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Synthesis of Indole Alkaloid Analogues: Novel Domino Stereoselective Electrophile Addition−Cyclizations of Tryptophan-Derived α-Amino Nitriles

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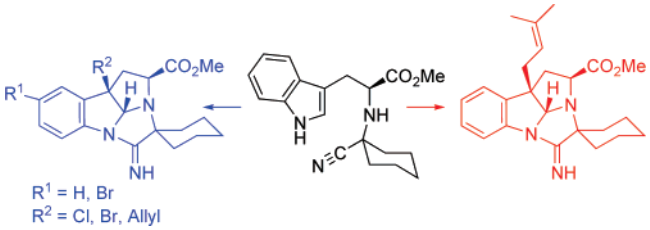
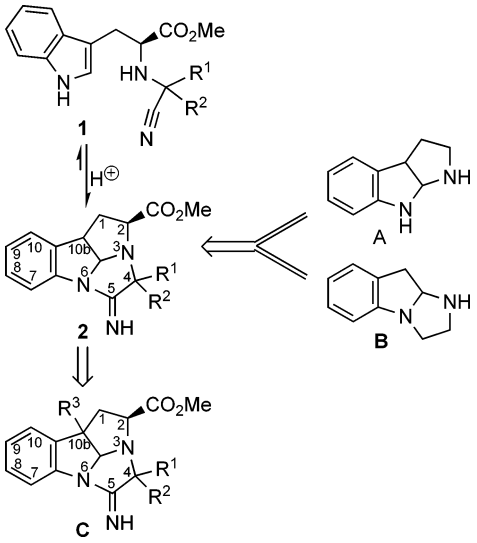
Received April 3, 2007



The synthesis of new indole alkaloid analogues, containing a 1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo-[1,2-*a*]indole skeleton, via highly stereoselective novel domino cyclative halogenation or prenylation reactions of tryptophan-derived α-amino nitriles, is described.

We have recently described the stereoselective synthesis of compounds of general formula **2** (Scheme 1), which contain the novel tetracyclic system 1,2,4,5,10b,10c-hexahydropyrrolo-[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole, via an acid-promoted domino tautomerization of tryptophan-derived α-amino nitriles **1**.[1] This novel ring system could be considered as a hybrid of the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**A**) and the 2,3,9,9a-tetrahydroimidazo[1,2-*a*]indole (**B**), both present in a growing class of indole alkaloids with a wide range of biological activities. Thus, for example, the hexahydropyrrolo[2,3-*b*]indole (**A**) is present in the acetylcholinesterase inhibitor physostigmine,[2] in the multidrug resistance reversal agents ardeemins,[3] or in diverse peptides which contain modified tryptophan residues, such as himastatin[4] or the *Bacillus subtilis* pheromone ComX.[5] The tetrahydroimidazo[1,2-*a*]indole (**B**) is present, among others, in the cholecystokinin antagonists asperlicins,[6] in the antifungic agents fumiquinazolines,[7] or in the substance P antagonists fiscalins.[8] Most of these alkaloids have substituents at the indoline C-3 position, which in the case of the hexahydropyrrolo[2,3-*b*]indole derivatives most frequently is a prenyl or reverse-prenyl group. This fact and the novelty of the aforementioned tetracyclic ring system pushed us to study the synthesis of 1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indoles **C** substituted at the 10b position.

SCHEME 1. General Access to 1,2,4,5,10b,10c-Hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indoles



Our first goal was the introduction of a prenyl or reverse-prenyl group, for which we devised a strategy similar to the two-step procedure developed by the Danishefsky group for the synthesis of hexahydropyrrolo[2,3-*b*]indoles substituted at the C-3a position.[9] This strategy involved a first step of domino electrophilic selenation-cyclization of tryptophan derivatives, by treatment with *N*-phenylselenophthalimide (*N*-PSP), followed by the replacement of the phenylselenyl radical by the appropriate functionality. According to this precedent, initially, we tried the reaction of the amino nitrile **1a** (Scheme 2) with commercial *N*-PSP in the presence of *p*-toluenesulfonic acid (*p*-TSA) or pyridinium *p*-toluenesulfonate (PPTS). However, in both cases the amino nitrile was recovered unaltered. Then, we decided to replace *p*-TSA by TFA, one of the acids that induces the cyclative tautomerization of amino nitriles **1**.[1a] Surprisingly, as shown in Scheme 2, after 7 days of treatment with 1.5 equiv of that commercial *N*-PSP in a (1:4) mixture of TFA/CH_2Cl_2, the amino nitrile **1a** provided 47% of a (∼1:1) mixture of the 2-*exo*/2-*endo* diastereoisomers of the 10b-chloropyrroloimidazoindoles **3a** and **4a**, along with 25% of the unsubstituted compound **2a**. An investigation of the origin of the chloro in this reaction led us to the commercial *N*-PSP. The ^{1}H NMR and ES-MS analyses of this reagent showed that it contained important percentages of PhSeCl (∼35%) and potassium phthalimide (∼50%), which are used as starting materials in the preparation of *N*-PSP.[10] The chlorination reagent could have been PhSeCl or *N*-

