi cross-coupling reactions[10] of the cyclic zinc intermediate with iodo-benzene for the preparation of proline-phenylalanine chimeras. This cross-coupling was successful using in situ generated Pd(0) from $Pd_2(dba)_3$ and tri-*o*-tolylphosphine.[11] However, these conditions failed for coupling indole rings. In that case, the formation of the *exo*-3-methylene-prolinate **4** and the reduced indole ring **5** was observed together with the hydrolysis product **3**, whatever the protecting group on the indole nitrogen (Scheme 1).

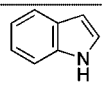
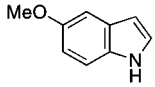
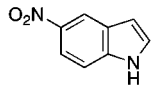
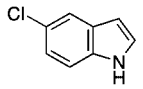
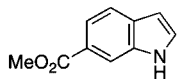
This observation can be explained by considering the rapid *β*-hydride elimination that has been reported with secondary alkyl ligands on Pd[12] (Scheme 2). This *β*-hydride elimination, competing with the reductive elimination, was not observed through coupling of aryl-iodide to zinc intermediate [**2**].

To avoid this side reaction, the use of Pd catalysts derived from Buchwald's Ru-phos, Hartwig's Q-phos and Fu's [(*t*-Bu_3PH)]-BF_4 have been reported in the α-arylation of *N*-Boc-pyrrolidine via transmetalation/Negishi coupling.[13] Fu's catalyst was chosen for reasons of cost, availability, and ease of use, and thus we considered the coupling of indole rings using this air-stable trialkylphosphonium salt[14] as described in Scheme 3 and Table 1.

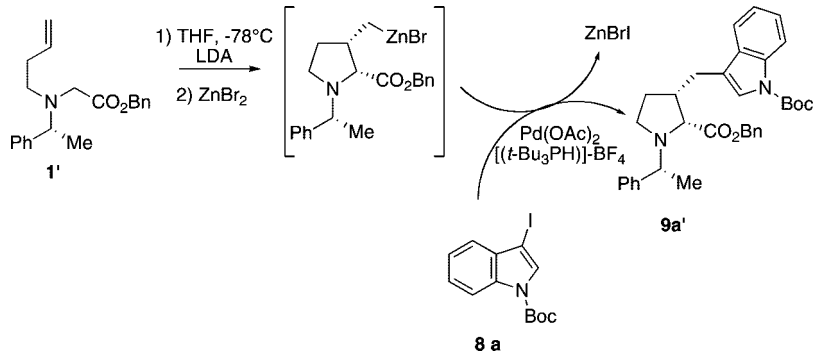
The zinc intermediate [**2**] was generated starting from the commercially available olefin **1**.[15] Carbocyclization was performed after the deprotonation/transmetalation sequence (Scheme

(9) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
(10) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
(11) Quancard, J.; Magellan, H.; Lavielle, S.; Chassaing, G.; Karoyan, P. *Tetrahedron Lett.* **2004**, *45*, 2185.
(12) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.
(13) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538.
(14) Netherton, M.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.
(15) Genzyme Pharmaceuticals, Eichenweg 1, CH-4410 Liestal, Switzerland.

TABLE 1. Yields of Iodation, Boc Protection, and Negishi Coupling of Indol Rings

Indoles	entry	Iodination yields (**7**)	Boc protection yields (**8**)	Cross-coupling yields (**9**)
	**a**	96%	95%	60%
	**b**	94%	83%	52%
	**c**	95%	90%	35%
	**d**	88%	90%	43%
	**e**	92%	87%	23%

