Unprecedented Stereospecific Synthesis of a Novel Tetracyclic Ring System, Hybrid of Tetrahydropyrrolo[2,3-*b*]indole and Tetrahydroimidazo[1,2-*a*]indole, Via a Domino Reaction upon a Tryptophan Derived Amino Nitrile

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SUPPORTING INFORMATION:

Contents: Experimental procedures and characterization data for the new compounds **1-10**, and 1D NOESY spectra of **2a** and **6a,b**.

Synthesis of *N*-(1-cyanocyclohexyl)-*L*-tryptophan methyl ester (1**) and its enantiomer **1c**.** TEA (0.77 mL, 5.5 mmol) was added to a solution of H-*L*- or -*D*-Trp-OMe·HCl (1.400 g, 5.5 mmol) in dry CH₂Cl₂ (45 mL). After 30 min of stirring at room temperature under argon, cyclohexanone (0.517 mL, 4.99 mmol) was added, and the stirring was maintained for 3 h. Then, the solution was cooled to -23 °C, and ytterbium triflate (76 mg, 0.12 mmol) and trimethylsilylcyanide (TMSCN, 1.04 mL, 8.13 mmol) were added. After stirring successively 1 h at -23 °C and 20 h at room temperature, the mixture was evaporated to dryness. The residue was dissolved in CH₂Cl₂ (20 mL), the solution was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, and evaporated. The residue was purified by flash chromatography, using 20-50% gradient of EtOAc in hexane as eluant, to yield the corresponding α -amino nitrile **1** or **1c**.

N-(1-cyanocyclohexyl)-*L*-tryptophan methyl ester (**1**). Yellow solid (1.290 g, 80%); mp 114-116 °C (CCl₄-hexane); $[\alpha]_D^{20} = +8.13$ (*c* 1.1, MeOH). RP-HPLC [Novapak C₁₈ (3,9 x 150 mm, 4 μ m), (A:B, 30:70)] $t_R = 5.70$ min. ¹H RMN (200 MHz, CDCl₃) $\delta = 1.09$ -1.96 [m, 10H, 2-, 3-, 4-, 5-, 6-H (cyclohexyl)], 2.07 (bs, 1H, α -NH), 3.01 [dd, 1H, *J* = 7 and 14 Hz, β -H (Trp)], 3.12 [dd, 1H, *J* = 7 and 14 Hz, β -H (Trp)], 3.60 (s, 3H, OCH₃), 3.78 [t, 1H, α -H(Trp)], 7.00 [d, 1H, *J* = 2.5 Hz, 2-H (indole)], 7.07 [dd, 1H, *J* = 7 and 8 Hz, 6-H (indole)], 7.11 [dd, 1H, *J* = 7 and 8 Hz, 5-H (indole)], 7.27 [d, 1H, *J* = 7 Hz, 7-H (indole)], 7.54 [d, 1H, *J* = 7 Hz, 4-H(indole)], 7.99 [bs, 1H, 1-H(indole)]. ¹³C-RMN (50 MHz, CDCl₃) $\delta = 22.1$ and 21.9 [C₃ and C₅(cyclohexyl)], 24.8 [C₄(cyclohexyl)], 30.3 [C $_{\beta}$ (Trp)], 35.8 and 36.3 [C₂ and C₆(cyclohexyl)], 56.4 [C₁(cyclohexyl)], 57.2 [C $_{\alpha}$ (Trp)], 110.5 [C₃(indole)], 111.1 [C₇(indole)], 118.6 [C₆(indole)], 119.4 [C₄(indole)], 121.6 (CN), 122.6 [C₅(indole)], 122.9 [C₂(indole)], 127.5 [C_{3a}(indole)], 136.0 [C_{7a}(indole)], 175.2 (CO₂CH₃). EM-ES *m/z* (%): 326.2 (100) [M+1]⁺. Anal. Calcd for C₁₉H₂₅N₃O₂ (%): C 69.70, H 7.70, N 12.83. Found: C 69.87, H 7.45, N 13.00.

N-(1-cyanocyclohexyl)-D-tryptophan methyl ester (1c). Yellow solid (1.273 g, 79%); $[\alpha]_D^{20} = -8.04$ (*c* 1.03, MeOH).