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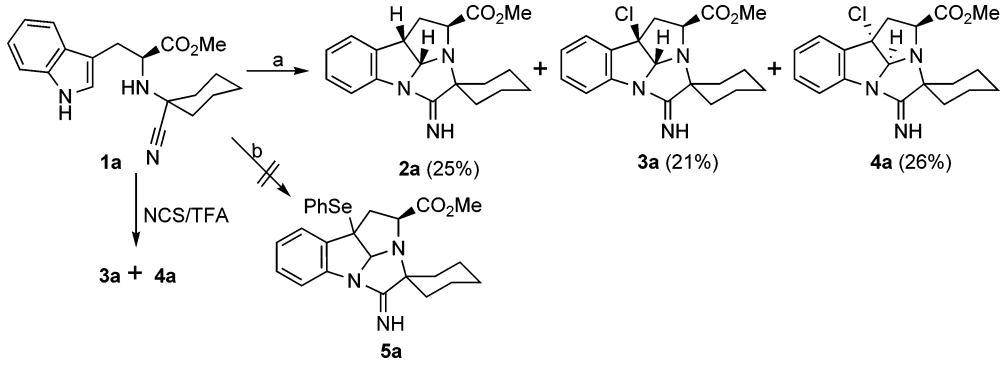
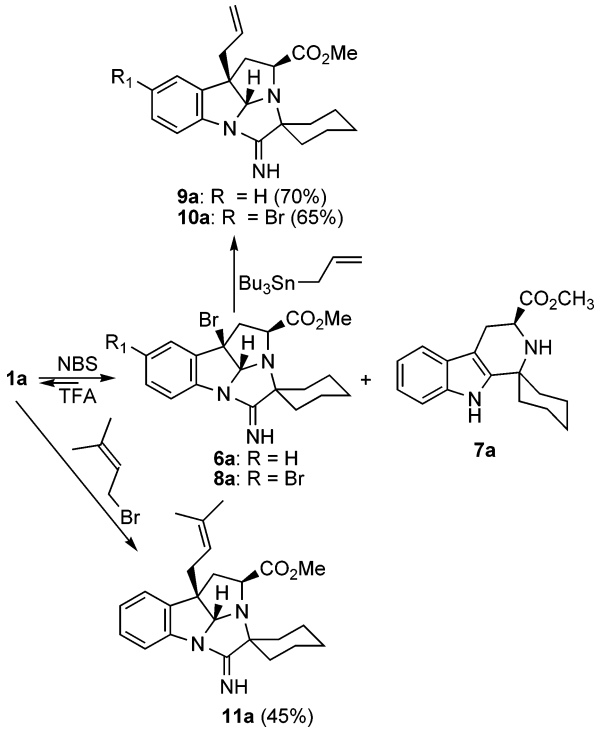
10.1021/jo070684u CCC: $37.00
Published on Web 06/19/2007

SCHEME 2. Cyclative Chlorination of α-Amino Nitrile 1a[a]



[a] *N*-PSP (A = *N*-PSP + PhSeCl + phthalimide potassium salt), TFA, CH_2Cl_2. [b] *N*-PSP (B), TFA, CH_2Cl_2.

