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Synthesis of indole alkaloid analogues containing the novel hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole skeleton by ring-closing reactions of tryptophan-derived α-amino nitriles

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Abstract—New indole alkaloid analogues, containing a 10b-methyl- or a 10b-hydroxy-1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indole skeleton, have been obtained by highly stereoselective electrophile addition–cyclization reactions of a tryptophan-derived α-amino nitriles.

1. Introduction

We have recently described the stereoselective synthesis of compounds of general formula **1** (Fig. 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] This novel ring system could be considered as a hybrid of 1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indole and 2,3,9,9a-tetrahydroimidazo[1,2-*a*]indole, both present in a growing class of indole alkaloids with a wide range of biological activities. The hexahydropyrrolo[2,3-*b*]indole is present, among others, in the acetylcholinesterase inhibitor physostigmine (**3**),[2] which has a methyl group at position 3a, and in diverse alkaloids that possess a hydroxy group at that position, such as alline (**4**),[3] flustraminol,[4] gypsetin,[5] okaramins,[6] brevianamide E (**5**),[7] and several peptides, which contain modified tryptophan residues.[8] On the other hand, the 9-hydroxy-tetrahydroimidazo[1,2-*a*]-indole is present in the cholecystokinin antagonist asperlicin (**6**),[9] in the antifungic agents fumiquinazolines,[10] or in the substance P antagonists fiscalins (**7**).[11] In the preparation of novel indole alkaloid analogues, we have explored and reported herein the synthesis of 1,2,4,5,10b,10c-hexahydropyrrolo-[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole derivatives **2** substituted with a methyl or hydroxy group at the 10b position, by ring-closing reactions of tryptophan-derived α-amino nitriles.

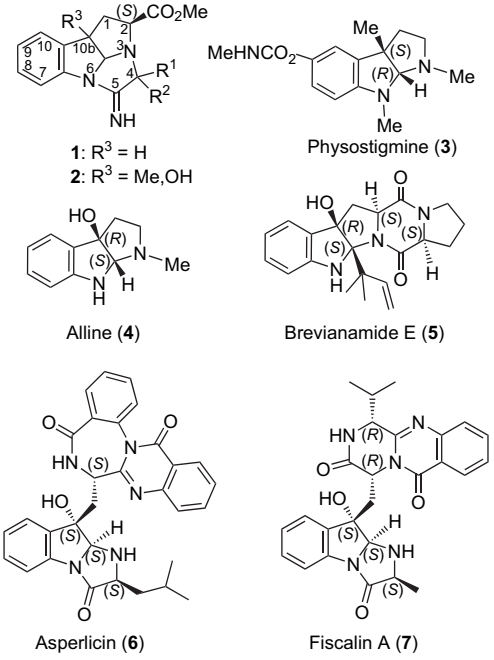

Figure 1. General formulas of hexahydropyrroloimidazoindoles and examples of related indole alkaloids.

2. Results and discussion

The construction of the 10b-methyl-hexahydropyrroloimidazoindole system was envisaged by applying a strategy similar to that reported by the Nakagawa's group for the synthesis of physostigmine.[12] This strategy involves the