Acid promoted tautomerization of α -amino-nitriles **1 and **1c**. Synthesis of **2-4**.** Concentrated H₂SO₄, 85% H₃PO₄, or TFA (the amount was calculated according to the % in CH₂Cl₂ indicated in the Table 1 of the communication) was added to a solution of the Trp-derived amino nitrile **1** or **1c** (20 mg, 60 μ mol) in CH₂Cl₂ (2 mL), except for reactions in neat TFA. The mixture was stirred at room temperature or 50 °C, and for a variable time, as specified in Table 1 of the communication. Afterward, the reaction mixture was sequentially poured into ice, neutralized with NH₄OH (for H₂SO₄ and H₃PO₄) or saturated solution of NaHCO₃ (for TFA), and extracted with CH₂Cl₂ (20 mL). The organic extracts were successively washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄, and evaporated to dryness. The residue was analyzed by ¹H NMR and RP-HPLC, to determine the ratio of the reaction products **2-4**, and purified by circular chromatography, using 45-100 % gradient of EtOAc in hexane as eluant. Significant analytical and spectroscopic data of the hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indole derivatives **2a**, **2b**, and **2c** are summarized in Table 1.

N-(1-Carbamoylcyclohexyl)-L-tryptophan methyl ester (3). Yellow solid (3.91 mg, 19 %); mp 157-158 °C (CCl₄); $[\alpha]_D^{20} = +13.72$ (*c* 1, MeOH); RP-HPLC [Novapak C₁₈ (3,9 x 150 mm, 4 μ m), (A:B, 30:70)]: *t_R* = 14.41 min. ¹H-RMN (200 MHz, CDCl₃) δ = 1.19-1.82 [m, 10H, 2-, 3-, 4-, 5-, 6-H (cyclohexyl)], 2.19 (bs, 1H, α -NH), 2.96 [dd, 1H, *J* = 8.5 and 14 Hz, β -H (Trp)], 3.11 [dd, 1H, *J* = 6 and 14 Hz, β -H (Trp)], 3.52 [t, 1H, α -H (Trp)], 3.64 (s, 3H, OCH₃), 4.77 and 6.45 (bs, 2H, CONH₂), 7.00 [d, 1H, *J* = 2 Hz, 2-H (indole)], 7.11 [dd, 1H, *J* = 8 and 9 Hz, 6-H (indole)], 7.18 [dd, 1H, *J* = 7 and 8 Hz, 5-H (indole)], 7.33 [d, 1H, *J* = 9 Hz, 7-H (indole)], 7.59 [d, 1H, *J* = 8 Hz, 4-H (indole)], 8.21 [sa, 1H, 1-H (indole)]. ¹³C-RMN (50 MHz, CDCl₃) δ = 21.6 and 21.4 [C₃ and C₅ (cyclohexyl)], 25.2 [C₄(cyclohexyl)], 31.8 and 34.6 [C₂ and C₆ (cyclohexyl)], 31.0 [C β (Trp)], 57.1 [C α (Trp)], 61.7 [C₁(cyclohexyl)], 111.2 [C₃(indole)], 111.4 [C₇(indole)], 118.8 [C₆(indole)], 119.7 [C₄(indole)], 122.3 [C₅ (indole)], 123.0 [C₂(indole)], 127.4 [C_{3a}(indole)], 136.0 [C_{7a}(indole)], 176.7 (CO₂CH₃), 179.4 (CONH₂). EM-ES *m/z* (%): 326.2 (100) [M+1]⁺. Anal. Calcd for C₁₉H₂₅N₃O₃ (%): C 66.45, H 7.34, N 12.24. Found: C 66.41, H 7.57, N 11.98.

(3*S*)-3-Methoxycarbonyl-tetrahydro- β -carboline-1-spiro-cyclohexane (**4**, reference 25 of the communication). Yellow solid (3.91 mg, 19 %). mp 173-174 °C (benzene), lit^[25] mp 173-175 °C (benzene); $[\alpha]_D^{20} = -52.18$ (*c* 0.57, MeOH); RP-HPLC [Novapak C₁₈ (3,9 x 150 mm, 4 μ m), (A:B, 50:50)]: *t_R* 1.61 min. ¹H-RMN (200 MHz, CDCl₃) δ = 1.20-1.97 [m, 10H, (cyclohexyl)], 2.74 (dd, 1H, *J* = 11 and 15 Hz, 4-H), 3.08 (dd, 1H, *J* = 4.5 and 15 Hz, 4-H), 3.83 (dd, 1H, 3-H), 3.81 (s, 3H, OCH₃), 7.07 (dd, 1H, *J* = 7 and 8 Hz, 7-H), 7.14 (dd, 1H, *J* = 7.5 and 8 Hz, 6-H), 7.31 (d, 1H, *J* = 8