SCHEME 3. Synthesis of 10b-Substituted Hexahydropyrroloimidazoindoles



chlorophthalimide; this last could be formed in the reaction medium. When we repeated the reaction, using commercial *N*-PSP from a different supplier, whose purity had been previously checked, the unsubstituted pyrroloimidazoindole **2a** was the only reaction product (23%). Although the unreactivity of **1a** toward *N*-PSP denied us the access to 10b-substituted compounds via phenylselenyl derivatives, the unexpected chlorination opened a possible alternative access via replacement of the halogen. Hence, we studied the optimization of the electrophilic chlorination−ring-closing reaction, focusing our attention on its stereocontrol and on the introduction of other halogens. Toward this goal, *N*-chlorosuccinimide (NCS) was first used as chlorination reagent. The treatment of the amino nitrile **1a** with 1 equiv of NCS in 10% TFA in CH_2Cl_2, at room temperature for 30 min, led to 90% of a (4:1) mixture of the diastereoisomeric chlorides **3a** and **4a**, which was chromatographically resolved. Interestingly, after 5 days at room temperature, the diastereomeric ratio in the reaction mixture evolved to a (3:2) proportion. However, pure diastereoisomers **3a** and **4a** in solution of 10% TFA in CH_2Cl_2 were stable at room temperature, and no interconversion was observed after 7 days. With the aim of improving the stereocontrol, the chlorination was then carried out under kinetic control conditions (−40 °C), which led exclusively and quantitatively to the 2-*exo* diastereoisomer **3a** after 3 h of reaction.

TABLE 1. Optimization of Bromination Conditions for 1a

				yield[a] (%)		
entry	NBS (equiv)	*T* (°C)	t (h)	**6a**	**7a**	**8a**
1	1	25	96	4	25	0
2	1	50	24	7	30	0
3	1	−40	3	91	0	0
4	2	−40	3	0	0	94

[a] Isolated yields.

A similar and parallel study was carried out for the bromination−cyclization of **1a** with *N*-bromosuccinimide (NBS) also in 10% TFA in CH_2Cl_2. The results were somewhat different. Thus, at room temperature, a complex reaction mixture was obtained from which only 4% of the 10b-bromo derivative **6a**, with a 2-*exo* configuration, and 25% of the tetrahydro-*β*-carboline derivative **7a**[1a,11] (Scheme 3) could be isolated. As shown in Table 1, the increase in the reaction temperature along with the decrease in reaction time did not improve the bromination yield (entry 2). However, the use of 1 equiv of NBS at −40 °C yielded 91% of the monobrominated compound **6a**, whereas the use of 2 equiv of NBS led to the 9,10b-dibrominated derivative **8a** in 94% yield, also with a 2-*exo* configuration. All attempts of similar iodocyclization of **1a**, by reaction with *N*-iodosuccinimide (NIS), were unsuccessful.

Taking into account the good yields obtained in the synthesis of 10b-bromopyrroloimidazoindoles **6a** and **8a**, we next explored the utility of these compounds for the replacement of the 10b-bromo by allyl- and alkyl-substituted allyl groups, by reaction with the appropriate allylstannane derivative in the presence of the free radical initiator AIBN. Initially, under the reaction conditions described for the allylation of 3a-bromohexahydropyrrolo[2,3-*b*]indoles,[12] **6a** and **8a** were recovered unaltered after 2 days of treatment with allyltributyltin in refluxing benzene. A similar result was obtained when the

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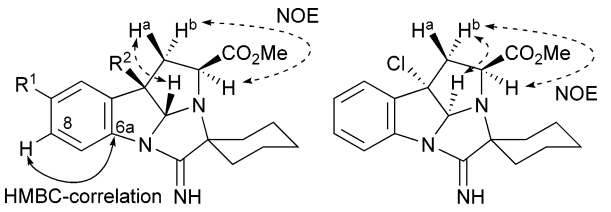

3a, **6a**, **8a-11a** **4a**

FIGURE 1. Structure assignment of the 10b-substituted hexahydropyrroloimidazoindoles.

benzene was replaced by toluene. However, when this reaction was carried out in refluxing xylene the corresponding 10b-allyl derivatives **9a** and **10a** (Scheme 3) were obtained in 70 and 65% yield, respectively. Nevertheless, when we tried a similar bromo to prenyl replacement, by reaction with prenyltributylstannane, the bromo derivatives **6a** and **8a** were recovered unchanged.

Finally, the procedure developed by the Casnati group for the insertion of isoprene units into the indole C-3 position[13] was explored as an alternative for the direct introduction of the prenyl group into the α-amino nitrile **1a**, by reaction with prenyl bromide in AcOH buffer. In the case of tryptophan or tryptamine derivatives, this methodology, via a domino prenylation−cyclization, leads to 3a-prenylhexahydropyrroloindoles, as described for the synthesis of pseudophrynaminol[14] and tryprostatin B,[15] although in low yields. As shown in Scheme 3, the treatment of **1a** with prenyl bromide and $Mg(NO_3)_2 \cdot 6H_2O$ in AcOH/AcONa buffer led with complete stereoselectivity to the 2-*exo*-10b-prenylpyrroloimidazoindole **11a** in 45% yield.