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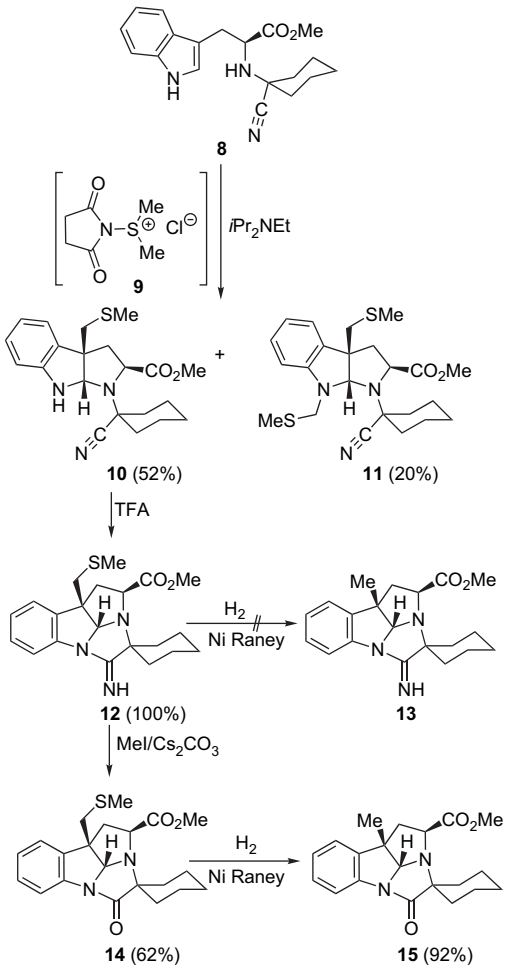
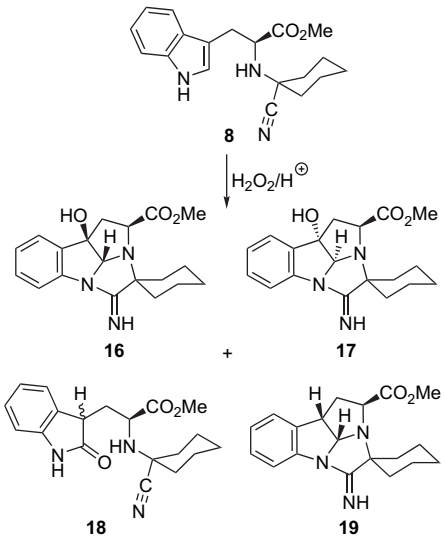
introduction of a methylthiomethyl group in tryptophan derivatives by a cyclative alkylation with the Corey–Kim reagent,[13] followed by reductive desulfurization of the methylthiomethyl to a methyl group. The tryptophan- and cyclohexanone-derived α-amino nitrile **8** was used as a substrate for the study of this methodology. As shown in Scheme 1, the reaction of amino nitrile **8** with 2 equiv of the Corey–Kim reagent (**9**) [prepared in situ by reaction of *N*-chlorosuccinimide with dimethyl sulfide in the presence of 2.4 equiv of diisopropylethylamine (DIEA)] led to a mixture of 52% of the 3a-monoalkylated-hexahydropyrrolo[2,3-*b*]indole **10**, along with 20% of the 3a,8-dialkylated product **11**. With the aim of avoiding the formation of this dialkylation product, the reaction was also performed using only 1 equiv of the Corey–Kim reagent. However, in this case the conversion was very low, obtaining only 16% of **10**, and recovering 53% of the starting amino nitrile. Interestingly, the ring-closing alkylation proceeded with complete stereoselectivity toward the 2-*exo*-diastereoisomer, while the Nakagawa's group, under the same reaction conditions, reported a (≈1:1) 2-*exo*/2-*endo* diastereoisomeric ratio.[12] In the next step, the treatment of the 3a-monoalkylated compound **10** with 10% solution of trifluoroacetic acid (TFA) in CH_2Cl_2 quantitatively led to the 5-imino-pyrroloimidazoindole derivative **12**, a tautomer of **10**, which results from the electrophilic cyclization of indole NH onto the protonated cyano group. All attempts of reductive desulfurization of the methylthiomethyl group of **12**, by heating in the presence of Raney Ni[14] or by catalytic hydrogenation in the presence of this catalyst[12] were unsuccessful, recovering the starting material unchanged. As we had previously observed for the hydrogenolysis of a benzyloxycarbonyl-protecting group from a pyrroloimidazoindole containing a *N*-Z-Ala residue,[15] the difficulty of catalytic reductive desulfurization could be due to catalyst poisoning by the amidine group. Hence, we turned our attention from the amidine to the lactam analogue **14**, which was obtained in 62% yield by alkylative hydrolysis of the amidine group of **12**, carried out by treatment with MeI and Cs_2CO_3 in CH_3CN at 80 °C for two days.[1a] Then, the hydrogenolysis of the methylthiomethyl group of **14** to the methyl of **15** was successfully achieved by hydrogenation in the presence of Raney Ni, in EtOH at 80 °C under 2 atm of H_2.



Scheme 1. Synthesis of 10b-methyl-hexahydropyrroloimidazoindoles.

The synthesis of the 10b-hydroxy-hexahydropyrroloimidazoindole skeleton was first attempted by applying the Crich's methodology of oxidation of hexahydropyrrolo[2,3-*b*]indoles with ceric ammonium nitrate (CAN)[16] to the 10b-unsubstituted hexahydropyrroloimidazoindoles **1**. However, these compounds were recovered unaltered after three days of treatment with 5 equiv of CAN. Then, the introduction of the hydroxy group was approached by cyclative oxidation of the corresponding tryptophan-derived α-amino nitrile. We decided to try H_2O_2 as an oxidizer, a commercial, cheap and environmental friendly reagent. Taking into account that, as above mentioned, the cyclization to the hexahydropyrroloimidazoindole system requires the cyano activation by protonation, this oxidation was studied in acid media. As shown in Scheme 2, the treatment of amino nitrile **8**, dissolved in a 10% solution of TFA in CH_2Cl_2, with 4% of H_2O_2 (33% solution in H_2O) at 0 °C led, after 3 h of reaction, to the two diastereoisomeric 10b-hydroxy-hexahydropyrroloimidazoindoles **16** (54%) and **17** (13%), along with the 2-oxoindolines **18** (11%), traces of the 10b-unsubstituted hexahydropyrroloimidazoindole **19**[1a] (1%) and 21% of H–Trp–OMe, resulting from the amino nitrile degradation in



Scheme 2. H_2O_2-mediated oxidation of the tryptophan-derived α-amino nitrile **8**.