Hz, 8-H), 7.45 (d, 1H, J = 7.5 Hz, 5-H), 7.74 (bs, 1H, 9-H). ^{13}C -RMN (125 MHz, CDCl_3) δ = 21.4, 21.1, 25.6, 38.7 and 34.7 (cyclohexyl), 26.3 (C_4), 52.1 (C_3 and OCH_3), 52.6 (C_1), 106.8 (C_{4a}), 110.8 (C_8), 118.1 (C_7), 119.5 (C_5), 121.7 (C_6), 127.1 (C_{9a}), 135.6 (C_{4b}), 140.5 (C_{8a}), 174.3 (CO_2CH_3). EM-ES m/z (%): 299.3 (100) $[\text{M}+1]^+$.

Synthesis of (2*S*,10*bS*,10*cR*)-2-methoxycarbonyl-5-oxo-hexahydropyrrolo[1',2',3':1,9*a*,9]-imidazo[1,2-*a*]indole-4-spiro-cyclohexane (5). Cs_2CO_3 (146 mg, 0.45 mmol) and MeI (168 μL , 2.7 mmol) were added to a solution of **2a** (97 mg, 0.3 mmol) in dry CH_3CN (4 mL), and this mixture was stirred at 80 °C in a pressure tube for 2 days. Afterward, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (20 mL), and the resulting solution was 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 15-25% gradient of EtOAc in hexane as eluant. Significant analytical and spectroscopic data of **5** are summarized in Table 1.

Methylation of the amidine group. Synthesis of *Z*- and *E*-(2*S*,10*bS*,10*cR*)-5-methylimino-2-methoxycarbonyl-hexahydropyrrolo[1',2',3':1,9*a*,9]-imidazo[1,2-*a*]indole-4-spiro-cyclohexane (6*a* and 6*b*). MeI (112 μL , 1.8 mmol) was added to a solution of **2a** (97 mg, 0.3 mmol) in dry CH_3CN (4 mL), and this mixture was stirred at 80 °C in a pressure tube for 24 h. Afterward, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (20 mL), and the resulting solution was 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 2-15% gradient of MeOH in CH_2Cl_2 as eluant, to yield the unresolved (5:1) mixture of **6a** and **6b**. Significant analytical and spectroscopic data of this mixture are summarized in Table 1.

Synthesis of (2*S*)-2-(indol-3-yl)methyl-3,5-dioxo-1,4-diazaspiro[5.5]undecane (7). A solution of **2a** (200 mg, 0.62 mmol) in 1N HCl (3 mL) was refluxed at 100 °C for 2 days. After cooling at room temperature, the solution was extracted with CH_2Cl_2 (20 mL). The organic extract were successively washed with H_2O (5 mL), saturated NaHCO_3 (5 mL), H_2O (5 mL), and brine (5 mL), dried over Na_2SO_4 , and evaporated to dryness. The residue was purified by flash chromatography, using 15-25% gradient of EtOAc in hexane as eluant. Foam (143 mg; 74 %). $[\alpha]_{\text{D}}^{20}$ = -23.74 (c 1, MeOH). RP-HPLC [Novapak C_{18} (3,9 x 150 mm, 4 μm), (A:B, 50:50)]: t_{R} 2.68 min. ^1H -RMN (200 MHz, CDCl_3) δ = 1.16-2.00 (m, 10H, 7-, 8-, 9-, 10- and 11-H), 3.30 (dd, 1H, J = 6 and 14.5 Hz, 2- CH_2), 3.39 (dd, 1H, J = 4.5 and 14.5 Hz, 2- CH_2), 3.80 (dd, 1H, J = 4.5 and 6 Hz, 2-H), 7.01-7.09 [m, 2H, 2- and 6-H (indole)], 7.14 [dd, 1H, J = 7 and 8 Hz, 5-H (indole)], 7.30 [d, 1H, J = 8 Hz, 7-H (indole)], 7.64 [d, 1H, J = 7 Hz, 4-H (indole)], 7.75 (bs, 1H, 4-H), 8.10 [bs, 1H, 1-H(indole)]. ^{13}C -RMN (50 MHz, CDCl_3) δ = 20.2 and 20.7 (C_8 and C_{10}), 25.4 (C_9), 25.9 (2- CH_2), 29.8 and 33.3 (C_7 and C_{11}), 54.2 (OCH_3), 58.1 (C_6), 110.5 [C_3 (indole)], 111.4 [C_7 (indole)], 119.1 [C_6 (indole)], 119.9 [C_4 (indole)], 122.4 [C_5 (indole)], 123.8 [C_2 (indole)], 127.9 [C_{3a} (indole)], 136.3 [C_{7a} (indole)], 173.9

(C₃), 177.2 (C₅). EM-ES m/z (%): 312.3 (100) [M+1]⁺. Anal. Calcd for C₁₉H₂₅N₃O₃ (%): C 69.43, H 6.80, N 13.49. Found: C 69.52, H 7.00, N 13.60.