The structural assignment of the pyrroloimidazoindoles herein described was based on their ES-MS and NMR data. The ^{1}H NMR spectra showed the disappearance of the indole NH and 2-H protons and the appearance of a singlet (δ ∼5.42−6.00 ppm), corresponding to 10c-H, while the ^{13}C NMR spectra showed the conversion of the nitrile carbon (121.6 ppm) into the amidine carbon (172−176 ppm) and the transformation of the aromatic indole C_3 and C_2 carbons into the two new aliphatic carbons C_{10b} (53−73 ppm) and C_{10c} (90−96 ppm), respectively. The stereochemistry at these fusion carbons was established on the basis of the NOE correlations observed in the 1D NOESY spectra (Figure 1). Furthermore, as has been described for hexahydropyrrolo[2,3-*b*]indole derivatives[16] and for unsubstituted pyrroloimidazoindoles **2**,[1b] the 2-*endo*-10b-chloro derivative **4a** showed an upfield shift of 0.61 ppm for the MeO signal in the ^{1}H NMR spectrum, and it was significantly less levorotatory than its respective 2-*exo* isomer **3a**. The bromination position at the aromatic ring in the dibrominated compound **8a** was established on the basis of the ^{1}H, ^{13}C correlations observed in its HMBC spectrum.

The new hexahydropyrroloimidazoindoles herein described were included in screening assays for antitumorals. Interestingly, the dibromo derivative **8a** and the allyl derivative **9a** showed micromolar cytotoxicity values in human lung carcinoma (A549) and colon carcinoma (HT-29) cell lines. Furthermore, **8a**, **9a**, and **11a**, at a 10 μg/mL concentration produced higher than 50% inhibition of the epidermic growth factor receptor (EGFR).[17] In view of these preliminary results, studies on the scope and versatility of novel domino electrophile addition−cyclizations for the synthesis of diverse pyrroloimidazoindole derivatives and on their antitumoral activity are in progress.

Experimental Section

Synthesis of (2*S*,10b*R*,10c*R*)- and (2*S*,10b*S*,10c*S*)-10b-Chloro-5-imino-2-methoxycarbonyl-1,2,4,5,10b,10c-hexahydropyrrrolo-[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole-4-spirocyclohexane (3a and 4a). NCS (65.1 mg, 0.49 mmol) and TFA (500 μL) were added to a solution of *N*-(1-cyanocyclohexyl)-L-tryptophan methyl ester (**1a**, 158.7 mg, 0.59 mmol) in CH_2Cl_2 (4.5 mL), and the mixture was stirred at room temperature for 30 min. Then, the reaction mixture was poured into ice (∼10 g), neutralized with concentrated ammonium hydroxide, and extracted with CH_2Cl_2 (20 mL). The organic extracts were successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by circular chromatography, using 30−70% gradient of EtOAc in hexane as eluant, to give the chloro derivatives **3a** (126.7 mg, 72%) and **4a** (31.7 mg, 18%) as foams whose analytical and spectroscopic data are summarized in Tables 2 and 3. When this procedure was carried out at −40 °C for 3 h, the 2-*exo* isomer **4a** was exclusively and quantitatively obtained.

Optimized Synthesis of (2*S*,10b*R*,10c*R*)-10b-Bromo-5-imino-2-methoxycarbonyl-1,2,4,5,10b,10c-hexahydropyrrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole-4-spirocyclohexane (6a). NBS (29.2 mg, 0.16 mmol) and TFA (500 μL) were added to a −40 °C cooled solution of *N*-(1-cyanocyclohexyl)-L-tryptophan methyl ester (**1a**, 53.3 mg, 0.16 mmol) in CH_2Cl_2 (4.5 mL), and the mixture was stirred at that temperature for 3 h. Then, the reaction mixture was poured into ice (∼10 g), neutralized with concentrated ammonium hydroxide, and extracted with CH_2Cl_2 (20 mL). The organic extracts were successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by circular chromatography, using 30−65% gradient of EtOAc in hexane as eluant, to give the 10b-bromo derivative **6a** (58.7 mg, 91%) as a foam whose analytical and spectroscopic data are shown in Tables 2 and 3.