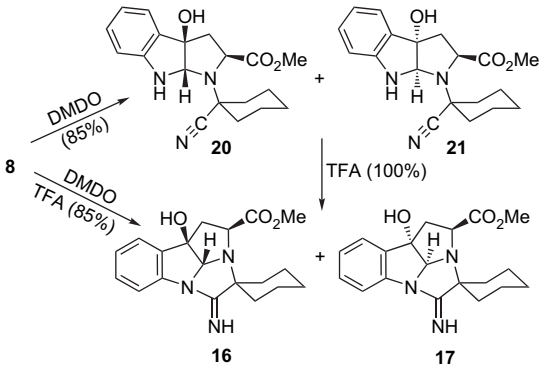
the acid medium. Diastereoisomers **16** and **17** were chromatographically resolved; however, the epimeric mixture of 2-oxoindolines **18** could not be resolved. To minimize the amino nitrile degradation and the formation of oxoindolines, a reaction condition optimization study was carried out. The results of this study (Table 1) showed that the increase of the H_2O_2 concentration lowered the overall yield of **16** and **17** due to the increase in oxoindolines **18**, while the increase of the TFA concentration or the temperature led to an increase in degradation products. Finally, the replacement of TFA by 85% H_3PO_4 as acid medium (entry 9) produced a significant increase in the overall yield of the desired **16** and **17** (86%).

Table 1. Optimization of reaction conditions for the H_2O_2-mediated oxidation of **8**

Entry	Acid	Acid concn[b] (%)	H_2O_2 concn[b] (%)	T (°C)	t (h)	Yield[a] (%)				
						16	**17**	**18**	**19**	H–Trp–OMe
1	TFA	10	4	0	3	54	13	11	1	21
2	TFA	10	10	0	2	23	10	19	12	36
3	TFA	10	20	0	3	30	16	24	8	22
4	TFA	10	35	0	3	32	18	50	0	0
5	TFA	10	35	25	1	23	6	46	3	22
6	TFA	20	10	0	2	16	8	13	12	51
7	TFA	40	4	0	2	6	3	17	4	70
8	TFA	40	35	25	1	10	3	8	7	72
9	H_3PO_4	10	4	0	5	56	30	9	1	4

[a] Yields were determined by ^{1}H NMR analysis, except for entries 1 and 9, where yields are of isolated compounds.
[b] Percentage in CH_2Cl_2 solution.

Having in mind that nowadays dimethyldioxirane (DMDO), due to its good efficacy and selectivity, is the most used oxidizer of tryptophan derivatives to 3a-hydroxy-pyrroloindoles,[17] we decided to study the oxidation of amino nitrile **8** also with this non-commercial reagent, which was freshly prepared as a 0.05 M solution in acetone.[18] Under the reaction conditions reported by the Danishefsky's group,[17a,b] the treatment of **8**, dissolved in CH_2Cl_2, with 1.2 equiv of the acetone solution of DMDO at −78 °C gave 85% of a (7:1) diastereomeric mixture of the 3a-hydroxy-hexahydropyrrolo[2,3-*b*]indoles **20** and **21** (Scheme 3), which could not be separated. TLC and ^{1}H NMR analysis showed the instability of this mixture and the appearance of degradation products. Therefore, without further purification, it was treated with a 10% solution of TFA in CH_2Cl_2. This treatment quantitatively produced the corresponding 10b-hydroxy-hexahydropyrroloimidazoindoles **16** and **17**. The parallel treatment of amino nitrile **8** with DMDO in the presence of a 10% of TFA at −78 °C led directly to **16** and **17**, in the same 2-*exo*/2-*endo* diastereomeric ratio (7:1) and in the same overall yield (85%). Interestingly, both H_2O_2 and DMDO gave similar overall yield of 10b-hydroxy-hexahydropyrroloimidazoindoles, although the stereoselectivity of DMDO for the 2-*exo*-diastereoisomer **16** was higher. This higher stereoselectivity is related with the lower reaction temperature, which favors this kinetic control product. In the case of using H_2O_2, the aqueous phase that contains this reagent froze below 0 °C and the oxidation did not take place.



Scheme 3. DMDO-mediated oxidation of α-amino nitrile **8**.

The structural assignment of pyrroloimidazoindoles **12** and **14–17** 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 ($\delta \approx 5.32$–6.77 ppm), corresponding to the 10c-H, while the ^{13}C NMR spectra showed the conversion of the nitrile carbon (121.6 ppm) into the amidine or lactam carbon (172–182 ppm), and the transformation of the aromatic indole C_3 and C_2 carbons into two new aliphatic carbons C_{10b} (49–85 ppm) and C_{10c} (89–94 ppm), respectively. The stereochemistry at these fusion carbons was established on the basis of the NOE correlations observed in the 1D NOESY spectra (Fig. 2). Furthermore, as it has been described for hexahydropyrrolo[2,3-*b*]indole derivatives[19] and for unsubstituted pyrroloimidazoindoles **1**,[1b] the 2-*endo*-10b-hydroxy-pyrroloimidazoindole **17** showed an upfield shift of 0.64 ppm for the MeO signal in the ^{1}H NMR spectrum, and it was significantly less levorotatory than its respective 2-*exo*-diastereoisomer **16**.