SCHEME 4. Synthesis of Enantiomer 9a′



3). The *cis*-stereochemistry observed during the cyclization process of the linear α-amino-ester **1** was initially attributed to a chair-like transition state involving O-metalated species.[16] Recent studies realized by Chemla and co-workers concluded that C-metalated species explain the stereochemistry observed in carbocyclizations involving zinc-enolates.[17] Anyway, the absolute configurations of both chiral centers created during the cyclization process depend on the chiral auxiliary used in this reaction, (*S*)-α-methyl-benzylamine, leading to *cis*-3-substituted proline derivatives with a 2*S* absolute configuration. The cross-coupling reaction was realized at room temperature, with first iodo-indole **8a** prepared by direct iodination of compounds **6a** followed by Boc-protection of the indole nitrogen.[18] Boc protection was required to achieve the cross-coupling reaction. Only trace amounts of cross-coupling product were observed with unprotected indole **7a**, the major compound being the hydrolysis product **3**, and no reaction occurred with *N*-benzyl-protected indole (not reported in Scheme 3 and Table 1). These results may be linked to the electron-withdrawing character of the *N*-Boc group, which favors the oxidative addition step of the palladium catalyst into the indoyl-iodine bond and thus favors the overall catalytic process. Compound **9a** was obtained with good yields after isolation and purification by flash column chromatography. *N*-Boc-protected indoles **8b**−**e** were prepared using the same procedure. These indoles were engaged in the cross-coupling reaction leading to compounds **9b**−**e** with good to low yields. The lower yields may be explained by considering that if electron-withdrawing character of the *N*-Boc group favors the oxidative addition step, electron-withdrawing groups on the aromatic ring might disfavor the reductive elimination process leading to the cross-coupling products; a balance between electron-donating or -withdrawing effects is required to achieve the reaction with satisfactory yields.

The same procedure was used to prepare compound **9a′**, the enantiomer of compound **9a**, starting from the commercially available linear α-amino ester **1′** (Scheme 4).

The prolino-homotryptophane chimera **9a′** was obtained with satisfactory yields, as for its enantiomer **9a**. Finally, both enantiomers (**9a** and **9a′**) were debenzylated by catalytic hydrogenation over palladium charcoal (Scheme 5). The orthogonally protected compounds **10** and **10′** were obtained after Fmoc protection of the pyrrolidine ring nitrogen.

In conclusion, the syntheses of *cis*-3-substituted prolino-homotryptophane chimeras were considered via AZEE cyclization and Negishi cross-coupling reaction. Despite the failure of classical Pd catalyst for Negishi cross-coupling reaction, Fu's catalyst allowed the introduction of indoles rings on the pyrrolidine cycle. Orthogonally protected and optically pure

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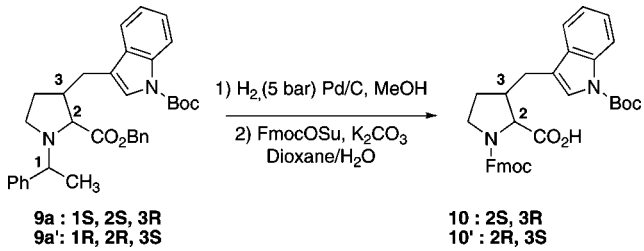
(17) Sliwinski, E.; Prian, F.; Denes, F.; Chemla, F.; Normant, J.-F. *C. R. Chim.* **2003**, *6*, 67, and ref 8.

(18) Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473.

SCHEME 5. Orthogonally Protected Prolino-homotryptophanes Derivatives



9a : 1S, 2S, 3R
9a': 1R, 2R, 3S

10 : 2S, 3R
10' : 2R, 3S

compounds were obtained, and their use in SAR studies of biologically active peptides is currently underway.