Synthesis of (2*S*,10b*R*,10c*R*)-9,10b-Dibromo-5-imino-2-methoxycarbonyl-1,2,4,5,10b,10c-hexahydropyrrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indole-4-spirocyclohexane (8a). NBS (56.9 mg, 0.32 mmol) and TFA (500 μL) were added to a −40 °C cooled solution of *N*-(1-cyanocyclohexyl)-L-tryptophan methyl ester (**1a**, 53.3 mg, 0.16 mmol) in CH_2Cl_2 (4.5 mL), and the mixture was stirred at that temperature for 3 h. Then, the reaction mixture was processed as indicated for the synthesis of **6a** to give the 9,10b-dibromo derivative **8a** (72.6 mg, 94%) as a foam whose analytical and spectroscopic data are shown in Tables 2 and 3.

General Procedure for the Bromo Replacement by the Allyl Group. Synthesis of the 10b-Allyl Derivatives 9a and 10a. AIBN (43.3 mg, 0.27 mmol) and allyltributyltin (828 μL, 2.7 mmol) were added to a solution of the corresponding 10b-bromopyrroloimidazoindole **6a** and **8a** (0.45 mmol) in xylene (5 mL), and the mixture was stirred under reflux for 2 days. Afterward, the solvent was removed under reduced pressure, and the residue was dissolved in diethyl ether (10 mL). This solution was stirred with 15% aqueous solution of potassium fluoride dihydrate (10 mL) for 24 h. Then, the organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by circular chromatography, using 15−45% gradient of EtOAc in hexane as eluant, to give the 10b-allyl derivatives **9a** and **10a** as foams whose analytical and spectroscopic data are shown in Tables 2 and 3.

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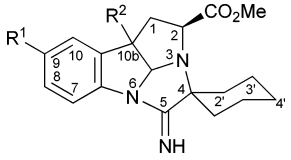
TABLE 2. Analytical Data of 10b-Substituted Hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole Derivatives



compd[a]	R^1	R^2	config 2	config 10b	config 10c	formula[b]	yield (%)	ES-MS $[M+1]^+$	$[\alpha]^{20}_D$	HPLC t_R (min) (A:B)[c]
3a	H	Cl	*S*	*R*	*R*	$C_{19}H_{22}ClN_3O_2$	100[d]	360.0	−52.3 (*c* 0.6, MeOH)	2.68 (40:60)
4a	H	Cl	*S*	*S*	*S*	$C_{19}H_{22}ClN_3O_2$	18[e]	360.0	−0.84 (*c* 1, MeOH)	3.42 (40:60)
6a	H	Br	*S*	*R*	*R*	$C_{19}H_{22}BrN_3O_2$	91	404.0	−64.31 (*c* 0.9, MeOH)	2.72 (50:50)
8a	Br	Br	*S*	*R*	*R*	$C_{19}H_{21}Br_2N_3O_2$	100	484.0	−47.30 (*c* 1.2, MeOH)	3.83 (50:50)
9a	H	Allyl	*S*	*S*	*R*	$C_{22}H_{27}N_3O_2$	70	366.2	−70.79 (*c* 1, MeOH)	2.59 (50:50)
10a	Br	Allyl	*S*	*S*	*R*	$C_{22}H_{26}BrN_3O_2$	89	444.1	−105.9 (*c* 0.9, MeOH)	3.33 (25:75)
11a	H	Prenyl	*S*	*S*	*R*	$C_{24}H_{31}N_3O_2$	37	394.2	−91.36 (*c* 1, MeOH)	4.08 (25:75)

[a] Foams. [b] Satisfactory analysis for C, H, N. [c] Novapak C_{18} (3.9 × 150 mm, 4 μm). Flow rate = 1 mL/min. A = CH_3CN, B = 0.05% TFA in H_2O. [d] Yield when the reaction temperature was −40 °C. [e] Yield for the reaction at room temperature.

TABLE 3. Significant Spectroscopic NMR Data of 10b-Substituted Hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole Derivatives