In conclusion, herein we describe highly stereoselective electrophilic alkylative and oxidative ring-closing reactions of a tryptophan-derived α-amino nitrile to 10b-methyl- and 10b-hydroxy-1,2,4,5,10b,10c-hexahydropyrrolo-[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indoles, respectively, which give easy access to new indole alkaloid analogues.

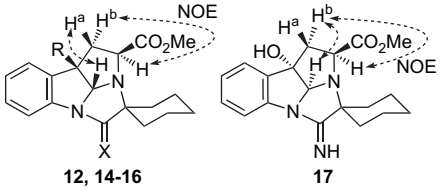


Figure 2. Configuration assignment of 10b-substituted-hexahydropyrroloimidazoindoles.

3. Experimental

3.1. General

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with 0.2 mm layer of silica gel 60 F_{254}. Silica gel 60 (230–400 mesh) was used for flash chromatography. Preparative radial

chromatography was performed on 20 cm diameter glass plates coated with 1 mm layer of silica gel PF_{254}. Analytical RP-HPLC was performed on a Novapak C_{18} (3.9×150 mm, 4 μm) column, with a flow rate of 1 mL/min, and using a tunable UV detector set at 214 nm. Mixtures of CH_3CN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phases. ^1H NMR spectra were recorded at 300, 400, or 500 MHz, using TMS as reference, and ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. The NMR spectra assignment was based on COSY and HSQC spectra. ESI-MS spectra were performed, in positive mode, using MeOH as solvent.

3.2. Synthesis of methyl (2*S*,3a*R*,8a*S*)-1-(1-cyanocyclohexyl)-3a-(methylthiomethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-yl-carboxylate (10) and methyl (2*S*,3a*R*,8a*S*)-1-(1-cyanocyclohexyl)-3a,8-bis(methylthiomethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-indol-2-yl-carboxylate (11)

Dimethyl sulfide (81 μL, 1.11 mmol) was added to a cooled solution (−78 °C) of *N*-chlorosuccinimide (123.2 mg, 0.92 mmol) in CH_2Cl_2 (3 mL) and the solution was stirred at that temperature for 1 h. Then, a solution of α-amino nitrile **8** (150.1 mg, 0.46 mmol) in CH_2Cl_2 (2 mL) and DIEA (189.5 μL, 1.11 mmol) were added and the stirring was maintained at −78 °C for 2 h. Afterward, the reaction mixture was brought to room temperature, diluted with CH_2Cl_2 (20 mL), successively washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 5–15% EtOAc gradient in hexane as eluant, to give the title compounds.

3.2.1. Methyl (2*S*,3a*R*,8a*S*)-1-(1-cyanocyclohexyl)-3a-(methylthiomethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-yl-carboxylate (10). Foam (92.1 mg, 52%); $[\alpha]_D^{20}$ −110.41 (*c* 0.9, MeOH); HPLC [Novapak C_{18} (3.9× 150 mm, 4 μm), (A:B, 50:50)] t_R 3.58 min; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23–1.86 (m, 9H, cyclohexyl), 2.00 [s, 3H, 3a-(CH_2–S–CH_3)], 2.18 (dd, 1H, *J*=7 and 13 Hz, 3-H), 2.24 (m, 1H, 2′or 6′-H^{ec}), 2.46 (dd, 1H, *J*=8.5 and 13 Hz, 3-H), 3.03 (d, 1H, *J*=12.5 Hz, 3a-CH_2), 3.08 (d, 1H, *J*=12.5 Hz, 3a-CH_2), 3.70 (s, 3H, OCH_3), 3.85 (dd, 1H, *J*=7 and 8.5 Hz, 2-H), 4.33 (d, 1H, 8-H), 5.48 (d, 1H, *J*= 3.5 Hz, 8a-H), 6.65 (d, 1H, *J*=8 Hz, 7-H), 6.75 (t, 1H, *J*=7 Hz, 5-H), 7.07 (t, 1H, *J*=8 Hz, 6-H), 7.10 (d, 1H, *J*=7 Hz, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 [3a-(CH_2–S–CH_3)], 22.3 and 22.7 ($C_{3'}$ and $C_{5'}$), 24.5 ($C_{4'}$), 34.9 and 36.7 ($C_{2'}$ y $C_{6'}$), 42.0 (3a-CH_2), 43.1 (C_3), 52.2 (OCH_3), 56.4 (C_{3a}), 58.5 ($C_{1'}$), 60.6 (C_2), 84.4 (C_{8a}), 110.3 (C_7), 119.4 (C_5), 120.9 (CN), 122.6 (C_4), 128.7 (C_6), 132.5 (C_{3b}), 148.5 (C_{7a}), 175.5 (CO_2); ES-MS *m*/*z* 386.2 (100) $[M+1]^+$. Anal. Calcd for $C_{21}H_{27}N_3O_2S$: C, 65.42; H, 7.06; N, 10.90. Found: C, 65.76; H, 7.35; N, 11.23.