Experimental Section

***tert*-Butyl 3-(((2*S*,3*R*)-2-(Benzyloxycarbonyl)-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)methyl)-1*H*-indole-1-carboxylate 9a.** LDA (12 mL, 24 mmol) was added at −78 °C to a solution of (*S*)-benzyl 2-(but-3-enyl(1-phenylethyl)amino)acetate **1** (6.47 g, 20 mmol) in dry THF (30 mL) under argon. $ZnBr_2$ (1.2 M in Et_2O, 50 mL) was then added at the same temperature. The reaction mixture was stirred overnight at room temperature under argon. *tert*-Butyl 3-iodo-1*H*-indole-1-carboxylate **8a** (8.92 g, 26 mmol) in dry THF (10 mL), $Pd(OAc)_2$ (180 mg, 0.80 mmol), and tBu$_3$P-HBF$_4$ (290 mg, 1.0 mmol) were then successively added, and the mixture was stirred overnight at room temperature under argon. Et_2O was added, and the organic layer was washed with NH_4Cl, dried over $MgSO_4$, and concenterd in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 95:5) to give a yellow oil (6.45 g, 60%). $[\alpha]^{20}_D$ −37.9 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.09 (d, 1H, J = 8.0 Hz), 7.38−7.16 (m, 14H), 5.10 (AB, 2H, J = 12 Hz), 3.73 (q, 1H, J = 6.8 Hz), 3.55 (d, 1H, J = 7.7 Hz), 3.09 (m, 1H), 2.91 (m, 1H), 2.81−2.73 (m, 2H), 2.36 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.64 (s, 9H), 1.35 (d, 3H, J = 6.8 Hz). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 173.2, 149.8, 144.5, 135.9, 135.5, 130.5, 128.9, 128.6, 128.4, 127.5, 127.2, 124.4, 122.8, 122.4, 119.0, 115.3, 83.5, 66.7, 66.0, 61.6, 50.1, 41.8, 30.2, 28.3, 26.4, 22.9. HRMS calcd for $C_{34}H_{38}N_2O_4$ [MH$^+$]: 539.2904. Found: 539.2910.

***tert*-Butyl 3-(((2*S*,3*R*)-2-(Benzyloxycarbonyl)-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)methyl)-5-methoxy-1*H*-indole-1-carboxylate 9b.** Same protocol as for **9a**: LDA (2 mL, 4 mmol), (*S*)-benzyl 2-(but-3-enyl(1-phenylethyl)amino)acetate **1** (647 mg, 2 mmol), THF (5 mL), $ZnBr_2$ (1 M, 6 mL), *tert*-butyl 3-iodo-5-methoxy-1*H*-indole-1-carboxylate **8b** (821 mg, 2.2 mmol), $Pd(OAc)_2$ (18 mg, 80 μmol), and tBu$_3$P-HBF$_4$ (29 mg, 100 μmol). A yellow oil (593 mg, 52%) was obtained after the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate 9:1). $[\alpha]^{20}_D$ −35.3 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.01 (d, 1H, J = 9.0 Hz), 7.35−7.25 (m, 11H), 6.93 (dd, 1H, J = 9.0 Hz, J = 2.5 Hz), 6.88 (d, 1H, J = 2.5 Hz), 5.13 (AB, 2H, J = 12,D Hz), 3.86 (s, 3H), 3.77 (q, 1H, J = 6.8 Hz), 3.59 (d, 1H, J = 7.5 Hz), 3.13 (m, 1H), 2.95 (m, 1H), 2.85−2.75 (m, 2H), 2.38 (m, 1H), 1.96 (m, 1H), 1.82 (m, 1H), 1.66 (s, 9H), 1.39 (d, 3H, J = 6.8 Hz). ^{13}C NMR (250 MHz, $CDCl_3$, Boc *cis*/*trans* isomerization) δ: 173.1, 155.7, 149.7, 144.3, 135.8, 131.3, 130.2, 128.8, 128.5, 128.4, 128.0, 127.5, 127.1, 123.5, 118.9, 116.0, 115.9, 112.7, 101.9, 83.2, 66.7, 66.6, 66.0, 61.6, 61.4, 55.9, 55.7, 50.0, 41.7, 30.2, 28.3, 28.2, 26.4, 22.9, 22.8. HRMS calcd for $C_{35}H_{40}N_2O_5$ [MH$^+$]: 569.3010. Found: 569.3018.