General procedure for the synthesis of the *N*-acetyl and -benzyloxycarbonyl derivatives **8 and **9**.** Propylene oxide (147 μ L, 2.1 mmol) and the corresponding acylating agent (chloroacetyl chloride or benzyl chloroformate, 2.1 mmol) were successively added to a 0 °C cooled solution of **2a** (97.5 mg, 0.3 mmol) in dry CH₂Cl₂ (3 mL). After 6 h of stirring at room temperature, the mixture was evaporated to dryness, and the residue was purified by circular chromatography, using 20-50% gradient of EtOAc in hexane as eluant. Significant analytical and spectroscopic data of the acetyl (**8**) and benzyloxycarbonyl (**9**) derivatives are summarized in Table 1.

Saponification of **2a. Synthesis of the sodium salt of *Z*-(2*S*,10*bS*,10*cR*)-5-imino-hexahydropyrrolo[1',2',3':1,9*a*,9]-imidazo[1,2-*a*]indole-4-spiro-cyclohexane-2-carboxylic acid (**10**).** 1N NaOH (1.53 mL, 1.5 mmol) was added to a solution of **2a** (50 mg, 0.15 mmol) in (2:1) MeOH/H₂O (3 mL). After 6 h of stirring a room for 10 h, the MeOH was evaporated. The residue was diluted with H₂O (4 mL), and the resulting solution was neutralized to pH 7 with acid resin Dowex 50W X4. The resin was filtered off, and the filtrate was lyophilized. Significant analytical and spectroscopic data of **10**, contaminated with $\approx$ 10% of L-tryptophan, are shown in Table 1.

Table 1: Analytical and spectroscopic data of the hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]-indole derivatives **2**, **5**, **6**, and **8-10**.

	2a	2b	5	6a	6b	8	9	10
R	Me	Me	Me	Me	Me	Me	Me	Na
X	(<i>Z</i>) NH	(<i>E</i>) NH	O	(<i>Z</i>) N-Me	(<i>E</i>) N-Me	(<i>Z</i>) N-Ac	(<i>Z</i>) N-Z	(<i>Z</i>) NH
Formula ^a	C ₁₉ H ₂₃ N ₃ O ₂	C ₁₉ H ₂₃ N ₃ O ₂	C ₁₉ H ₂₂ N ₂ O ₃	C ₂₀ H ₂₅ N ₃ O ₂	C ₂₀ H ₂₅ N ₃ O ₂	C ₂₁ H ₂₅ N ₃ O ₃	C ₂₇ H ₂₉ N ₃ O ₄	C ₁₈ H ₂₀ N ₃ NaO ₂
Yield (%)	100 ^b	7 ^c	95	75	14	65	100	87
mp (°C)	108-110 (cyclohexane)	97-99 (CH ₃ Ph/hexane)	foam	127-129 (cyclohexane)		foam	foam	amorphous
ESI-MS (<i>m/e</i>) [M+1] ⁺	326.1	326.1	327.2	340.3		369.2	459.2	334.2
[α] _D ²⁰	-102.64 ^d (<i>c</i> 1.01, MeOH)	-23.02 (<i>c</i> 0.7, MeOH)	-62.20 (<i>c</i> 1.07, MeOH)	--		-133.06 (<i>c</i> 1.06, MeOH)	-76.04 (<i>c</i> 1.29, MeOH)	--
<i>t</i> _R (min) (A:B) ^e	2.02 (50:50)	1.69 (50:50)	4.69 (50:50)	2.14 (50:50)	2.68 (50:50)	4.16 (50:50)	16.77 (50:50)	2.29 (25:75)
¹ H-NMR ^f								
1-H	2.01-2.13 2.43	2.12-2.17 2.52	2.16 2.44	2.19 2.54	2.19 2.54	2.16 2.54	2.07-2.18 2.49	1.97-2.08 2.35
2-H	3.21	3.37	3.39	3.48	3.48	3.30	3.38	3.13
7-H	7.32	7.68	7.42	7.05	7.77	7.30	7.42	7.68
8-H	7.18	7.32	7.25	7.13-7.20	7.24	7.22	7.12-7.17	7.29
9-H	6.98	7.15	7.08	7.00	7.02	7.07	7.03	7.16
10-H	7.11	7.22	7.18	7.13-7.20	7.13-7.20	7.17	7.15	7.34
10b-H	3.76	3.87	3.83	3.89	3.80	3.82	3.78	3.91
10c-H	5.82	5.97	5.97	5.68	5.87	5.92	5.89	5.98
R	3.64	3.70	3.69	3.70	3.70	3.70	3.65	
Cyclohex.	1.37-2.13	1.23-2.17	1.12-2.02	1.12-2.15	1.12-2.22	1.22-2.24	1.04-2.18	1.13-2.16
X	--	--	--	3.55	3.41	2.21	5.19, 7.30	--
J _{1,2}	6 and 11.5	6 and 11	6 and 11.5	10 and 5.5	--	6 and 11	6 and 11	6 and 10
J _{1,10b}	0 and 8.5	0 and 8	1 and 8.5	0.5 and 7.5	0 and 6	1 and 8.5	0 and 8.5	0 and 8
J _{10b,10c}	7	7	7.5	6.5	7	7	7	7