3.2.2. Methyl (2*S*,3a*R*,8a*R*)-1-(1-cyanocyclohexyl)-3a,8-bis(methylthiomethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-yl-carboxylate (11). Foam (41.7 mg, 20%); $[\alpha]_D^{20}$ +96.83 (*c* 1.1, MeOH); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 50:50)] t_R 5.76 min; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23–2.04 (m, 9H, cyclohexyl), 2.06 [s, 3H, 8-(CH_2–S–CH_3)], 2.09 [s, 3H, 3a-(CH_2–S–CH_3)], 2.36 (dd, 1H, *J*=5 and 13 Hz, 3-H), 2.55 (dd, 1H, *J*=8 and 13 Hz, 3-H), 2.61 (m, 1H, 2′ or 6′-H^{ec}), 3.06 (d, 1H, *J*=12.5 Hz, 3a-CH_2), 3.18 (d, 1H, *J*=12.5 Hz, 3a-CH_2), 3.38 (s, 3H, OCH_3), 4.20 (dd, 1H, *J*=5 and 8 Hz, 2-H), 4.43 (d, 1H, *J*=14 Hz, 8-CH_2), 4.69 (d, 1H, *J*=14 Hz, 8-CH_2), 5.59 (s, 1H, 8a-H), 6.48 (d, 1H, *J*=8 Hz, 7-H), 6.64 (t, 1H, *J*=7.5 Hz, 5-H), 7.04 (d, 1H, *J*=8 Hz, 4-H), 7.05 (t, 1H, *J*=7.5 Hz, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 [8-(CH_2–S–CH_3)], 17.1 [3a-(CH_2–S–CH_3)], 22.9 and 23.0 ($C_{3'}$ and $C_{5'}$), 24.5 ($C_{4'}$), 36.5 and 37.1 ($C_{2'}$ and $C_{6'}$), 41.0 (3a-CH_2), 42.4 (C_3), 48.2 (8-CH_2), 52.0 (OCH_3), 57.1 (C_{3a}), 60.5 ($C_{1'}$), 62.7 (C_2), 86.2 (C_{8a}), 106.6 (C_7), 117.9 (C_5), 122.3 (CN), 122.9 (C_4), 128.7 (C_6), 130.7 (C_{3b}), 148.1 (C_{7a}), 173.7 (CO_2); ES-MS *m*/*z* 468.2 (100) $[M+Na]^+$. Anal. Calcd for $C_{23}H_{31}N_3O_2S_2$: C, 61.99; H, 7.01; N, 9.43. Found: C, 61.74; H, 7.37; N, 9.79.

3.3. Synthesis of (2*S*,10b*R*,10c*R*)-5-imino-2-methoxycarbonyl-10b-methylthiomethyl-1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole-4-spirocyclohexane (12)

TFA (500 μL) was added to a solution of **10** (82.4 mg, 0.21 mmol) in CH_2Cl_2 (4.5 mL) and the mixture was stirred at room temperature for 30 min. Then, the mixture was poured into ice (≈10 mg), neutralized with NH_4OH, and extracted with CH_2Cl_2 (20 mL). The organic extracts were successively washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 30–80% EtOAc gradient in hexane as eluant, to give the title compound as a foam (80.9 mg, 100%); $[\alpha]_D^{20}$ −109.17 (*c* 0.9, MeOH); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 50:50)] t_R 2.54 min; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.80 and 2.05 (m, 10H, cyclohexyl), 2.04 [s, 3H, 10b-(CH_2–S–CH_3)], 2.24 (dd, 1H, *J*=6 and 12 Hz, 1-H), 2.35 (t, 1H, *J*=12 Hz, 1-H), 3.01 (d, 1H, *J*=12.5 Hz, 10b-CH_2), 3.22 (d, 1H, *J*=12.5 Hz, 10b-CH_2), 3.24 (dd, 1H, *J*=6 and 12 Hz, 2-H), 3.67 (s, 3H, OMe), 5.65 (s, 1H, 10c-H), 7.07 (dt, 1H, *J*=1 and 7.5 Hz, 9-H), 7.24 (d, 1H, *J*=7.5 Hz, 10-H), 7.28 (dt, 1H, *J*=1 and 7.5 Hz, 8-H), 7.41 (d, 1H, *J*=7.5 Hz, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3 [10b-(CH_2–S–CH_3)], 21.9, 22.2, 25.4, 29.4, 34.0 (cyclohexyl), 45.0 (C_1), 52.2 (OMe), 54.4 (C_{10b}), 61.9 (C_2), 72.4 (C_4), 91.0 (C_{10c}), 114.9 (C_7), 123.5 (C_{10}), 124.1 (C_9), 129.0 (C_8), 136.4 (C_{10a}), 144.5 (C_{6a}), 173.7 (CO_2), 174.0 (C_5); ES-MS *m*/*z* 386.2 (100) $[M+1]^+$. Anal. Calcd for $C_{21}H_{27}N_3O_2S$: C, 65.42; H, 7.06; N, 10.90. Found: C, 65.63; H, 7.01; N, 10.73.