***tert*-Butyl 3-(((2*S*,3*R*)-2-(Benzyloxycarbonyl)-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)methyl)-5-nitro-1*H*-indole-1-carboxylate 9c.** Same protocol as for **9a**: LDA (2 mL, 4 mmol), (*S*)-benzyl 2-(but-3-enyl(1-phenylethyl)amino)acetate **1** (647 mg, 2 mmol), THF (5 mL), $ZnBr_2$ (1 M, 6 mL), *tert*-butyl 3-iodo-5-nitro-1*H*-indole-1-carboxylate **8c** (854 mg, 2.2 mmol), $Pd(OAc)_2$ (18 mg, 80 μmol), and tBu$_3$P-HBF$_4$ (29 mg, 100 μmol). A yellow oil (412 mg, 35%) was obtained after the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate 9:1). $[\alpha]^{20}_D$ −34.7 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.28 (m, 1H), 8.18 (m, 2H), 7.40−7.22 (m, 11H), 5.12 (AB, 2H, J = 12.2 Hz), 3.78 (q, 1H, J = 6.8 Hz), 3.56 (d, 1H, J = 7.5 Hz), 3.12 (m, 1H), 2.95 (m, 1H), 2.81−2.71 (m, 2H), 2.39 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.75 and 1.66 (2s, 9H, Boc *cis*/*trans* isomerization), 1.36 (d, 3H, J = 6.8 Hz). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 172.8, 148.9, 144.3, 143.4, 138.6, 135.7, 130.4, 128.8, 128.6, 128.4, 127.4, 127.2, 125.6, 120.0, 119.7, 115.4, 115.3, 84.9, 66.4, 66.0, 61.4, 49.8, 41.6, 30.1, 28.2, 26.1, 22.9. HRMS calcd for $C_{34}H_{37}N_3O_6$ [MH$^+$]: 584.2755. Found: 584.2764.

***tert*-Butyl 3-(((2S,3R)-2-(Benzyloxycarbonyl)-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)methyl)-5-chloro-1*H*-indole-1-carboxylate 9d.** Same protocol as for **9a**: LDA (2 mL, 4 mmol), (*S*)-benzyl 2-(but-3-enyl(1-phenylethyl)amino)acetate **1** (647 mg, 2 mmol), THF 51 mL), $ZnBr_2$ (1 M, 6 mL), *tert*-butyl-5-chloro-3-iodo-1*H*-indole-1-carboxylate **8d** (831 mg, 2.2 mmol), $Pd(OAc)_2$ (18 mg, 80 μmol), and tBu$_3$P-HBF$_4$ (29 mg, 100 μmol). A yellow oil (495 mg, 43%) was obtained after the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate 9:1). $[\alpha]^{20}_D$ −35.2 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.03 (d, 1H, J = 8.5 Hz), 7.36−7.25 (m, 13H), 5.16 (AB, 2H, J = 12.2 Hz), 3.77 (q, 1H, J = 6.5 Hz), 3.57 (d, 1H, J = 7.5 Hz), 3.13 (m, 1H), 2.97 (m, 1H), 2.84−2.67 (m, 2H), 2.31 (m, 1H), 1.96 (m, 1H), 1.77 (m, 1H), 1.76 and 1.66 (2s, 9H, Boc *cis*/*trans* isomerization), 1.38 (d, 3H, J = 6.5 Hz). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 173.0 149.4, 144.4, 135.8, 133.8, 131.7, 128.9, 128.6, 128.5, 128.4, 128.1, 127.5, 127.2, 124.5, 124.0, 118.6, 118.5, 116.3, 83.8, 66.5, 66.0, 61.5, 49.9, 41.6, 30.1, 28.2, 26.2, 22.9. HRMS calcd for $C_{34}H_{37}ClN_2O_4$ [MH$^+$]: 573.2515. Found: 573.2524.