Table 1 (Continuation)

	2a	2b	5	6a	6b	8	9	10
¹³ C-NMR ^g								
C ₁	40.0	39.9	38.7	40.2	39.8	42.5	39.2	40.3
C ₂	61.0	61.4	60.9	60.0	62.0	61.7	61.6	61.5
C ₄	72.7	74.6	72.1	71.9	71.9	76.0	76.6	74.3
C ₅	173.9	173.3	173.5	168.8	168.8	160.6	165.4	173.9
C _{6a}	144.0	140.7	141.0	145.2	145.2	141.8	141.3	140.4
C ₇	114.9	115.4	115.2	114.0	115.4	116.2	116.5	115.0
C ₈	128.5	129.1	128.7	128.6	128.5	128.6	128.6	128.3
C ₉	124.1	125.1	125.1	123.5	124.3	125.0	124.5	125.5
C ₁₀	124.7	125.7	124.8	125.3	125.3	124.7	125.1	125.5
C _{10a}	135.2	135.7	134.7	134.8	135.2	135.8	135.9	136.7
C _{10b}	43.0	42.6	42.7	42.0	42.0	39.4	42.5	41.8
C _{10c}	87.3	89.4	85.2	89.3	87.8	88.4	88.4	89.6
Cyclohex.	22.0, 22.4, 25.6, 29.7, 34.3	21.7, 22.3, 25.2, 29.1, 33.8	21.5, 22.4, 25.2, 29.1, 32.7	21.9, 22.2, 25.0, 30.3, 36.1	21.9, 22.2, 25.8, 30.5, 36.1	21.6, 22.4, 25.3, 28.8, 33.4	21.5, 22.3, 25.2, 28.6, 32.7	21.2, 22.0, 25.0, 28.3, 33.1
R	52.1, 174.1	52.5, 173.4	52.4, 180.7	52.2, 174.2	52.2, 173.9	52.4, 173.6	52.2, 173.5	--
X	--	--	--	42.9	32.6	27.2, 181.4	67.9, 128.2, 128.4, 128.9, 135.8, 173.5	--

^aSatisfactory analyses for C, H, N, except for **10**. ^bYield obtained in the treatment of **1** with 85% H₃PO₄ or neat TFA. ^cYield obtained in the treatment of **1** with 50% TFA in CH₂Cl₂. ^d[α]_D²⁰ of the enantiomer **2c** = +101.18 (*c* 1.1, MeOH). ^eNovapak C₁₈ (3.9 × 150 mm, 4μm). A = CH₃CN, B = 0.05 % TFA in H₂O. ^fSpectra registered at 400 or 500MHz in CDCl₃ for **2**, **5**, **6**, **8-9**, and in D₂O for **10**. Assigned with the help of COSY spectra. ^gSpectra registered at 100 or 125MHz in CDCl₃ for **2**, **5**, **6**, **8-9**, and in D₂O for **10**. Assigned with the help of HSQC y HMBC spectra.

1D NOESY spectrum of **2a**, using the DPGSE-NOE sequence with a mixing time of 800 ms

1D NOESY spectrum of **6a** + **6b**, using the DPGSE-NOE sequence with a mixing time of 800 ms

1D NOESY spectrum of **6a** + **6b**, using the DPGSE-NOE sequence with a mixing time of 800 ms