3.4. Synthesis of (2*S*,10b*R*,10c*R*)-2-methoxycarbonyl-10b-methylthiomethyl-5-oxo-1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole-4-spirocyclohexane (14)

Cs_2CO_3 (87.6 mg, 0.27 mmol) and MeI (100.8 μL, 1.62 mmol) were added to a solution of **12** (70.3 mg, 0.18 mmol) in dry CH_3CN (3 mL), and this mixture was stirred at 80 °C in a pressure tube for two days. Afterward, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (10 mL), and the resulting solution was successively washed with H_2O (3 mL) and brine (3 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 15–25% gradient of

EtOAc in hexane as eluant, to yield the title compound as a foam (45.2 mg, 65%); $[\alpha]_D^{20}$ −48.01 (*c* 0.7, MeOH); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 50:50)] t_R 14.34 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–2.02 (m, 10H, cyclohexyl), 2.03 [s, 3H, 10b-(CH_2–S–CH_3)], 2.30 (d, 2H, *J*=9 Hz, 1-H), 3.00 (d, 1H, *J*=12.5 Hz, 10b-CH_2), 3.22 (d, 1H, *J*=12.5 Hz, 10b-CH_2), 3.37 (t, 1H, *J*=9 Hz, 2-H), 3.68 (s, 3H, OMe), 5.77 (s, 1H, 10c-H), 7.11 (t, 1H, *J*=7.5 Hz, 9-H), 7.25 (d, 1H, *J*=7.5 Hz, 10-H), 7.28 (t, 1H, *J*=7.5 Hz, 8-H), 7.45 (d, 1H, *J*=7.5 Hz, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 [10b-(CH_2–S–CH_3)], 21.9, 22.8, 25.7, 29.4, 33.0 (cyclohexyl), 44.8 (C_1), 52.8 (OMe), 55.0 (C_{10b}), 62.3 (C_2), 72.2 (C_4), 89.2 (C_{10c}), 115.7 (C_7), 124.1 (C_{10}), 125.6 (C_9), 129.6 (C_8), 136.4 (C_{10a}), 142.2 (C_{6a}), 173.4 (CO_2), 181.4 (C_5); ES-MS *m/z* 387.1 (100) $[M+1]^+$. Anal. Calcd for $C_{21}H_{26}N_2O_3S$: C, 65.26; H, 6.78; N, 7.25. Found: C, 65.60; H, 6.89; N, 7.23.

3.5. Synthesis of (2*S*,10b*S*,10c*R*)-2-methoxycarbonyl-10b-methyl-5-oxo-1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole-4-spirocyclohexane (15)

Ni Raney (125 mg), previously washed with EtOH, was added to a solution of **14** (29.9 mg, 0.08 mmol) in EtOH (10 mL) and the reaction mixture was hydrogenated at 80 °C under 2 atm of H_2 for 3 h. The catalyst was filtered off and washed with EtOH (10 mL). The combined filtrates were evaporated to dryness and the residue was purified by circular chromatography, using 5–25% gradient of EtOAc in hexane as eluant, to yield the title compound as a foam (27.2 mg, 92%); $[\alpha]_D^{20}$ −63.20 (*c* 1, MeOH); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 50:50)] t_R 5.85 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40–2.05 (m, 10H, cyclohexyl), 1.61 (s, 3H, 10b-CH_3), 2.18 (t, 1H, *J*=12 Hz, 1-H), 2.28 (dd, 1H, *J*=6 and 12 Hz, 1-H), 3.37 (dd, 1H, *J*=6 and 12 Hz, 2-H), 3.69 (s, 3H, OMe), 5.53 (s, 1H, 10c-H), 7.12 (t, 1H, *J*=7 Hz, 9-H), 7.17 (d, 1H, *J*=7 Hz, 10-H), 7.26 (t, 1H, *J*=7 Hz, 8-H), 7.44 (d, 1H, *J*=7 Hz, 7-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.3, 25.2, 29.0, 32.6 (cyclohexyl), 25.5 (10b-CH_3), 45.9 (C_1), 52.3 (OMe), 49.4 (C_{10b}), 62.2 (C_2), 71.9 (C_4), 91.1 (C_{10c}), 115.1 (C_7), 123.0 (C_{10}), 125.2 (C_9), 128.6 (C_8), 139.0 (C_{10a}), 140.7 (C_{6a}), 173.3 (CO_2), 180.9 (C_5); ES-MS *m/z* 341.2 (100) $[M+1]^+$. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.49; H, 7.34; N, 7.99.