1-*tert*-Butyl 6-Methyl 3-(((2*S*,3*R*)-2-(Benzyloxycarbonyl)-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)methyl)-1*H*-indole-1,6-dicarboxylate 9e. Same protocol as for **9a**: LDA (500 μL, 1 mmol), (*S*)-benzyl 2-(but-3-enyl(1-phenylethyl)amino)acetate **1** (162 mg, 0.5 mmol), THF (1 mL), $ZnBr_2$ (1 M, 1.5 mL), 1-*tert*-butyl-6-methyl-3-iodo-1*H*-indole-1,6-dicarboxylate **8e** (241 mg, 0.60 mmol), $Pd(OAc)_2$ (4 mg, 20 μmol), and tBu$_3$P-HBF$_4$ (7 mg, 30 μmol). A yellow oil (70 mg, 23%) was obtained after the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate 9:1). $[\alpha]^{20}_D$ −23.4 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.82 (s, 1H), 7.89 (dd, 1H, J = 8.5 Hz, J = 1.5 Hz), 7.43−7.22 (m, 12H), 5.11 (AB, 2H, J = 12 Hz), 3.94 (s, 3H), 3.74 (q, 1H, J = 6.5 Hz), 3.55 (d, 1H, J = 7.5 Hz), 3.11 (m, 1H), 2.94 (m, 1H), 2.79−2.73 (m, 2H), 2.37 (m, 1H), 1.92 (m, 1H), 1.80 (m, 1H), 1.79 and 1.67 (2s, 9H, Boc *cis*/*trans* isomerization), 1.36 (d, 3H, J = 6.5 Hz). ^{13}C NMR (250 MHz, $CDCl_3$, Boc *cis*/*trans* isomerization) δ: 173.0, 167.7, 149.3, 144.3, 135.8, 134.9, 134.1, 128.8, 128.6, 128.4, 127.5, 127.2, 126.0, 125.8, 125.7, 123.6, 123.5, 119.1, 118.7, 117.2, 84.1, 66.6, 66.5, 66.0, 61.6, 61.4, 52.2, 52.0, 49.9, 41.7, 30.1, 28.3, 28.1, 26.2, 22.9, 22.8. HRMS calcd for $C_{36}H_{40}N_2O_6$ [MH$^+$]: 597.2959. Found: 597.2969.

***tert*-Butyl 3-(((2*R*,3*S*)-2-(Benzyloxycarbonyl)-1-((*R*)-1-phenylethyl)pyrrolidin-3-yl)methyl)-1*H*-indole-1-carboxylate 9a′.** Same protocol as for **9a** starting from (*R*)-benzyl 2-(but-3-enyl(1-phenylethyl)amino)acetate **1′** yielding a yellow oil. $[\alpha]^{20}_D$ 39.6° (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.09 (d, 1H, J = 8.0 Hz), 7.38−7.16 (m, 14H), 5.10 (AB, 2H, J = 12 Hz), 3.73 (q, 1H, J = 6.8 Hz), 3.55 (d, 1H, J = 7.7 Hz), 3.09 (m, 1H), 2.91 (m, 1H), 2.81−2.73 (m, 2H), 2.36 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.64 (s, 9H), 1.35 (d, 3H, J = 6.8 Hz). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 173.2, 149.8, 144.5, 135.9, 135.5, 130.5, 128.9, 128.6, 128.4, 127.5, 127.2, 124.4, 122.8, 122.4, 119.0, 115.3, 83.5, 66.7, 66.0, 61.6, 50.1, 41.8, 30.2, 28.3, 26.4, 22.9. HRMS calcd for $C_{34}H_{38}N_2O_4$ [MH$^+$]: 539.2904. Found: 539.2911.