	3a	**4a**	**6a**	**8a**	**9a**	**10a**	**11a**
^{1}H NMR[a]							
1-H	2.67, 2.84	2.71, 3.20	2.79, 3.00	2.77, 2.98	2.20, 2.27	2.17, 2.26	2.19, 2.27
2-H	3.17	4.10	3.16	3.13	3.23	3.18	3.21
7-H	7.43	7.46	7.39	7.31	7.40	7.30	7.39
8-H	7.29	7.26	7.31	7.41	7.26	7.35	7.25
9-H	7.10	7.01	7.18	-	7.07	-	7.05
10-H	7.35	7.27	7.41	7.51	7.15	7.24	7.12
10c-H	5.80	5.65	6.00	5.97	5.49	5.46	5.42
OCH_3	3.64	3.03	3.69	3.69	3.67	3.66	3.66
cyclohexyl	1.38−1.93, 1.99	1.27−1.78, 2.05	1.37−1.84, 2.05	1.37−1.82, 2.04	1.27−1.82, 2.05	1.29−1.79, 2.01	1.39−1.80, 2.03
$J_{1,2}$ (Hz)	11.5 and 5.5	9 and 0	12.5 and 5.5	12.5 and 5	12 and 6	12 and 6	12 and 6
$J_{1,1}$ (Hz)	12.5	13.5	12.5	12.5	12	12	12
R^1					2.63, 2.72, 5.06, 5.14, 5.60	2.60, 2.74, 5.09, 5.16, 5.60	1.60, 1.63, 2.63, 2.65, 4.94
^{13}C NMR[b]							
C_1	49.2	48.3	50.7	50.5	45.3	45.2	45.4
C_2	61.8	63.0	61.8	61.7	61.8	61.6	61.7
C_4	72.9	70.2	72.4	72.3	72.5	72.3	72.4
C_5	172.8	175.7	173.2	173.2	174.3	173.3	173.7
C_{6a}	142.9	147.0	142.9	142.1	144.4	143.7	144.3
C_7	115.6	114.5	115.3	117.0	114.9	116.4	114.6
C_8	130.5	130.5	130.3	133.2	128.5	131.3	128.2
C_9	124.5	124.0	125.3	117.2	124.2	116.4	124.0
C_{10}	125.1	124.5	125.0	128.2	123.4	126.3	123.3
C_{10a}	135.2	134.8	136.0	138.0	137.4	139.6	137.9
C_{10b}	72.0	73.4	61.4	60.2	53.0	53.0	53.4
C_{10c}	95.1	94.5	95.6	95.6	90.5	90.4	90.9
OCH_3	52.5	51.5	52.5	52.5	52.2	52.2	52.2
$C_{2'}$, $C_{6'}$	29.1, 34.0	29.5, 34.5	29.2, 34.0	21.9, 33.9	29.5, 34.1	29.4, 33.9	29.5, 34.0
$C_{4'}$	25.3	25.5	25.3	25.2	25.5	25.3	25.4
$C_{3'}$, $C_{5'}$	21.8, 22.1	22.1, 23.1	21.8, 22.1	21.8, 22.0	22.0, 22.3	21.1, 21.9	21.9, 22.2
R^1					42.4, 119.0, 133.7	42.1, 119.4, 133.2	18.3, 25.8, 36.7, 119.3, 134.9
CO_2	172.1	172.9	172.0	171.7	173.6	173.3	174.4

[a] Spectra registered at 200, 300, or 400 MHz in $CDCl_3$, assigned with the help of COSY spectra. [b] Spectra registered at 75 or 100 MHz in $CDCl_3$, assigned with the help of HSQC and HMBC spectra.

Synthesis of (2*S*,10b*S*,10c*R*)-5-Imino-10b-(3-methyl-2-buten-1-yl)-2-methoxycarbonyl-1,2,4,5,10b,10c-hexahydropyrrrolo-[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole-4-spirocyclohexane (11a). Prenyl bromide (267 μL, 2.28 mmol) was dropwise added to a vigorously stirred solution of *N*-(1-cyanocyclohexyl)-L-tryptophan methyl ester (**1a**, 124.4 mg, 0.38 mmol) and magnesium nitrate hexahydrate (489 mg, 1.9 mmol) in acetic acid/sodium acetate buffer (pH 2.9, prepared from 8 g of sodium acetate, 100 mL of acetic acid, and 20 mL of H_2O, 15 mL) under argon. After 2 h of stirring at room temperature, the reaction mixture was sequentially neutralized with Na_2CO_3 and extracted with CH_2Cl_2 (20 mL). The organic extracts were successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 12−50% gradient of EtOAc in hexane as eluant, to give the 10b-prenyl derivative **11a** as a foam whose analytical and spectroscopic data are shown in Tables 2 and 3.

Acknowledgment. This work was supported by CICYT (SAF2006-01205). J.A.G.-V. held a postgraduate I3P fellowship from the CSIC. The antitumoral evaluation was carried out by Pharma Mar, S.A.

Supporting Information Available: General methods, combustion analysis data, and ^{1}H NMR and ^{13}C NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070684U