3.6. General procedure for the H_2O_2-mediated oxidation of amino nitrile 8

Aqueous solution of 33% H_2O_2 (according to the percentage indicated in Table 1) and the appropriate acid (TFA or 85% H_3PO_4 in the percentage indicated in Table 1) were successively added to a solution of amino nitrile **8** (81.3 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred under the reaction conditions indicated in Table 1. Afterward, this mixture was sequentially poured into ice (≈10 mg), neutralized with NH_4OH, and extracted with CH_2Cl_2 (20 mL). The organic extracts were successively washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was analyzed by ^{1}H NMR and HPLC to determine reaction product proportions and, in some cases, was purified by circular chromatography, using 20–60% EtOAc gradient in hexane as eluant, to give **16**–**19** and H–Trp–OMe in the yield indicated in Table 1.

3.6.1. (2*S*,10b*R*,10c*R*)-10b-Hydroxy-5-imino-2-methoxycarbonyl-1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indole-4-spirocyclohexane (16). Foam; $[\alpha]_D^{20}$ −124.5 (*c* 0.6, MeOH); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 25:75)] t_R 2.88 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–2.01 (m, 10H, cyclohexyl), 2.43 (dd, 1H, *J*=6 and 12.5 Hz, 1-H), 2.56 (dd, 1H, *J*=10.5 and 12.5 Hz, 1-H), 3.29 (dd, 1H, *J*=6 and 10.5 Hz, 2-H), 3.70 (s, 3H, OMe), 5.49 (s, 1H, 10c-H), 7.13 (t, 1H, *J*=7 Hz, 9-H), 7.37 (d, 1H, *J*=7 Hz, 10-H), 7.34 (t, 1H, *J*=7 Hz, 8-H), 7.38 (d, 1H, *J*=7 Hz, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.2, 25.4, 29.1, 34.3 (cyclohexyl), 45.6 (C_1), 52.4 (OMe), 61.6 (C_2), 71.8 (C_4), 85.5 (C_{10b}), 93.4 (C_{10c}), 115.7 (C_7), 123.6 (C_9), 124.8 (C_{10}), 130.3 (C_8), 136.4 (C_{10a}), 143.6 (C_{6a}), 173.4 (CO_2), 172.9 (C_5); ES-MS *m/z* 342.2 (100) $[M+1]^+$. Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.99; H, 7.07; N, 12.56.

3.6.2. (2*S*,10b*S*,10c*S*)-10b-Hydroxy-5-imino-2-methoxycarbonyl-1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indole-4-spirocyclohexane (17). Foam; $[\alpha]_D^{20}$ +7.99 (*c* 1.2, MeOH); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 25:75)] t_R 3.64 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–2.06 (m, 10H, cyclohexyl), 2.39 (d, 1H, *J*=13.5 Hz, 1-H), 2.95 (dd, 1H, *J*=9.5 and 13.5 Hz, 1-H), 3.06 (s, 3H, OMe), 4.14 (d, 1H, *J*=9.5 Hz, 2-H), 5.32 (s, 1H, 10c-H), 7.05 (t, 1H, *J*=7 Hz, 9-H), 7.30 (d, 1H, *J*=7 Hz, 10-H), 7.33 (t, 1H, *J*=7 Hz, 8-H), 7.46 (d, 1H, *J*=7 Hz, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 23.1, 25.5, 29.4, 34.6 (cyclohexyl), 44.3 (C_1), 51.3 (OMe), 62.6 (C_2), 70.4 (C_4), 85.7 (C_{10b}), 92.8 (C_{10c}), 114.6 (C_7), 123.6 (C_9), 123.6 (C_{10}), 130.4 (C_8), 136.1 (C_{10a}), 147.8 (C_{6a}), 173.7 (CO_2), 176.0 (C_5); ES-MS *m/z* 342.2 (100) $[M+1]^+$; Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.87; H, 6.59; N, 12.13.