(2*S*,3*R*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-3-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)pyrrolidine-2-carboxylic Acid 10. A mixture of compound **9a** (6.25 g, 11.6 mmol) and 10% Pd/C (1.16 g) in MeOH (58 mL) was stirred for 90 h under 5 bar

hydrogen. After filtration over a Celite pad, the solvent was concentrated. A white powder, (2*S*,3*R*)-3-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)pyrrolidine-2-carboxylic acid (2.60 g, 73%), was obtained after crystallization from Et_2O/pentane.

(2*S*,3*R*)-3-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)pyrrolidine-2-carboxylic acid (1.12 g, 3.25 mmol) was dissolved in 30 mL of water and in 30 mL of dioxane. FmocOSu (1.32 g, 3.9 mmol) was slowly added, and then K_2CO_3 (7.15 g, 7.15 mmol) was added. The solution was stirred overnight at room temperature. The solvent was evaporated, and the residue was taken up in water. The aqueous layers were extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. A white powder (1.43 g, 78%) was obtained after purification by flash chromatography (CH_2Cl_2/MeOH/acetic acid, 95:5:0.1). Mp, degradation over 90 °C. $[\alpha]^{20}_D$ 7.8 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.13 (d, 1H, $J = 8.0$ Hz), 7.77−7.06 (m, 12H), 4.59−4.12 (m, 4H), 3.76 (m, 1H), 3.40 (m, 1H), 3.08 (m, 1H), 2.82 (m, 1H), 2.54 (m, 1H), 1.96 (m, 2H), 1.67 and 1.58 (2s, 9H, Fmoc and Boc *cis*/*trans* isomerization). ^{13}C NMR (250 MHz, $CDCl_3$, Fmoc and Boc *cis*/*trans* isomerization) δ: 176.0, 175.5, 155.3, 154.5, 149.8, 144.1, 143.9, 143.8, 141.4, 135.5, 130.3, 127.8, 127.2, 125.3, 124.6, 123.3, 122.6, 120.1, 118.9, 118.3, 118.2, 115.5, 115.0, 83.8, 67.9, 62.5, 62.1, 47.2, 46.4, 46.1, 42.9, 41.8, 30.2, 28.6, 28.4, 25.4. HRMS calcd for $C_{34}H_{34}N_2O_6$ [MNa^+]: 589.2309. Found: 589.2319.

(2*R*,3*S*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-3-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)pyrrolidine-2-carboxylic Acid 10′. Same protocol as for **10** starting from **9a′** yielding a white powder. Mp, degradation over 90 °C, $[\alpha]^{20}_D$ −11.0 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.13 (d, 1H, $J = 8.0$ Hz), 7.77−7.06 (m, 12H), 4.59−4.12 (m, 4H), 3.76 (m, 1H), 3.40 (m, 1H), 3.08 (m, 1H), 2.82 (m, 1H), 2.54 (m, 1H), 1.96 (m, 2H), 1.67 and 1.58 (2s, 9H, Fmoc and Boc *cis*/*trans* isomerization). ^{13}C NMR (250 MHz, $CDCl_3$, Fmoc and Boc *cis*/*trans* isomerization) δ: 176.0, 175.5, 155.3, 154.5, 149.8, 144.1, 143.9, 143.8, 141.4, 135.5, 130.3, 127.8, 127.2, 125.3, 124.6, 123.3, 122.6, 120.1, 118.9, 118.3, 118.2, 115.5, 115.0, 83.8, 67.9, 62.5, 62.1, 47.2, 46.4, 46.1, 42.9, 41.8, 30.2, 28.6, 28.4, 25.4. HRMS calcd for $C_{34}H_{34}N_2O_6$ [MNa^+]: 589.2309. Found: 589.2319.

Acknowledgment. C.M. is grateful to Genzyme Pharmaceutilcals for financial support of her Ph.D. P.K. thanks Jean-Claude Tabet and his team for the HRMS analysis.

Supporting Information Available: General considerations, iodo-indoles syntheses, and NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801006A