3.6.3. Methyl (2*S*)-2-(1-cyanocyclohexylamino)-3-[(3*RS*)-2-oxoindolin-3-yl]propanoate (18). Foam; HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 25:75)] t_R 3.55 (68%) and 4.59 (32%) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77–1.84 (m, 10H, cyclohexyl), 2.05–2.25 (m, 2H, 3-H), 3.59 [dd, 1H, *J*=4 and 8 Hz, 3-H (indoline)], 3.67 and 3.68 (2s, 3H, OCH_3), 3.70–3.80 (m, 1H, 2-H), 6.82 [t, 1H, *J*=7.5 Hz, 5-H (indoline)], 6.97 and 6.98 [2t, 1H, *J*=7.5 Hz, 6-H (indoline)], 7.14–7.29 [m, 2H, 4-H and 7-H (indoline)], 7.98 and 8.13 [2br s, 1H, 1-H (indoline)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 21.8, 22.3, 22.4, 24.8, 24.9, 34.7, 35.2, 37.0, 37.3, 55.6 and 56.4 (cyclohexyl), 33.8 and 34.0 (C_3), 42.4 and 42.8 [C_3 (indoline)], 52.1 and 52.2 (OCH_3), 53.0 (C_2), 109.6 and 109.7 [C_5 (indoline)], 121.3 and 121.5 (CN), 122.4 and 122.5 [C_6 (indoline)], 124.0 and 124.1 [C_4 (indoline)], 128.1 and 128.3 [C_7 (indoline)], 129.3 and 129.6 [C_{3a} (indoline)], 141.2 and 141.6 [C_{7a} (indoline)], 174.9 and 175.2 (CO_2CH_3), 179.5 and 179.8 [C_2 (indoline)]; ES-MS *m/z* 342.2 (100) $[M+1]^+$.

3.7. General procedure for the DMDO-mediated oxidation of amino nitrile 8. Method A: synthesis of methyl (2*S*,3a*RS*,8a*SR*)-1-(1-cyanocyclohexyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-yl-carboxylate (20 and 21)

A 0.05 M solution of DMDO[18] in acetone (2.4 mL, 0.12 mmol) was added under argon to a cooled solution (−78 °C) of amino nitrile **8** (50.1 mg, 0.12 mmol) in CH_2Cl_2 (5 mL); the mixture was stirred at that temperature for 3 h and, then, it was evaporated to dryness. The residue was purified by circular chromatography, using 20–50% EtOAc gradient in hexane as eluant, to give the diastereoisomeric mixture of **20** and **21** as a foam (34.8 mg, 85%), which could not be resolved and resulted to be unstable. HPLC [Novapak C_{18} (3.9×150 mm, 4 μm), (A:B, 25:75)] t_R 11.22 (74%, **20**) and 12.12 (11%, **21**) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–2.26 (m, 10H, cyclohexyl), 2.26 (dd, 0.88H, J=1.5 and 14 Hz, 3-H), 2.36 (dd, 0.12H, J=8 and 13 Hz, 3-H), 2.46 (dd, 0.88H, J=9 and 14 Hz, 3-H), 2.69 (dd, 0.12H, J=7.5 and 13 Hz, 3-H), 3.53 and 3.80 (s, 0.37 and 2.63 H, OCH_3), 4.08 (dd, 1H, J=1.5 and 9 Hz, 2-H), 4.31 (br s, 1H, OH), 4.50 (s, 1H, 8-H), 5.25 (d, 1H, J=3 Hz, 8a-H), 6.62 (d, 1H, J=8 Hz, 7-H), 6.80 (t, 1H, J= 7.5 Hz, 5-H), 7.12 (t, 1H, J=8 Hz, 6-H), 7.26 (d, 1H, J=7.5 Hz, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 and 23.1 ($C_{3'}$ and $C_{5'}$), 24.8 ($C_{4'}$), 35.3 and 37.8 ($C_{2'}$ and $C_{6'}$), 43.0 (C_3), 53.2 (OCH_3), 59.1 ($C_{1'}$), 61.5 (C_2), 88.3 (C_{3a}), 89.3 (C_{8a}), 111.3 (C_7), 119.8 (C_5), 120.5 (CN), 122.6 (C_4), 129.5 (C_6), 130.9 (C_{3b}), 147.6 (C_{7a}), 177.2 (CO_2); ES-MS m/z 342.2 (100) $[M+1]^+$.

3.8. General procedure for the DMDO-mediated oxidation of amino nitrile 8. Method B: synthesis of the hexahydropyrroloimidazoindole derivatives 16 and 17

A 0.05 M solution of DMDO[18] in acetone (1.8 mL, 0.09 mmol) and TFA (500 μL) were successively added under argon to a cooled solution (−78 °C) of amino nitrile **8** (30.2 mg, 0.09 mmol) in CH_2Cl_2 (4.5 mL); the mixture was stirred at that temperature for 3 h and, then, it was processed as indicated for the H_2O_2-mediated oxidation, to give the hexahydropyrroloimidazoindoles **16** (19.1 mg, 88%) and **17** (2.9 mg, 12%).

3.9. General procedure for the cyclization of the hexahydropyrrolo[2,3-*b*]indoles 20 and 21 to the hexahydropyrroloimidazoindoles 16 and 17

TFA (500 μL) was added to a solution of the epimeric mixture of pyrrolo[2,3-*b*]indoles **20** and **21** (30 mg, 0.09 mmol) in CH_2Cl_2 (4.5 mL) and the reaction mixture was stirred at room temperature for 30 min. Then, the mixture was processed as indicated for the H_2O_2-mediated oxidation, to give the hexahydropyrroloimidazoindoles **16** (26.1 mg, 87%) and **17** (3.9 mg, 13%).

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